Chapter 1 . Introduction and Aims

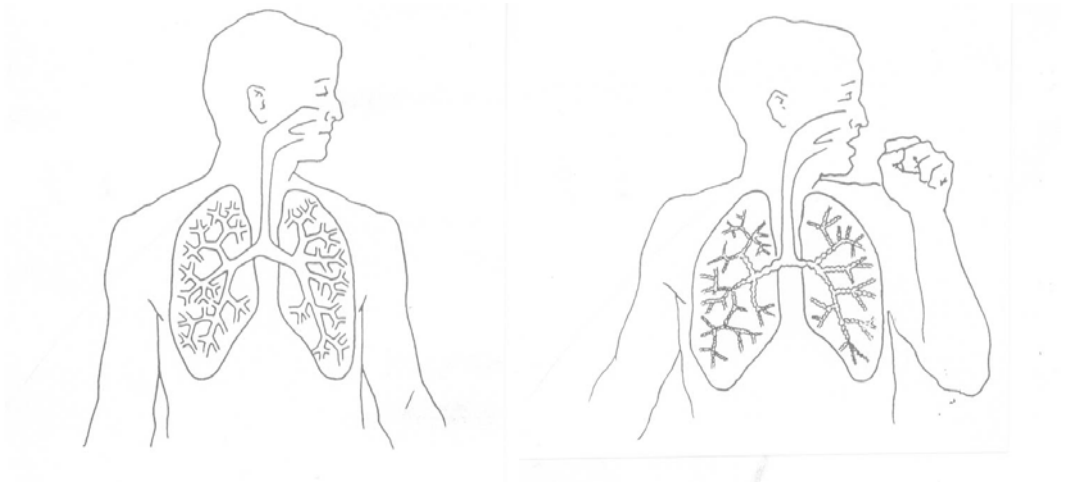
1.1 Respiratory illness including Asthma

The major functions of the respiratory system are to supply the body with oxygen and dispose of carbon dioxide. The secondary organs of the respiratory system include the nose and nasal cavity, the pharynx, the larynx, and the trachea. The primary organ of respiration is the lung, composed of bronchii, bronchioles, and the terminal air sacs involved in air exchange, known as the alveoli. Respiratory illness results from an impaired respiratory system. It is a broad term that includes mild complaints such as hayfever and sinusitis, as well as life-threatening conditions such as tuberculosis, chronic obstructive pulmonary disease (COPD), and asthma.

Asthma is an important respiratory illness. It is an inflammatory disease of the airways, characterised by periodic attacks of wheezing, shortness of breath, chest tightness and coughing (Marieb 2001). Once someone has asthma, the inflammation persists even during symptom-free periods and makes the airways hypersensitive to many irritants. When asthma is under control, the airways are clear and air flows easily in both directions. The aetiology of asthma is unclear, but current theories suggest it is due to environmental, lifestyle and/or genetic factors. Typical environmental and lifestyle factors include immune system reaction due to an infection in early life, diet, indoor and outdoor pollutants and aeroallergens.

Asthma attacks involve excessive mucus production, swelling of the airways due to an inflammatory response, and constriction of bronchial passages (Marieb 2001). As a result, less air can enter and leave the lungs (Figure 1.1). The airway narrowing is usually reversible either spontaneously or with medication (Marieb 2001). Asthmatic wheezing results from the narrowing airways creating a higher velocity flow, while chest tightness occurs from the irritation of nerve receptors. Coughing develops as asthma improves, dislodging thickened mucus plugs from the trachea-bronchial area (Marieb 2001).

Figure 1.1. Normal lungs and lungs during an asthma attack



When asthma is under control, the airways are clear and air flows easily in and out

When asthma is not under control, the sides of the airways in the lungs are thick and swollen

Reproduced from (Global initiative for Asthma 1995)

1.2 Burden of illness

Numerous studies of the prevalence of asthma have been undertaken, yet it remains difficult to state with confidence how many people suffer from the disease. Asthma prevalence can be measured in terms of self-reported wheeze, doctor-diagnosed asthma, or a combination of symptoms and lung function abnormality (Toelle *et al.* 1992). Some of the variation in reported prevalence rates is attributable to differing approaches to measuring the prevalence rates, differences in the age groups studied, and variation in settings in which the studies have been conducted. Another likely reason for the inconsistencies in prevalence rates is that there is no agreed definition of asthma (Woolcock 1987).

The Australian Bureau of Statistics 1995 National Health Survey estimated that 11.3% of all Australians (2.04 million people) had asthma. This represented an increase from the 1989-90 National Health Survey, which estimated 8.5% of Australians (1.04 million people) had the condition. However, this apparent change may have been due in part to heightened awareness of the condition or improved identification. The prevalence of asthma is highest in those aged less than 25 years, peaking at 19% in the 5-14 years age group (Australian Bureau of Statistics 1997). In fact asthma is the most common chronic disorder of school-age children, and it is a major cause of school absences.

While the incidence of asthma is increasing, there has been a reduction in mortality from asthma over recent times. Asthma accounted for only 0.3% of deaths in 1999, an approximate halving since 1989 (Australian Bureau of Statistics 2002). This decrease has been attributed to an increased understanding of the triggers of asthma, and more effective management of the illness.

The total cost burden of asthma to the Australian community in 1991 was estimated to be $650 million (National Asthma Campaign Australia 1992). The cost is approximately equally divided between medical related costs (including medications, medical consultations, and hospitalisations) and indirect costs (including lost productivity due to absenteeism, and time off work to attend consultations). The cost of the disease is comparable with that of coronary heart disease, which amounts to $623 million annually (Crowley *et al.* 1992).

Asthma is the sixth most common condition seen by general practitioners, accounting for 32 of every 1,000 consultations (Britt *et al.* 1999). It is also among the top five reasons for doctors to refer patients to hospital. During 1997-98, asthma was the principal diagnosis in 1.1% of all hospital separations, with an average stay of 3.5 days (Australian Bureau of Statistics 1997).

Although asthma incidence has been rising in the western world, it has remained low in developing countries. The International Study of Asthma and Allergies in Childhood (ISAAC) was conducted in 56 countries across all continents during 1994-1995 (ISAAC Steering Committee 1998; Robertson *et al.* 1998). In this study, the prevalence of any wheeze in the past 12 months was used as an outcome measure. This is a sensitive, but not specific measure of asthma, as it may include some very mild wheezing. Amongst 13-14 year olds, it ranged from under 5% in Albania, China, Greece, Georgia, Indonesia, Romania and Russia to 29-32% in Australia, New Zealand, Republic of Ireland and the UK. The prevalence of 4 or more attacks in the past 12 months is a more specific indication of clinically important asthma. This ranged from 1% in the non-English speaking countries to over 9% in Australia, New Zealand, UK and Canada. There were some interesting patterns across countries in the ratio of prevalence of asthma diagnosis to prevalence of frequent wheezing. For example, Malta and Kuwait had a low asthma to wheeze ratio while Oman and Singapore had a high asthma to wheeze ratio. This is likely to be due in part to differences in diagnostic practice.

1.3 Diagnosis and management

Lung function tests are usually performed to diagnose asthma and also to measure progress in treatment. Once diagnosed with asthma, it is recommended that the general practitioner devise an asthma action plan. The aim of the plan is for patients to learn to control their asthma by recording their peak flow levels in a booklet twice-daily. Under normal circumstances asthmatics can lead a full and productive life. The majority of children with mild asthma will not be troubled by it in later life, but the majority of children with moderate to severe asthma are likely to continue to have symptoms in adult life (Robertson 2002).

Medications may be used to both relieve symptoms and to prevent them from occurring. Medications used to treat asthma may be broken up into 2 drug classes: bronchodilators and anti-inflammatory agents. Most Bronchodilators provide immediate relief of asthma symptoms and so are often referred to as relievers. They work by opening up the bronchial tubes - the air passages in the lungs - so that more air can flow through. Anti-inflammatory agents reduce the inflammation in the airways, thereby treating the underlying problem rather than just treating the symptoms. There are four types of medicines in the anti-inflammatory class – inhaled corticosteroids, oral corticosteroids, cromolyns and leukotriene-receptor antagonists. Both bronchodilators and anti-inflammatory agents are usually prescribed as an inhaler, but may also be nebulised, taken orally or given intravenously in severe acute attacks to rapidly control symptoms.

Atopy, a form of allergy, is an important factor in many people with asthma, especially children. In addition to asthma it can cause hayfever and eczema. Antihistamines, corticosteroid nasal sprays and decongestants are used to relieve or prevent the symptoms of hayfever and other allergies. They predominately work by blocking the effects of histamine, a substance produced by the body during an allergic reaction. These medications come in various forms and are available both over-the-counter and by prescription.

1.4 Risk factors

An asthma attack can be triggered by a number of factors, including allergens, weather conditions, viral infections, irritants and exercise. An allergen is a substance that can cause an allergic reaction. House dust mites are the most common potential allergen. Outdoor allergens include pollens from trees, grasses and weeds, feathers and mould spores. Inhaled cool and dry air is a strong asthma trigger. Changing weather conditions, including changes in temperature, barometric pressure, humidity, and strong winds can also trigger asthma. Viral infections of the

respiratory tract often act as a major aggravating trigger of asthma. This is usually due to direct infection of the lower respiratory tract, although a nasal blockage may prevent air from being humidified and warmed in the nose. Exercise can also trigger an asthma attack, with an estimated 80% of allergic asthmatics having symptoms of wheeze following exercise (Panditi and Silverman 2003). Tobacco smoke, whether directly or passively inhaled, has harmful effects on the airways and is especially irritating for many patients with asthma. Indoor and outdoor irritants such as strong odours and sprays, like perfumes, household cleaners, cooking fumes and paints may aggravate individuals who have asthma. Air pollution, including particulate matter, sulphur dioxide (SO_2), nitrogen dioxide (NO_2), and ozone (O_3) have been associated with exacerbation of asthma (Bates 1995). Avoiding exposure to known allergens and respiratory irritants has been shown to substantially reduce asthmatic symptoms (Boner *et al.* 1998; Gold 2000).

1.5 Respiratory illness related to the environment

The effect of air pollutants on respiratory health was dramatically demonstrated in the London smog of 1952, which was caused mainly by inefficient combustion of coal on open domestic fires. More than 4,000 deaths were associated with the resultant pollution that occurred during a few days in the month of December. Whilst most deaths occurred in individuals with pre-existing heart and lung disease, there were many deaths in apparently healthy children and adults. Current concentrations of air pollution are greatly reduced in comparison to the levels observed in the 1950s.

Human exposure to polluted air chiefly affects the lungs, eyes and skin. It also indirectly affects the heart and other organs, and general bodily health. Air pollution is of particular concern to people with asthma, as even low concentrations may increase the risk of developing asthma, or exacerbate existing conditions (Brimblecombe 1986; Elsom 1992). The actual biological pathway is not well understood but three respiratory effects are thought to result from exposure to air pollution:

- Direct irritation of the sensitive airways
- A toxic effect, causing cellular damage and inflammation of the airways
- Modification of the immune system, resulting in greater susceptibility to other asthma triggers, especially entry of allergens (Wardlaw 1993).

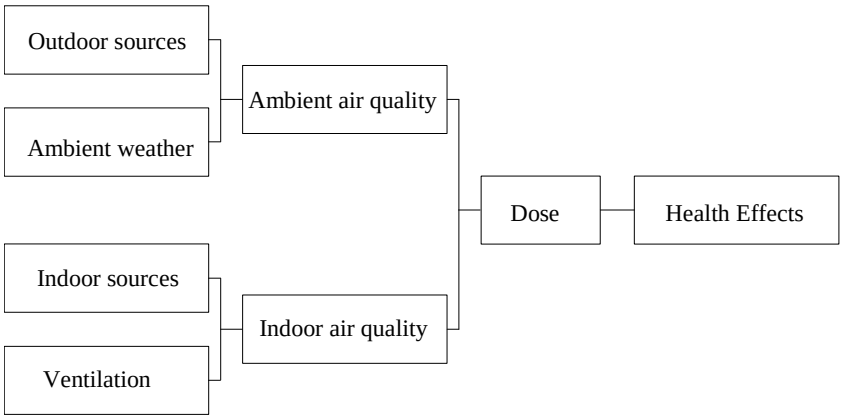
Many epidemiological studies have modelled the effect of air pollution on health and they have been reviewed on several occasions (Holland *et al.* 1979; World Health Organization Regional

Office for Europe 1987; Lipfert 1993; Ostro 1993; Dockery and Pope 1994; Schwartz 1994b; Katsouyanni *et al.* 1995; Smith *et al.* 1999). The consensus has been that particulates at current observed levels can pose a greater danger to human health than the better-known kinds of air pollution, such as ozone, sulphur dioxide and carbon monoxide, though the biological mechanism is still not clear. By comparison, there have been relatively few studies and no reviews examining the effect of pollen or spore counts on health. The following sections summarise the evidence for each of the exposures measured in this study.

1.5.1 Air pollution

Air pollution is defined as the increased presence of atmospheric solids, liquids, or gaseous compounds within the atmosphere (Crawford 1976). Mobile and stationary sources emit primary pollutants directly into the atmosphere. These pollutants are principally carbon monoxide, nitrogen oxides, hydrogen sulphide, sulphur oxides, hydrocarbons, particulate matter, and heavy metals such as lead. Photochemical reactions in the atmosphere produce secondary pollutants such as ozone. The concentrations of primary and secondary pollutants determine air quality. The effect of emissions on air quality is strongly mediated by weather and climatic conditions (inversion level height, mixing, wind speed and direction, air pressure, and precipitation). Figure 1.2 summarises the suspected causal relationships.

Figure 1.2. Determinants of exposure to air pollution that underlie the development of health effects



The concentration of air pollutants is expressed by either weight per volume of air (micrograms per cubic metre; $\mu g/m^3$) or by volume as parts per hundred million (pphm). A description of the

pollutants of most concern to asthmatics, namely particulates, sulphur dioxide, nitrogen dioxide, and ozone is provided below.

Particulate Matter, including PM10

"Particulate matter" (PM) or particulates, are fine solid or liquid particles that occur in many sizes. It is a general term used to describe tiny bits of matter (up to 100 μm) floating in the atmosphere, such as smoke, fine ash, soot, dirt, dust and liquid droplets. It also includes aerosols that are formed in the atmosphere from gaseous combustion by-products such as volatile organic compounds, sulphur dioxide and nitrogen oxides. Not all particulates result from human activities. They also include natural sources such as soil dust, sea salt spray, pollens and moulds. Whilst individual particles cannot be seen with the naked eye, collectively they can appear as black soot, dust clouds, or grey hazes.

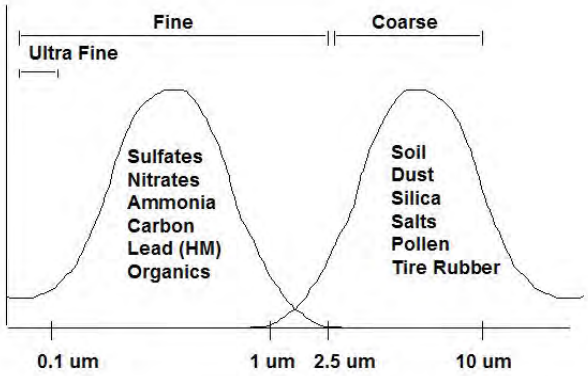
There are several ways of measuring particulates. The coefficient of haze, or smoke shade, is an average index of particulates that does not provide any information about particle size or chemical composition – factors which toxicological studies have shown to be of great importance in producing physiological effects. Total suspended particulates (TSP) are measured using filters.

Because of their weight, particulates larger than 10 micrometres (μm) are affected by gravity and velocity. If inhaled, they tend to collect in the throat or get caught by nasal hairs, and are eliminated from the body by sneezing, coughing, nose blowing or through the digestive system. For this reason, the measurement of particulates usually focuses on matter with a mass median aerodynamic diameter less than 10 μm, so called PM10. For comparison, a human hair is about 75 μm in diameter.

Particulates that are 2.5 μm or smaller (PM2.5) are sometimes referred to as the fine fraction of PM10. They can remain suspended in the air for days or weeks and can travel long distances. They are of special concern to the protection of lung health as they are easily inhaled deeply into the lungs where they can be absorbed into the bloodstream or remain embedded within the terminal airways. Both PM10 and PM2.5 are measured using high volume samplers with special filters, or more complex instruments such as the Tapered Element Oscillating Microbalance (TEOM) or nephelometer.

Figure 1.3 shows the size distribution of particulate matter, where the conventional distinction between “fine” and “coarse” particles is indicated. Fine particles (considered in the air quality context as those less than 2.5 μm) are mainly anthropogenic, whereas PM10 includes a significant amount of natural particulate matter in the range 2.5 to 10 μm. The load of natural particles is even higher in TSP.

Figure 1.3. PM10 air pollution size and composition



Reproduced from (California Environmental Protection Agency 2001)

Early research into particulate pollution focused on TSP but was gradually refined to PM10, which are more likely to enter the lungs. More recently, PM2.5 have begun to replace PM10 as the particulate measured (Dockery *et al.* 1993; Pope *et al.* 1995b) and there has been some evidence of associations between PM2.5 and mortality, rather than the course fraction of PM10 (Schwartz *et al.* 1996a).

Until about 1980, analyses suggested that mortality and morbidity were not associated with particulates and other pollution until high levels were reached (Holland *et al.* 1979). However, a number of more recent epidemiological studies have established mortality and morbidity associations with lower levels of particulate air pollution (Pope *et al.* 1991; Dockery *et al.* 1993; Koenig *et al.* 1993; Pope *et al.* 1995b). Remarkable consistency and coherence in the results support the evidence for substantial adverse health effects due to air pollution (Bates *et al.* 1990). There is good epidemiological evidence that short-term increases in PM10 concentrations are associated with increases in: total mortality, as well as mortality from respiratory or cardiac disease; respiratory and probably cardiac hospitalisations; emergency room visits for asthma and other respiratory conditions; functional limitation as reflected by restricted activity days and school absenteeism; and the daily prevalence of respiratory

symptoms (Dockery and Pope 1994). Short-term increases in PM10 are also associated with small decreases in the level of pulmonary function in children and in adults with obstructive airways disease (Dockery and Pope 1994). These results have been observed in cross-sectional, cohort, time series, case-control studies and air pollution episodes (Pope *et al.* 1995a).

Most of the evidence shows increasing mortality due to particles starting above a PM10 concentration of 20 $\mu g/m^3$. Although there is no evidence of a value of PM10 below which no population impacts are detectable (Schwartz and Marcus 1990). The association is essentially linear in the ranges observed with no plateau. In a major review, it was shown that a 10 $\mu g/m^3$ increase in PM10 concentration is associated with a 1.0% increase in total deaths per day (Dockery and Pope 1994). Stronger associations have been observed with cardiovascular disease (1.4% per 10 $\mu g/m^3$ PM10) and respiratory disease (3.4% per 10 $\mu g/m^3$ PM10). The estimated impacts on mortality, hospitalisation and emergency room visits are relatively small compared to estimates on school absenteeism and incidence of respiratory illness (Table 1.1).

Table 1.1. Summary of the health effects of PM10 on respiratory outcomes (per 10 $\mu g/m^3$ increase in PM10)

	Estimate of effect	
Respiratory outcome	**Overall**	**Asthmatics**
All causes mortality	1.0%	n.a.
Respiratory mortality	3.4%	n.a.
Cardiac mortality	1.4%	n.a.
Respiratory hospital admissions	0.8%	1.9%
Emergency department visits	1.0%	3.4%
Asthma attacks	n.a.	3.0%
Bronchodilator use	n.a.	3.0%
Lower respiratory symptoms	n.a.	3.0%
Upper respiratory symptoms	n.a.	0.7%
Cough	1.2%	2.5%
School absenteeism	4.1%	n.a.
Peak expiratory flow	0.08%	n.a.

Source: (Dockery and Pope 1994)
n.a. Not applicable as no results were reported for this outcome.

Some population subgroups are particularly sensitive to PM10 effects, and experience more severe adverse health effects for a given particle exposure. These include the elderly, subjects with pre-existing lung or heart disease, and asthmatics. Younger children may also be more sensitive. This may be a result of children breathing more air per body weight than adults, or because their respiratory systems are still developing (Schwartz 2004).

Independent studies with different investigators in different settings have found consistent estimates of the health effects of PM10 (Dockery and Pope 1994). This suggests that the concentration level of particulates may be more responsible for the observed associations than the chemical mix. In addition, since similar results have been obtained in all climates (warm, cold, dry and moist), it suggests that either climatic factors are not important confounders, or that the statistical models used have adjusted adequately for them.

The findings of the scientific health studies on particulates have generated a great deal of criticism and debate (Dockery *et al.* 1993; Dockery and Schwartz 1995; Moolgavkar *et al.* 1995a; Moolgavkar *et al.* 1995b; Samet 1995; Moolgavkar and Luebeck 1996; Moolgavkar *et al.* 1996). Criticisms have mainly concerned the statistical approaches used, such as inadequate adjustment for additional factors, such as other pollutants, or changes in weather, that could alternatively explain the findings. Of special concern is that different statistical methods on the same datasets have produced inconsistent results in some instances. However, a recent reanalysis of a large body of data has produced supportive evidence for significant health effects at current levels of particulate pollution (Samet *et al.* 2000a).

Sulphur dioxide

Sulphur dioxide is a colourless gas with strongly acidic properties, and is generated from natural sources such as volcanoes, tidal flats and decomposing organic material, and anthropogenic sources such as coal and oil combustion (Butler 1979). It is characterised by a very pervasive and offensive odour in ambient air. The term oxide refers to the family of compounds including sulphur dioxides, sulphuric acid, and various sulphate salts. Sulphur dioxide is the main sulphur oxide emitted by fossil fuel combustion.

There are several methods of measuring sulphur dioxide including the conductrimetric method and reference method (pararosaniline method), although the conductrimetric method is highly unreliable at low levels of sulphur dioxide (Fox and Jeffries 1979). Sulphur dioxide is recorded in parts per hundred million (pphm) or $\mu g/m^3$. Because sulphur dioxide and sulphates may be

transported long distances before being removed from the atmosphere, and because there is conversion of sulphur dioxide to sulphates during the transport period, there is not always a close relationship between ambient concentrations of the sulphates and emissions of sulphur dioxide in the immediate vicinity.

Sulphur dioxide is a major air pollutant in many parts of the world and its effect on health has been well documented. Long-term exposure has been shown to damage the cells lining the airways in animals. Also, short-term exposure to sulphur dioxide leads to constriction of the airway bronchioles, which can produce symptoms of asthma. Asthmatics respond in a similar way to non-asthmatics with the development of bronchoconstriction, but at lower concentrations (World Health Organization Regional Office for Europe 2000).

In a review of 46 daily time series studies Stieb reported that a 0.94 pphm increase in SO_2 was associated with a 0.9% (95% CI: 0.7 to 1.2%) increase in mortality (Stieb *et al.* 2002). Stronger associations have been observed between sulphur dioxide and mortality in Athens where annual SO_2 concentrations are approximately 3 pphm (Touloumi *et al.* 1994) but not in the United States, where the concentrations are much lower (Samet *et al.* 2000a). Toxicological studies have shown that the oxidation products of sulphur dioxide, namely sulphuric acid and sulphates are more likely to have harmful health effects than sulphur dioxide itself. The association between sulphur dioxide and daily mortality or morbidity sometimes disappeared when particulates were included in the regression model (Schwela 2000) but the relative contribution of sulphur dioxide and particulate matter to acute adverse health effects is difficult to disentangle (Kjellstrom *et al.* 2002). Particulates are known to act as precursors, increasing the sensitivity of the respiratory tract to the effects of sulphur dioxide. This is widely termed a synergistic effect on health, and in a statistical regression model it is expressed as an interaction between PM10 and SO_2. In a review of forty health studies, it was confirmed that the respiratory effects of sulphur dioxide were enhanced in the presence of total suspended particulates (Zmirou and Dechenaux 1991).

Nitrogen dioxide and nitrates

Nitrogen dioxide (NO_2) is an oxidant gas, derived by the combustion of atmospheric nitrogen and formed by oxidation of nitric oxide (NO) in the presence of ozone and ultra-violet light. In Australia, the major outdoor sources of nitrogen oxides are motor vehicles. Common indoor sources are unvented gas appliances, such as gas stoves and heaters. Another important indoor source of personal NO_2 exposure is cigarette smoke.

The health effects of inhaled NO_2 are not well understood despite extensive research in laboratories and in various clinical and epidemiological settings (Samet and Utell 1990; Berglund *et al.* 1993). Experimental animal studies have suggested that pro-inflammatory toxicity in the lower respiratory tract, increased susceptibility to bacterial lung infections, and irreversible emphysema-like structural changes may occur. Amongst people with asthma, the resulting impaired lung function may make them more susceptible to the effect of other allergens (Folinsbee 1992). There have been several epidemiological studies examining the effects of NO_2 from automotive and indoor sources (Braun-Fahrlander *et al.* 1992; Rossi *et al.* 1993) but very few examining nitrates. In a study of Denver asthmatics over a 3 month period, an association was found between fine nitrates and both asthma symptoms and bronchodilator use (Perry *et al.* 1983).

Ozone

Ozone is generated when oxides of nitrogen and hydrocarbon compounds react in the presence of sunlight. In Australia, the major source of ozone is vehicle exhausts. Ozone causes irritation of the eyes and the respiratory tract, and has been associated with increased rates and episodes of asthma (Woodward *et al.* 1995; McDonnell *et al.* 1999).

1.5.2 Aeroallergens

An aeroallergen is any airborne substance that can cause an allergic response. In this thesis the term aeroallergen refers to pollen and fungi.

Pollen

Pollens are small, egg-shaped male cells of flowering plants which are necessary for plant fertilization. Their diameter is typically in the range of 10 to 50 μm. The pollen from plants with bright flowers, such as roses, usually does not cause allergic problems, since these flowers have large and waxy pollens that are carried from plant to plant by insects such as bees. Conversely, many trees, most grasses, and certain low-growing weeds are primarily wind-pollinated, as the small, light, dry pollens of these plants are well suited for dissemination by wind currents. These are the pollens that cause allergies.

Each plant has a period of pollination, which does not vary greatly from year to year, although weather conditions can affect the amount of pollen in the air at any one time. The pollinating

season starts in spring, with trees pollinating earliest. The pollen of trees such as western red cedar and cypress is often the cause of early spring seasonal hayfever. Grasses follow next in the cycle, and are usually the cause of late spring and early summer hayfever. Weeds usually pollinate in late summer and early autumn. A species of weed pollen, called Asteraceae, has been identified as the most allergenic plant in NSW. This is a very large family of plants, and includes Ragweed, which is responsible for hayfever (Bass *et al.* 2000).

Fungi

Fungi, or moulds are another inhaled allergen that may trigger asthma. They are parasitic, and consist of microscopic fungi without stems, roots or leaves. They can be found in soil, vegetation and rotting wood. Their spores float in the air like pollen. Outdoor fungi spores reach their peak in late summer and autumn. The common fungi are Alternaria, Cladosporium and Aspergillus species.

General comments on aeroallergens

The amount of airborne allergens present in the air can be measured in a variety of ways, including suctional trap devices, gravitational slides, or rotating rods prepared with an adhesive. They are typically reported daily as pollen grains and fungal spores per cubic metre of air. Sampling techniques such as the type of device used and its location within the community affect counts. Symptoms may be affected by recent exposure to other allergens, personal intensity of pollen exposure, and individual clinical sensitivity. Pollen concentrations of 50 grains/m^3 are associated with symptoms in all susceptible people (Parikh and Scadding 1997). Pollen counts may vary widely from day to day during a season, and are most prevalent between the hours of 5:00-10:00 am (University of Melbourne 2003).

There have been few studies examining the effect of pollen and fungi counts on health. Some studies have adjusted particulates for the effect of pollens (Rossi *et al.* 1993; Gielen *et al.* 1997). Some studies have suggested that air pollutants adhering to pollen grains may increase their impact (Kjellstrom *et al.* 2002). Several studies have noted increased asthma admissions following thunderstorms and this is thought to be due to pollens breaking up and producing fine allergic particles (Bellomo *et al.* 1992). In Melbourne, starch granule concentrations have been found to be approximately fifty times greater following periods of rainfall (Suphioglu *et al.* 1992). They have been examined in very few daily diary studies (Delfino *et al.* 1997; Epton *et al.* 1997). In a study of 22 asthmatics in Southern California a 4000 grain/m^3 increase in pollen

was associated with a 0.36 increase in symptom score, a 0.33 increase in inhaler use, and a 12.1 L/min decrease in peak flow (Delfino *et al.* 1997).

1.6 Modelling the effect of air quality on health outcomes

From a statistical point of view, determining the association between ambient air quality and respiratory health may be broadly construed as a regression problem with "respiratory health" as the dependent variable and features of "ambient air quality" as the independent variable(s). Measurements of the pollutants are taken at air monitoring stations located at fixed points in an air pollution control district. Measurements of many pollutants are taken almost continuously in time. Health effects data are reported for discrete times and may be measured on a continuous scale (e.g. lung function) or dichotomous (e.g. cough symptom). A linear regression of effects (or their logarithms) on exposure levels (or their logarithms) and other variables of interest yields the estimated association. Investigations comparing acute respiratory events with pollution levels should continue, using better design, analysis and exposure techniques (Whittemore 1981).

1.7 Air pollution standards

An important step in environmental protection is regulation. This requires distinguishing between pollutant levels that will and will not be tolerated by the population. The core indicators for metropolitan air quality are generally in the form of the number of days on which relevant air quality monitoring goals are exceeded at air quality monitoring sites operated by the Environmental Protection Agency (EPA).

In the USA, National Ambient Air Quality Standards (NAAQS) in the form of air quality regulations have been in place since the 1970s for several pollutants including particulate matter, sulphur dioxide (SO_2), ozone (O_3), and nitrogen dioxide (NO_2). Their standards are based on a synthesis of available scientific information on health effects of air pollution, which are reviewed every 5 years. In 1987 the United States EPA standard for total suspended particulates (TSP) was revoked in favour of a PM10 standard (Chow 1995). This PM10 air quality standard was introduced following studies that established that the particles of greatest health concern were those equal to, or less than 10 μm in aerodynamic diameter (so called PM10) that can penetrate into sensitive regions of the respiratory tract (Dockery and Pope 1994; Chow 1995). In 1997 the United States EPA again revised the NAAQS, and the particulate matter standard based on PM10 was replaced with one that was perceived as much more stringent, based on PM2.5 (diameter less than 2.5 micrometres).

Prior to 1998, the NSW EPA data were reported against air quality goals set by the National Health and Medical Research Council (NHMRC) and key international agencies such as the World Health Organization (WHO) and the United States EPA (New South Wales Environment Protection Authority 1995). The NSW EPA had guidelines for both total suspended particulates (TSP) and PM10. The 24-hour average TSP goal was set at 260 $\mu g/m^3$, based on the United States EPA standard prior to its revocation in 1987. The annual average goal for TSP was 90 $\mu g/m^3$, based on the recommendations of the NHMRC. The standard for PM10 was actually composed of both an acute (24-hour allowable average) and a chronic component (annual allowable average). The EPA 24-hour standard for PM10 was 150 $\mu g/m^3$, not to be exceeded more than once a year. The annual arithmetic average of PM10 was not to exceed 50 $\mu g/m^3$.

In 1998, the National Environmental Protection Council (NEPC) developed Australia's first national ambient air quality standards. The standards are legally binding and must be met by the year 2008. Those relating to the air pollutants associated with asthma are listed in Table 1.3. There is no longer a guideline for TSP, and the 24-hour goal for PM10 has been reduced from 150 $\mu g/m^3$ to 50 $\mu g/m^3$. The 24-hour goal for sulphur dioxide has been reduced from 14 pphm (NAAQS) to 8 pphm.

Table 1.2. National ambient air quality standards

Air pollutant	Averaging period	Maximum ambient concentration	Goal by 2008
PM10 †	24-hours	50 $\mu g/m^3$	5 days per year
Sulphur dioxide	1-hour	20 pphm	1 day per year
	24-hour	8 pphm	1 day per year
Nitrogen dioxide	1-hour	12 pphm	1 day per year
	12 months	3 pphm	None
Ozone	1-hour	10 pphm	1 day per year
	4-hour	8 pphm	1 day per year

pphm. Parts per hundred million
†. Measured using a Tapered Element Oscillating Microbalance (TEOM)

Recommended air quality levels do not take into account the increased individual sensitivity caused by a disease such as asthma, as they were not set with more vulnerable individuals in

mind. It is possible that asthmatics may have increased asthma symptoms with levels of pollution at or below the recommended ambient air quality levels.

1.8 The Hunter Perspective

The Hunter Region is located on the east coast of Australia in the state of New South Wales, between 31.5^{o} and 33^{o} south, and between 150^{o} and 152^{o} east. The Region's total population was 540,490 in the 1996 census and 563,586 in the 2001 census (Hunter Valley Research Foundation 2003). At the time of this study, it had a steel industry base and residential areas adjacent to heavy industry. Air quality monitoring during the 1980s and early 1990s showed the local communities were exposed to air pollution at levels approaching or exceeding existing guidelines. TSP concentrations in inner Newcastle were equivalent to those in more polluted cities, such as Copenhagen and Denver. SO_2 concentrations measured in the inner Newcastle area were slightly above those for Toronto, Canada (Bridgman *et al.* 1992). The city has a regular succession of calms (inversions) and winds, thus providing the large temporal and spatial range needed for regression analysis.

In recent years, researchers in the Hunter have carried out studies of air pollution and airways problems in school children in the vicinity of Lake Munmorah power station, Nelson Bay and Dungog (Henry *et al.* 1991a; Henry *et al.* 1991b) using protocols similar to those used in Belmont, Wagga Wagga and other areas of NSW (Woolcock 1987).

The differences in air pollution sources, climate and geography in the Hunter Region challenged the generalisability of overseas findings to the Australian setting. There was also community pressure to implement a research study, as there was general concern about the possible health effects of industrial air pollution. In 1992 the NSW Government established the Metropolitan Air Quality Study (MAQS) and Health and Air Research Program (HARP) to investigate and address urban air quality in NSW metropolitan areas. The MAQS study, conducted by the NSW Environmental Protection Agency (EPA), aimed to develop a detailed knowledge of urban pollutant chemistry and meteorology. The HARP study, undertaken by the NSW Health Department, examined the effect of air pollution on asthma (New South Wales Environment Protection Authority 1996). The Hunter-Illawarra Study of Airways and Air Pollution (HISAAP), a sub-study of HARP, examined asthma and air pollution in the Newcastle and Wollongong regions of NSW. These areas are exposed to industrial sources of air pollution. A similar study was conducted in Sydney which examined transport associated pollution (Jalaludin *et al.* 2000).

1.9 Aims

The aims of Phase II of the HISAAP study were to:

1. document changes in symptoms and lung function over time in symptomatic children;
2. report daily 24-hour averages of PM10 and SO_2 to which children are exposed;
3. report the number of days when the pollution level exceeded the NSW EPA guideline for TSP, PM10 and $SO_{2;}$
4. estimate the change in lung function on days with poor air quality (e.g. higher outdoor particulates, higher exposures of SO_2) compared to days with lower exposures. Similarly, estimate the risk of worsening respiratory symptoms and increased medication usage as a result of poor air quality. This will be done for each child, and for the symptomatic group as a whole.

The aims of this thesis were the same as those for Phase II of the HISAAP study, but the examination of item 4 was limited to lung function (evening peak flow), respiratory symptom (day cough) and medication (bronchodilator use). The focus of the thesis is the statistical analysis of the data, and a comparison of the available methods to analyse longitudinal data.

This thesis describes the analysis of a study in which the parents of a group of primary school children recorded information in a daily diary and the data that were recorded were compared to daily measures of air pollution. The study was the second in a program that addressed questions related to the health effects of current levels of ambient air pollution on the respiratory system. In keeping with many previous studies on this topic, the subjects were young children.

The protocol for the study was prepared by the principal investigator, Professor Michael Hensley, together with Dr Peter Lewis and Dr John Wlodarczyk. The project was funded by a 1993 Environmental Trusts Grant. The candidate was awarded a scholarship from the project team in 1997 to collate all data received, perform the data management and analysis on the project.

1.10 Structure of thesis

A full description of the Hunter component of the HISAAP study is provided in Chapter 2. In Chapter 3 a summary of the statistical methods used to examine the effect of air pollution (focusing on PM10 and SO_2) and aeroallergens (pollen and fungi) on respiratory health is provided. Chapter 4 describes the data management and statistical methods used in the analysis of the data. The statistical results are presented in Chapters 5 to 9. Chapter 10 discusses the findings and limitations of the study, and suggests possibilities for further research.

Chapter 2 . Study Methods

This chapter will detail the sampling methods used in the Hunter component of the Hunter Illawarra Study of Airways and Air Pollution (HISAAP) study (Section 2.1). The methods of conducting the initial interview, follow-up interviews, and final interview are described as well as the instructions given in completing the daily diary (Section 2.2). The five study areas that were chosen for the study will be briefly described (Section 2.3). Each of the study and outcome factors will be presented (Section 2.4). The measurement of particulates and sulphur dioxide as part of the Newcastle air quality network will be explained. In addition, the measurement of pollens, and the species of pollens and fungi collected, will be described (Section 2.5). Some information collected in Phase I was used in the analysis and this is described in Section 2.6. Many data sources were used to obtain the air quality data and these are described in Section 2.7.

2.1 Sampling Methods

This study was conducted as part of the HISAAP project. HISAAP aimed to provide evidence on the association between primary school children's lung health and outdoor air quality, in particular sulphur dioxide and particulates. In this thesis, analyses are limited to the Hunter Region of NSW, Australia.

Study areas were selected based on exposure and non-exposure to industry generated air pollution. Three areas were exposed: Stockton, Mayfield, and North Lake Macquarie. Control areas were sought that had similar socio-economic profiles and existing air quality monitoring stations. The control areas that were selected were Wallsend and Beresfield (Figure 2.1).

All primary schools within a 3.5 km radius of air quality monitoring stations were approached to be involved in the study. All 18 eligible schools participated: Stockton (2), Wallsend (4), Mayfield (4), Beresfield (4), and North Lake Macquarie (4). The names of the schools involved in the study and their distance from industry and air quality monitoring stations are listed in Appendix A Table A1.1.

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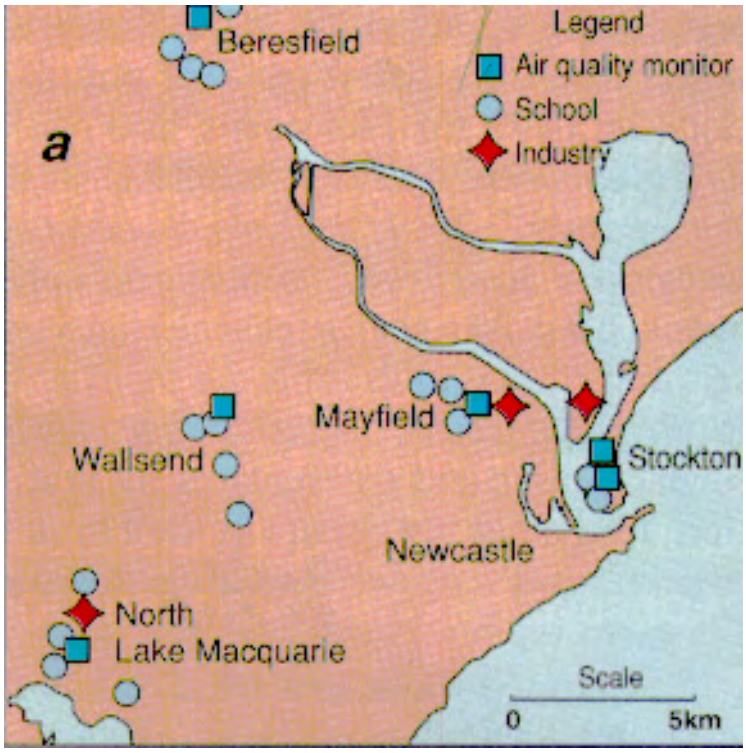
Figure 2.1. The study areas showing the positions of air quality monitoring sites, industrial sites and the schools involved in the study



Reproduced from (Lewis *et al.* 1998)

All children enrolled in years 3 or 4 at each of the primary schools within the five areas were eligible to participate. Year 5 students at Stockton and North Lake Macquarie were also enrolled, in order to achieve an adequate sample size.

Phase I was a cross-sectional study which aimed to investigate the association between outdoor air pollution and the respiratory health of children. It was conducted from October to December 1993. Children received consent forms and questionnaires at school. Parents completed the questionnaires, and children returned them to their teachers. If a questionnaire was not returned after two weeks, a copy was posted to the parents for completion, with a request that it be returned by reply-paid post. The three main outcome measures were:

- 4 or more episodes of wheeze;
- 4 or more chest colds;
- night-time cough, without a cold, for more than 2 weeks; all within the previous twelve months.

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Analysis of the data revealed an association between the average level of particulates and the prevalence of chest colds and night-time cough. However, no association was found between SO_2 and any of the outcomes (Lewis *et al.* 1998).

The target population for Phase II of the study comprised those children identified from Phase I who had at least one of the three respiratory symptoms listed above.

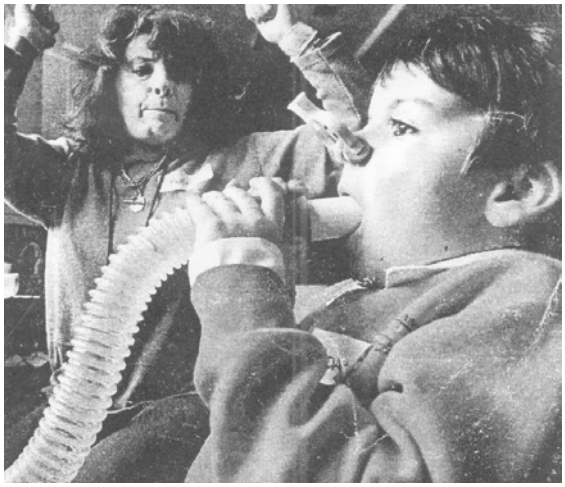
2.2 Study methods

Preliminary results of Phase I were presented to the schools' Parents and Friends Association prior to Phase II commencing. All children defined as being symptomatic in Phase I were identified, after which the study team sent a letter to each child's parents or legal guardian describing the study procedures for Phase II. Parents or guardians were then contacted by phone and invited to attend an appointment at the child's school whereby the study was explained in more detail. The information and introduction letters used are in Appendix B1 and Appendix B2.

2.2.1 Initial interview

If written consent (form in Appendix B3) was obtained at the initial interview, the interviewer conducted baseline measures of each child's lung function. The forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1) were obtained using a Vitalograph spirometer (Figure 2.2). Children were required to exert maximum effort throughout expiration. After at least one trial blow three values were obtained. The highest FEV_1 and FVC were recorded, which is considered standard practice (Quanjer *et al.* 1997). The predicted spirometry values were recorded using a standard formula based on the child's sex, age and height. For children with abnormal spirometry, a letter was sent to their own doctor with the results (form in Appendix B4).

Figure 2.2. Spirometry measured at initial interview



Reproduced from Newcastle Herald, 25 July 1997.

During the initial interview, the parents and children were also trained in the study methods. Training involved the correct use of the Mini-Wright peak expiratory Flow Meter to obtain peak expiratory flow (PEF), and completion of the daily diary. Parents were asked to complete the diary, or at least closely supervise their child's diary keeping and PEF measurements. Subjects were instructed to leave the diary blank if they forgot to complete it on any particular day, and not to fill it in retrospectively. The dose, frequency and brand name of any regular medications that the children were taking were also recorded. There was no definition of "regular" provided. The data collection form used for the initial interview is in Appendix B5.

2.2.2 Follow-up interviews

Fortnightly contact was maintained throughout the study period (including school holidays) by the same interviewer, and the contact alternated between telephone and personal visits to the schools. During the monthly visits to the schools, the diary cards were collected and reviewed for compatibility with the previous phone contact. New cards were given out, with each child receiving a maximum of eight cards in total throughout the study, allowing for 8 months of data collection. The team member also observed the child's PEF measurement technique and recorded a grade of competence. Any change to medication use was recorded in the follow-up interviews. Refer to Appendix B6 for the data collection forms used in telephone interviews and personal interviews.

2.2.3 Final Interview

Each child's spirometry, as well as height and weight measurement was repeated at the conclusion of the study. Refer to Appendix B7 for the form used to record these measurements.

2.2.4 Diary

The daily diary that the children completed was based on one that was used in the Lake Munmorah study of asthmatic symptoms and air pollution (Henry *et al.* 1991b). Modifications incorporated into the design of the new diary card included additional questions relating to irritation of mucous membranes, and whether they slept at home. Refer to Appendix B8 for the diary card used. Each parent was instructed to complete the diary twice daily, when the child woke up in the morning and in the evening before going to bed. For each peak flow recording, the child was asked to perform 3 PEF measurements in the standing position. The largest value was recorded in the diary, which is standard practice (Brunekreef and Hoek 1993). The diary also used the same symptom severity scale that was used in the Lake Munmorah study – the scale ranged from 0 (absent, no discomfort at all) through to 6 (most severe discomfort ever).

Subjects were asked to report each morning on events that had occurred during the night (approximately 8 pm to 8 am). They recorded cough, wheeze, chest tightness and breathlessness symptoms, peak flow, and whether they had slept the preceding night in their home suburb.

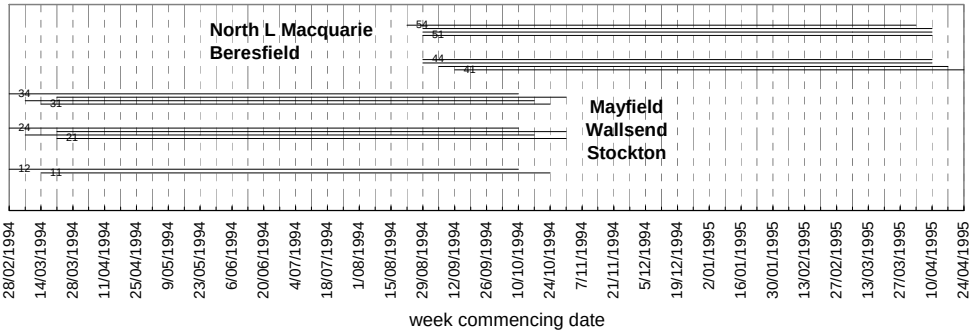
In the evenings, subjects reported on events that had occurred during the day (approximately 8 am to 8 pm). They recorded the presence or absence of the same symptoms as for the morning, and their peak flow measurements. They also recorded any eye and nose symptoms (scale 0 to 6), absences from school, visits to the doctor or hospital. The perceived amount of pollution was recorded on a scale from 0 (none at all) to 3 (a lot).

Daily recordings were made of the number of times that reliever medications were taken, with separate records for the number of puffs and for the number of occasions that a nebuliser was used. The number of times that inhaled corticosteroids were taken was recorded in the "office use only" section, as the question was added after printing of the diary cards. Parents were instructed to circle the trade-name of any medications taken during the four-week period covered by the diary card. Medication options included bronchodilators, inhaled corticosteroids, oral corticosteroids, cromolyns, nasal preparations for hayfever, antihistamines/decongestants or antibiotics.

The study was initially designed to obtain daily diary information from all children over the same 12-month period. However, this was not feasible for two reasons. Firstly, the project team recognised that it was unrealistic to expect primary school children to accurately report their symptoms for 12 months. In addition, there were insufficient staffing resources to complete the study according to the original proposal. Only three members of the team were available to cover the five geographical areas and it was considered necessary to have one member assigned exclusively to each area for most of the study period.

Therefore, the project investigators decided to modify the study design so that each area participated for 7 months. Children attending school at Stockton, Mayfield, and Wallsend kept diaries from February to October 1994. Children at Beresfield and North Lake Macquarie kept diaries from August 1994 to April 1995. Hence, diaries were completed over the four seasons with a slight overlap between the two waves. The schools within the same area did not all start the study at exactly the same time, due to staff constraints. However, the starting date was consistent within each school (Figure 2.3). The aim was to obtain 30 weeks of data from each subject.

Figure 2.3. Time period of data collection, by school



Each horizontal line represents 32 weeks duration. This was the longest period of follow-up achieved at any school in the Hunter. Subjects were requested to complete the diary for 30 weeks.
School IDs are displayed in this figure. Refer to Appendix A Table A1.1 for the coding scheme applied.

2.3 Study Areas

The Hunter Region's principal source of air pollution is industry. The main sources of industry in each of the study areas during the period of the study (1994/1995) are described below. Note that most of this information is still current, except for the closure of the Broken Hill Proprietary

(BHP) steelworks plant in Mayfield in September 1999. A list showing the location of industry in each of the study areas is provided in Appendix A Table A1.2.

2.3.1 Stockton

Stockton is located in close proximity to the industrial areas of Mayfield and Kooragang Island. The population of Stockton were exposed to industrial air pollution from Mayfield and Kooragang Island when the prevailing winds were from the northwest, which occurs frequently during the cooler months of the year, from April to October. Incitec, an industrial fertilizer plant, was based at Kooragang Island. Part of the site was used to store and grind the rock phosphate used to manufacture Single Superphosphate at Incitec's Cockle Creek site at North Lake Macquarie. Incitec manufactured specialty granulated ammonium phosphate/sulphate fertilizers and also stored and dispatched ammonium phosphate fertilizers and blended fertilizers. The Kooragang and Inner Newcastle Airshed Study (KINAS), which was conducted in this area in 1990, found that the Stockton area had higher levels of SO_2 and NO_2 than Mayfield at that time.

2.3.2 Wallsend

There was no industry within a 5 km radius of the air quality monitoring device at Wallsend.

2.3.3 Mayfield

At Mayfield the main industry was BHP (Figure 2.4). Steelmaking commenced in the Hunter Region with the opening of the BHP works at Newcastle in 1915. The plant was always structured as a fully integrated steelworks, combining coke ovens, blast furnaces, steel making vessels and rolling mills. Corporate reorganisation of the BHP group in 1985 resulted in the Newcastle works becoming a stand-alone division specialising in Rod and Bar products.

Figure 2.4. BHP Steelworks at Mayfield in 1997

Photograph taken by the candidate September 1997

The KINAS study identified the main pollutants for the Mayfield area as SO_2, oxides of nitrogen (NO_x) and particulates. Mayfield had the highest level of particulates in the Hunter area. The major source of SO_2 emissions in Mayfield was the BHP Rod and Bar industrial complex, which contributed 93% of emissions. Approximately 81% of NO_x emissions were from BHP Rod and Bar stacks, whilst rail activities comprised 11% and traffic comprised 5%. The main sources of particle emissions were industrial roads (33%), open surface areas (31%) and BHP Rod and Bar stacks (29%).

2.3.4 Beresfield

The socio-economic profile of Beresfield was similar to the study areas that were exposed to industrial air pollution. The location of this area with no nearby heavy industry, ensured a low level of air pollution when compared to the Stockton, Mayfield and North Lake Macquarie areas.

There were two light industries operating in this area - Beresfield Crematorium and Steggles Chicken factory. Poultry farms generated odours as part of their daily activities. Wet litter and manure, which contain high levels of organic matter, were two major sources of odour. Dust expelled from sheds could also transmit odours and cause discomfort to humans within the vicinity.

2.3.5 North Lake Macquarie

Two industries operated in the North Lake Macquarie area. They were Pasminco Metals-Sulphide (PMS) and Incitec.

Pasminco Metals-Sulphide started its operation as The Sulphide Corporation in 1897, and has operated the smelter in North Lake Macquarie since 1962 (Figure 2.5). One of the by-products of the smelting process was sulphur dioxide (SO_2). The SO_2 was used to manufacture sulphuric acid, which was also produced commercially at the plant. Data supplied by the EPA showed that ambient air levels of SO_2 in the areas surrounding the smelter regularly exceeded the recommended maximum levels for ten minute and one hour periods since 1990 (Nigel Holmes and Associates 1994). The EPA data suggested that this area had one of the highest levels of SO_2 pollution in the state. In 1994, Pasminco began a $41M upgrade and expansion of the site. These improvements were expected to reduce SO_2 levels by one-third by 1997 (Dames and Moore 1994).

Figure 2.5. Industry at North Lake Macquarie in 1997

Photograph taken by the candidate September 1997
One of the primary schools participating in the study is in the foreground, and the local industry Pasminco Metals-Sulphide is in the background.

Incitec was also situated at North Lake Macquarie. Its key activity was the manufacture of super phosphate fertilizers. The phosphate rock used in the process can produce odours as a result of Hydrogen Oxide, which can be unpleasant to members of the residential community. The level of SO_2 emissions from Incitec was very small in comparison with that from Pasminco Metals-Sulphide.

2.4 Description of outcomes

Seventeen outcomes were measured in Phase II of the HISAAP study. They included morning and evening PEF; morning and evening symptoms (cough, wheeze, chest tightness, and breathlessness); daily nose and eye symptoms; absence from school; doctor or hospital visits; and medication usage (bronchodilator, inhaled corticosteroid, and cromolyns) (Table 2.1). The outcomes investigated in this thesis were evening peak flow, day cough, and number of times a bronchodilator was used. These outcomes were chosen for three reasons:

- the study outcomes were all highly clinically relevant;
- they enabled variety in the statistical procedures adopted;
- the number of statistical analyses was manageable within the time period of the thesis.

Table 2.1. List of outcomes for Phase II of study

Outcome	Frequency of measurement	Type of variable
Peak flow	Twice daily	Continuous
Cough symptoms	Twice daily	Ordinal 0 to 6*
Wheeze symptoms	Twice daily	Ordinal 0 to 6*
Chest tightness	Twice daily	Ordinal 0 to 6*
Breathlessness	Twice daily	Ordinal 0 to 6*
Nasal symptoms	Daily	Ordinal 0 to 6*
Eye irritation	Daily	Ordinal 0 to 6*
School absence	Daily	Part-day / full-day / no
Doctor or hospital visit	Daily	Doctor / hospital / no
Bronchodilator usage	Daily	Count ¶
Inhaled corticosteroid usage	Daily	Count ¶
Cromolyns	Monthly	Yes / no

*. Analysed as a binary variable, which was 1 if the symptom score reported was between 1 and 6 (symptom present), and 0 if the symptom score reported was 0 (symptom absent)
¶. Analysed as a binary variable, which was 1 if some medication was taken, and 0 if no medication was taken

2.4.1 Lung function

Children recorded their PEF twice daily. The morning and evening peak flow were analysed separately, as the deviation from the respective mean peak flow. For each day, this was calculated by subtracting the child's mean over the entire study from their PEF for that day. For example, if a child's average evening peak flow over the whole study period was 320 L/min and

they recorded 280 L/min on a given day, the evening peak flow deviation would be –40 L/min on that day. Hence, negative numbers indicated poorer than average peak flow.

2.4.2 Cough symptoms

Morning and evening symptoms were recorded at 6 levels of severity; (0) absent; (1) barely noticeable; (2) very mild discomfort; (3) mild discomfort; (4) moderate amount of discomfort; (5) a great deal of discomfort; (6) most severe discomfort ever. These were combined as (0) absence and (1-6) presence for all analyses.

2.4.3 Bronchodilator medication usage

Subjects were instructed to record the number of puffs they required daily from inhaled bronchodilators. These were grouped into two categories, “none” and “one or more”, for the analyses.

2.5 Measurement of air quality and meteorological data

Phase II required that daily measures of particulate pollution, sulphur dioxide, pollens (speciated), mould (Alternaria) and meteorological data (temperature and rainfall) be taken for each of the study areas for the periods that children were keeping diaries.

The Newcastle and Hunter Valley Air Pollution Monitoring Networks consisted of a combination of industry maintained self-monitoring sites, and sites independently operated by the EPA (Figure 2.6). Negotiation took place with industry and the EPA during the planning of this study in order to ensure that particulates, sulphur dioxide and some meteorological variables would be measured at each site during the data collection periods of the study. The EPA sites were at Wallsend and Beresfield and these were established with the guidance of the Health and Air Research Program (HARP) group. The industry owned sites were at BHP (Mayfield), PMS (North Lake Macquarie) and Incitec (Stockton). Industries were only required by the EPA to measure TSP as a daily load on a 6-day rotating basis (6d-TSP). That is, the particles were collected for a 24-hour period every 6 days. However, all sites offered to expand their usual monitoring program to daily monitoring for particulates for the duration of the study in their areas.

Figure 2.6. Monitoring Station at North Lake Macquarie in 1997

Photograph taken by the candidate September 1997
Pasminco Metals-Sulphide is in the background

Data were also collected from the Newcastle City Council site at Mayfield and the Lake Macquarie City Council site at North Lake Macquarie. The Australian Nuclear Science and Technology Organisation (ANSTO) was awarded a contract to measure PM2.5 at Mayfield and Wallsend for the duration of the study as part of the Aerosol Sampling Project (ASP).

Standard parameters were air quality parameters determined by continuous sampling instruments, with records made every 15 seconds or 2 minutes. These samples were averaged over 10 minutes. The 10-minute averages were further averaged over 1-hour periods and if a 10-minute average was missing, the hourly average was calculated on the remaining values in the hour. If all 10-minute averages were missing the hourly value was set to missing. Ten-minute and hourly averages were available, but hourly averages were more frequently used. Standard parameters included PM2.5 (measured using nephelometry, or NEPH), PM10 (measured using Tapered Element Oscillating Microbalance, or TEOM), ozone, nitrogen oxide, sulphur dioxide, carbon monoxide, total hydrocarbons, non-methanic hydrocarbons, and lead. Also included were the meteorological parameters wind speed, wind direction, temperature, relative humidity and solar radiation.

TSP, PM10 (measured using SSI) and PM2.5 (measured using SSI) were not standard parameters as they were determined by analysis of filters. For this reason they were usually only available as a daily load on a 6-day rotating basis.

The NSW Health Department tendered a contract for pollen monitoring as part of its Health and Air Research program in 1993 (McShane and Cripps 1997). Pollen monitoring was carried out in all study areas for the duration of the study.

The data were sent to the study team at the conclusion of Phase II in electronic format by the various sources. The locations of the monitoring stations are listed in Appendix A Table A1.3. Once all available data were received and collated for each study area, the core air pollution data to be included in the analyses were decided by the research team (as described in Chapter 4).

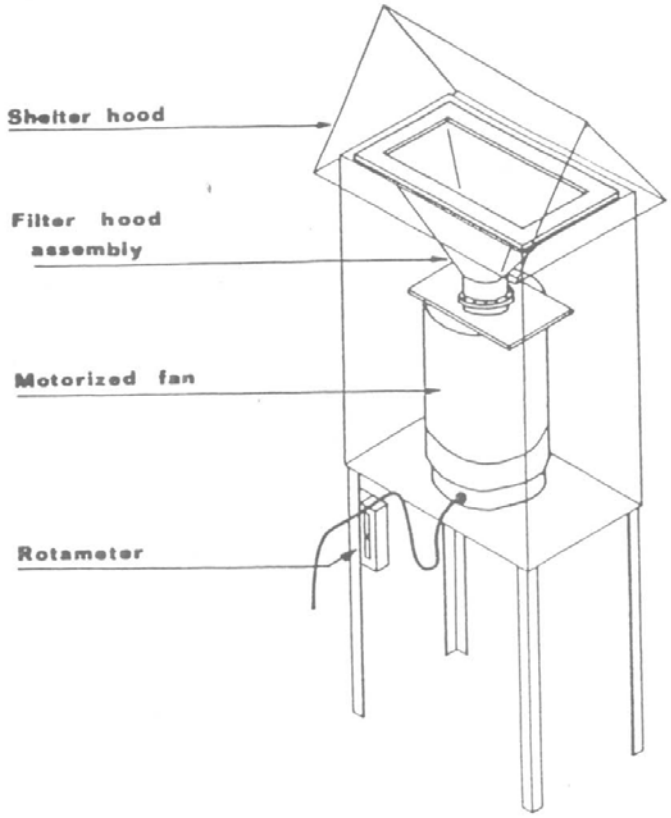
2.5.1 Measurement of particulates

Four types of particulates were measured in the Hunter Region (TSP, PM10, PM2.5 and nephelometry). TSP was measured in the industrial areas of Stockton, Mayfield, and North Lake Macquarie using a high volume sampler (HVS) following a standard protocol (Australian Standard 2724.3). The EPA monitoring stations at Wallsend and Beresfield used a Tapered Element Oscillating Microbalance (TEOM) to measure PM10, whereas Lake Macquarie City Council used a high volume sampler with a size-selective inlet (SSI) attached (Australian Standard 3580.9.6). PM2.5 were measured indirectly at EPA sites using an Integrating Nephelometer (Australian Standard 2724.4) and directly using a size-selective inlet by ANSTO.

High volume sampler

The high volume sampler method of measuring particulates was labour intensive. Prior to each day's field sampling, the filter was calibrated, dried, and weighed. It was then placed in the high volume sampler (Figure 2.7). Sample air was drawn at a flow rate of approximately 1 cubic metre per minute through a glass-fibre paper mounted beneath a protective hood to prevent material falling directly onto the paper. After a 24-hour period, the filter was taken out and placed in a dust-proof container. Each sample was weighed and the mass of the unexposed filter paper subtracted to determine the mass of the sample collected. These data, together with the total volume of air drawn in the 24-hour period, yielded the concentration (Australian Standard 2724.3). The major sources of error were from variations in flow, wind velocity, and direction relative to the orientation of the shelter. The accuracy has been reported to be within +/- 20 percent (Australian Standard 2724.3).

Figure 2.7. Schematic of a high-volume air sampler used to measure Total Suspended Particulates



Reproduced from lecture notes prepared by Dr Howard Bridgman, University of Newcastle, 1996.

Particles in the approximate size range 0.1 μm to 50 μm were collected. The TSP concentration was calculated as TSP ($\mu g/m^3$) = 10^6 * (W_f-W_i)/(Q_{std}*T) where Q_{std} was the standard mean flow rate of the air sampler; W_i was the initial mass of filter, in grams; W_f was the final mass of filter, in grams; and T was the sampling time, in hours.

Size-Selective inlet

Samples were collected and weighed as for TSP but using a high volume sampler to which a size-selective inlet (SSI) was attached. The SSI made use of the aerodynamics of particles of different sizes to ensure that only those with a diameter less than 10 μm were collected (Australian Standard 3580.9.6).

Fine particles (PM2.5) were collected on 25 mm diameter stretched Teflon filters using a cyclone size-selective inlet with a pumping rate of 22 L/min (Cohen 1999).

Tapered Element Oscillating Microbalance (TEOM)

The TEOM consisted of a sensor unit and control unit. The sensor unit contained the sample inlet and the microbalance that provided the sensitive mass measurement. The control unit housed the processing hardware and flow components. The filter was held on the end of a tapered tube. One end of the tube was free to oscillate while the other end was clamped. As particles landed on the filter, the filter mass change was detected as a frequency change in the oscillation of the tube. Combining the mass change with the flow rate through the system, provided a measure of the particle concentration. Some volatile solids at ambient temperature can vaporise at the temperature to which the air was heated and so were not counted.

Integrating Nephelometer (NEPH)

Nephelometers measure the scattering of light by atmospheric particles and gases, so called aerosol back-scattering (Australian Standard 2724.4). Air was heated to 10 degrees Celsius above air-conditioned ambient air and passed through a cone containing a light source of 530nm wavelength, a green light-filter, and a light detector. Light absorption by gases was discounted and the mass of dry particles <2.5 $\mu g/m^3$ of air was then calculated using the particle scattering extinction coefficient. Particles of 2.5 μm or less absorb virtually all the light that strikes them. Larger particles tend to reflect light and so were not counted. Further, some volatile solids at ambient temperature can vaporise at the temperatures to which the air is heated during this process resulting in an underestimation of the PM2.5 concentration. PM2.5 were recorded as coefficient of light scattering by fine particles per 10 km.

2.5.2 Measurement of sulphur dioxide

Sulphur dioxide (SO_2) was measured at all sites using pulsed fluorescent spectrophotometry (Australian Standard 3580.4.1). A stream of sample air was drawn through a cell where it was exposed to pulsed ultraviolet light, resulting in excitation of sulphur dioxide molecules. These molecules subsequently re-emit light at a different wavelength and therefore fluoresce. The intensity of the fluorescent light measured by a photomultiplier tube is proportional to the concentration of sulphur dioxide in the sample air. Concentration was recorded in parts of SO_2 per hundred million parts of air (pphm).

2.5.3 Measurement of nitrogen oxide and nitrogen dioxide

Oxides of nitrogen were measured using chemiluminescence (Australian Standard 3580.5.1).

2.5.4 Measurement of ozone

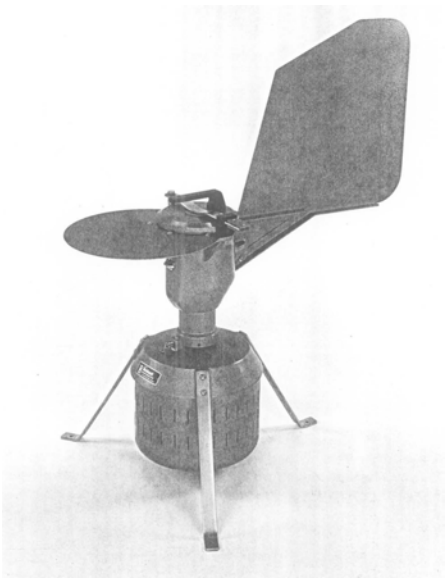
Ozone was measured by ultraviolet spectroscopy (Australian Standard 3580.6.1).

2.5.5 Measurement of aeroallergens

Pollen grains and fungal spores were collected in each area using a Burkard 7-Day volumetric spore trap (Burkard Manufacturing Co 1953). All traps were at a height of approximately 3m above ground level, in accordance with Australian Standard AS2922-1987.

The Burkard traps had a 7-day sampling cycle, which continuously presented a clean adhesive surface to impinging particles (Figure 2.8). The 1 mm wide sampling tape carrying the adhesive surface was collected on a weekly basis at approximately the same time each week. A record was kept of any abnormalities found with the traps or on the sampling tapes, such as heavy deposits of particulate matter. The sampling tape was cut into 48 mm lengths corresponding to a 24-hour interval, mounted onto microscope slides, then stained to visualise the pollen grains more easily, and the slide cover-slipped. Each slide was then scored with pollen being identified and classified by the technician. Scoring involved two sweeps of each 48 mm slide using the x40 objective of a stereo microscope. Each sweep was 0.5 mm wide so as to cover the 1 mm width of tape.

Figure 2.8. Burkard Spore Trap



Reproduced from: (Burkard Manufacturing Co 1953)

The drum speed was one revolution per 7 days (equivalent to 2 mm per hour) and the throughput of air was theoretically 10 Litres per hour. This flow rate was equivalent to a volume of 14.4 cubic metres of air in each 24-hour period if the trap was 100% efficient. The efficiency varied however depending on the state of the pump, wind speed and spore size and was quoted to be 70% +/- 20% (Burkard Manufacturing Co 1953). Grain and spore concentrations quoted therefore may be below the true value.

Daily pollen counts were performed for a variety of tree, grass, and weed pollens that were identified as most allergenic, prior to the commencement of the study (Table 2.2). Alternaria spores were the only fungus identified during the study period. Pollen grains not easily identified or not listed in the table were counted and placed in a miscellaneous group. Total pollen counts were calculated as the sum of all identified species and miscellaneous (unclassified) pollens. All counts were subsequently converted to a 24-hour count per cubic metre of air.

Table 2.2. Families of pollen grains monitored during the study period

Family	Examples
Weed pollen	
Asteraceae (Compositae)	Ragweed, goldenrod, ragwort, daisy
Boraginaceae	Paterson's Curse
Chenopodiaceae	Saltbush, burrs, fat-hen, goosefoot
Plantaginaceae	Plantains
Polygonaceae	Docks, sorrels
Urticeae	Nettles
Tree pollen	
Casuarinaceae	Australian pine family such as the she-oak
Cupressaceae (Cupressus pine)	Cypress, juniper pines and red cedar
Mimosaceae	Wattle
Myrtaceae	Eucalypts, bottle brushes, callistemons, melaleucas
Oleaceae	Privet, ligustrum
Grass pollen	
Poaceae (Gramineae)	Rye grass, Bermuda grass

2.6 Description of other study factors

Information collected in Phase I allowed assumptions to be made about potential exposure to indoor nitrogen dioxide. This was obtained from information on the type of cooking and heating in the home. Details of cigarette smoking inside the home, and whether the child had been diagnosed as having asthma were also obtained. The analysis of Phase II also incorporated data obtained in Phase I regarding maternal allergy and the presence of cats in the subjects' homes. Maternal allergy has been shown to be a determinant of respiratory symptoms in the child, presumably through the increased risk of atopy, and hence the child is more likely to be susceptible to pollens (Lewis *et al.* 1998). Information about household cats was also included, as cat allergy has been found to be a risk factor for emergency visits with asthma (Pollart *et al.* 1989). The data collection instrument used in Phase I is in Appendix C.

2.7 Description of air quality and meteorological data received

Many data sources were used to obtain the air quality data. Each of the data sources is described below, and is summarised in Table 2.3 and Table 2.4.

2.7.1 Australian Nuclear Science and Technology Organisation (ANSTO)

The data were received as two Microsoft Excel files. It contained daily minimum and maximum temperature readings, flow rate, volume of air and PM2.5 from the Wallsend and Mayfield sites. Documentation provided with the data indicated that if the flow rate through the unit was not between 20 and 24 L/min, the measurement of PM2.5 was unreliable.

2.7.2 Broken Hill Proprietary (BHP)

The data were received as 10 floppy disks containing 58 data files. Daily TSP data were supplied on hardcopy, which the candidate subsequently entered into the database. In the period March to May 1994, quality control data were collected by BHP, during which time they ran two high volume samplers side by side to collect daily TSP, PM10 and PM2.5. Hourly SO_2, NO_2, NO_x, hydrogen sulphate, and ozone data were also received. Ten-minute meteorological data were received, including wind speed, wind direction, temperature, and rainfall. Documentation provided with the data indicated that TSP concentrations were determined in accordance with Australian Standard 2724.3 using a protocol developed by the company laboratory (protocol LTS-PC158). The filters were changed at midnight (D Richards, BHP, pers. com., 1997).

2.7.3 NSW Environmental Protection Agency (EPA)

The NSW EPA provided several datafiles on standard parameters. Some files contained data on all sites in NSW, and others were limited to the three sites of interest to the study, which were Wallsend, Beresfield and the mobile unit at Mayfield. The EPA sent data relating to a total of 18 standard parameters for 1994 and 1995. These included carbon monoxide, PM2.5 (measured using nephelometer), nitric oxide, nitrogen dioxide, total oxides of nitrogen, ozone, sulphur dioxide, PM10 (measured using TEOM), total hydrocarbons, dry bulb temperature, wind speed, wind direction, humidity, and net solar radiation. The data consisted of daily summary data for the period midnight to midnight, and daytime summary data for the period 6am to 9pm. It included the maximum value recorded within the period (24 hours or 15 hours), the mean value recorded during the period, and the proportions of hourly data that were readable during the period, and this was termed the capture rate. For 1995 only, hourly data were also received for all 18 standard parameters. Following discussions with the EPA regarding the quality of data provided for both 1994 and 1995, the EPA provided another dataset that contained hourly PM10 and sulphur dioxide data for the period 1994 and 1995.

The EPA also monitored the non-standard parameters TSP (using a high volume sampler) and PM10 (using a size-selective inlet) once every six days for 24 hours, from midnight to midnight. These data have been denoted 6d-TSP and 6d-PM10.

2.7.4 Hunter Valley Research Foundation (HVRF)

The HVRF recorded meteorological data from its site at Maryville. Data relating to daily minimum, mean and maximum temperatures and rainfall were requested. As the cost of the data was estimated to be $120 and resources were limited, the study team decided not to purchase it.

2.7.5 Incitec

The data were received as 10 floppy disks containing 23 data files. Incitec sent data on the following measures: wind speed, wind direction, sulphur dioxide (hourly), nitrous oxide, nitrogen oxides (hourly), 6d-TSP (measured using HVS), phosphate content, and nitrate content. Documentation provided with the data indicated that sulphur dioxide was limited to +/- 0.1 pphm and oxides of nitrogen to +/- 0.2 pphm.

2.7.6 Lake Macquarie City Council (LMCC)

The data were received as 1 floppy disk containing one Microsoft Excel file. It contained daily measures of TSP and PM10 (using a size-selective inlet).

2.7.7 National Climate Centre / Bureau of Meteorology

Data relating to measures that were recorded at all Bureau sites across NSW were received as three floppy disks. Measures that were received included dry bulb temperature, wet bulb temperature, and dew point temperature. The data were recorded 3-hourly (6 am, 9 am, 3 pm, 6 pm, and 9 pm), and recoded as daily minimum, maximum, and mean.

2.7.8 Newcastle City Council (NCC)

Data were received as two floppy disks containing six data files. The data consisted of daily TSP and 6d-TSP at Stockton, 6d-TSP at Wallsend, and 6d-TSP from three sites at Mayfield. The filters were changed daily at 9am (C Robson, NCC, pers. com., 1997).

2.7.9 Wallsend Primary School

Rainfall was measured by one of the primary schools involved in the study. These data were received by the study team but were subsequently lost and so could not be used in the analysis.

2.7.10 NSW Health Pollen Study

The pollen data were received as 2 floppy disks containing seven data files. The measures included Asteraceae, Boraginaceae, Casuarinaceae, Chenopodiaceae, Cupressaceae, Mimosaceae, Myrtaceae, Oleaceae, Plantaginaceae, Poaceae, Polygonaceae, Urticaceae, Miscellanous, and Alternaria. Daily pollen counts were received from all locations. Comments recorded by the technician were also entered as well as the time the sampling tape carrying the adhesive surface was changed. Quality control data from the North Lake Macquarie site (where a six week repeat and a three week repeat was conducted) were also received.

2.7.11 Pasminco Metals-Sulphide (PMS)

The data were received as five floppy disks containing 49 data files. Measures that were recorded included 10-minute measurements of rainfall, temperature, humidity, wind speed, gust, and wind direction. Both 10 minute and hourly data were supplied for SO_2. Daily and 6-daily records of TSP were measured using a high volume sampler at various locations in North Lake Macquarie (NLM). They were measured from 9am to 9am (J Watson, PMS, pers. com., 1997).

Table 2.3. Sources of air quality data for Phase II of study

	Study area				
	S	**W**	**M**	**B**	**NLM**
Particulates					
6d TSP	NCC (2) Incitec	NCC	NCC (3)	-	PMS (5)
D TSP	NCC	-	BHP BHPQ	-	PMS (2) LMCC
6D PM10 using SSI	-	EPA	-	EPA	-
D PM10 using SSI	-	-	BHPQ	-	LMCC
D PM10 using TEOM	-	EPA	-	EPA	-
PM2.5 using NEPH	-	EPA	EPA*	-	-
PM2.5 using SSI	-	ANSTO	ANSTO BHPQ	-	-
Sulphur dioxide	Incitec	EPA	BHP EPA*	EPA	PMS (3)
Nitrogen dioxide	Incitec	EPA	BHP EPA*	EPA	-
Ozone	-	EPA	BHP	EPA	-
Aeroallergens	NSW Health Pollen Study	NSW Health Pollen Study	NSW Health Pollen Study	NSW Health Pollen Study	NSW Health Pollen Study

The number of monitoring stations (in parentheses) are reported if there was more than one station in the area.
Measurements of particulates are made every 6 days (6d) or daily (d). Measuring devices are size-selective inlet (SSI), Tapered Element Oscillating Microbalance (TEOM) and nephelometer (NEPH).
Sources are: Australian Nuclear Science and Technology Organisation (ANSTO). BHP Quality Program (BHPQ), NSW Environmental Protection Agency (EPA), Lake Macquarie City Council (LMCC), Newcastle City Council (NCC), Pasminco Metals-Sulphide (PMS).
*. Mobile unit

Table 2.4. Sources of meteorological data for Phase II of study

	Study area				
	S	**W**	**M**	**B**	**NLM**
Temperature	-	EPA ANSTO	EPA* ANSTO BHP	EPA	PMS
Rainfall	-	-	BHP	-	PMS
Humidity	-	EPA		EPA	PMS
Wind speed	Incitec	EPA	BHP	EPA	PMS
Wind direction	Incitec	EPA	BHP	EPA	PMS
Gust	-	-	-	-	PMS
Sigma-theta	-	-	-	-	PMS

Sources are: Australian Nuclear Science and Technology Organisation (ANSTO). NSW Environmental Protection Agency (EPA), and Pasminco Metals-Sulphide (PMS).
*. Mobile unit

2.8 Summary

The study was carried out in five areas in the Hunter Region, selected on the basis of known particulate and sulphur dioxide concentrations obtained from the network monitoring of local air quality. Three study areas were exposed to industrial sources of air pollution and two study areas served as controls. The children who participated were a subgroup of a previous large cross-sectional study, who had been identified as having persistent respiratory symptoms. Following an initial assessment by questionnaire and spirometry lung function, respiratory symptoms and medications were recorded twice daily in a diary for seven months either by the parents or by the children closely supervised by the parents. The study was conducted in two waves, with the first wave commencing late February 1994, and the second wave commencing in August 1994. The outcomes considered were evening peak flow, day cough and bronchodilator usage. Concurrent exposure to particulates, ambient sulphur dioxide, pollens, and fungi were measured in each of the study areas. The children's daily exposure to particulates was assessed by total suspended particulates (Stockton, Mayfield, and North Lake Macquarie) using a high volume sampler, or particulate matter less than 10μm (Wallsend and Beresfield) using the TEOM. Pollen and spore counts were recorded using a Burkhard spore

trap. Meteorological data including temperature and rainfall were collected from two of the study areas.

The study design of HISAAP was based on that undertaken by overseas investigators including Doug Dockery from Harvard School of Public Health. An overview of the HISAAP study design is also provided on page xxiv of this thesis for ease of reference. The next chapter reviews the study methodologies used to investigate the association between air quality and health, and the statistical techniques to analyse the data.

Chapter 3 . Literature Review

This chapter reviews the study methodologies used to investigate the association between air quality and health, and the statistical techniques to analyse the data. The first section describes the different epidemiological study designs that have been used (Section 3.1). A literature review of diary studies (the design used in Phase II of the HISAAP study) is presented in Section 3.2. This review was not intended to be an exhaustive review of the published literature, but rather to highlight statistical issues inherent in these types of studies. Section 3.3 describes issues relating to the measurement of exposures. The outcomes recorded in diary studies will be discussed in Section 3.4. Section 3.5 discusses issues regarding statistical adjustment for meteorological confounders such as temperature and other modelling procedures. The final section of this chapter (Section 3.6) focuses on the types of statistical models used in diary studies.

3.1 Study designs

The investigation of the effects of inhaled air pollutants on human health has followed a multidisciplinary approach using animal toxicology, molecular and cellular biology, controlled human exposure studies, and epidemiology. Each approach has specific strengths and weaknesses in evaluating the human health effects of air pollution. Epidemiological studies of air pollution have largely focused on the association between exposure and health effects in the community setting. Accurate estimation of exposure to a pollutant is usually difficult, as it is often estimated from fixed monitoring sites.

The health effects associated with ambient air quality in epidemiological studies can be divided into short-term and long-term effects, according to the investigated period of exposure. Short-term effects usually concern changes in mortality, symptoms, and pulmonary function in association with assessed hourly peak, daily or weekly exposure. Long-term effects are mainly reported as the prevalence of symptoms or disease in association with annual exposure.

Epidemiological study designs used to explore the short-term effects of pollution have included time series and longitudinal studies. In time series studies, daily counts of mortality or hospital admissions are compared to daily concentrations of air pollutants. In longitudinal studies, a cohort of symptomatic people are followed over a period of time and daily reports of symptoms or peak flow are compared to daily concentrations of air pollutants. Longitudinal studies are often referred to as panel studies.

In panel studies, the unit of observation is the person-day. The data are frequently collapsed to daily measures so that the unit of analysis is the day, and the data can then be analysed in a similar way to time series studies. The durations of panel studies (3.1.1) tend to be up to four months, whereas the durations of time series studies (3.1.2) are usually between 2 and 5 years. Other study designs used to explore short-term effects are episode studies and case-crossover designs (3.1.3). Panel and time series studies examine the acute effects of exposure. Long-term exposure to pollution can reduce life expectancy and study designs used to explore long-term affects are cross-sectional and cohort studies (3.1.4). Each study design is described below.

3.1.1 Panel studies including diary studies

Panel studies include diary studies, where the participant records symptoms and/or their peak flow on a daily or twice-daily basis. Camp studies are another type of panel study, where the participants are children attending summer camp and any measures of lung function are undertaken daily by trained personnel. They typically last for less than 2 weeks. Children during these camps spend a large proportion of their day outside being physically active, and so tend to inhale more outdoor air than they usually would. A recent review identified 31 panel studies published between 1980 and 1998 that investigated the association between air quality and respiratory health (Desqueyroux and Momas 1999).

There have been several large panel studies conducted in the United States including NCICAS (National Cooperative Inner-City Asthma Study), which was conducted in eight urban areas in the United States (Mortimer *et al.* 2000), the 24 cities study (Neas *et al.* 1995), the Harvard Six Cities Study (Dockery *et al.* 1982), the EPA-CHESS study (Korn and Whittemore 1979), and the Los Angeles Student Nurse Study (Hammer *et al.* 1974). There have also been large panel studies conducted in Europe including the PEACE (Pollution Effects on Asthmatic Children in Europe) study in which 14 European centres collaborated (Roemer *et al.* 2000). Most panel studies have focused on children and there are several reasons for this. In adults, personal cigarette smoking and occupational exposures may confound the estimate of the effect of air pollution on respiratory symptoms and lung function. In addition, asthma is more prevalent in young children and hence they may be more sensitive to air pollution. Finally, schools provide easy accessibility to children for study investigators.

3.1.2 Time series studies

Time series are often used to study the short-term association between ambient air pollution levels and aggregated health data. Health endpoints are usually daily mortality or daily hospital admissions using data from routine health registers. There have been considerably more time series studies than panel studies due to the comparatively inexpensive nature of data collection.

In mortality studies, the three outcomes most frequently examined are daily number of deaths from all causes, deaths from cardiovascular disease, and deaths from respiratory disease. Investigators sometimes include a control condition such as cause of death relating to the digestive system. Some studies restrict their analysis to the very old (aged over 65 or 70 years), or the very young (aged under 5 years). Typically, time series studies exclude non-residents. In morbidity studies, the outcome is usually the daily number of emergency department admissions for asthma.

The increased mortality associated with particulate air pollution generally occurs in the elderly or those with chronic cardiac or respiratory disease. It is unclear whether the increased mortality seen with short-term episodes of pollution cause significant premature mortality, or merely advance death by a few days or weeks (Smith *et al.* 1999; Schwartz 2001). The latter alternative is known as the mortality displacement or the harvesting effect. Interestingly, the people who are considered to be at risk of dying from particulate exposure are ill, and likely to be indoors during air pollution episodes. However, it has been shown that concentrations of very fine particles (PM2.5) are present indoors in similar concentrations as outdoors (Janssen *et al.* 2000).

Time series studies assume that the demographic and socio-economic profile of an area is stable. Hence, factors that are often thought to influence the health of the population, such as prevalence of smoking, income level, occupational exposure to pollutants, access to medical care and age distribution, do not need to be incorporated into the analysis as they are considered to remain relatively constant within the study area over time. For a factor to be a confounder, it must vary over the study period (Katsouyanni *et al.* 1996) and typically, the only other factors aside from pollution that are included in these models are climate-related variables.

The approach used in time series studies is similar to that used in ecological studies. However, rather than being based on geographical unit of aggregation, time series analysis is based on aggregation by time. As time series studies do not face the problems inherent in traditional ecological studies such as confounding by personal risk factors such as smoking, they are

instead referred to as semi-individual studies rather than ecological studies (Kunzli and Tager 1997).

The methodologies appropriate for time series data have been summarised previously (Schwartz *et al.* 1996b). The APHEA project (Air Pollution and Health a European Approach) developed strict guidelines for the process of model building in mortality studies (Katsouyanni *et al.* 1995) and all centres participating in the APHEA project were required to adhere to these guidelines (Katsouyanni *et al.* 1996). These are now standard methods for the analysis of time series data. Because the outcomes are counts (number of events per day) and are small compared to population sizes, Poisson regression is the suitable statistical method to analyse time series studies. Results are usually expressed as relative risks or percent increases in mortality. Time series studies are usually based on large datasets, so that there is sufficient power to detect even weak associations so although the regression models may be statistically significant, they typically explain only a small amount of the variability in daily mortality.

3.1.3 Episode studies and case-crossover design

Another study design identifies days at emergency departments where extraordinarily large numbers of visits for respiratory conditions (e.g. asthma) have occurred. If a similar pattern is seen in other areas within the city, it can be inferred that a common environmental factor such as pollution or unusual weather took place over the entire city. A search for the common factor on the particular days can then be instituted. These are called episode studies. In the case-crossover study design, persons with an asthma-related event are enrolled, and the pollution levels at the time of their event are compared to that prior to their event using conditional logistic regression (Lumley and Levy 2000).

3.1.4 Cross-sectional studies and cohort studies

The work presented in this thesis focuses on the acute effects of air pollution. In order to assess the effects of long-term exposure to pollutants, cross-sectional or cohort studies can be used. Two cross-sectional studies have been conducted in the Hunter, including Phase I of the HISAAP study (Lewis *et al.* 1998) and Phase I of the Lake Munmorah Study (Henry *et al.* 1991a). In cross-sectional analysis, the pollution effects are estimated by regressing the subject's responses (e.g. whether they had experienced wheeze in the previous year) against the corresponding yearly pollution exposures in their area. Several study areas are required so that a gradient of exposure can be obtained. With cross-sectional data, pollution effects are underestimated if susceptible persons have moved to areas with better air quality.

Measuring the effects of chronic exposure requires a long-term prospective study in which a population sample is followed for long enough to allow chronic effects to develop and manifest. Three such studies have been completed to date: the Harvard Six Cities Study, which followed participants over the course of 15 years (Dockery *et al.* 1993), the Seventh Day Adventist study in California (Abbey *et al.* 1995), and a study by the American Cancer Society, which lasted approximately 8 years (Pope *et al.* 1995b).

3.2 Overview of longitudinal studies

A literature review of all diary studies published prior to January 2002 was undertaken using the PubMed database. Seventy-five manuscripts were identified that related to 72 unique studies. A summary of key points regarding these studies is provided in Table 3.1. Several camp studies were identified (Table 3.2), and there were also some panel studies where the diary was completed on a weekly basis, but exposures were obtained daily; the statistical methods used were similar to that used in diary studies (Table 3.3). Throughout the remainder of this chapter, examples will be cited from these three tables.

Table 3.1. Summary of statistical methods used in diary studies investigating the association between air pollution and respiratory health

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Agocs *et al.* 1997)	Hungary (Budapest)	60 asthmatic children	3 months (winter)	TSP, SO_2 (m24h). Took average daily reading from 8 monitors.	2D diary. PEF (% deviation from the mean) Exclusions: First 2 days of subjects' data excluded; Days where subject spent more than 4 hours away.	Adjustments a: Temp (quartiles), humidity (quartiles), weekend/weekday, time-trend, sinusoidal terms, AR-1. Adjustments b: Cold. Aggregate Non-aggregate: K-W fixed, K-W random
(Bjerknes-Haugen *et al.* 1995)	Norway (Grenland region)	85 COPD aged 4-75 yrs & 280 randomly selected aged 18-75 yrs.	4 months (winter/spring)	SO_2, NO_x +Indoor air quality	1D diary. PEF	Adjustments: previous day PEF Non-aggregate: K-W Subgroup: by study design, medication use.
(Boezen *et al.* 1999)	Netherlands (three rural and two urban)	632 children aged 7-11 years	3 months	PM10, BS, SO_2, NO_2	2D diary PEF (decrease of 10% or more below the 95th percentile of an individual child). Exclusions: Subject excluded if diary completion < 60% of study period; same peak flow for more than 1 week.	Each area analysed separately and pooled using fixed effects approach. Non-aggregate: PROC MODEL. Subgroups: bronchial hyper-responsiveness and high serum total IgE (i.e. atopy).

[1] Abbreviations used in {column description} "Sample" include: Chronic obstructive pulmonary disease (COPD)
[2] Duration refers to the length of measurement for each subject
[3] Abbreviations used in {column description} "Exposure measurement" include: Mean 24-hour values (m24h), Mean 12 hour values (m12h), Maximum hourly values over 24 hours (max1h), Black smoke / coefficient of haze (BS), Carbon monoxide (CO), Hydrogen ion (H+), Nitric oxide (NO), Nitrogen dioxide (NO_2), Oxides of nitrogen (NO_x), Ozone (O_3)
Particulate matter less than 10μm in size (PM10), Particulate matter less than 2.5μm in size (PM2.5), Particulate matter of various sizes (PMx), Total suspended particulates (TSP), sulphur dioxide (SO_2), Sulphate (SO_4).
[4] Abbreviations used in {column description} "Outcome measurement" include: Completed twice-daily (2D diary), Completed once a day (1D diary), Upper respiratory tract illness (URT), Lower respiratory tract illness (LRT), Peak Expiratory flow (PEF).
[5] Abbreviations used in {column description} "Modelling procedures and types of models" include: Autoregression term (AR), Korn-Whittemore – where a separate regression model is fitted for each subject (K-W), Generalised estimating equations (GEE), Generalised linear mixed model (GLMM), Standard error (SE), polynomial distributed lag (PDL), missing at random (MAR).

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Braun-Fahrlander *et al.* 1992)	Switzerland (Basel & Zurich)	625 children from 4 locations aged 0-5 yrs.	1.5 months.	TSP, SO_2, NO_2 (m24h). + Indoor air quality	1D diary. Symptoms: day cough, night cough, sore throat, runny nose, fever, earache, breathlessness, URI (prevalence, incidence, duration)	Non-aggregate: GEE
(Clench-Aas *et al.* 1999)	Norway (Oslo)	2300 school-aged children	6 weeks (winter)	PM2.5, NO_2 Personal exposure estimated by dispersion model Daily exposure to passive smoking.	Symptoms: sneezing, sore throat, & earache.	Adjustments: daily exposure to passive smoking (y/n). Non-aggregate: GEE
(Delfino *et al.* 1996)	USA (San Diego – California)	12 asthmatic children	2 months.	PM2.5, NO_2, O_3, SO_4, pollen, Alternaria (m24h). + Personal O_3	1D diary. Symptoms: (0 to 5) $Beta_2$-agonist inhaler.	All outcomes assumed Gaussian. Non-aggregate: GLMM with time-dependant covariates fixed; SAS procedure PROC MIXED.
(Delfino *et al.* 1997)	USA (Alpine - California)	22 asthmatics aged 9-46 yrs.	2 months.	PM10, fungi, pollen (m24h); O_3 (m12h).	2D diary. PEF Symptom (0 to 5) $Beta_2$-agonist inhaler (puffs)	All outcomes assumed Gaussian. Non-aggregate: both K-W (SAS procedure PROC AUTOREG) and GLMM (SAS procedure PROC MIXED).
(Delfino *et al.* 1998)	USA (California)	25 asthmatic children	3 months	PM10, O_3, fungi.	1D diary Nocturnal wakening	Non-aggregate: GEE Subgroups: anti-inflammatory medication
(Delfino *et al.* 2002)	USA (California)	22 asthmatic children living in non-smoking households	2 months	PM10 (1hr, 8hr, 24hr) NO_2, O_3, pollen, fungi		Non-aggregate: GEE Subgroup: subjects on anti-inflammatory medication.
(Downs *et al.* 2001)	Australia (Victoria)	399 children sensitive to aeroallergen	1 month.	Alternaria.	Airway responsiveness to histamine Symptoms: wheeze Bronchodilator use	Non-aggregate: GEE Subgroup: Sensitised to Alternaria
(Dusseldorp *et al.* 1995)	Netherlands	32 asthmatic adults	2.5 months.	PM10, manganese.	1D diary. PEF Symptoms Increased medication use.	Non-aggregate (PEF): K-W using PROC AUTOREG Non-aggregate (symptoms, medication): logistic regression using PROC MODEL and linear regression gave similar results

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Epton *et al.* 1997)	New Zealand (Blenheim)	139 asthmatic adults	12 months	Pollen, fungi	2D diary PEF Symptoms: nocturnal wakening Medication use	Non-aggregate: K-W
(Forsberg *et al.* 1993)	Sweden (Pitea)	31 asthmatic (any age)	2 months.	Particulates, BS, SO_2, NO_2 (m24h).	1D diary. Symptoms: any (incident y/n), cough (y/n)	Aggregate: observed/expected Non-aggregate: random intercept model with common slope
(Frezieres *et al.* 1982)	USA (Los Angeles)	34 asthmatic volunteers	8 months.	Sulphates, pollen.	1D diary. Symptoms Medication use	Unknown
(Gielen *et al.* 1997)	Netherlands (Amsterdam)	61 children (77% were taking asthma medication)	2 months (summer).	PM10, BS, pollen (m24h); O_3 (max1h).	2D diary. PEF (deviation from the mean) Symptoms: URS, LRS Bronchodilator use (prevalence, deviation from the mean number of puffs) Exclusions: Subject excluded if diary completion < 60% of study period Exclusions: First 11 days of subjects' data excluded	Adjustments: AR-1, grass pollen (log transformed), time trend, weekday/weekend Lags O_3: same day, lag 1, lag 2. Lags PM10: same day, lag 1, lag 2, 5-day average. Non-aggregate: K-W using PROC AUTOREG Subgroup: excluded children who used asthma medication during study period.
(Gold *et al.* 1999)	Mexico (Mexico City)	40 children	Unknown	PM10, PM2.5, O_3	2D measurements PEF (deviation from the mean) Symptoms: phlegm	Lags: moving average, PDL Aggregate
(Hammer *et al.* 1974)	USA (Los Angeles) Los Angeles Student Nurses Study Reanalysed by (Schwartz *et al.* 1988)	LA student nurses	3 years	NO_2, O_3 (max1h), CO	1D diary Symptoms: headache, eye irritation, cough, chest discomfort (prevalence)	Aggregate: Ignored serial correlation; used linear regression; prevalence only; referred to as "hockey stick approach". Morbidity-adjusted: excluded all days when the symptom was reported in conjunction with an illness e.g. fever.
(Henry *et al.* 1991b)	Australia (NSW)	99 children	12 months.	SO_2, NO_x.	1D diary. PEF Symptom (y/n)	Non-aggregate: K-W fixed (inverse variance weights)

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Higgins *et al.* 1995)	UK	75 adults with asthma or COPD	1 month	NO_2, SO_2, O_3 (m24h).	PEF Symptoms: wheezing Bronchodilator use	Subgroup: bronchial hyperactivity
(Higgins *et al.* 2000)	UK	35 adults with asthma/COPD & bronchial hyperactivity	1 month	NO_2, O_3, pollen, spore.	PEF Symptoms: wheeze, dyspnoea, cough, throat irritation, eye irritation	Unknown
(Hiltermann *et al.* 1998)	Netherlands (Leiden)	60 adult non-smoking asthmatics	3 months.	PM10, BS, SO_2, NO_2, (m24h); O_3 (max8h).	2D diary. PEF (morning to evening change) Symptoms Medication use.	Lags: Lag0, lag 1, lag 2, 7-day mean. Adjustments: exposure to outdoor aeroallergens, exposure to environmental tobacco smoke. Aggregate: PROC MODEL Subgroups: (2)
(Hoek and Brunekreef 1993)	Netherlands (Wageningen)	112 children	5 months	PM10, BS, SO_2, NO_2	Symptoms 1D; Spirometry every 3 weeks	Non-aggregate (Spirometry): K-W Aggregate (symptoms): PROC MODEL
(Hoek and Brunekreef 1994)	Netherlands (three non-industrial and one industrial community)	1078 children over three years winter 1987 (308), winter 1988 (381), winter 1989 (390)	3 months.	PM10, SO_2, NO_2 (m24h).	1D diary. Spirometry occasionally; Symptoms 1D.	Each area analysed separately and pooled using fixed effects approach. Non-aggregate (spirometry): K-W fixed (unweighted); test of heterogeneity. Aggregate (symptoms): PROC MODEL
(Hoek and Brunekreef 1995)	Netherlands (two rural towns Deurne & Enkhuizen)	300 school children aged 7-11 yrs.	3 months	PM10, SO_2, NO_2, (m24h); O_3 (max1h). Missing exposure data imputed using SAS procedure PROC EXPAND.	1D diary. Symptoms: any, LRS (incidence, prevalence)	Aggregate: logistic regression using PROC MODEL and linear regression using PROC ARIMA & PROC AUTOREG; adjustment for autocorrelation.
(Hoek *et al.* 1998)	Reanalysis of five panel studies that were conducted in Utah, Pennsylvania, and Netherlands.	Children from 5 panel studies	Various	PM10	PEF (binary more than 10% or 20% below the median)	Lag: 0,1, 5-day average Non-aggregate: logistic regression with allowance for overdispersion, AR-1.

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Jalaludin *et al.* 2000)	Australia (Sydney, NSW)	148 symptomatic children (history of wheeze)	11 months.	PM10, pollen (m24h); O_3 (max1hr,m24h) Multiple stations.	2D diary. PEF (two alternatives) Symptoms.	Lag: 1,2,3,4,5,6,7,average2-8. Aggregate: outcome is standardised mean deviation of PEF; exposure is average across multiple stations; weighted by number of PEF recordings for the day. Non-aggregate: outcome is PEF; exposure is closest monitor to child's school; GEE. Subgroup: bronchial hyperreactivity & asthma diagnosis.
(Korn and Whittemore 1979)	USA (California) EPA-CHESS	Panel of asthmatics	7 months	TSP	1D diary Symptoms: asthma attack	Non-aggregate: K-W fixed & K-W random effects Subgroup: sex, age, hayfever, increased attacks during cold weather, increased attacks during periods of emotional stress.
(Krzyzanowski *et al.* 1992)	USA (Tucson – Arizona)	287 children & 523 non-smoking adults	12 days.	PM10, O_3 (m24h).	2D diary. PEF (morning and evening in same model)	Adjustments (Time-varying): Temp, time of day, time spent outdoors, respiratory illness, time of day (morning or evening) Non-aggregate: Random effects model, analysis of covariance. Adjustments (Time-stationary): Gender, age, diagnosis (y/n), smoke (y/n), spring season (y/n).
(Lebowitz *et al.* 1985)	USA (Tucson – Arizona)	211 children & adults	2 years	TSP, NO_2, O_3, CO. +Indoor air quality	1D diary PEF (standardised deviation)	Non-aggregate: ANOVA
(Lebowitz *et al.* 1987)	Unknown	204 adults (asthmatic/allergic/COPD)	Unknown	TSP, CO (m24h); NO_2, O_3 (max1h). + Indoor air quality	1D diary PEF Symptoms.	Subgroup: asthmatics
(Luck 1997)	Australia (Hunter Region - NSW)	28 symptomatic children	7 months	PM10, SO_2	Symptoms: day cough, night cough, runny nose (score 0 to 18)	Aggregate only
(Mortimer *et al.* 2000)	USA (eight urban areas) NCICAS	846 symptomatic children	3 months	O_3	PEF Symptoms	Subgroups: born > 3 weeks premature, birth weight < 5.5 pounds, no medication, use of corticosteroids but not bronchodilators.

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Mortimer *et al.* 2002)	USA (eight urban areas) NCICAS	846 symptomatic children	3 months	PM10, SO_2, NO_2, O_3	PEF (%change from median, incidence of 10% decline from median) Symptoms (incidence) Exclusions: Values < 70 or >450 L/min were considered to be implausible and were deleted	Non-aggregate (continuous outcome): mixed linear models using PROC MIXED Non-aggregate (binary): GEE with independence covariance structure
(Moseholm *et al.* 1993)	Denmark (Copenhagen)	27 non-allergic asthmatic adults	8 months.	SO_2, NO_2 (m24h).	1D diary. Symptoms Medication.	Principal-component analysis & neural network techniques
(Neas *et al.* 1995)	USA (Pennsylvania) Identified from 24 cities study	60 symptomatic children not taking asthma medication & 23 asymptomatic children	1.5 months (summer).	PM10, PM2.5, SO_4 O_3, H+ (m12h). Exposure weighted by # hrs subject spent outdoors in previous 12 hour period.	2D diary. PEF (standardised deviation) Symptoms: cough, wheeze, cold (incidence) Exclusions: Subject excluded if diary completion < 30% of study period. In sensitivity analysis also excluded children who reported little variation in PEF measurements, reported PEF in multiples of 50 L/min.	Adjustments: temp, trend, AR-2 Evening & morning measures included in same model by using an indicator variable Non-aggregate: K-W (unit weights, inverse variance weights), GEE Weighted by number of subjects. Weighted by number of hours spent outside. Subgroup: symptomatic / asymptomatic
(Neas *et al.* 1996)	USA (Pennsylvania) Identified from 24 cities study	62 symptomatic children not taking asthma medication & 46 asymptomatic children	1.5 months (summer).	PM10, PM2.1, SO_4, aeroallergens, pollens, fungal spores, cladasporium spore.	2D diary. PEF Symptoms: cough, wheeze, cold (incidence) Exclusions: Subject excluded if diary completion < 30% of study period	Both morning and evening PEF in same model Adjustments: AR-# Lags: chosen after fitting 2nd order polynomial distributed lag. Aggregate: PROC AUTOREG and PROC NLIN Non-aggregate: K-W (inverse variance weights)

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Neas *et al.* 1999)	USA (Pennsylvania)	children	Unknown	Particulates, Sulphates	2D diary PEF (height adjusted)	Unknown
(Neukirch *et al.* 1998)	France (Paris)	40 non-smoking mild to moderate asthmatics who were being treated with inhaled corticosteroids.	6 months	PM10, BS, SO_2, NO_2	PEF Symptoms	Non-aggregate: GEE Subgroup: inhaled bronchodilators
(Ostro *et al.* 1991)	USA (Denver-Colorado)	207 adult asthmatics	4 months (winter).	PM2.5, Particulates, H+, Nitric acid, Sulphates, and nitrates. Incorporated time spent outside, exercise intensity into daily measure of exposure.	1D diary. Symptoms: cough, breathlessness; medication use.	Non-aggregate:
(Ostro *et al.* 1993)	USA (California)	321 non-smoking adults	6 months	SO_2, BS, NO_2, SO_4, H+ (m24h). O_3 (max1h)	1D diary Symptoms: URS, LRS.	Subgroups: no residential a/c, pre-existing respiratory infection.
(Ostro *et al.* 1994)	USA (Denver-Colorado)	164 adult asthmatics	2.5 months.	Indoor air quality.	1D diary. Symptoms: (0-4, y/n) Work absence Doctor visit	Adjustments (time-varying): gas stove use Non-aggregate: Naïve and GEE Subgroups: concurrent cold, oral corticosteroids
(Ostro *et al.* 2001)	USA (Los Angeles)	138 African-American children	3 months	PM2.5, PM10, NO_2, O_3, pollens, moulds (Cladosporium and Alternaria)	Symptoms (incidence): cough Extra medication	Non-aggregate: GEE Subgroups: anti-inflammatory medication, asthma severity, income
(Pekkanen *et al.* 1997)	Finland (Kuopio) PEACE study	39 asthmatic children	57 days.	PM10, BS, PM0.01 to PM10 (m24h).	1D diary. PEF (deviation from the mean)	Lags: tried various. Aggregate: Weighted by daily numbers of participants; PROC MODEL.
(Penttinen *et al.* 2001)	Finland (Helsinki)	57 adult asthmatics	6 months	PM10, PM_x, pollen	1D diary PEF Symptoms Medication	Lags: lag 0, lag 1, lag 2, lag 3, 5-day average. Aggregate: weighted by daily numbers of participants

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Perry *et al.* 1983)	USA (Denver-Colorado)	24 adult asthmatics	3 months	Particulates, Nitrates.	2D diary. PEF Symptom score Bronchodilator (nebuliser), which was recorded automatically by machine.	Adjustments: temp, barometric pressure, weekend (y/n), sinusoidal terms Non-aggregate: K-W with previous day's outcome as a covariate
(Peters *et al.* 1996)	Czech Republic (Sokolov) & Germany (Erfurt & Weimar)	155 asthmatic children & 102 asthmatic adults	82 days (Sept 1990 to June 1992, winters only?)	TSP, PM10, SO_2, SO_4 (m24h). Three monitors - analysed separately.	2D diary. PEF (deviation from the mean) Symptoms score (deviation from the mean) Exclusions: Subject excluded if diary completion < 25% of study period Exclusions: First 2 weeks of subjects' data excluded	Separate analysis for each area and pooled across study areas using fixed effects. Adjustments: controlling for trend, meteorology, & autocorrelation. Sinusoidal terms fitted. Lags: same day, cumulative (5-day average), polynomial distributed lag. Some adjustment made for having two study areas Aggregate: with weighting
(Peters *et al.* 1997a)	Czech Republic (Sokolov)	82 children who were mildly asthmatic	2.5 months. (winter '91/'92).	TSP, PM10, PM2.5, SO_2, NO_2, O_3, SO_4, H+ (m24h). If exposure missing imputed average.	PEF (deviation) Symptoms: runny nose $Beta_2$-agonist (puffs) Exclusions: Subject excluded if diary completion < 14% of study period Exclusions: First 2 weeks of subjects' data excluded	Adjustments: Linear trend, mean temp, weekend/weekday Lags SO_2: 5-day average Non-aggregate: GEE Adjustments: prevalence of fever Subgroup: medication use
(Peters *et al.* 1997b)	Czech Republic (Sokolov)	89 asthmatic children.	7 months (winter '91/'92)	TSP, PM10, SO_2, SO_4 (m24h).	2D daily. PEF Symptoms (y/n) Theophylline or $beta_2$-agonist use (y/n) School absence; fever	Adjustments a: linear trend, mean temperature, weekend, AR, weights for # subjects participating. Lag: current day, 5-day average, polynomial distributed lags. Aggregate Adjustments b: respiratory infection, fever.
(Peters *et al.* 1997c)	Germany (Erfurt)	27 adult non-smoking asthmatics	(winter '91/'92)	PM2.5, PM10 (m24h).	1D diary PEF Symptoms	Lags: 5-day average

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Pope *et al.* 1991)	USA (Provo-Utah)	66 grade 4,5 symptomatic school children (34?) 66 any age, asthmatic (21?)	3.5 months. (winter '89/'90)	PM10, SO_2, NO_2, O_3 (m24h).	1D diary. PEF (deviation) Symptom: any (y/n), LRS Any medication use (y/n), Bronchodilator use (y/n). Exclusions: Subject excluded if diary completion < 55% of study period	Adjustments: autocorrelation, min temp & linear trend Lags: single-period models, polynomial distributed lag, 5-day moving average models. Non-aggregate: random intercept model, K-W
(Pope and Dockery 1992)	USA (Orem, Lindon - Utah)	33 children with respiratory symptoms (not taking medication) & 33 children with no respiratory symptoms.	3.5 months (winter '90/'91).	PM10 (m24h). Two stations - used one only as shown to be similar.	1D diary. PEF (deviation) Symptom (y/n) -LRS, URS, cough	Separate estimates for symptomatic & asymptomatic subjects Lags: single period, 5-day average (moving average), polynomial distributed lag models. Adjustments: min temp, AR-1, linear time trend variable Aggregate (PEF): Heteroscedasticity (i.e. unequal day specific variance) a concern as can produce biased SEs of regression coefficients so weighted least squares regression models - using inverse of SEs; PROC AUTOREG Non-aggregate (PEF): K-W Non-aggregate (symptom): Logistic regression with subject-specific indicator variables (Bonney 1987), and GEE.
(Riediker *et al.* 2001)	Switzerland (Zurich)	15 pollen-sensitised allergic patients	(spring/summer '98)	PM10, NO_x, O_3, pollen count; airborne allergen concentrations.	2D diary Symptoms: rhinoconjunctivitis (score of 0 to 20) Medication.	Transformation: All exposures were log transformed. Time spent outdoors Non-aggregate: K-W
(Roemer *et al.* 1993)	Netherlands (Wageningen & Bennekem)	73 symptomatic/ asthmatic children.	2.5 months. (winter '90/'91)	PM10, BS, SO_2 (m24h).	2D diary. PEF Symptom Bronchodilator.	Lags: same day, one day, one week average. Unknown

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Romieu *et al.* 1996)	Mexico (Mexico City)	71 asthmatic children	Unknown	PM10, PM2.5, SO_2, NO_2 (m24h); O_3 (max1h).	PEF Symptoms: cough, phlegm production, wheeze, breathlessness, LRI	Unknown
(Romieu *et al.* 1997)	Mexico (Mexico City)	65 mild asthmatic children.	2 months	PM10, SO_2, NO_2, (m24h); O_3 (max1h).	1D diary. PEF (z-score) Symptoms. Bronchodilator use (y/n)	Adjustments: Min temp, AR Lags: up to two days Non-aggregate: GEE Sensitivity: Excluded observations of children who had used bronchodilators on a given day.
(Scarlett *et al.* 1996)	UK (Surrey - England)	154 children	1.5 months (summer '94).	PM10, NO_2, O_3, pollen (m24h).	1D diary (school days only). Spirometry.	Adjustment: temperature, humidity, pollen count. Lags: one or two days Non-aggregate: K-W (various weights used); test of heterogeneity Subgroup: children with wheeze
(Schwartz *et al.* 1988)	USA (Los Angeles) Los Angeles Student Nurses Study Reanalysis of (Hammer *et al.* 1974)	30 student nurses	3 years.	SO_2, O_3, NO_2, CO	1D Diary. Symptom (y/n)	Adjustments: AR-#, weighted Aggregate only
(Schwartz and Zeger 1990)	USA (Los Angeles) Los Angeles Student Nurse Study	100 student nurses	3 years.	Unknown	1D Diary. Symptoms: number of incidents; duration of episode; incidence of symptom (0-4, y/n). Exclusions: First 2 months of subjects' data excluded	Non-aggregate: GEE; stratify by SS covers; weight by N subjects in strata with an indicator variable for strata. Linear regression of log duration Vs covariates (with adjustment for multiple episodes) Subgroups: To identify subject-specific covariates the # incidents over period for each subject was regressed on subject-specific covariates (Poisson regression)
(Schwartz *et al.* 1991)	USA (Los Angeles) Los Angeles Student Nurse Study	Unknown	Unknown	Unknown	1D diary Symptoms: (incidence, prevalence)	Non-aggregate: K-W

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Schwartz *et al.* 1994)	USA (six US cities) Six cities study	1844 school children in six cities (300 per city).	1 year	PM10, PM2.5, SO_2, NO_2, O_3, SO_4, H+ (m24h).	1D diary. Symptoms: LRS, cough only, URS, rhinitis only. Exclusions: analysis was restricted to data from the non-winter months (5 months only)	Adjusted for mean temperature (quadratic term based on previous day), day of week, & city (city of residence was treated as a categorical explanatory variable), AR-1. Lags (PM10): previous day, current day, mean of up to 4 previous days (chosen by goodness of fit). Non-aggregate: Logistic regression using GEE, local smoothing using generalised additive models.
(Schwartz *et al.* 2000)	Finland (Kuopio)	169 children (74 with asthmatic symptoms & 95 with cough symptoms)	3 months	Environmental Tobacco Smoke	2D diary PEF Symptoms: phlegm production Bronchodilator	Analysis was performed separately for the asthma cohort & the cough only cohort. Non-aggregate (PEF): a random subject effect using PROC MIXED and a random intercept model. Non-aggregate (symptoms, medication): random intercept model.
(Schwartz and Neas 2000)	Reanalysis of 3 panel studies that were conducted in USA	Children from 3 panel studies	Various	PM2.1, PM2.5, PM2.1 to PM10, PM2.5 to PM10	PEF Symptoms: LRT	Unknown
(Segala *et al.* 1998)	France (Paris)	84 infant asthmatics	6 months.	PM13, SO_2, NO_2 (m24h).	2D Lung function Symptoms Extra $beta_2$-agonists.	Non-aggregate: GEE
(Shamoo *et al.* 1994)	USA (Los Angeles)	49 adult asthmatics	Unknown	PM10 (m24h); SO_2, NO_2, O_3 (max1h).	Symptoms Medication	Activity patterns
(Silverman *et al.* 1992)	Canada (Toronto)	36 severe asthmatics any age	20 days.	Personal exposure to particulates.	1D diary. Lung function.	Adjustments: Medication Non-aggregate: ANOVA, K-W.
(Smith *et al.* 2000)	Australia (Port Adelaide – SA)	125 asthmatics any age	1.5 months	Outdoor pollutants, Spores + Indoor NO_2	Symptoms: 7 classifications including chest tightness, breathlessness, daytime asthma attack.	Used multiple imputation to adjust for outcomes not being MAR. Non-aggregate: GEE Subgroups: age <= 14 years; 35-49.

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(Tarlo *et al.* 2001)	Canada (Vancouver-British Columbia)	57 asthmatics any age	Unknown	SO_2, NO, pollen, fungi	2D PEF Symptoms: colds Medication use.	Unknown
(Timonen and Pekkanen 1997)	Finland (Kuopio) PEACE study	74 symptomatic children (wheezing, breathlessness or asthma diagnosis) & 95 with cough only from two towns.	3 months (winter '94)	PM10, BS, SO_2, NO_2, (m24h). Lags: 2 days.	2D Diary. PEF Symptoms: URS.	Morning & evening evaluated separately Separate models for urban & suburban areas Adjustments a: time trend, min temperature, relative humidity, & AR-1. Lags: lag 0, lag 1, lag 2, 4-day average. Aggregate (PEF): PROC MODEL; weighted by number of observations that day. Non-aggregate (PEF): analysis of covariance, indicator variable for each subject. Aggregate (symptom): PROC MODEL and PROC NLIN; weighted. Subgroup: doctor-diagnosed asthma
(Vedal *et al.* 1987)	USA (Pennsylvania)	School-aged children (3 panels – without respiratory symptoms; symptoms of persistent wheeze; cough or phlegm production but without persistent wheeze)	8 months (PEF for 2 months only)	BS, SO_2, NO_2, O_3 (max1h).	1D diary. PEF Symptom (y/n).	Adjustments: min temp Aggregate Non-aggregate: K-W (inverse variance weights) Subgroup: systems of persistent wheeze.
(Vedal *et al.* 1998)	Canada (Vancouver Island)	4 types of children Asthmatic (75), exercise induced fall in FEV_1 (57), airway obstruction (18), and controls (56).	18 months.	PM10 (m24h). EM algorithm to impute values where missing exposure data	2D diary. PEF (took max of evening & morning peak flow) Symptoms: cough, phlegm, sore throat.	Lags: up to 15 days considered. Adjustments: Mean temp, humidity, wind speed, wind direction, rain, day of week, season Aggregate Non-aggregate: K-W (unweighted average), modified GEE with fixed offset. The offset was the estimated intercept obtained in K-W (autocorrelation: IND and AR-1). Subgroup: asthmatic
(Vichit-Vadakan *et al.* 2001)	Thailand (Bangkok)	3 panels (school children, nurses, adults).	3 months	PM10, PM2.5.	Symptoms: URS, LRS.	Prevalence, incidence.

Reference	Country (city) Name of study	Sample [1]	Duration[2]	Air quality measurement[3]	Outcome measurement [4]	Modelling procedures and types of models[5]
(von Klot *et al.* 2002)	Germany (Erfurt)	53 adult asthmatics	6 months	PM0.1, PM2.5	Symptoms Medication: bronchodilator, corticosteroid use	Non-aggregate: GEE with adjustment for heteroscedasity. In medication analysis, limited it to people who used meds at some stage during the study
(Whittemore and Korn 1980)	USA (Los Angeles) EPA-CHESS	443 asthmatics (from 16 panels - 4 areas & over 4 different years 1972-1975).	8 months.	TSP	1D diary. Symptom (y/n) Exclusions: days where the subject was out of town.	Adjustments: humidity, wind speed, day of week, time since start of study. Non-aggregate: K-W Subgroup: age, sex, hayfever status, self-assessed attack precursors.

Table 3.2. Summary of statistical methods used in summer camp studies investigating the association between air pollution and respiratory health

Reference	Country (city)	Sample[1]	Duration[2]	Air quality measurement[3]	Outcome measurement[4]	Modelling procedures and types of models[5]
(Higgins *et al.* 1990)	USA (California)	43 children	Summer camp	TSP, PM10, SO_2, NO_x, O_3	Spirometry	Non-aggregate: K-W
(Kinney *et al.* 1996)	USA (Six studies)	6 groups of infants	Summer camp	O_3 (max1h).	Spirometry	Each study analysed separately and in one analysis all studies combined. Non-aggregate: random intercept model
(Klabuschnigg *et al.* 1981)	Europe	40 asthmatic children	6 weeks	Pollen, fungi	Symptoms Medication use	Unknown
(Lioy *et al.* 1985)	USA (Pennsylvania)	62 children in summer camp	2 weeks	O_3	Spirometry	Non-aggregate: K-W
(Spektor *et al.* 1988)	USA (New Jersey)	91(37) children at summer camp	1 month.	PM15, O_3, H^+ (m24h).	Spirometry	Non-aggregate: K-W Adjustment for: temp, humidity, # hrs of activity
(Spektor *et al.* 1991)	USA (New Jersey)	91 children at summer camp	1 month.	O_3 (m24h)	Spirometry	Non-aggregate: K-W
(Studnicka *et al.* 1995)	Austrian Alps	Children from three consecutive summer camps Panel 1 (47), Panel 2 (45) and Panel 3 (41)	3 weeks	PM10, O_3, H+, pollen	Spirometry	Analysed as three separate panels Non-aggregate: GEE Subgroups: medication
(Thurston *et al.* 1997)	USA (Connecticut River Valley)	166 children from three consecutive summer camps June 1991 (52), June 1992 (58) & June 1993 (56). Most had moderate to severe asthma	1 week	O_3 (max1h); PM2.5, Sulphates, H^+, pollens (m12h).	PEF Symptoms: chest symptoms Unscheduled medications.	Adjustments: Max temperature Aggregate Non-Aggregate (symptoms, med): Number of symptoms / unscheduled medications per day per child; Poisson regression (PROC NLIN)

1-5. Refer to footnote to Table 3.1 for explanation

Table 3.3. Summary of statistical methods used in air pollution episode studies investigating the association between air pollution and respiratory health

Reference	Country (city)	Sample[1]	Duration[2]	Air quality measurement[3]	Outcome measurement[4]	Modelling procedures and types of models[5]
(Dockery *et al.* 1982)	USA (Steubenville – Ohio) Six cities study Reanalysed by (Brunekreef *et al.* 1991)	200 children	3 years: fall '78, fall '79, spring '80, fall '80.	TSP	Weekly Spirometry	Non-aggregate: K-W
(Brunekreef *et al.* 1991)	USA (Steubenville - Ohio) Reanalysis of (Dockery *et al.* 1982)	200 children from general population	Unknown	TSP (m24h).	PEF	Adjustments: AR-# Lags: 5-day average. Non-aggregate: K-W with test for heterogeneity of response of lung function

1-5. Refer to footnote to Table 3.1 for explanation

Table 3.4. Summary of statistical methods used in unclassified panel studies investigating the association between air pollution and respiratory health

Reference	Country (city)	Sample[1]	Duration[2]	Air quality measurement[3]	Outcome measurement[4]	Modelling procedures and types of models[5]
(Desqueyroux *et al.* 2002)	France (Paris)	60 severe asthmatic adults	13 months	PM10, O_3	Asthma attack	Non-aggregate: GEE
(Hoek *et al.* 1993a)	Netherlands	83 children	Weekly diary Winter	PM10, NO_x, O_3.	PEF	The difference of PEF before and after training
(Hoek *et al.* 1993b)	Netherlands (three non-industrial towns)	533 children	3 months	O_3	Spirometry occasionally	Non-aggregate: K-W Subgroup: chronic respiratory symptoms
(Kinney *et al.* 1989)	USA (Tennessee) Six Cities Study	154 children from six cities study	2 months.	O_3 (m24h).	Weekly measurements. Spirometry	Transformation: Lowess. Non-aggregate: K-W
(Koenig *et al.* 1993)	USA (Seattle)	326 children (which included 24 asthmatics)	3 measurements only	PM2.5	Spirometry	Unknown
(Linn *et al.* 1996)	USA (three communities in Los Angeles)	269 children	Daily for one week over three seasons	PM, NO_2, O_3	2D Spirometry Symptoms	Adjusted for year, season, day of week, year by season interaction
(Lawther *et al.* 1970)	Unknown	Unknown	Unknown	Particulates	Symptoms-bronchitis	Adjustments: AR-#
(Moseler *et al.* 1994)	Germany (Freiburg)	361 asymptomatic children and 106 symptomatic children	2.5 years	NO_2 Concentration at subject's residence was estimated using modelling techniques.	Every 11 months (3 measurements per child) Spirometry	Subgroup: asthmatics.
(Neas *et al.* 1991)	USA (six cities) Harvard six cities study	1567 children	Weekly for two weeks over two seasons	Indoor NO_2	Spirometry Symptoms: LRS	Unknown
(Ponka 1990)	Finland (Helsinki)	1532 infants	Weekly for one year	SO_2, NO_2.	Symptoms: URS, LRS Absenteeism.	Unknown
(Robertson and Lebowitz 1984)	USA (Tucson)	Selection of 80 adults each week	Weekly	TSP, CO, NO	Various symptoms	Fourier analysis
(Samet *et al.* 1993)	New Mexico	1205 asymptomatic children	Diary	Indoor NO_2	Symptoms: LRS	Unknown

Reference	Country (city)	Sample[1]	Duration[2]	Air quality measurement[3]	Outcome measurement[4]	Modelling procedures and types of models[5]
(Taggart *et al.* 1996)	UK	38 adult non-smoking asthmatics	Summer '93	SO_2, NO_2, O_3, pollen (m24h)	Bronchial hyper-responsiveness Pulmonary function.	Unknown
(von Mutius *et al.* 1995)	Germany (Leipzig)	1854 children	Unknown	PMx, SO_2, NO_x	Symptoms: URS recorded by physician	Analysed winter & summer separately

1-5. Refer to footnote to Table 3.1 for explanation

3.3 Air quality measurement

The types of air pollution that have been typically investigated in studies of air pollution and health include particulates (such as TSP, PM10, and PM2.5), sulphur dioxide (SO_2), nitrogen oxides (NO_x), nitrogen dioxide (NO_2), and ozone (O_3). Black smoke (BS), which includes particulates less than 4μm in size, was also sometimes measured. In addition, some studies studied acidic aerosols, which included hydrogen ion (H+), hydrogen sulphide (H_2S), sulphate (SO_4^{2-}), ammonium (NH_4^+), and sulphuric acid (H_2SO_4). It has been suggested that particles from industrial sources (e.g. from iron/steel emissions) and from coal production are more significant contributors to human mortality than soil-derived particles (Ozkaynak and Thurston 1987). There is also some evidence that concentrations of smaller particles (e.g. PM2.5) may be more hazardous than course particles. An explanation for this may be that the measures have different chemical composition or that they are deposited differently within the respiratory system. This has been examined in several diary studies whereby the effect of fine particles (e.g. PM2.5) on respiratory health was compared to the effect of course particles (e.g. PM2.5 to PM10) (Peters *et al.* 1997c; Neas *et al.* 1999; Schwartz and Neas 2000).

Several diary studies have also obtained pollen and fungi measurements. These have been conducted in California (Delfino *et al.* 1996; Delfino *et al.* 1997; Delfino *et al.* 1998; Delfino *et al.* 2002), Pennsylvania (Neas *et al.* 1996), Netherlands (Gielen *et al.* 1997) and Victoria (Downs *et al.* 2001).

3.3.1 Approach

In all study designs, it is necessary to obtain an estimate of each subject's exposure to various pollutants. Subjects will differ in the amount of time spent outdoors, the types of activities they engage in outside, their exposure to indoor pollution, and time spent in the immediate area. The exposure can be assessed by either direct, indirect-individual, or group-level exposure methods. Direct methods include personal monitoring, however this was not used in the panel studies. Indirect-individual methods refer to estimating personal exposure based on concentrations in various environments by using atmospheric or dispersion models. This was used in one diary study where time-activity logs and indoor sources of air pollution were used to estimate personal exposure to pollutants (Clench-Aas *et al.* 1999). In group-level methods, a single measure is assigned to all subjects in an area or city based on levels recorded using stationary monitoring. If more than one monitor exists in the area, an average or population-weighted average can be used (Katsouyanni *et al.* 1995). Many studies have shown that stationary

monitoring can represent the ambient exposure of individuals reasonably well. In the case of ambient ozone pollution, central-site monitoring has been justified as a regional measure of exposure, based partly on grounds that correlations between concentrations at neighbouring sites measured over time are usually high (U.S. EPA. 1996), though this may be due in part to common seasonal variation at all sites (U.S. EPA. 2001). In general, it has been found that indoor pollutant concentrations (PM10 and NO_2) vary in the same way as outdoor concentrations (Jamriska *et al.* 1999; Leaderer *et al.* 1999). However, there are exceptions: in very warm and very cold climates, and where there are high levels of indoor pollutants such as from cigarette smokers in the household or from the use of a gas stove (Wallace 2000; Wallace and Howard-Reed 2002). Furthermore, non-differential misclassification of exposure due to imprecise exposure estimation would tend to weaken any association between exposure and disease, and so bias the results towards the null. The likely consequence of using ambient monitors has been shown to underestimate pollutant effects on mortality (Zeger *et al.* 2000). Some daily diary measurements included the time spent outdoors by the subject prior to completion of the diary. A diary study of children in Pennsylvania found that when the concentration of air pollution was weighted by time spent outdoors, this strengthened the associations between ambient air pollution and peak flow (Neas *et al.* 1995).

Several studies examined more than one geographic area in their analysis. Two approaches were used: analysing each area separately (area-specific analysis); combining across areas (multi-area analyses). These two approaches will now be discussed.

In *area-specific analyses*, separate analyses are done for each area. The results may then be pooled across areas using a method analogous to random effect meta-analysis, whereby the mean of each city's regression coefficient is weighted by the inverse of its variance, allowing for additional between-cities variance as necessary (Peters *et al.* 1996; Schwartz *et al.* 1996a). Analogous methods were used to pool the results from the six European cities participating in the APHEA project (Anderson *et al.* 1997). There are other, more complex statistical methods such as mixed models, where area may be modelled as a fixed or random effect (Mortimer *et al.* 2002). Alternatively, data may be analysed using a fixed effects approach whereby a term is included in the model to indicate city of residence (Schwartz *et al.* 1994). Other studies chose not to pool across the different areas because markedly different coefficients were observed between the cities (Wojtyniak and Piekarski 1996).

In *multi-area analyses,* the same pollutant levels are assigned to all areas in the study. This approach was used in the studies of asthma mortality and morbidity in the Sydney population (Morgan *et al.* 1998a; Morgan *et al.* 1998b), and mortality in Athens (Hatzakis *et al.* 1986). However, this approach ignores spatial variation in pollutant levels. Residents living in Sydney's southwest, for example, were likely to be exposed to a very different cocktail of pollutants (and allergens) than residents living in Sydney's inner suburbs. An alternative study design would have been to separate Sydney into regions that had a monitor and analyse them separately.

3.3.2 Averaging time of pollutants

When pollutants are recorded each hour, a number of daily measures can be modelled in the analyses. These include the daily mean (average of the hourly measures), the daily maximum (maximum hourly measure over a 24-hour period), the daytime mean (average of the hourly measures over an 8-hour period 9am to 5pm), and the daytime maximum reading (maximum hourly measure over an 8-hour period). Most diary studies report associations between daily mean PM10 and respiratory health, and there are two advantages of using this measure. Firstly, it is the standard reported by government authorities. Secondly, there are advantages of using the same standard so that different studies can be compared and pooled together. However, there are no experimental studies to support this standard. In fact, shorter averaging times may be better proxies for exposure than daily averages. For instance, daytime means are more intuitively appealing because during the hours 9am and 5pm children are outdoors and physically active thus potentially having higher doses. One hour peaks may be more influenced by local point sources near the monitoring station and so may not be as good in representing regional exposures.

Some studies have tested associations between pollutants (PM10 and SO_2) for different averaging times. For instance, PM10 was analysed as both the daily maximum and daily mean in Sydney (Morgan *et al.* 1998a; Morgan *et al.* 1998b). Diary reports of cough were associated somewhat more strongly with an increase in daily maximum PM10 than with an increase in daily mean PM10 (Delfino *et al.* 1998). Most robust particulate effects were seen for daytime maximum exposures than daily maximum or daily mean (Delfino *et al.* 2002). Stronger associations were found between daily mean PM10 and respiratory health outcomes than daily maximum PM10 (Ostro *et al.* 2001).

3.3.3 Missing air quality data

If an exposure (PM10 in this study) is not measured on a particular day then the observations on that day will not be included in the analysis unless imputation is used. There have been several methods developed to impute missing values including those based on spatial correlation and temporal correlation. In spatial correlation, the values from close monitoring stations are used based on spatial statistic techniques. In temporal correlation, the previous day's values may be used from the same monitoring site, or statistical procedures may be used to interpolate between the two sequential non-missing values, and this approach has been used in some diary studies (Hoek and Brunekreef 1995; Vedal *et al.* 1998). Other studies have imputed the mean of available measurements from the monitor (Peters *et al.* 1997a) but this may result in standard errors which are too low.

3.4 Outcome measurement

The outcomes considered in panel studies include lung function, symptoms, and medication use. Each of these outcomes is described below, together with techniques for modelling them.

3.4.1 Lung function

Peak flow measurements have been widely used as a simple, cheap indicator of acute changes in lung function. They are used in diary studies, whilst other types of panel studies used spirometry measures as recorded by a trained technician (Koenig *et al.* 1993). Typically, peak flow measurements are made in both the morning and the evening. As a measure, morning peak flow may have some advantages over evening peak flow, as it is less likely to be affected by medication or daily activities, and asthma attacks tend to be more severe in the morning (Timonen and Pekkanen 1997). Stronger pollutant effects have been observed for symptoms compared to peak expiratory flow (PEF), suggesting that peak flow monitoring is not as sensitive as a symptom diary for revealing acute exacerbations of asthma. However, a reanalysis of five panel studies found that when peak flow was modelled as a dichotomous variable stronger effects were seen than when it was modelled as a continuous variable and these effects were of similar magnitude to symptoms (Hoek *et al.* 1998).

Separate models are typically fitted for morning and evening peak flow but it is possible to incorporate both in the one model (Neas *et al.* 1995). Other studies have taken the outcome to be the maximum of the evening and morning peak flow (Vedal *et al.* 1998), or the change in peak flow from evening to morning (Thurston *et al.* 1997). Although peak flow has traditionally

been analysed as a continuous measure, it has recently been analysed as dichotomous. The definition of an exacerbation has included a decrease of 10% or more below the 95th percentile of an individual subject (Boezen *et al.* 1999), or more than 10% or 20% below the median for an individual subject (Hoek *et al.* 1998). A 30% decrease in PEF from a subject's best reading has been the criterion for defining an acute exacerbation based on supporting symptom data (Chan-Yeung *et al.* 1996).

When analysed as a continuous variable, peak flow has been expressed in various forms including the raw peak flow, peak flow deviation or standardised peak flow deviation. Each of these outcomes is approximately normally distributed, and will now be defined. Say Y_{it} is the peak flow for subject i on day t, and $\overline{Y}_i$ and S_i are the mean peak flow observed across the study period for subject i, and the standard deviation respectively. Then the peak flow deviation for subject i on day t is:

$$Z_{it} = Y_{it} - \overline{Y}_i \qquad (1a)$$

This has been used as the outcome in several studies (Pope *et al.* 1991; Pope and Dockery 1992; Peters *et al.* 1997b; Timonen and Pekkanen 1997). There are some statistical advantages of standardising the outcome variable in any regression analysis and this approach has been used in many diary studies. The standardised deviation $Z_{it}^{'}$ (typically referred to as the normalised deviation) is defined as the deviation divided by the subject's overall mean and then multiplied by the mean for all subjects in the study, $\overline{Y}$ i.e.

$$Z_{it}^{'} = (Z_{it} / \overline{Y}_i) \times \overline{Y} \qquad (1b)$$

This has also been the outcome in several studies (Neas *et al.* 1995; Neas *et al.* 1996; Jalaludin *et al.* 2000) and is useful when the size of the deviation is related to the mean. Other studies have used the Z-score (Lebowitz *et al.* 1985) or the percent deviation (Agocs *et al.* 1997) defined respectively as:

$$Z_{it} / S_i \qquad (1c)$$

$$(Z_{it} / \overline{Y}_i) \times 100 \qquad (1d)$$

If the subject's mean peak flow $\overline{Y}_i$ is equal to the overall mean $\overline{Y}$ then from equation (1b) it can be seen that the standardised deviation will equal the absolute deviation. For a given absolute deviation, the standardised deviation will be larger in absolute value if the subject's overall mean peak flow is low relative to the group mean and vice-versa, i.e.

$$\text{if } \bar{Y}_i << \bar{Y} \text{ then } |Z_{it}'| >> |Z_{it}|$$

$$\text{if } \bar{Y}_i >> \bar{Y} \text{ then } |Z_{it}'| << |Z_{it}|$$

3.4.2 Symptoms

Symptoms are typically recorded in a daily diary on a Likert scale of severity of three or six points. They are often divided into upper respiratory tract (URT) and lower respiratory tract (LRT) symptoms for analysis. Upper respiratory symptoms include runny or stuffy nose, sneezing, sore throat, earache, head cold, hayfever, and burning or red eyes. Lower respiratory symptoms include wheezing, phlegm, dry or persistent cough, shortness of breath, and chest tightness. Stronger effects for PM10 have been found for lower rather than upper respiratory symptoms. Cough is the most frequent symptom examined, and is often analysed separately. One study examined the outcome cough in the presence of no other symptom (Schwartz *et al.* 1994).

In most of the published material, symptoms were analysed on a dichotomous or binary scale as the presence or absence of a symptom. Some investigators have experimented with different cut-offs in the scale to obtain the binary measure (Delfino *et al.* 2003). Binary outcome data such as this allows for the use of logistic regression modelling. The continuation odds model, the cumulative logit, and polychotomous logistic regression would make use of the ordinal nature of the symptom data but have not been used in the air quality literature presumably because of the added model complexity. For more information on these models, refer to the text by Agresti (Agresti 1996). For binary data, logistic regression is the most popular tool as the coefficients can be interpreted as odds ratios, and as a result alternatives such as the probit and complementary log-log models (Collett 1991) have not been used in the air quality literature. In logistic regression, the log linear scale forces predicted values to fall between 0 and 1. Another alternative is to model the number of subjects having the symptom by applying the Poisson model. This has not been used in panel studies, as the outcomes are not rare. One diary study examined symptom prevalence as a linear model as event rates were high (Gielen *et al.* 1997).

Other studies have analysed symptoms by keeping the scale as a continuous measure as recorded in the Likert Scale (Delfino *et al.* 1997). Symptoms scores which are sums of individual symptom items have also been used (Luck 1997) and the deviation from the child's mean symptom score has also been used (Peters *et al.* 1996). In one study, the observed number of patients with symptoms on each day was compared to that expected to have symptoms, based

on the overall occurrence of symptoms for each subject; the ratio of the two values were then modelled using least squares regression (Forsberg *et al.* 1993).

Although early work focused on prevalence measures, attention was drawn to incidence measures in the 1990s (Schwartz and Zeger 1990). Incidence has been defined as the presence of a symptom on a given day when the previous day (Schwartz and Zeger 1990; Braun-Fahrlander *et al.* 1992) or previous two days (Hoek and Brunekreef 1994) were symptom free. The prevalence is a function of both the incidence and the duration of the symptom. The incidence analyses investigate whether the pollutant is related to precipitating an attack; whereas the prevalence analysis indicates whether the pollutant is related to precipitating and prolonging an attack. An episode is defined as a set of days in which a symptom was continuously present, and duration is the number of days in the episode.

3.4.3 Medication use

Medication usage has been used as an outcome measure in many studies (Table 3.1). For asthmatic children this is thought to be the most appropriate outcome (Pope *et al.* 1991). It is typically expressed as the number of puffs of reliever (bronchodilator) medication taken each day, or whether unscheduled (extra) medication was required on a given day (Thurston *et al.* 1997). In one study medication usage was analysed as the daily mean deviation from the overall mean daily number of puffs of bronchodilator medication (Gielen *et al.* 1997). Usually all subjects were included in the analysis, however one study limited the analysis to people who used asthma-medication at some stage during the study (von Klot *et al.* 2002). One study found similar results between doing the analysis both ways (Peters *et al.* 1997a). Medication was usually recorded by the subject but one study used an automated device (Perry *et al.* 1983).

Medication use has also been treated as a confounder or effect modifier in some analyses where the outcome has been peak flow or symptoms and this is discussed in Section 3.5.10.

3.4.4 Criteria for exclusion of outcome data and exclusion of subjects

In the daily diary studies, the first two of weeks of the subject's data were typically excluded from analyses due to probable learning effects. The exclusion time ranged from 2 days (Agocs *et al.* 1997) to 2 months in a three year panel study of student nurses (Schwartz and Zeger 1990). To ensure data integrity, some data were excluded:

- dates where the peak expiratory flow (PEF) values were the same for more than 14 days (Peters *et al.* 1997b)

- dates where the PEF on a given day was more than 120% of the overall mean for the subject (Jalaludin *et al.* 2000)
- dates where values fell outside the range of 70 to 450 L/min (Mortimer *et al.* 2002).

In addition, some studies excluded dates where the subject spent more than 4 hours away from the area (Agocs *et al.* 1997), or dates where the subject spent any time away from the area (Whittemore and Korn 1980).

Subjects who provided minimal data were removed. The actual criteria varied between studies, from less than 14% of the study period (Peters *et al.* 1997b) to less than 75% of the study period (Agocs *et al.* 1997). Subjects for whom an incorrect PEF technique was observed were excluded (Neas *et al.* 1996). Subjects who reported little variation in PEF, or only reported PEF in multiples of 50 L/min, were excluded in a small sensitivity analysis (Neas *et al.* 1995). Subjects who moved out of the area were excluded (Pope *et al.* 1991), as were subjects who resided outside the community for more than 2 days (Neas *et al.* 1996). In one study subjects who were exposed to indoor sources of air pollution including coal or wood heating were excluded (Agocs *et al.* 1997). This has the advantage of reducing potential confounding by indoor air pollution, but as a disadvantage, generalisability of results may be reduced, as they may have been a more susceptible subgroup of the population (Rothman and Greenland 1998a).

3.5 Modelling procedures

Panel studies involving repeated observations of susceptible population subgroups have been used to investigate the health effects of air pollution since the 1970s. Initially, the statistical method most frequently used was linear regression of the daily symptom event rate in the panel, against ambient air quality and meteorological measurements. If c_t is the number of subjects with symptoms on day t and n_t is the number of subjects observed on day t, the event rate can be expressed as $G_t = c_t / n_t$. This is analysed on a linear scale by modelling

$$G_t = X_t \beta + \varepsilon_t \qquad (2)$$

Where: $X_t = (X_{1,t}, ..., X_{Q,t})$ denotes the explanatory variables on day t

$\beta = (\beta_0, \beta_1, ..., \beta_Q)$ denotes a vector of parameters to be estimated

ε_t are independent with distribution $\varepsilon_t \sim IN(0, \sigma^2)$.

There were at least two problems with this approach. Firstly, it required that the event rates on successive days were statistically independent with constant variability about the expected value. This is an invalid assumption as asthmatics are significantly more likely to have an attack on days following an attack compared to days after an attack-free day. The second problem with this approach was that it is undesirable to represent proportions as linear functions (Cox 1970). It was generally agreed that the methodology for collecting and analysing the data from these studies had not been adequately developed (Stebbings and Hayes 1976). More sophisticated models have since been developed and these will be discussed in the remainder of this section and Section 3.6.

The typical analysis of diary studies includes both Aggregate and non-aggregate approaches. In an Aggregate analysis the data are summarised to obtain daily summary measures, for example, the average evening peak flow deviation across all participants recording data on a given day. The coefficients from these Aggregate models indicate how the average risk over the population changes with increased levels of the pollutant. It is common to start with an Aggregate analysis of the data and then move on to the more complex non-aggregate analyses. Several modelling issues are relevant to diary studies and these will now be discussed in Sections 3.5.1 to 3.5.10. Note that the issues discussed in Section 3.5.1 to Section 3.5.8 are also relevant to time series studies. In Section 3.6 a description is given of the various modelling approaches.

3.5.1 Removing seasonality and trend

Temperature typically has a “U-shaped” association with morbidity and mortality, whereby higher levels of both outcomes are observed on very cold and very hot days. The weather can affect respiratory health directly, indirectly, or through broad seasonal effects:

- Direct effects – occur when the weather alone affects respiratory health. Temperature and other meteorological variables such as humidity, rainfall, wind-speed, and wind-chill factor, are likely to directly affect health indices. It is generally accepted that sharp temperature changes or cold temperatures can induce asthma attacks. One study reported that 61% of children identified weather changes as a significant factor influencing an asthma attack (Mercer and van Niekerk 1991). An earlier study found that paediatric emergency room visits in New York were associated with temperature fluctuations (Ribon *et al.* 1972). A Danish study identified that pulmonary impairment in asthmatics occurred during frost periods (Moseholm *et al.* 1993).
- Indirect effects – occur when weather promotes the formation, or increases the concentration of pollutants and other allergens, e.g. photochemical smog. Housing studies

have shown that increases in humidity may increase the propagation of biological triggers, such as dust mites and moulds (Bjornsson *et al.* 1995). In cold weather there are higher emissions of pollutants as a result of the use of wood heating. The concentrations of these pollutants that remain in the ambient air are in turn influenced by wind-speed, precipitation, and inversion height.

- Broad seasonal effects – occur when seasonal patterns provide direct changes in the biophysical environment, e.g. spring pollen period.

A critical task in a time series analysis involves dealing with the seasons of the year. There have been several papers discussing this issue and these have been summarised (Pope and Schwartz 1996). Many outcomes have pronounced seasonal patterns, with peaks in respiratory complaints often being observed in winter. Several pollutants also exhibit seasonal patterns. If these seasonal patterns are not controlled for in the analysis, this may result in spuriously positive (if pollutants also peak in winter), or negative (if the pollutant peaks in summer) findings. For example, if ozone levels were low in winter and high in summer, a crude analysis would suggest that ozone was protective against respiratory epidemics. To adjust for season, indicator variables can be used, however they are often inadequate as they specify a pattern in which the level of the outcome variable is constant in each season. More sophisticated seasonal models, such as the use of month indicator variables, smoothing or filtering are often appropriate. An alternative is to fit sinusoidal terms of the form:

$$\sum_{k=1}^{K}\left[\gamma_k \cos(2\pi kt/365) + \theta_k \sin(2\pi kt/365)\right] \qquad (3)$$

where K is estimated using spectral analysis (Diggle 1990). This approach has mainly been used in time series studies (Katsouyanni *et al.* 1996), but has also used in one diary study (Peters *et al.* 1996).

Temperature has been modelled in various ways in the literature, including the minimum daily temperature, maximum daily temperature, and mean daily temperature. Sharp temperature changes measured by the gap (maximum value minus minimum value of the day) was used in one study conducted in Australia (Luck 1997). Many of the studies have been conducted during one season only, or their analyses has been restricted to only one season (Schwartz *et al.* 1994). Temperature has been fitted as a continuous variable, or using quartiles (Morgan *et al.* 1998a; Morgan *et al.* 1998b), or with quadratic indicator terms. Most investigators modelled the current day's temperature, although one study used the previous day's (Thurston *et al.* 1992). Binary variables were sometimes included to indicate temperature extremes (Ostro *et al.* 1996).

Rainfall was typically modelled as a binary indicator with dry or light days of fall (classed as up to 1 or 2 mm) or heavy (classed as more than 1 or 2 mm) (Neas *et al.* 1996). Adjustments were also made for humidity, day of the week, wind direction (important when local sources of pollution dominate air quality), and sunny days (defined by the amount of solar radiation) (Neas *et al.* 1996).

Any two variables showing a time trend will be correlated, so it is important to remove long-term trends from time series data. Diary studies involving children, particularly those with a diary collection period greater than 100 days, will generally show an upward trend in peak flow levels. This is most likely due to the children's growth, and a learning effect in the first part of the study. This combination will probably present as a non-linear time trend. To adjust for trend, a variable that represents the nth day of the study is often fitted. In addition, the residuals should be plotted against trend and temperature to check that the model properly adjusts for trend and seasonality.

3.5.2 Autocorrelation

When time series data are analysed using regression models, often the error term is not independent across time. Positive autocorrelation of the errors generally tends to make the estimate of the error variance too small and so the true null hypothesis is rejected with a higher probability than the stated significance level. It is the correlation of the fitted model's error term, not the correlation of the outcome that is of primary concern. Hence, the degree of autocorrelation is a reflection of the model itself and once the confounders are taken into account the autocorrelation will generally be reduced (Katsouyanni *et al.* 1996). There are two general approaches to allow for autocorrelation in model fitting.

The *first approach*, which was used in earlier studies, was:

$$Y_t = X_t\beta + \alpha Y_{t-1} + \varepsilon_t \qquad (4a)$$

where: β denotes a vector of parameters

ε_t is normally and independently distributed with mean 0 and variance σ^2 i.e.

$\varepsilon_t \sim IN(0, \sigma^2)$.

The *second approach* involves incorporating autoregressive parameters into a model to deal with autocorrelation. This approach allows greater flexibility than the first approach. The model has the form:

$$Y_t = X_t\beta + \vartheta_t \quad (4b)$$

where: β denotes a vector of parameters

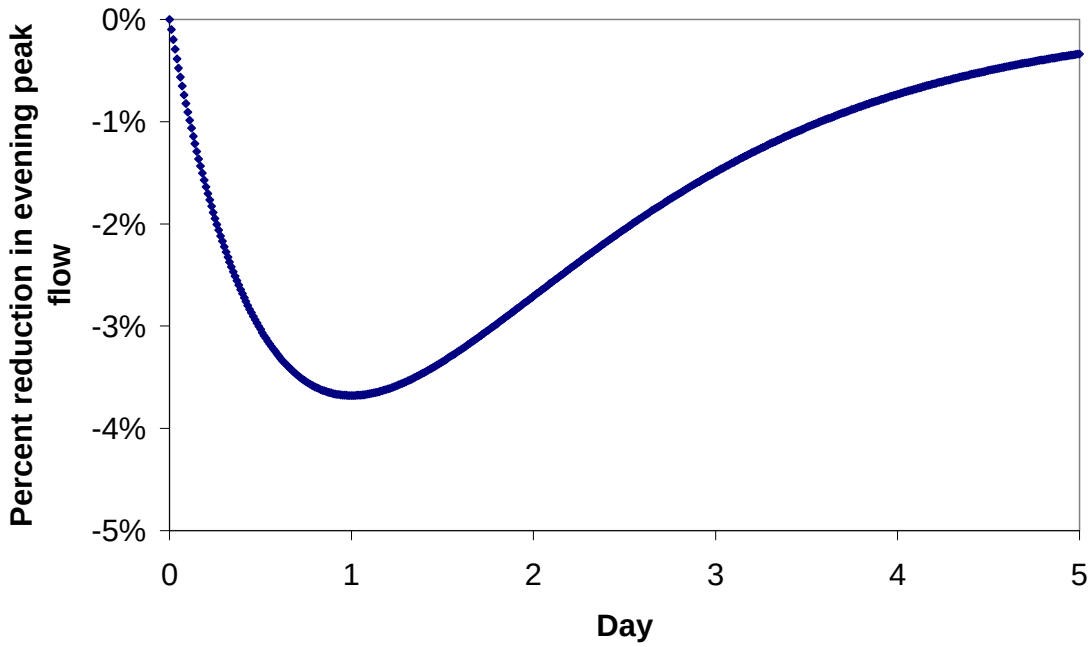
ϑ_t is a latent process allowing autocorrelation in Y_t.

Diary studies typically assume the error term is an autoregressive process of order 1, denoted AR-1, and this can be written as $\vartheta_t = -\varphi_1\vartheta_{t-1} + \varepsilon_t$ where $\varepsilon_t \sim IN(0, \sigma^2)$. An AR-1 model indicates the residuals at day *t* are highly correlated with those at day (*t*-1), but less with those at day (*t*-2). To choose the appropriate order the partial autocorrelation function (PACF) can be used, which describes the serial correlation of a time series at each lag with the value at each lag corrected for the previous lags. If the errors from the fitted regression model are uncorrelated, the value of the Durbin-Watson test statistic will be close to 2. Schwartz *et al*. found that models with incidence of symptoms as the outcome were not as correlated as models with prevalence of symptoms as the outcome (Schwartz *et al.* 1991).

3.5.3 Lag effect of pollutants

While exposure to air pollution may cause an immediate physiological response, the evidence of these changes may only be apparent a day or two later. In addition, the associated respiratory health outcomes may persist for more than one day. Both these factors indicate a lagged effect may exist whereby the effect of an increase in pollution concentration on a single day is distributed across several subsequent days. Currently, no biological evidence supports a particular lag although toxicological data also suggest that effects of exposure may be seen over several subsequent days. In general, the shape of the distribution of effect of air pollution on evening peak flow may be similar to that displayed in Figure 3.1. The effect rises in absolute value, and then falls, possibly with a long tail. The pollutant variables can be analysed at different lag-times to account for short latency periods in the manifestation of diseases. Knowing the correct lag has two advantages: the length of the effect may be of biological interest, and the overall effect of the pollutant may be more accurately estimated. Various exposure-lag structures have been discussed in the pollution literature (Pope and Schwartz 1996; Samet *et al.* 2000b) and are summarised here.

Figure 3.1. Graphical illustration of the hypothesised impact of PM10 on evening peak flow over time



This figure is a modification of the figure reported by Schwartz (Schwartz 2000).

In general, the variable Y (e.g. evening peak flow) may be modelled as a linear function of the same day X (e.g. PM10), the first lag of X, the second lag of X, and so on up to the P th lag of X as

$$Y_t = a + \beta_o X_t + \beta_1 X_{t-1} + \beta_2 X_{t-2} + ... + \beta_P X_{t-P} + \varepsilon_t \qquad (5a)$$

where X_{t-P} is the PM10 concentration P days before the respiratory outcome. This may also be expressed as:

$$Y_t = a + \sum_{i=0}^{P} \beta_i X_{t-i} + \varepsilon_t \qquad (5b)$$

The overall effect of a one unit increase in X (say PM10) on a single day is its impact on that day as well as subsequent days. This may be expressed as the estimates $\sum_{p=0}^{P} \beta_i$. The data analyst specifies the constant P a priori. The analyst also determines the form of the constraint on β. There are five general approaches:

- *Same day lag:* The model is constrained to assume the effect all occurs on one day.

$$Y_t = a + \beta_o X_t + \varepsilon_t \qquad (5c)$$

- *Single day lags:* In a single day lag of order d days then

$$Y_t = a + \beta_d X_{t-d} + \varepsilon_t \qquad (5d)$$

- *Unrestricted lag:* each parameter (β_i) is estimated independently of its neighbours. The problem is that X_t is correlated with X_{t-1},…., X_{t-P} and the high degree of collinearity will result in unstable estimates of the X_t. Both the β_i and sum of β_i however, will be unbiased estimators of the effects of each lag and of overall effects. One disadvantage is that the estimated shape is often noisy. These have been fitted in time series studies of mortality (Schwartz 2000) and morbidity (Samet *et al.* 2000b).
- *Polynomial distributed lag (PDL):* parameters are constrained to follow a polynomial curve over time,

$$\beta_i = \sum_{r=0}^{R} a_r i^r \qquad (5e)$$

where *R* is the degree of the polynomial used. R can be determined using stepwise increases in the degree of the polynomial and testing the significance of $\hat{\alpha}_r$, stopping when $\hat{\alpha}_r$ is no longer statistically significant. Models of this kind are referred to as Almon lag models in the econometric literature. In the air pollution literature both quadratic distributed lag models (R=2) and cubic distributed lag models (R=3) have been fitted. Endpoint restrictions can be imposed on a polynomial distributed lag model to require that the lag coefficient is zero at certain lags. This type of modelling is only appropriate when the pollutant is fitted as a continuous term, and hence is not appropriate if the pollutant is fitted using indicator variables. These may be implemented in SAS using PROC PDL or PROC MODEL.

- *Moving average*: In a moving average lag model of P days all the parameters (β_i) are constrained to be equal

$$Y_t = a + \beta \times \left[(X_t + X_{t-1} + X_{t-2} + ... + X_{t-P}) / (P+1) \right] \qquad (5f)$$

For example, the 5-day moving average model is fitted by regressing the outcome against the average of the current and preceding four days and is sometimes called the 5-day cumulative lag (Pope and Dockery 1992).

In epidemiological studies examining the effects of acute exposures to particulates, lagged effects of two or three days are common, and several studies have reported effects after five or more days (Dockery and Pope 1994). It is common to consider same day models as well as single day lags of up to 5 days, although one diary study considered lags of up to 15 days

(Vedal *et al.* 1998). Cumulative lags, calculated using moving averages of up to five days are also commonly used. Many studies have found the strongest association between particulate matter and lung function based on 5-day moving average models (Brunekreef *et al.* 1991). Such long-term average exposure variables may be less affected by exposure misclassification (Delfino *et al.* 1998). The coefficients, regardless of the outcomes and exposures, are typically reported in the epidemiological studies for same day (lag 0), one-day lag (lag 1), and five-day moving average models. Polynomial distributed lag models have been used in very few diary studies (Pope *et al.* 1991; Peters *et al.* 1996). Such models have the advantage of allowing a graphical display of the lag effect, and may indicate which single-day lag or moving average model would be most appropriate to fit. Schwartz found that models examining same day pollutants tend to underestimate the effect of the pollutant compared to models using polynomial distributed lag models (Schwartz 2000). The factors considered when choosing the lag structure to be reported have varied. Some studies have based it on an a priori specification or the Goodness of Fit test (Spix *et al.* 1993). Other studies have chosen the lag with the largest effect estimate in the hypothesised direction (Morgan *et al.* 1998a), however this method can bias the results towards finding statistically significant associations. A more consistent and statistically rigorous approach using polynomial distributed lag models has been advocated to facilitate combining evidence across studies (Schwartz 2000).

3.5.4 Model representation of air quality and meteorological variables

One of the first steps in the analysis is to determine whether the association between each air quality (e.g. PM10) and meteorological variable with the outcome variable is linear. Graphical tools such as scatterplots, conditioning plots and partial-residual plots can be useful in this regard. There are also formal tests for non-linearity available, and these will be discussed later in this section. Linearity of the air quality variable may also be investigated by seeing if the association remains significant for those days with lower say PM10 values. This can be done by fitting the pollutant as a linear term in the model and if a statistically significant linear relationship is found, the change in the pollutant's regression coefficient is studied after successive deletion from the regression model of the days with the highest values (Hatzakis *et al.* 1986). If the coefficient remains stable to the deletions then the relationship is in fact linear. A linear relationship is of clinical interest as it indicates that there is no evidence of a "safe" threshold level. If the relationship between the pollutant and outcome variable is linear then the pollutant should be fitted as a linear rather than as a categorical variable in the relevant models. There are several reasons for this. Firstly, the resulting coefficient is more easily interpreted. Secondly, it allows for easy pooling of the coefficients across study areas using meta-analytic

techniques. Lastly, fewer degrees of freedom are used in the model and so the power to detect significant differences is greater. Results are usually expressed as the change in the outcome corresponding to a change from the 5^{th} to the 95^{th} centile or interquartile range (25^{th} to the 75^{th} centile) of the pollutant's distribution.

When the covariate effects are not linear, several approaches can be undertaken. The non-linearity may be handled within the linear model framework by using one of these techniques: *transformations, polynomial regression, use of indicator terms*. Alternatively, nonparametric regression techniques may be used. Nonparametric regression methods do not impose a priori assumptions about the association between the outcome and explanatory variables. The graphical displays from nonparametric regression are useful but its disadvantage is that it does not provide an estimate of effect of the pollutant on respiratory health. Nonparametric regression methods include: *local polynomial regression, smoothing splines*, and *generalised additive models*. These six different approaches will now be discussed.

Transformations of the pollutant such as logarithms may be used. Particulates and sulphur dioxide were linearly related to the respiratory health outcomes in most time series and panel studies. For this reason they have rarely been transformed. However, in a study examining short-term effects of air pollution on both hospital admissions and mortality in Italy, both TSP and SO_2 showed evidence of a curvilinear relationship, with a smaller slope at higher concentrations and consequently, both pollutants were logarithmically transformed in the regression analysis (Vigotti *et al.* 1996). A log-linear relationship was also found between SO_2 and emergency admissions for wheeze (Buchdahl *et al.* 1996). In diary studies pollen counts have been log-transformed (Gielen *et al.* 1997) and square-rooted (Downs *et al.* 2001).

Polynomial regression is an extension of linear regression, where parameters are added which represent different parts of the trend for a particular covariate. For every bend in the curve, another term is added to the model. For example, when there is only one bend in the curve, a quadratic term can be added to the model, and then one can test whether it accounts for the non-linearity.

An alternative is to break the data up into ranges within which the relationship is relatively linear, by using *indicator variables*. If the pollutant needs to be fitted as a categorical variable, the choice of cutpoints needs to be justified. Some studies have modelled PM10 as quartiles

(Pope and Dockery 1992). Pollens have been modelled as a presence/absence binary indicator variable (Jalaludin *et al.* 2000).

One type of nonparametric regression is *local polynomial regression*, or lowess (locally weighted scatterplot smoothing) which was originally developed by Cleveland (Cleveland 1979). In this method, a polynomial regression is fitted for each data point using kernel functions, and then the fitted values are joined together. The basic approach of these methods is to estimate peak flow at a particular pollution level by a weighted average of peak flow values over a range of values of pollution including the specified pollution level. The choice of weighting and the bandwidth of the pollution determine the amount of smoothing carried out. This can be done in SAS using the SAS procedure PROC LOESS.

In *smoothing splines*, the data are partitioned and separate nonparametric regressions are fitted in each section. They are smoothed together where they join. The amount of smoothing done depends on the location of the breakpoints to form the sections and the choice of spline. Splines can also help determine which transformation to consider or how to chose cutpoints to set up indicator variables in parametric regression (Wypij 1996).

Although these two nonparametric methods are unable to account for correlation among repeated measures on subjects, graphical presentations of the fitted model are useful to illustrate the relationship between the pollutant and outcome. However, it is not straightforward to do multivariable regression using these nonparametric methods. *Generalised additive models* (GAMs) are an extension of lowess and smoothing splines for application to multivariable regression, and generalised linear models (Hastie and Tibshirani 1990). These methods can be applied to any generalised linear model and so are appropriate for Gaussian, as well as binary and Poisson responses. In a linear GAM the following model is fitted:

$$Y_t = g_0 + \sum_{q=1}^{Q} g_q(X_{q,t}) + \varepsilon_t \qquad (6)$$

where each g_q is a smooth, possibly non-linear univariate function. The application of generalised additive models to air pollution studies has been discussed (Schwartz 1994a). A GAM can be used to fit peak flow as a sum of smooth functions of air pollution, temperature, as well as additional covariate effects added on a linear scale. Any nonparametric smoothing method can be used to estimate $g_q(X_{q,t})$ using the backfitting estimation procedure. The generalised additive model test for non-linearity compares the fit of the linear model with the fit

of the nonparametric model. Generalised additive models can be fitted in SAS using the procedure PROC GAM from Release 8.2. Generalised additive models have recently been extended to accommodate longitudinal responses. Those based on the generalised linear mixed models are referred to as generalised additive mixed models (Lin and Zhang 1999) and these can be fitted using a modification of the SAS procedure PROC MIXED. Those based on generalised estimating equations are referred to as additive generalised estimating equations (Wild and Yee 1996). Both generalised linear mixed models and generalised estimating equations will be discussed in Section 3.6.

In one panel study a statistically significant non-linearity was found between sulphur dioxide and incidence of cough when using generalised additive models (Schwartz *et al.* 1994). Many mortality studies have included adjusted nonparametric smooth plots to show the relationship between the pollutant and outcome (Hoek *et al.* 1997). A method (Schwartz and Zanobetti 2000) has been developed to detect whether a threshold exists using GAMs in the application of situations where the investigator seeks to pool estimates of coefficients across multiple cities using hierarchical models.

3.5.5 Assessment of effect modification by climate-related factors and pollutants

There is some evidence to suggest that the effects of particulates and SO_2 on respiratory mortality are dependent on season (Stieb *et al.* 2002). That is, weather may act synergistically with pollutants to produce adverse health effects. In a mortality study in Athens, stronger associations between pollutants and deaths were found when the mean daily temperature exceeded 30 ^{O}C (Katsouyanni *et al.* 1993). The synergistic effects of the pollutants can be investigated by including interaction terms in the regression model and assessing their statistical significance.

There has also been some evidence of effect modification by pollutants. In one study, when particulate concentrations were greater than 60 $\mu g/m^3$, the joint effect of PM10 and SO_2 on mortality was increased (Zmirou *et al.* 1996). A study of bronchial hyperactive patients reported that the effect of pollen on peak flow was stronger when the previous day's ozone levels were high (Higgins *et al.* 2000).

3.5.6 Model fit

The Akaike's Information Criterion (AIC) can be used for variable selection. The AIC of a model is calculated as the sum of the deviance of the model and two times the number of degrees of freedom. The AIC is used to evaluate whether the decrease in deviance of a model, resulting from the use of an additional parameter, is worth the use of an additional degree of freedom. Therefore, the model with the lowest AIC is preferred.

3.5.7 Sensitivity analyses

It has been suggested that a sensitivity analysis should be conducted on the final model. This may involve including alternative pollutant averaging times, alternative methods of adjusting for season and trend, and alternative model representation of pollutant variables. The results from the final model should be robust to alternate methods of estimation and weather control.

Several reanalyses have been undertaken to determine whether the use of alternative statistical methodologies alter the results substantially. The mortality data from the winters of 1958 to 1972 in London have been independently analysed by four investigators (Mazumdar *et al.* 1982; Ostro 1984; Schwartz and Marcus 1990; Lippmann and Ito 1995). The mortality data at Steubenville, Ohio from 1974 to 1984 have been analysed by two investigators (Schwartz and Dockery 1992b; Moolgavkar *et al.* 1995b). The mortality data from Philadelphia 1973 to 1990 has also been reanalysed (Schwartz and Dockery 1992a; Li and Roth 1995; Moolgavkar *et al.* 1995a). Data from panel studies have also been reanalysed (Hoek *et al.* 1998).

3.5.8 Overdispersion

A frequent concern when fitting Poisson models is the possible presence of overdispersion. This tends to result, when ignored, in standard errors which are too low (Agresti 1996). To avoid such a problem, the standard errors can be multiplied by a correction factor called a scale parameter (Thall and Vail 1990). By default, this scale parameter is usually constrained to equal 1. This issue of overdispersion is less of a concern in panel studies where the outcomes are usually binary or continuous. A recent study which pooled the data from several diary studies allowed for overdispersion when modelling the binary outcome measure (Hoek *et al.* 1998).

3.5.9 Missing outcome data

Longitudinal studies frequently have missing outcome data due to participant dropouts and intermittent missing values. If the cause of the missing data is related to the values not observed, and there is a substantial amount of missing data, this may bias the results (Diggle *et al.* 1994).

For example, it is probable that a subject's decision to complete the diary is dependent on their health that day; for instance, worry about illness may lead to neglect of the diary which may lead to biased estimates.

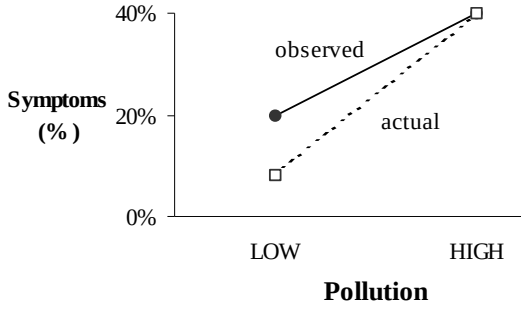
Of principle concern is that the proportion of missing data on a given day may be related to the level of pollutants (e.g. PM10) on that day. If a subject only completes the diary on days that they are sick and these correspond to days of relatively high PM10, this will result in a bias towards the null. This is illustrated in Figure 3.1(a). If a lower weight was applied to values where few subjects respond, this would reduce the bias. Conversely, a subject may not complete a diary on days when they are sick. High pollution days would then be expected to have a lower proportion of sick subjects responding compared to low pollution days, resulting again in a bias toward the null. This is illustrated in Figure 3.1 (b). In both situations, the bias would be less evident if during the analysis the daily observations were weighted by the number of subjects responding.

Figure 3.2. Effect of missing outcome data on the estimate of effect of pollution on respiratory health

∘ Actual value; • Observed value

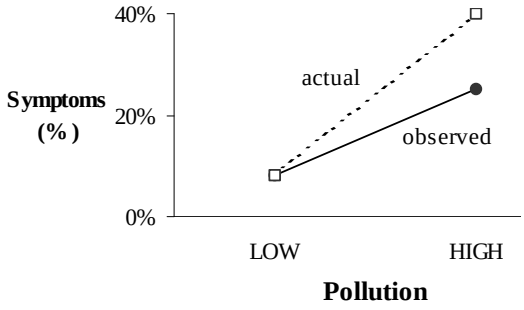
(a) Bias toward null

Symptomatic people *more* likely to respond on days with high pollution than on days with low pollution



(b) Bias away from null

Symptomatic people *less* likely to respond on days with high pollution than on days with low pollution



Missing data are not a problem as long as the non-response is non-informative. Missing data in longitudinal studies has been defined as either missing completely at random (MCAR), missing at random (MAR), or non-ignorable (Little and Rubin 1987). Consider two variables **X** and **Y** where **X** may be PM10 and **Y** may be presence of symptoms. Missing data are said to be MCAR when the probability of response is independent of variables **X** and **Y**. Missing data are

considered to be MAR when the probability of response depends on **X** but not on **Y**. Lastly, missing data are considered to be non-ignorable when the probability of response depends on **X** and **Y**. The various modelling approaches differ in their assumptions of "missingness" and this will be discussed in Section 3.6.

Several procedures are available for handling data that are missing. The most common approach is to simply omit those records with missing data and to run the analysis with what remains. This is termed list-wise deletion, and is the default in statistical packages. However, omitting records may introduce bias, to the extent that the unobserved records differ systematically from the observed ones. Treatment of missing data follows two general approaches: weighting and imputation. Weighting methods discard incomplete data and weight observed data inversely to the probability of observation, and imputation methods impute missing values. When using imputation, it is not appropriate to impute the overall mean as this may distort the marginal distribution for **Y**, covariances and correlations with other variables (Schafer 1997). Considerable research has focused on modelling the drop out process (Lindsey 2000) however, dropouts are not a problem encountered in the diary studies in the air quality literature.

To examine the direction of the bias that could result from non-random missing data, the models can be refit using imputed values based on the methodology of 'across-wave imputation' from panel surveys (Lepkowski 1989) whereby on each day where the subject is missing outcome data, the value from the preceding day under three different kinds of assumptions can be used. These assumptions are: symptom did not change from previous day (so called last observation carried forward), symptom improved, or symptom worsened. Examining the results from the three models gives some sense of the bias that potentially exists.

The issue of missing data has largely not been examined in panel studies. One strategy used to examine whether data are MCAR was to examine whether missing reporting periods are correlated with the ambient pollutant levels (Neas *et al.* 1995). Specifically, if there is a correlation between the proportion of subjects completing the diary each day and ambient pollutant levels that day then they cannot be MCAR, and must be MAR or non-ignorable. There was only one diary study in which the symptoms were found to be non-ignorable, in this study multiple imputation was used to determine the likely size and direction of the bias (Smith *et al.* 2000).

3.5.10 Subgroup analysis, adjustment for confounding and effect modification by non-climate-related factors

Diary studies often present analyses based on the entire sample, as well as a subgroup. The estimates are frequently stronger in these subgroups, and significant effects are often only seen in these groups. Children with mild respiratory disease and no treatment with asthma medication have been found to be a sensitive subgroup in many studies (Pope *et al.* 1991; Pope and Dockery 1992; Neas *et al.* 1995). In a panel study of children aged 7-12 years with chronic respiratory symptoms in Finland, daily NO_2 concentrations were significantly associated with declines in morning PEF among children with asthmatic symptoms (wheezing, breathlessness or asthma diagnosis), but not among children with cough symptoms only (Timonen and Pekkanen 1997). Other sensitive subgroups have included bronchial reactive subjects (Higgins *et al.* 1995); subjects with a history of wheeze, positive histamine challenge and doctor diagnosed asthma (Jalaludin *et al.* 2000); subjects with bronchial hyperresponsiveness and atopy (Boezen *et al.* 1999); and subjects born premature or with low birthweight (Mortimer *et al.* 2000). In one study the number of occurrences of symptoms for each subject was modelled against various subject characteristics in order to identify potential subgroups using Poisson regression (Schwartz and Zeger 1990). The use of interaction terms is preferred to stratification of the data, as it allows the model to be fitted for all observations, and increases the stability of the estimates (Mortimer *et al.* 2002).

The covariates can be classified as either time-stationary or time-varying. Time-stationary or between-subject covariates do not change over time and include terms such as gender. Time-varying or within subject covariates change over time and include meteorological variables. Some studies have included diary-based time-varying covariates in the regression model. In a panel study examining the effect of nitrogen dioxide on symptom reporting, the regression model adjusted for exposure to passive smoking which was recorded each day (Clench-Aas *et al.* 1999). In a panel study of 164 children in Denver, the regression model adjusted for current cold (Ostro *et al.* 1994). A number of studies have adjusted for presence of fever in the analysis (Schwartz *et al.* 1988; Peters *et al.* 1997a; Peters *et al.* 1997b) or excluded data on days a participant reported fever (Dusseldorp *et al.* 1995).

There are special issues regarding medication use and perception of air pollution. These will now be discussed.

Special issues relating to use of asthma medication

People diagnosed with asthma are advised to take bronchodilator medication when symptomatic. This should result in peak flow increase and reduced severity of symptoms as part of drug efficacy. It has been found in human experimental studies that the adverse effect of sulphur dioxide on lung function can be reduced through use of medication (Koenig *et al.* 1992). If this medication use was ignored in an analysis with peak flow or symptoms as an outcome, the results may be biased towards the null. Because medication adds complexity to the analysis and interpretation of results, some studies have excluded subjects that have taken asthma medication (Pope and Dockery 1992; Neas *et al.* 1995; Neas *et al.* 1996). However, this type of exclusion leads to loss of generalisability of results.

Several approaches may be used to adjust for medication use. The first approach is to include medication as an outcome as discussed earlier in Section 3.3.3. The second approach is to examine whether medication use is a confounder by including use of bronchodilators as a time-varying covariate within the regression model. One study found that medication use did not prevent decreases in PEF and increases in symptoms attributable to particulate air pollution, meaning that medication use was not a confounder (Peters *et al.* 1997a). A third and final approach is to examine whether medication use was an effect modifier in the association between air pollution and lung function or respiratory symptoms. To examine effect modification, subjects are classified into one of two groups depending on whether they took any medication during the study. The effect of air pollution on lung function or symptoms can then be examined for the two groups separately in a stratified analysis. In a panel study of adult asthmatics, persons on oral corticosteroids were less susceptible to indoor pollutants when compared to persons not on oral corticosteroids (Ostro *et al.* 1994). This has been replicated in diary studies stratifying by use of any anti-inflammatory asthma medication (Delfino *et al.* 2002) or use of any asthma medication (Roemer *et al.* 1999). There have been some studies, including a panel study in Amsterdam (Gielen *et al.* 1997), that have found associations in the opposite direction, where subjects using bronchodilators were more susceptible to pollutants when compared to subjects not using bronchodilators, although these studies have been few in number.

Special issues relating to perception of air pollution

The person completing the diary may be able to perceive ambient pollution. This may result in symptom reporting to be biased. Hence, there is concern for the reliability and validity of the outcome, which may potentially result in the effect of the pollutant on symptoms to be biased

away from the null. Very few studies have sought to determine whether the subject's perception of air pollution modified the association between air pollution and the primary health outcomes. In a study examining respiratory morbidity in Merseyside school children, the subjects were asked whether they considered coal dust exposure to be a health problem (Brabin *et al.* 1994). In a study of Californian households located near a waste disposal site there was an overall increase in reported symptoms by respondents living near the site (Baker *et al.* 1988) and the authors concluded that this elevation might reflect increased perception or recall of conditions by respondents living near the site. This was a particular concern as the aim of their study was expressed to the participants. In a study of childhood asthma hospitalisations in California, the effect of pollution was much greater for children of lower socio-economic status (Neidell 2002). One explanation given was that high socio-economic families exhibit air pollution avoidance behaviour. Based on this, perception of air pollution might be a potential modifier in the association between air pollution and respiratory health.

3.6 Type of models used in diary studies

The defining characteristic of a longitudinal study is that individuals are measured repeatedly through time. Various techniques are available to analyse longitudinal data. The statistical method used must account for the high correlations between measurements taken from the same subject at different time points. In diary studies, both the outcomes and pollutants are highly correlated across time. The scientific objectives of diary studies can be formulated as a regression problem whose purpose is to describe the dependence of the response on the explanatory variables. Both the time dependence and the covariance structure are regarded as "nuisance parameters" in this regression.

Generalised linear models for uncorrelated data were introduced in the 1970s (Nelder and Wedderburn 1972). The linear, logistic and Poisson models all belong to this family. They are solved using maximum likelihood. For standard linear models this will give the same result as generalised least squares. Only the first two moments of the outcome variable are specified; specifically the mean Y_i is set to equal to some "link" function of the Q covariates X_i i.e. $g(\mu_i) = X_i\beta$ and the variance is set to be a function of the mean (and if necessary a scale parameter). Estimates of β are then obtained from the solution to a set of "quasi-score" equations. Generalised linear models were extended to a broader range of applications and solved using quasi-likelihood (McCullagh and Nelder 1989).

The issue of random and fixed effects is very relevant to non-aggregate models. If the effect of an explanatory variable (e.g. PM10) is thought to be the same for all subjects then it may be modelled using fixed effects. That essentially means the covariate is modelled by a fixed unknown parameter and called a fixed effect (Longford 1993). If though, the effect of the covariate differs among subjects this can be modelled by a random variable (random slope and/or intercept). Random effects are useful to identify sensitive subgroups or individuals most severely affected by high air pollution. Typically, the random variable is assumed to be normally distributed, and its variance is the parameter of interest because it describes the variability amongst the subjects. The normality assumption is not essential, though it allows generalisations and further extensions. Such a random variable is called a random effect. There are two variance parameters, one within the subject and one between subjects. Random effects models are particularly useful when inferences are to be made about individuals. Random effects models are sometimes also referred to as mixed models.

In non-aggregate analyses the approach used may be population-averaged (PA) or subject-specific (SS) as defined by Zeger (Zeger *et al.* 1988). Population-average estimates characterise changes in the prevalence of an outcome in the population (e.g. cough) that are associated with changes in the level of a covariate (e.g. PM10) regardless of whether they are within or between subject changes. Hence, population-average coefficients have the same interpretation as coefficients from Aggregate models. The PA approach is to fit marginal models which relate the marginal distribution of an individual's multinomial response at time t to the covariates. Subject-specific coefficients indicate how one subject's risk changes if pollution increases, and are sometimes also referred to as cluster-specific coefficients. Subject-specific estimates are the average changes in the probability of cough that are associated with within-subject changes in exposures given the individual effect of a subject. The SS approach is to fit a random effects model. Population-averaged and subject-specific estimates are identical under a linear regression model, but they are different under a logistic regression model. Typically, PA coefficients are closer to the null than SS coefficients. Population-average approaches do not take advantage of directly observable within-subject effects. In situations where the association between the response and within-subject variation in a predictor is of primary interest, the modelling of SS effects is appropriate. Opinions vary on the appropriateness of fitting SS models in diary studies where the exposure is monitored at fixed sites. From a clinical perspective, one can use PA associations to measure population-wide effects of say reducing PM10 pollution. Whereas in a SS model, the assumption is that all subjects within an area are exposed to the same amount of ambient pollution, which is not a valid assumption.

Subjects who report no symptoms during the study period pose special problems in the model fitting. These subjects are sometimes referred to as non-informative clusters. In SS approaches (conditional likelihood methods) they contribute no information, but in mixed effects and PA (population-averaged) approaches the information from non-informative subjects is used.

There are nine approaches to dealing with longitudinal data. These include (1) Aggregate analysis, (2) naïve analysis, (3) the use of robust standard errors, (4) random intercept models, (5) Korn-Whittemore approach, (6) generalised estimating equations, (7) generalised linear mixed models, (8) transitional models and (9) multilevel models. Each of these approaches will be discussed in this section. A summary of the relevant statistical issues is provided in Table 3.5. Some diary studies used alternative methods such as ANOVA (Lebowitz *et al.* 1985) and principal components (Moseholm *et al.* 1993) but these do not allow estimate of effect and so are not discussed further here.

Table 3.5. Review of statistical approaches that can be used to analyse data from panel studies investigating the association between air pollution and respiratory health

Statistical approach	Description	Advantages	Disadvantages
(1) Aggregate analysis Also known as analysis of summary measures	The outcome considered for each day is an average of all subjects' individual outcomes on that day. In the case of PEF, the outcome is the average PEF across all children on that day. Estimation via maximum likelihood (MLE). Assumes outcome data are MAR Autoregressive linear models are implemented in SAS using PROC AUTOREG (continuous outcome). Autoregressive logistic models are implemented in SAS using PROC NLIN or PROC MODEL (binary outcomes).	The intracluster correlation in outcomes is naturally accounted for. Smoothing of exposure variables (e.g. PM10) can be incorporated in available software (e.g. GAMs)	Loss of information, by letting a large group of responses be represented by one summary measure. This is especially problematic if number of subjects responding each day is highly variable. To examine the effect of subject level covariates, need to split the population into distinct sub-populations, which becomes rather tedious.
(2) Naïve analysis Ignore that it is longitudinal.	The observations within the subject are assumed to be independent. Coefficients are calculated using maximum likelihood estimation (MLE) Implemented in SAS using PROC REG (continuous outcome) and PROC LOGISTIC (binary outcome)	If the within-subject correlations are low, then estimates will have high efficiency	If the within-subject correlations are high the estimated standard error will be too small.

Statistical approach	Description	Advantages	Disadvantages
(3) The use of robust standard errors. Also known as Huber-White correction. Estimates are also referred to as "sandwich", "empirally-corrected", and "empirical variance" estimators.	Ignore that it is longitudinal but report a robust standard error. e.g. (Huber 1967; White 1980; White 1982). The estimated coefficients are the same as (2). The observations within the subject are assumed to be independent, but the standard error is adjusted. The adjustment is the inflation factor which is $\sqrt{1+(m-1)\rho}$, where *m*=average number of observations per subject and ρ is estimate of intra-cluster correlation. Implemented in SAS using PROC GENMOD and specifying robust variance estimator; independent correlation.	More appropriate than Naïve analysis	Does not model the error structure directly
(4) Random intercept models	A single regression model is fitted for all subjects allowing each subject to have a different intercept. It includes indicator variables for each subject; If there are *n* subjects then (*n*-1) indicator variables are required. Assumes outcome data are MAR	Interaction terms between subject-level covariates and pollutant can test for sensitive subgroups.	Loss of power as (*n*-1) degrees of freedom is used. Estimate obtained will be dependent on which subject was chosen as the reference.
(5) Korn-Whittemore (K-W) modelling approach Also known as subject-specific regression modelling; two-stage regression.	A separate regression model is fitted for each subject (different slope and intercept) using MLE. Subject-specific estimates are then pooled to obtain a summary estimate under fixed or random effects using meta-analytic techniques. Introduced by Korn & Whittemore (Korn and Whittemore 1979); an extension of Cox (Cox 1970). Heterogeneity of estimates can be tested. Plots of regression coefficients versus time-stationary variables may indicate sensitive subgroups (e.g. medicated subjects). Assumes outcomes are MAR	If the number of repeated observations is large, GEE are not applicable. Assumes MAR only.	Cannot include time-stationary variables in model. In binary models requires exclusion of subjects for which outcome is infrequent or frequent.

Statistical approach	Description	Advantages	Disadvantages
(6) Generalised Estimating Equations (GEEs) Also known as marginal mean models	Introduced by Liang and Zeger (Zeger and Liang 1986). A generalisation of the widely used generalised liner model for uncorrelated data (McCullagh and Nelder 1989). Only the first two moments of the outcome variable are specified. The mean is equal to some link function of the covariates *X*. The variance is set to be a function of the mean (and if necessary a scale parameter). The robust estimate is consistent even if the correlation is misspecified. It is a marginal model. Estimation via quasi-likelihood. Implemented in SAS using PROC GENMOD or PROC MIXED. Assumes outcomes are MCAR	Do not need to specify distributions, just the relationship between mean and variance. They give valid parameter estimates even if the specified correlation structure is not correct. Describes the average population response with respect to changes in the covariates. Straightforward to adjust for subjects' time-varying covariates (e.g. current cold). A potential advantage of GEEs over robust standard errors (3) is its ability to use information about the nature of the intracluster dependence to recover more precise estimates of the coefficients.	Not suitable to describe individual changes; i.e. does not allow random effects. Are not appropriate if there are few subjects compared to number of days in study period. The regression estimates can be highly influenced by the presence of unusual data points and attention has to be paid to avoid misleading conclusions due to a few outlying points. Goodness of fit cannot be assessed. The estimates of correlation within subject (ICC) are not precise. May give biased results when data are not MCAR
(7) Generalised Linear Mixed Models (GLMM) Also known as Random effect models, Mixed models, and Mixed-effects models.	Each subject can have a different intercept and/or slope. It is a conditional model. Equation is solved by one of the following: Laplace approximation, Gaussian quadrature, iterative methods, or Monte Carlo simulations. It is the simplest form of a multilevel model (level 1 is time, and level 2 is subject). Implemented in SAS using the macro GLIMMIX (PROC MIXED), which uses PQL via the Laplace approximation. Robust estimation procedure has been recently proposed (Mills *et al.* 2002). Assumes outcomes are MAR.	The estimates of correlation within subject (ICC) are precise. Less restrictive with respect to missing data assumptions than GEE. They allow missingness to depend upon an individual's previously observed values of the dependent variable (Hu *et al.* 1998)	Random slope is only appropriate if individual exposure to the pollutant is monitored
(8) Transitional models Also known as conditional models and Markov models	The response on the previous day is treated as a covariate.	Generally easy to fit Nuisance parameters not included in model	Not relevant for diary studies No information on cross-sectional differences among subjects
(9) Multilevel models Also known as hierarchical linear models	Extension of GLMM where more than two-levels.	Allows for multiple levels of clustering The estimates of correlation within subject (ICC) are precise.	Usually requires specialist software Requires assumptions which may not always be met (normality of residuals, constant variance, no correlation between residuals at different levels)

Missing at random (MAR) and Missing completely at random (MCAR) are defined in (Little and Rubin 1987).
Maximum likelihood estimation (MLE), partial quassi-likelihood (PQL), Generalised additive models (GAMs), intracluster correlation coefficient (ICC).

Very few of the panel studies identified in Table 3.1 used a combination of approaches. In a study of Australian school children (Jalaludin *et al.* 2000) stronger associations between ozone and PEF were found in the Aggregate compared to the GEE models. In another panel study, very similar results for both PEF and symptoms were found with the Korn-Whittemore and GEE models (Neas *et al.* 1995). One study reported results from the Aggregate model but reported obtaining similar results with the Korn-Whittemore modelling approach (Neas *et al.* 1996). Another study found that under the GEE model, the estimated coefficients of the effect of indoor air quality on symptoms were smaller and standard error larger, compared to the naïve model (Ostro *et al.* 1994). A further study analysed symptoms using both the random intercept model and GEE, and analysed peak flow using both the Aggregate and Korn-Whittemore method (Pope and Dockery 1992). One panel study used Aggregate, Korn-Whittemore and GEE models but the estimated coefficient for the pollutant could not be directly compared as the models adjusted for different confounders (Vedal *et al.* 1998). Schwartz analysed PEF using both the mixed model with random intercept and the random intercept model, and analysed symptoms using the random intercept model only (Schwartz *et al.* 2000).

The terminology used in this section is that Y_{it} denotes the outcome for the i th subject on the t th day. There are n subjects observed on T occasions, of which T_i observations are non-missing. The T observations within the subject may be correlated with each other, but are independent of observations of other subjects. Let $X_{it} = \left(X_{1it}, X_{2it}, ..., X_{Qit}\right)$ be a vector of Q covariates (includes pollutant terms and meteorological terms) observed on day t for subject i, which are time-dependent. Let $S_i = \left(S_{1i}, S_{2i}, ..., S_{Ri}\right)$ be a vector of R covariates observed for subject i, which are time-independent, and G_t is the average response on day *t* i.e.

$$G_t = \sum_{i=1}^{n} Y_{it} \Big/ n$$

3.6.1 Aggregate analysis

In Aggregate analysis, the data are analysed using time series techniques. The outcomes are expressed as daily percentages (e.g. daily cough prevalence) or daily means (e.g. mean evening peak flow deviation). The units of analyses are populations or groups of people rather than individuals.

Aggregate models allow one to identify likely pollutants and confounders to be used in non-aggregate models. They also have the advantage of not being computationally intensive. However, variables that do not alter during the study period within a person, so called time-stationary covariates, cannot be examined unless the population is first stratified by the covariate. This approach has been used for smoking where the population is stratified into two groups based on whether they smoked during the study period, and then analysed as two separate groups and the estimates compared (Dusseldorp *et al.* 1995). With the aggregation, there is a loss of information since it cannot accommodate characteristics of subjects, and they are assumed stable across the study period. If the aggregated data are sufficient to answer the research question, this approach is suitable. In the field of meta-analysis, comparisons have been made between results from analyses based on aggregate data and those based on non-aggregate (i.e. individual level) data and it has been found that ecological bias exists (Berlin *et al.* 2002). Ecological bias is the bias that may occur when the results from ecological studies are extrapolated to individuals.

Data from panel studies are often aggregated for analysis. In Aggregate analysis, the chosen form for peak flow is averaged across all subjects recording a measurement on that day. Aggregate modelling was used extensively in all diary studies published prior to the mid 1980s. Since then, Aggregate modelling has been used in exploratory analysis, but the estimated coefficients have largely not been reported. Such exploratory analysis has been used for several purposes: to determine appropriate variables to remove seasonality and trend; to determine autocorrelation structure; to examine lag structures; and to determine the appropriate scale of the pollutants and climate-related covariates.

Modelling Lung function

Models discussed here assume lung function is analysed as a continuous measure and so linear models are appropriate. As discussed in Section 3.4.1 this is the most frequent method of analysis for panel studies of air pollution. Aggregated deviations are less likely to be influenced by missing data than aggregated means. For example, if, on a given day, a subject who tended to have a relatively high peak flow did not record their measurement, the cohort average would be inflated, and as a result, the estimate of the effect of air pollution could be biased. This would be less likely if the outcome was deviation rather than the mean. In simple linear regression this is

$$G_t = \beta_0 + \beta X_t + \varepsilon_t \qquad (7a)$$

where: G_t is the mean deviation at time t

X_t is the pollutant at time t

β is the regression coefficient

β_o is the intercept term.

$\varepsilon_t \sim IN(0,\sigma^2)$

The notation $\varepsilon_t \sim IN(0,\sigma^2)$ indicates each ε_t is normally and independently distributed with mean 0 and variance σ^2. The estimates of β_0 and β are obtained by the least squares method. In multivariable linear regression this may be expressed as:

$$G_t = \beta_0 + \beta_1 X_{1,t} + \beta_2 X_{2,t} + ... + \beta_Q X_{Q,t} + \varepsilon_t \quad (7b)$$

The standard regression model assumes the expected value of *G* has a linear form:

$$E(G_t / X_t) = X_t \beta \quad (7c)$$

where: X_t is a vector of various pollutants, temperature and other covariates

β is a vector of unknown regression coefficients

E denotes the expected value.

As discussed in Section 3.5.2 it is unlikely that the error terms are independent of each other. Instead of the usual regression model, the following autoregressive error model is used:

$$G_t = X_t \beta + \vartheta_t \quad (7d)$$

where: $\vartheta_t = -\varphi_1 \vartheta_{t-1} - \varphi_2 \vartheta_{t-2} - \varphi_m \vartheta_{t-m} + \varepsilon_t$ and $\varepsilon_t \sim IN(0,\sigma^2)$

Modelling symptoms

Models discussed here assume that the outcome is binary and analysed using logistic regression. As discussed in Section 3.4.2 this is the most frequent method of analysis for air pollution and health studies. The logistic regression model is:

$$\text{logit}\left[E(G_t / X_t)\right] = X_t \beta + \vartheta_t \quad (8)$$

where: ϑ_t is a latent process allowing autocorrelation in Y_t

$E(G_t / X_t)$ is the probability of reporting a symptom on the t th day

Modelling medication use

Medication use has been analysed as both a binary and continuous outcome. The models chosen for medication usage have been similar to those chosen for symptoms (when binary) and lung function (when continuous).

Incorporating weights

Typically, in a diary study, the number of subjects providing data will vary daily. This may be due to rolling enrolment, or dropouts, or it may be simply be due to subjects not responding due to weekends and school holidays for example. When the number of subjects varies daily the assumption of constant variance is violated. To adjust for this, weighting can be used whereby the weighted residual sum of squares is minimised:

$$\sum_{t=1}^{T} w_t (G_t - \hat{G}_t)^2 \qquad (9)$$

where: w_t is the value of the weight

G_t is the observed value of the outcome

$\hat{G}_t$ is the predicted value of the outcome.

The regression can be weighted by either the number of subjects at each observation point or using the inverse of the calculated standard errors. Using the number of subjects is equivalent to analytically weighted least squares (Johnston 1984). Maximum-likelihood estimates can be computed by iteratively re-weighted least squares, where the weights are the reciprocals of the variances (Nelder and Wedderburn 1972). In Aggregate analyses daily observations have been weighted by the number of subjects making a recording on that day (Jalaludin *et al.* 2000) or by the inverse of the standard error (Pope and Dockery 1992).

SAS procedures

The SAS procedure PROC AUTOREG fits linear regression models with allowance for autocorrelation. The coefficients are determined using the Yule-Walker estimating procedure. It gives efficient estimators even in the presence of missing exposure data. The SAS procedures PROC NLIN and PROC MODEL fit logistic regression models with allowance for autocorrelation where the outcome is binary such as the presence or absence of symptoms.

3.6.2 Naïve Analysis

Another analysis method is to keep the data in their original form but ignore the fact that they are longitudinal. This essentially means treating the repeated observations on the same individual as independent. For linear models:

$$Y_{it} = \beta_o + \beta_1 X_{1it} + \beta_2 X_{2it} + ... + \beta_Q X_{Qit} + \alpha_1 S_1 + ... + \alpha_R S_R + \varepsilon_{it} \qquad (10a)$$

where: $\varepsilon_{it} \sim IN(0, \sigma^2)$ and $\text{cov}(\varepsilon_{it}, \varepsilon_{ik}) \neq 0$.

This can also be expressed in matrix notation:

$$E(Y_{it} / X_{it}) = X_{it}\beta + S_i\alpha \quad (10b)$$

For non-linear models:

$$\text{logit}\left[E(Y_{it} / X_{it})\right] = X_{it}\beta + S_i\alpha \quad (10c)$$

where: ε_{it} are independent with a binomial distribution and $\text{cov}(\varepsilon_{it}, \varepsilon_{ik}) \neq 0$.

There are two consequences of ignoring the correlation when it exists in longitudinal data. If a suitable choice of the independent variables is made the estimated regression coefficients are consistent (i.e. their distribution converges on the true regression coefficient as sample size increases). However, since the specification of the variance structure will be incorrect the wrong standard errors for the estimates will be obtained and so the tests based on them are incorrect. The estimates of the standard error for the time-varying variables (e.g. PM10) will be conservative and the time-stationary variables (e.g. maternal hayfever) will be anti-conservative (Bellamy *et al.* 2000).

3.6.3 The use of robust standard errors

Another approach is to ignore the longitudinal nature of the data, but do a correction for correlation of errors within subjects (Williams 2000). Robust variance estimators give accurate assessments of the sample-to-sample variability of the parameter estimates even when the model is misspecified. Robust variance estimators come under various names, including Huber/White, Sandwich, and empirically-corrected estimators. This method provides no information about the components of variance and covariance. As long as the interest is in fixed effects, and not in the structure of the random effects, this is a valid approach. One diary study used this method after confirming the standard errors were insensitive to the use of several covariance structures in a GEE analysis (Mortimer *et al.* 2002).

3.6.4 Random intercept models

In a random intercept model, an indicator variable is fitted for each subject. Formally, if there are n subjects then $(n-1)$ indicator variables are required, denoted $N_1, N_2, ...N_{n-1}$ and

$$Y_{it} = \beta_0 + X_{it}\beta + n_1N_1 + n_2N_2 + ... + n_{n-1}N_{n-1} + \vartheta_{it} \quad (11)$$

where ϑ_{it} is a latent process allowing autocorrelation in Y_{it}

This is essentially a fixed effects approach as all subjects have the same effect estimate but a different intercept. Random intercept models are not practical for diary studies for two reasons. Firstly, there are typically large numbers of subjects and so the number of indicator variables fitted becomes excessive. In addition, in order for the model to converge, the outcome is required to be reasonably frequent. For instance, each subject would need to have a reasonable number of symptom free and symptom days. This method has only been used in one of the diary studies located (Forsberg *et al.* 1993).

3.6.5 Korn-Whittemore (K-W) modelling approach

Another approach that has been applied to diary data is the two-stage approach or analysis of summary measures. It is often referred to as the Korn-Whittemore approach as the authors were the first to apply the method to respiratory diary data in the EPA-chess study where children in several communities were followed for 8 months (Korn and Whittemore 1979). The methods have been subsequently refined (Stiratelli *et al.* 1984; Rosner *et al.* 1985). The Korn-Whittemore method involves firstly fitting a separate regression model for each subject in the study and so obtaining a separate effect estimate for each subject. In a linear model this may be expressed as:

$$Y_{it} = \beta_0^{(i)} + \beta_1^{(i)} X_{1it} + \beta_2^{(i)} X_{2it} + ... + \beta_Q^{(i)} X_{Qit} + \vartheta_{it} \qquad (12a)$$

where: $(X_{1it}, X_{2it}, ...X_{Qit})$ are time-dependent covariates

ϑ_{it} is a latent process allowing autocorrelation in Y_{it}. If AR-1 then

$\vartheta_{it} = -\varphi^{(i)} \vartheta_{i(t-1)} + \varepsilon_{it}$ and $\varepsilon_{it} \sim IN(0, \sigma^{2(i)})$.

The early diary studies crudely took into account autocorrelation by including the previous day's peak flow ($Y_{i(t-1)}$) as an explanatory variable in a Markov model (Section 3.6.8), but it is now routine practice to include an autoregressive term.

The distribution of the subject-specific estimates may be presented in a histogram to show the amount of between-subject variation. In the second stage, these estimates are pooled to obtain one summary measure using methods analogous to those used in meta-analysis. When pooling, the individual estimates are weighted by the inverse variance of the estimates. The K-W method has been applied to both binary and continuous outcomes. These types of models, as for the random intercept model, require excluding subjects with either a very high proportion or very low proportion of days with symptoms. Typically, it requires exclusion of subjects who have

symptoms on less than 5% or more than 95% of days so that models can converge (Henry *et al.* 1991b). A modification allows all the subjects to be included, but this is computationally intensive (Stiratelli *et al.* 1984). The number of time-dependent covariates considered for an individual must be smaller than the number of days of follow-up. Hence, this method is only suitable where the number of observations per individual is large relative to the number of variables considered for each subject.

In the Korn-Whittemore method, the coefficient of the pollutant for subject i is denoted by $\hat{\beta}^{(i)}$ and its standard error is s_i. This coefficient is asymptotically normally distributed with mean $\hat{\beta}^{(i)}$, the true coefficient for that individual and variance $\sigma^2{}_i$ i.e. $\hat{\beta}^{(i)} \sim N(\beta^{(i)}, \sigma^2{}_i)$. The coefficients are pooled using either fixed or random effects, which are now described.

In the *fixed effects* model, the single β is estimated which is the true regression coefficient for all the individuals. In this type of model, all $\beta^{(i)}$ are considered equal. It is appropriate for testing the null hypothesis that the covariate is not associated with response for any of the individuals i.e. that all $\beta^{(i)}$=0. Assuming that normality holds for the given sample estimates $\beta^{(i)}$, and that $\sigma^2{}_i$ are known, the maximum likelihood estimator $\hat{\beta}$ of β is given by a weighted average of the $\hat{\beta}^{(i)}$. This can be expressed as

$$\hat{\beta} = \sum_{i=1}^{n} w_i \hat{\beta}^{(i)} \Big/ \sum_{i=1}^{n} w_i \qquad (12b)$$

where w_i are the weights. If the weights are inversely proportional to the variances (i.e. $w_i = 1/s_i{}^2$), the estimate of β is unbiased and its variance is given by

$$\mathrm{var}(\hat{\beta}) = 1 \Big/ \sum_{i=1}^{n} s_i{}^{-2} \qquad (12c)$$

Other choices of the weight can be w_i=1 for unweighted pooling, w_i=T_i for weighting by the number of observations provided by the subject.

For the *random effects* model, $\beta^{(i)}$ are assumed to be a random sample from a normal distribution with mean β and variance η^2. The mean β represents the overall population association of the covariate with the response; the variance η^2 represents the variability of β from individual to individual. Note $\hat{\beta}^{(i)} \sim N(\beta, s_i{}^2 + \eta^2)$ for *i*=1,..,*n*. The random effects model is appropriate for testing the null hypothesis that the average effect of the covariate on the

response of all the individuals is zero. If there is much heterogeneity, subjects with small standard errors will be given a greater weight. If there is no heterogeneity then the estimates will be weighted equally, which will correspond to the fixed effect model.

The causes of heterogeneity can be examined by fitting the following model:

$$\hat{\beta}^{(i)} = \alpha_0 + \alpha_1 S_{1i} + \alpha_2 S_{2i} + ... + \alpha_R S_{Ri} \qquad (12d)$$

where: $(S_{1i}, S_{2i}, ...S_{Ri})$ are time-independent covariates for subject i

The Korn-Whittemore technique has been used in several panel studies, most recently in 1997 (Agocs *et al.* 1997; Gielen *et al.* 1997). It has been used to analyse both binary (cough) and continuous (peak flow) outcomes. Generally only fixed effects are reported, but one study reported both fixed and random effects (Agocs *et al.* 1997). The weights used to pool the subject-specific estimates have been based on the reciprocal of the number of observations (Neas *et al.* 1995; Neas *et al.* 1996), and the reciprocal of the variance of the estimates (Scarlett *et al.* 1996). Some investigators have reported a test of heterogeneity of the estimates (Brunekreef *et al.* 1991; Scarlett *et al.* 1996) and time-stationary terms are sometimes used to identify sensitive subgroups (Korn and Whittemore 1979; Vedal *et al.* 1987; Neas *et al.* 1995; Scarlett *et al.* 1996).

3.6.6 Generalised Estimating Equations (GEEs)

Generalised Estimating Equations (GEEs) were proposed by Zeger and Liang (Zeger and Liang 1986) as a method for obtaining parameter estimates in generalised linear models with correlated response data. They are based on marginal models that relate the expected value of an individual's response at time *t*, to the covariates at time *t*. In a linear model this can be expressed as:

$$E(Y_{it} / X_{it}) = \beta_o + \beta_1 X_{1it} + \beta_2 X_{2it} + ... + \beta_Q X_{Qit} \qquad (13a)$$

In logistic regression, this method models the logarithm of the odds of a symptom as a linear function of fixed covariates. It can be expressed as:

$$\text{logit}\left[E(Y_{it} / X_{it})\right] = \beta_o + \beta_1 X_{1it} + \beta_2 X_{2it} + ... + \beta_Q X_{Qit} \qquad (13b)$$

Pollution X_{it} may have no influence on cough Y_{it}. However, pollution may still increase prevalence of cough in the population as a whole, and this is the more pertinent question from the public health perspective.

The marginal approach has the advantage of separately modelling the mean and the within-subject correlation (covariance), that is, the correlation structure is not modelled in terms of parameters in the model. There are several possible correlation structures including independence, exchangeable, unstructured, and autoregressive (these are mutually exclusive). For longitudinal data analyses, the within-subject error structure is usually assumed to be autoregressive of order one, denoted AR-1 where correlation is lower for measurements that are further apart. The first-autoregressive model AR-1 has covariances of the form $Cov(Y_{it}, Y_{ik}) = \sigma^2 \rho^{|t-k|}$. The correlation between observations looks like (for four measurements per subject):

$$
\begin{array}{cc} & \text{Day} \\ & \begin{array}{cccc} 1 & 2 & 3 & 4 \end{array} \\ \begin{array}{c} \\ \text{Day} \\ \\ \\ \end{array} & \begin{array}{c} 1 \\ 2 \\ 3 \\ 4 \end{array} \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix} \end{array} \qquad \text{(13c)}
$$

The GEE approach accounts for the correlation structure in the data by using a specified working correlation model. These correlations are estimated from the model, and estimates of regression coefficients are then iteratively updated taking this correlation into account. Valid inferences about the coefficient can sometimes be made even when an incorrect form of the covariance is assumed. Correlations are treated as a nuisance that one must account for in order to get reasonable estimates of the regression parameters, and so GEEs are not appropriate when the primary interest centres on estimating the correlation. The data analyst estimates the correlation structure, but the results are often insensitive to the choice of correlation made, as robust variance estimates are computed using quasi-likelihood methods. Under misspecification of the correlation structure, the GEE approach will still yield a consistent estimate of β, although this estimate may not be as efficient as when the correlation structure is correctly specified. “Consistency” and “efficiency” are statistical terms whereby consistency refers to the coefficient and efficiency refers to the size of the standard error. If the working covariance matrix is chosen to be the actual covariance for observations in the subject then the estimate will be efficient (Liang *et al.* 1992).

Formally, GEEs are identical to standard models with robust standard error when the correlation structure is specified to be independent. A potential advantage of GEEs over simple robust

variance estimates is its ability to use information about the nature of the intra-subject dependence to recover more precise estimates of the coefficients.

The standard errors of regression coefficients produced using Generalised Estimating Equations are either model-based or empirical. Model-based standard errors are calculated using correlation structure estimates based on the data-analyst's pre-specified correlation (e.g. AR-1). Empirical (or robust) standard errors are calculated using correlation structure estimates based on the observed correlation structure of the residuals. Model-based standard errors are best if the assumed correlation structure is correct as they are usually more efficient than empirical standard errors. Empirical estimates give consistent estimates of coefficients and standard errors even when the assumed correlation is incorrect because the robust estimates of the standard errors of the regression coefficients are asymptotically valid irrespective of the working correlation used in the analysis and the actual correlation structure of the data. In practice, empirical standard errors are usually reported. The GEE models do not allow random effects. Generalised Estimating Equations can be analysed in SAS using the procedures PROC GENMOD and PROC MIXED.

Unlike random effect models marginal models give a population-averaged approach. The response can be continuous (linear model) or discrete (e.g. logistic model) as GEEs are based on generalised linear models (GLM) but their main advantage is in the analysis of discrete data. They are suitable for any generalised linear model and reduce to maximum likelihood estimation (MLE) if the outcome is normally distributed and the correlation is unstructured, provided there are no missing observations (Park 1993). Generalised Estimating Equations models were further refined to consider subject-level covariates (Liang and Zeger 1986; Prentice 1988; Zeger *et al.* 1988). There are no established summary statistics available for assessing the adequacy of a GEE model but one methods paper developed an extension of the Hosmer-Lemeshow statistic (Horton *et al.* 1999). Regression diagnostics may be used to identify subjects that influence estimates (Ziegler *et al.* 1998a). In GEE-2 the correlation is a parameter of interest rather than a nuisance (Prentice 1988).

Generalised Estimating Equations were used in several of the panel papers identified. Autocorrelation of order one (AR-1) is typically specified, although one study found that the same results were obtained when independence was assumed (Mortimer *et al.* 2002). Generalised Estimating Equations are not appropriate in situations where there are few subjects compared to number of days observed, as is sometimes the case with panel studies. One study

claimed to make allowance for this by writing a customised version of GEE code (Vedal *et al.* 1998). One diary study used GEEs for the analysis of peak flow (raw form i.e. not standardised) but allowed each subject to have a different intercept through the use of a fixed offset which were derived from the Korn-Whittemore analysis (Vedal *et al.* 1998). In GEE it is straightforward to test for sensitive subgroups and adjust for time-varying covariates as discussed in Section 3.5.10.

Generalised Estimating Equations assume missing outcome observations are MCAR. If this observation does not hold, their analysis may yield biased estimates. The assumption can be tested by fitting indicator variables for each missing data pattern and testing their significance in the regression model (Park and Lee 1997). There are a few methods available for rendering estimates from GEE analysis to be unbiased under MAR mechanisms. These methods include weighting (Robins et al 1995), mean imputation (Paik 1997) and multiple imputation (Paik 1997).

3.6.7 Generalised Linear Mixed Models (GLMMs)

In a generalised linear mixed model, the probability distribution of Y_{it} is modelled as a function of the covariates X_{it}, and parameters β_i specific to the i th subject. Generalised linear mixed models can incorporate both fixed and random effects, and the outcome can be continuous or discrete. The response for the i th subject is assumed to differ from the population mean by a subject effect, υ_{0i}, and a within subject measurement error ε_{it}. In a linear model, with a random intercept and fixed slopes, this can be expressed as:

$$Y_{it} = \beta_o + \beta_1 X_{1it} + \beta_2 X_{2it} + ... + \beta_Q X_{Qit} + \upsilon_{0i} + \varepsilon_{it} \qquad (14a)$$

where: $\upsilon_{0i} \sim IN(0, \sigma_0^{\,2})$

$\varepsilon_{it} \sim IN(0, \sigma^2)$

υ_{0i} and ε_{it} are independent

The random-effects model is essentially a set of separate regression models for each subject. In this way, the coefficients have a similar interpretation as that from the Korn-Whittemore modelling approach (12a). They will differ though, as the GLMM assumes σ^2 are equal for all subjects but the K-W modelling approach permits a different σ^2 for each subject (Burton *et al.*

1998). The term υ_{0i} is important for removing serial correlation. The model can also be expressed in matrix notation as:

$$E(Y_{it} / X_{it}, Z_i) = X_{it}\beta + Z_i\upsilon_i \qquad (14b)$$

where: β is the vector of fixed effect parameters

υ is the vector of random effect parameters

Now the variation in Y_{it} is made up of intersubject variability ($\sigma_0{}^2$) and intrasubject variability (σ^2). It can be shown that the following correlation structure results:

$$Var(Y_{it}) = \sigma^2{}_o + \sigma^2$$

$$Cov(Y_{it}, Y_{ik}) = \sigma^2{}_0$$

$$Corr(Y_{it}, Y_{ik}) = \sigma^2{}_0 / (\sigma^2{}_0 + \sigma^2)$$

A natural extension of the random intercept model is the random intercepts and slopes model. In a linear model this can be expressed as:

$$Y_{it} = \beta_o + \beta X_{it} + \upsilon_{0i} + \upsilon_{1i} X_{it} + \varepsilon_{it} \qquad (14c)$$

where: $\upsilon_{1i} \sim IN(0, \sigma_s{}^2)$

The slope for the *i*th subject is $\hat{\beta}^{(i)} = (\beta + \upsilon_i)$. Several methods have been developed to obtain solutions for the estimated coefficients. These include: using Taylor series approximation, penalised quasi-likelihood (PQL), Laplace integral approximation (Breslow and Clayton 1993), quadratic approximation of the likelihood surface in the region of the maximum, or repeated applications of linear mixed models to obtain approximate MLE/REML. Generalised Linear Mixed Models are based on a pseudo-likelihood approach (Wolfinger and O'Connell 1993). They can be implemented in SAS using the GLIMMIX macro, which calls the SAS procedure PROC MIXED and estimates the coefficients using PQL techniques. The SAS procedure PROC MIXED can be used for continuous outcomes only, and uses a ridge-stabilised Newton-Raphson algorithm to optimise a restricted maximum likelihood (REML) function. The general concept of REML is that firstly, the estimated fixed part of the model is subtracted, and then secondly, the likelihood of the remaining part is maximised. Since the maximising of the likelihood is restricted to the residual, REML is referred to as “residual” or “restricted” ML. The SAS procedure PROC NLMIXED can be used to estimate parameters when the outcome is binary.

Generalised linear mixed models are an extension of the linear mixed models that were developed by Laird and Ware (Laird and Ware 1982). Mixed linear regression models have been used where the regression coefficients can vary between individuals and where the residual errors can be correlated (Laird and Ware 1982). This type of random effect model was extended to allow for time dependent covariates and binary outcomes but it was computationally demanding because it was solved using the EM algorithm (Stiratelli *et al.* 1984). The approaches taken have been reviewed for both binary (Ware *et al.* 1988) and Gaussian (Ware 1985) models.

Generalised linear mixed models have not been used in any diary papers. Linear mixed models have been applied to PEF as a continuous measure in 4 of the diary studies (Delfino *et al.* 1996; Delfino *et al.* 1997; Schwartz *et al.* 2000; Mortimer *et al.* 2002). Each subject was modelled as a random effect but the time dependence was fixed in two of these studies (Delfino *et al.* 1996; Delfino *et al.* 1997) and it was unclear how it was modelled in the other two studies. One study did analyse symptom scores and bronchodilator dosage using GLMM but assumed the ordinal measures were in fact Gaussian for their model choice (Mortimer *et al.* 2002). The major problem with mixed models in the application to diary studies is that they assume that the individual exposure for each subject is the same as that for the population.

Sherrill and Viegi recommend random effect models in preference to GEEs for linear models because if there is a lot of missing data the random effect model generally yields parameter estimates with less bias than those obtained under GEE (Sherrill and Viegi 1996). The fixed effects and random effects are directed at different observations (Gibbons *et al.* 1993).

3.6.8 Transitional models

Transitional models model the mean as a function of covariates, as well as responses and covariates at previous days for the same subject (Bonney 1987). In a simpler model, the subject's outcome on day *t* does not depend on covariates observed on other days. In a linear model this can be expressed as:

$$E(Y_{it} / Y_{i(t-1)},..Y_{i1}, X_{it}) = \beta_o + BX_{it} + \varphi (Y_{i(t-1)} - \beta_o - BX_{i(t-1)}) \qquad (15a)$$

If there is an AR-1 structure then this can be expressed as:

$$E(Y_{it} / Y_{i(t-1)}, X_{it}) = \beta_o + BX_{it} + \varphi Y_{i(t-1)} \qquad (15b)$$

Transitional models are also sometimes known as conditional or Markov models. Transitional models combine the assumptions about the dependence of *Y* on *X* and the correlation among

repeated *Y*s into a single equation. This method is not appropriate for diary studies, as estimating the time dependence is not of primary importance.

A special type of transitional model, is the autoregressive model (Rosner *et al.* 1985). An *L*th order autoregressive model is expressed as:

$$Y_{it} = \beta_o + \sum_{i=1}^{L} \gamma_i Y_{i,t-i} + \beta X_{it} + \alpha X_{it} S_i + \varepsilon_{it} \qquad (15c)$$

where: $\varepsilon_{it} \sim IN(0, \sigma^2)$

This is used to examine if the estimate of the PM10-PEF effect is different for different subgroups. Specifically, it allows one to test whether the effects of the time dependent covariate X_{it} are the same in different subgroups defined by the covariate S_i.

3.6.9 Multilevel models

The generalised linear mixed model (14c) assumes that each subject has the same level 1 variance and the measurements for different subjects are independent i.e. $\varepsilon_{it} \sim IN(0, \sigma^2)$. In some situations these assumptions may not be valid and so multilevel models may be appropriate. The generalised linear mixed model (14c) can be expressed as:

$$Y_{it} = \beta_o + \beta X_{it} + \upsilon_{0i} + \upsilon_{1i} X_{it} + \varepsilon_{it} \qquad (16a)$$

where $\upsilon_{0i} \sim IN(0, {\sigma_0}^2)$

$\upsilon_{1i} \sim IN(0, {\sigma_s}^2)$

$\varepsilon_{it} \sim IN(0, \sigma^2)$

υ_{0i} and ε_{it} are independent; and υ_{1i} and ε_{it} are independent

$\mathrm{cov}(\upsilon_{0i}, \upsilon_{1i}) = \sigma_0 \sigma_s$

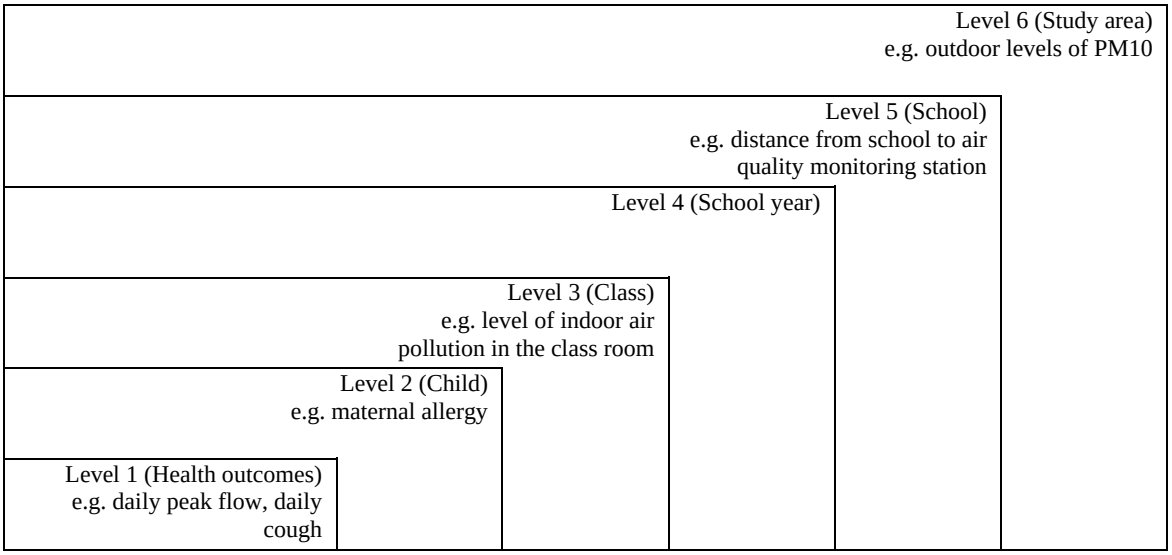
It is expected that some subject's responses will vary a lot over time, while other subject's responses vary very little. To account for this heterogeneity among the level 2 units (subjects) in level 1 variance a 2-level model can be fitted, which incorporates a function associated with level 1 residuals allowing these to vary between individuals:

$$Y_{it} = \beta_o + \beta X_{it} + \upsilon_{0i} + \upsilon_{1i} X_{it} + \delta_{it} \varepsilon_{it} \qquad (16b)$$

where: δ_{it} is some function of covariates associated with level 1 variance

The GLMM also assumes the measurements for different subjects are independent. However, in diary studies that involve children recruited from schools, the children in the same geographical area share the same absolute measure of air quality. In addition, children attending the same school may share certain common characteristics such as same distance from school to air quality device, similar time outdoors, and similar socio economic status. They may also share the same medical practitioner. Children in the same classroom are exposed to a similar amount of indoor air pollution. This dependence among subjects can be taken into account in multilevel models. Under the multilevel modelling framework, the hierarchy of the observations can be seen as a 6-stage multilevel model (Figure 3.3). In school-based diary studies, variables at level 1 are time-dependent, at level two they are student level variables, level three are class-level variables, level four are school year variables, level five are school-level variables, and level six are study area variables.

Figure 3.3. Diagrammatic illustration of 6-stage multilevel model



Study area and school class can be modelled as categorical variables or used to define a separate level in a multilevel model. If study area was incorporated to form a 3-level model, the simplest model may be expressed as:

$$Y_{itk} = \beta_o + BX_{it} + \nu_{0k} + \upsilon_{tk} + \varepsilon_{itk} \qquad (16c)$$

where: Y_{itk} denotes the outcome for the i th subject in the k th study area on day t

This can be extended to a random slopes model, and to include additional covariates. Random effects and random slopes are usually assumed to follow a multivariate normal distribution with mean zero and constant variance. However, some work has been done in removing this restriction to allow for intercepts and slopes that come from non-Gaussian distributions such as the gamma or exponential distributions. The type of modelling required has been called multilevel modelling, random coefficient models and Bayesian hierarchical models (Goldstein *et al.* 2002). Multilevel models can be fitted in SAS using PROC MIXED and there is also specialist software available (MLn and HLM).

Multilevel models have not been used in the diary studies. In situations where children were recruited from different areas the approach has been to either include an indicator term for city of residence (Schwartz *et al.* 1994) or to analyse each area separately and pool the estimates using meta-analysis techniques (Hoek and Brunekreef 1994). More sophisticated meta-smoothing techniques have recently been used to pool PM10-mortality estimates across cities (Schwartz and Zanobetti 2000). There may be gains in fitting a multilevel model to panel data where several areas had been sampled, as the estimate may be more robust and more precise.

3.7 Summary

Early diary studies examining the health effects of air pollution focused on using Aggregate analyses where the health endpoints on each day are aggregated across all participants. The Korn-Whittemore (K-W) approach of pooling coefficients from subject-specific regressions was introduced in 1979. There was then a transition to using generalised estimating equations following their introduction in 1986. Perhaps the future analyses will focus on generalised linear mixed models. The statistical methods used in the analysis of Phase II of the HISAAP study follow that used in the literature, and focus on the methodology of the Harvard Group (investigators Neas, Dockery and Schwartz). The Aggregate, Korn-Whittemore and GEE models were fitted for the outcomes peak flow, day cough and medication usage. It was of interest to see whether the estimate of the PM10-outcome coefficient and its standard error differed substantially between the different modelling approaches. Also examined, was whether the strength of the PM10-outcome association was greater among children with certain characteristics. The next chapter describes the data management undertaken and the statistical methods used.

Chapter 4 . Data management and Statistical methods

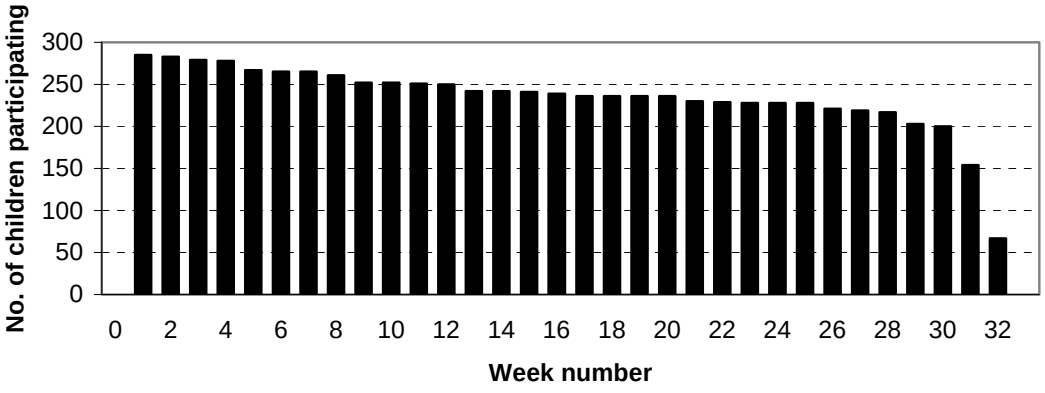
This chapter describes the data management undertaken on the various datasets and the statistical methods used. Section 4.1 and Section 4.2 describe the data management undertaken on the health survey data and environmental data respectively. Section 4.3 describes the statistical methods used to perform the descriptive analysis of the study population and health outcomes. Section 4.4 describes the statistical methods used to perform the descriptive analysis of the air quality data. In the remaining sections, the statistical methods used to determine the effect of air quality on each of the three health outcomes are described.

4.1 Data management of health data

4.1.1 Data collection period

The study period was from Monday 28th February 1994 to Sunday 23rd April 1995. The first wave (Stockton, Wallsend, Mayfield) commenced data collection on the 28th February 1994, and by the 21st March 1994, all schools in the three areas were participating. The second wave (Beresfield and North Lake Macquarie) commenced on the 29th August 1994, and by the 12th September, all schools were participating. Two hundred and eighty-five (285) subjects commenced the diary. Although participants were only required to complete the diary for 30 weeks, some subjects completed the diary for up to 32 weeks. A steady dropout rate was observed, with just over 200 subjects completing the diary in the 30th week, as shown in Figure 4.1.

Figure 4.1. Number of children participating, by week of study period *



*. Total of 285 children commenced the diary

4.1.2 Aggregate analysis period and non-aggregate analysis period

The first 2 weeks of data collection for each child was ignored for all analyses because during this time they may still be learning how to use the peak flow meter and to complete the diary. This has been done in previous diary studies, as discussed in Chapter 3. It was also decided to ignore data that was collected beyond 30 weeks, because the subjects had been asked to complete the diary for only 30 weeks and those completing the diary past the "cut-off day" were likely to be different to the majority.

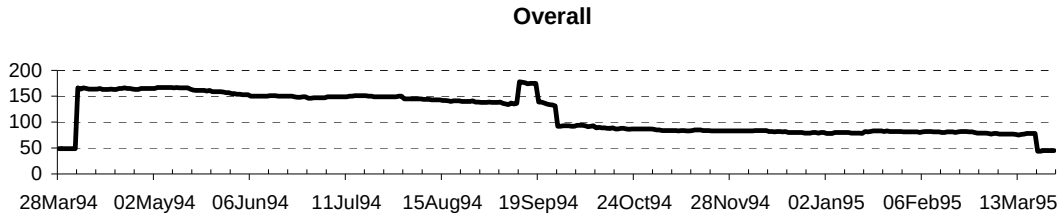
It is a requirement for aggregate analysis that a sufficient number of children provide informative data on each day in each area. Hence, the aggregate analysis period was defined as the area-specific time period where all schools were participating. Because of the poor completion rate in the last week at one of the schools at Stockton, data from this week were also excluded (Table 4.1).

Table 4.1. Aggregate analysis period, by study area

Study area	Period	Weeks
Stockton	28/3/94 to 18/9/94	25
Wallsend	4/4/94 to 25/9/94	25
Mayfield	4/4/94 to 25/9/94	25
Beresfield	26/9/94 to 26/3/95	26
North Lake Macquarie	12/9/94 to 19/3/95	27

The number of subjects completing the diary on each day during the aggregate analysis period is shown in Figure 4.2. The step occurred at the time of overlap of data for areas participating in Wave 1 and North Lake Macquarie in Wave 2.

Figure 4.2. Number of subjects completing the diary on each day during the aggregate analysis period *



*. Number of children giving informative responses

The non-aggregate analysis period was the 28-week period described in Table 4.2. The participation period for a child was defined as the number of months from first completing the diary to last completing the diary, inclusive of broken periods. Hence, a subject who completed a diary for two months then had a one-month lapse before recommencing in the fourth month and continuing for one month, had a participation period of four months. Children eligible for the non-aggregate analysis were required to have a participation period of at least 3 months and to give informative responses on at least 70% of the days in the participation period. Hence, children were required to supply informative data on at least 63 days (70% of 90 days) for inclusion. The criterion was decided upon after consideration of criteria used in other diary studies and that estimates from GEE tend to be biased when more than 20% of the data are missing (Rijcken *et al.* 1997). In the dataset used for the non-aggregate analysis, each record represented a child-day.

Table 4.2. Non-aggregate analysis period, by school

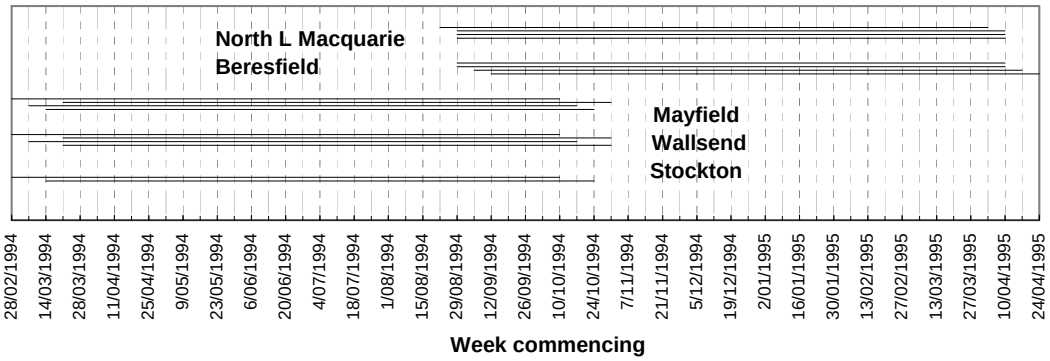
Study Area / school code	Period	Weeks
Stockton		
11	28/3/94 to 9/10/94	28
12	14/3/94 to 25/9/94	28
Wallsend		
21	4/4/94 to 16/10/94	28
22	21/3/94 to 2/10/94	28
23	4/4/94 to 16/10/94	28
24	14/3/94 to 25/9/94	28
Mayfield		
31	28/3/94 to 9/10/94	28
32	21/3/94 to 2/10/94	28
33	4/4/94 to 16/10/94	28
34	14/3/94 to 25/9/94	28
Beresfield		
41	26/9/94 to 9/4/95	28
42	19/9/94 to 2/4/95	28
43	12/9/94 to 26/3/95	28
44	12/9/94 to 26/3/95	28
North Lake Macquarie		
51	12/9/94 to 26/3/95	28
52	12/9/94 to 26/3/95	28
53	12/9/94 to 26/3/95	28
54	5/9/94 to 19/3/95	28

Refer to Table A1.1 for corresponding names of schools.

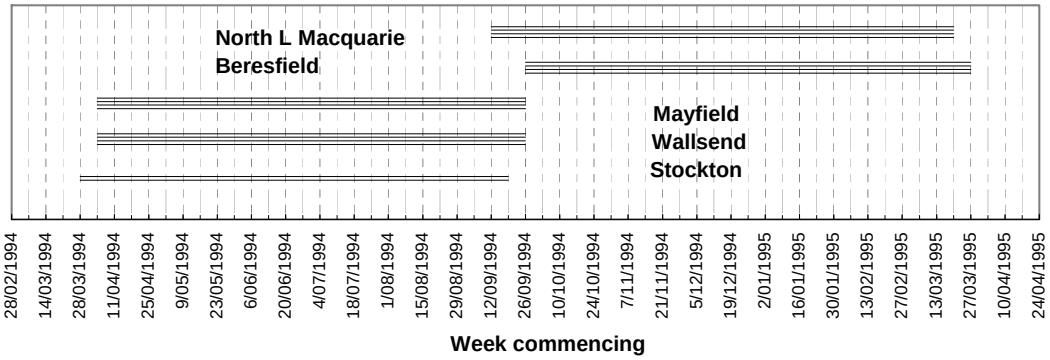
A comparison of the study period, aggregate analysis period and non-aggregate analysis period is given in Figure 4.3. In these graphs, each horizontal line indicates a school within the five study areas (total of 18 schools).

Figure 4.3. Description of study period, aggregate analysis period, and non-aggregate analysis period *

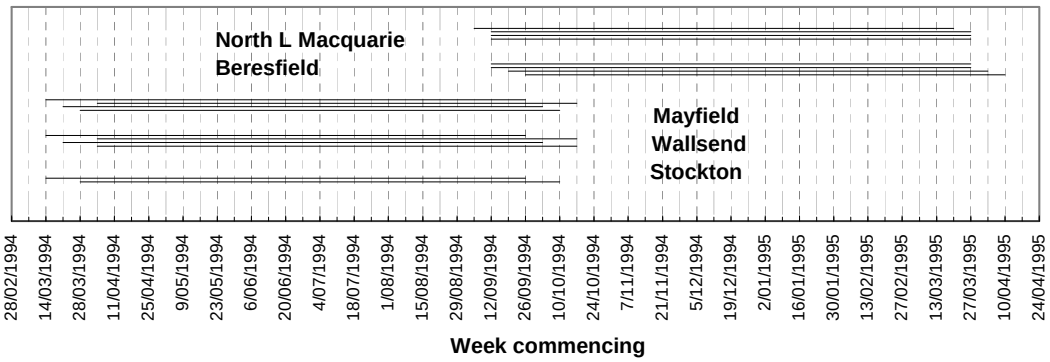
Study period (32 weeks at each study area)



Aggregate analysis period (25 weeks at Stockton, Wallsend and Mayfield; 26 weeks at Beresfield; 27 weeks at North Lake Macquarie)



Non-aggregate analysis period (28 weeks at each study area)



*. Each horizontal line indicates a school within the five study areas (total of 18 schools). Refer to Table A1.1 for corresponding names of schools.

4.1.3 Data management of diary information

A customised data entry program with existing range checks was written in FoxPro for the symptom and medication data prior to the commencement of the candidate. The same computer operator entered all of the data. A random sample of 20 diary cards was re-entered by another operator and compared for consistency. The overall error rate was less than three percent (310/10640), with a clinically relevant error rate of less than one percent. The monthly record of returned diary cards kept by the study team was cross-checked against the diary data-entry to check that all diary cards had been entered. The date of commencement of each diary card was checked for internal consistency within each school. Peak expiratory flow (PEF) control charts for individual children were plotted and PEF values above or below two standard deviations of the child's overall mean PEF were reviewed for data entry accuracy. Peak flows of less than 100 L/min were also reviewed if there was no accompanying symptom. During these reviews, the original data were edited when a data entry error was subsequently found. One child was identified as changing school during the study period so their diary data was deleted from the time of the move.

The data were entered such that each record represented one week of the diary for each subject. There were 7,663 records from 285 children. A SAS program was written by the candidate to merge the symptom and medication files together by a unique identifier based on study number and week number. These data were then expanded so that each record represented a unique study day for each child. If the subject did not complete the diary on a given day then the record corresponding to that day contained mainly missing data. Each child had 32 weeks (224 days) of observation, providing 63,840 records in total.

For the Aggregate analysis, a new dataset was created with each record representing an area-day. The number of data points per area ranged from 175 (corresponding to 25 weeks) to 189 (corresponding to 27 weeks), totalling 840 records. In addition, ten other datasets were created with the same structure, but based on various subpopulations within each area– e.g. children exposed to passive smoking, and children not exposed to passive smoking. Other stratifications included asthma medication usage, maternal allergy, a cat kept inside in the home, and gas appliance use inside the home. These stratification variables were considered in order to identify any subgroups particularly susceptible to pollutants and allergens (discussed in Section 4.6).

A further dataset that described subjects' health outcomes was created for the analysis. It summarised both the proportion of days across the study period the subject had symptoms and their mean peak flow reading. This dataset had 285 records – one for each subject.

4.1.4 Data management of other Phase II files

Several customised data entry programs were written in FoxPro to hold the remaining data collected in Phase II. These were written, and the data entered, before the candidate commenced work. The master file from each area contained the school and home address of each child eligible for Phase II, and their consent status. The initial interview file contained all the information collected in the initial interview. The only data entered from the final interview were the clinical measurements and monthly record of return of diary cards. A customised data entry program was written for the follow-up interviews. The only data entered from the follow-up interviews were the dates of contact.

Each of the eight files were exported into dbase format and then merged by a unique identifier (study number) in a SAS program.

4.1.5 Data management of the Phase I files

The data from the cross-sectional study (Phase 1) were entered into four different text files. A SAS program was written by the candidate to merge these files together by a unique identifier based on study number.

4.2 Data management of air quality and meteorological data

4.2.1 Data management of pollution data

The particulate, sulphur dioxide, nitrogen dioxide, and ozone data were received from various sources. They were provided as 10 minute, hourly, or daily data. The data were standardised as daily maximum, daily maximum for daytime period, daily arithmetic average, and daily arithmetic average for daytime period using a SAS program. The maximum reading for the 24-hour period or the daytime period was the highest of the hourly readings. The mean for the 24-hour period or the daytime period was the average of the hourly readings. Also calculated was the proportion of hourly data available for both the whole day and for the daytime period, and this was referred to as the capture rate. The data from 0:00 to 23:59 hours were used for daily values, and from 6:00 to 21:59 for daytime values. In the industrial study areas Stockton,

Mayfield, and North Lake Macquarie where TSP was monitored using a filter device, the only particulate measurement recorded was daily arithmetic average.

The air quality data set created had one record for each day during the study period, per study area - a total of 896 records. A data flag was set to identify when less than 80% of the hourly values were captured (Jalaludin *et al.* 2000).

4.2.2 Assessment of measurement error in pollution data

The air pollution data were reviewed by the candidate. Time plots of the data for each pollutant allowed the identification of outliers and any unusual patterns. Data management of each data source will now be described.

Incitec

The SO_2 data at Stockton were 100% complete, with a capture rate of 100% on each day. Documentation provided to the study team indicated that the only interruptions occurring in the SO_2 monitoring during the study period occurred on two days and lasted less than one hour.

Pasminco

The SO_2 data at North Lake Macquarie were 100% complete, with all dates having a capture rate of 100%. There was no documentation provided with the data and the provider was unable to be contacted. Given that on approximately 20% of these dates a zero concentration was recorded on each hour, there was concern that some of these values were actually missing data where the device had failed to record any value during the day.

EPA

There were some data outliers and unusual patterns in the data. These included a large amount of missing SO_2 and PM10 (using TEOM) data, unusually high mean daily TEOM values recorded at Wallsend in July 1994, and an unusual pattern in maximum SO_2 values at Wallsend. These problems are outlined below:

- There were high mean PM10 values observed at Wallsend on 19-22 July 1994 where all values were greater than 200 $\mu g/m^3$. None of the alternative particulate measures (6-daily TSP recorded by EPA, the PM2.5 recorded by ANSTO, and the nephelometry recorded by EPA) had high values recorded on these dates.

- The maximum SO_2 at Wallsend appeared to be incorrect between June and August 1994, with the values alternating between approximately 4 pphm and 0 pphm on successive days.

The EPA was contacted regarding these problems. They responded in June 1997 by supplying a dataset that had been cleaned more thoroughly than the one previously provided. The revised dataset was compared to the original and two differences were noted. Firstly, the maximum and mean PM10 values were the same except for the period 19 July 1994 to 22 July 1994 at Wallsend where the PM10 values had been set to missing, and 1 January 1995 at Beresfield where there was now a value recorded. Secondly, sulphur dioxide values at Wallsend were considerably different in the months of May, June, and July for 49 days, with the revised dataset having somewhat lower values. It had reset 84% of the values greater than 4 pphm to a value less than 2.0 pphm. This revised dataset was used for the analysis.

4.2.3 Data management of aeroallergen data

A comment field was included with the pollen and fungi data. If the tabled comment was “no trace” or “over-run”, the value for all species of pollens and Alternaria was recorded as zero on that day. After consultation with the technician, such data were deleted (L McShane, NSW Health Pollen Study, pers. com., 1997) because the equipment had failed. The raw counts were multiplied by 14/14.4 to enable the count to be expressed in grains per cubic metre of air (Burkard Manufacturing Co 1953; McShane and Cripps 1997). The analysis focused on grass pollen, weed pollen, and Alternaria (mould), as these were the most appropriate biologically and locally.

4.2.4 Data management of meteorological data

Meteorological data were received from various sources. They were provided as 10-minute average data from the industrial sites, and on a daily basis as mean, maximum and capture rate from the EPA. The measures included temperature, humidity, rainfall, wind-speed, wind direction and sigma-theta (standard deviation of wind direction). These last three measures were not analysed because they were not relevant to the objectives of the study.

The data from BHP (at Mayfield) and Pasminco (at North Lake Macquarie) were not used because the providers advised that the stations were not set up to measure temperature accurately (P Lewis, formerly HISSAP Study Group, pers. com., 1997). The maximum daily and mean daily temperature at Wallsend and Beresfield as measured by the EPA were within

one degree of each other on over 95% of dates during the study period. The agreement was therefore considered likely to be similar for all other study areas. Temperature data were also received from the Bureau of Meteorology based on recordings made at Nobbys Head Lighthouse and Signal Station. This Station was situated in the city of Newcastle, south of Stockton (refer to Figure 2.1 for study map). The maximum temperature at Nobbys correlated reasonably well with the maximum temperature at both Beresfield (r=0.87) and Wallsend (r=0.91). For these reasons, the average of maximum temperatures recorded at Wallsend and Beresfield was used for all the Hunter Region. Minimum temperature was available from the Bureau of Meteorology based on recordings made at Nobbys Head Lighthouse and Signal Station as dry bulb, wet bulb, and dew point temperature. Dry bulb temperature was used because it was modelled in a time series study of hospitalisations based in Melbourne, Australia (Erbas and Hyndman 2001).

Rainfall data were only available from North Lake Macquarie and Mayfield, where Pasminco and BHP own the monitoring stations respectively. North Lake Macquarie monitored rainfall from 23/8/94 to 31/3/95, and Mayfield from 28/2/94 to 30/10/94. No rainfall data were available for April 1995, at the end of the study period. The measured daily rainfall differed substantially between the two industrial sites (the difference ranged from 0 mm to 21.2 mm), during the 56 days in common. For this reason a binary indicator was created for rain days (any day with at least 1 mm of precipitation at either site) and heavy rain days (at least 20 mm of precipitation at either site).

The maximum daily relative humidity recorded by the EPA at Wallsend and Beresfield was over 99% on 199 days at Wallsend (81% of the study period) and on 195 days at Beresfield (82% of the study period). The EPA advised that there was a problem with the measuring device, and subsequent communication suggested that the mean would be more reliable (G Morgan, NSW Health, pers. com., 1997). For this reason, the average of the Wallsend and Beresfield mean daily measures was used for the whole of the Hunter Region.

In summary, the meteorological data representing the whole of the Hunter Region included the maximum, mean and minimum temperature, the mean relative humidity, and a binary indicator of rainfall (>1 mm), and a binary indicator of heavy rainfall (>20 mm).

4.3 Statistical methods: descriptive analysis of study population and health outcomes

A descriptive analysis of the health data was undertaken. Demographic characteristics of subjects eligible for the longitudinal study (Phase II) and those not eligible were compared using the chi-square statistic. The participation rates were described for each area. The children's home characteristics were compared across study areas, again using the chi-square statistic. Lung function results at the initial and final interview were expressed in their original scale, and as a percentage of predicted normal values for height and sex. These were normally distributed, and so means and standard deviations were reported. The number of days each child completed the diary over the study period was described. In addition, the proportion of subjects completing the diary for each day during the study period was plotted across time. The diary was considered to be completed on a given day if any of the 18 items had been completed. Also reported were summary statistics for each of the health outcomes. Mean evening peak flow, percentage of subjects with day cough symptoms, and percentage of subjects using inhaled bronchodilators were plotted across time to assess the extent of daily variation within each area.

Distance from home to school

It was assumed that the air quality monitoring stations would have provided a good estimate of the ambient concentrations at the schools because all schools were located within 2km of a monitor. It would also be expected that children attending school in the same area would be exposed to the same amount of air pollution during school hours. However, some children travelled from outside the area to go to school, and for these children the "out of school" measures would not be as reliable. The distance from each child's school to their home was estimated using a street directory (Gregory's Publishing Company 1989) and a ruler with reference to the scale provided for each map. The distances approximated this way were categorised as less than 1km, 1-5km, 6-10km, or more than 10km.

School term

The study period for both waves (Wave 1: February to October, Wave 2: August to April) included school holidays. It was anticipated that some analyses would be restricted to days during school term, and so this information was obtained from a 1994 and 1995 calendar (Table 4.3). A binary indicator was created for school term.

Table 4.3. School terms for New South Wales schools in 1994 and 1995

Term	Period
Term 1, 1994	Mon 31/01/94 to Thu 31/03/94
Term 2, 1994	Mon 11/04/94 to Fri 24/06/94
Term 3, 1994	Mon 11/07/94 to Fri 23/09/94
Term 4, 1994	Mon 10/10/94 to Fri 16/12/94
Term 1, 1995	Tue 31/01/95 to Thu 13/04/95
Term 2, 1995	Mon 24/04/95 to Fri 30/06/95

Medication

Medications that affect lung function were recorded in the initial interview and in the diary by trade name. For the analysis they were grouped into the following seven drug classes using the MIMS classification (MIMS Australia 1992) :

- Bronchodilators
- Inhaled corticosteroids
- Cromolyns
- Oral corticosteroids
- Nasal preparations for hayfever
- Antihistamines / decongestants
- Antibiotics.

The dosage was recorded during the fortnightly interviews, but the information was not of sufficient quality to accurately determine the daily dosage of each drug.

The number of children taking each of the medications was presented by drug class and by generic rather than trade name. Within the bronchodilator drug class, there were four different generic drugs: Salbutamol (Ventolin, Respolin, Medihaler), Terbutaline Sulfate (Bricanyl), Fenoterol hydronomide (Berotec), and Orciprenaline Sulfate (Alupent). There were two varieties of inhaled corticosteroids – Beclomethasone Dipropionate (Aldecin, Becotide, Becloforte) and Budesonide (Pulmicort). The only cromolyn medication used was Sodium Cromoglycate (Intal, Intal forte). Prednisone (Panafcortelone) was the only oral corticosteroid. Nasal preparations for hayfever included the corticosteroids Beclomethasone Dipropionate (Beconase) and Budesonide (Rhinocort), as well as Sodium Cromoglycate (Rynacrom). Medications used for symptomatic relief of various upper respiratory tract conditions included

Antihistamines, decongestants, and medications consisting of a combination of the two. These medications were not categorised by generic name (Avil, Benadryl, Demazin, Fabahistin, Polaramine, Teldane, Zadine, Hismanal, Phenergen and Other).

In the diary, the parent was asked to record the number of puffs of reliever medication (bronchodilators) taken during the day and the number of times inhaled corticosteroids were taken. Bronchodilators are typically taken as required, and their use was one of the main outcomes of the study. Corticosteroids are different to bronchodilators in that corticosteroids are used as a preventative treatment and are taken once or twice daily. It was anticipated that children who used inhaled corticosteroids, oral corticosteroids or cromolyns may be a less susceptible subgroup within a month of taking their medication, and so medication-use may be an effect modifier in the association between air pollution and respiratory health. However, it was also feasible that medication may be taken when pollution is perceived to be high; therefore, use of preventative treatment was considered a potential confounder in some analyses. As corticosteroids have long-term effects, it was sufficient to indicate whether they were used at anytime during the month by the use of a binary variable.

A child was considered asthma-medicated if they used a reliever (puffer or nebuliser), inhaled corticosteroids, oral corticosteroids, or cromolyns at any time during the study period. In determining the number of children taking each type of medication during the study period, both the name of the drug and its frequency of use needed to be recorded. There were 14 children with incomplete information, which may have resulted in an underestimate of the actual medication usage by those participants.

Peak flow

The within-subject coefficient of variation was calculated as an index of each subject's morning and evening PEF variability. For each child, this was defined as the standard deviation as a percentage of their mean PEF recorded across the study period (Higgins *et al.* 1989; Higgins 1997). This is appropriate because there was no correlation between the standard deviation and the mean (correlation=0.12 for the 285 subjects). The diurnal peak flow and the day-to-day peak flow were also calculated. Diurnal peak flow was the daily morning to evening change in peak flow (i.e. evening measure minus morning measure). Day-to-day peak flow was defined as the current day minus the previous day's recording.

The deviation in evening peak flow was calculated for each child-day by subtracting the child's mean evening peak flow over the entire study from the evening PEF for that day. The child-specific deviations were standardised by dividing by the child's mean PEF and then multiplying by 300 (Neas *et al.* 1995). This may be expressed as:

$$Y_{it}' = \frac{Y_{it} - \overline{Y_i}}{\overline{Y_i}} \times 300 \qquad (1)$$

Symptoms

Symptoms were recorded on a 6-point Likert scale but the categories were combined to form binary variables (0: absence of the symptom, 1-6: presence of the symptom) for most analyses. Any respiratory symptom was defined as the presence of cough, breathlessness, chest tightness, or wheeze during the day or night. The presence of a day symptom was defined as a cough, wheeze, chest tightness, breathlessness, sore/itchy red eyes, or runny/stuffy nose during the day.

The frequency of occurrence of each symptom for each child during the study was determined by expressing the number of days with the symptom as a proportion of the number of recorded days of observation. This was then categorised as never, less than once a week on average, 1-3 times a week on average, 4-6 times a week on average, and every day.

Both daily prevalence and incidence of symptoms were analysed (Schwartz *et al.* 1991). A symptom was defined as incident for an individual, if it was reported on the current day, but had not been reported on the previous day. The advantages of analysing daily symptom incidence rather than daily prevalence were the lower autocorrelation of residuals, and potential differential effects of air pollution on first occurrence and duration of symptoms, as discussed in Chapter 3.

The daily prevalence for each symptom was also determined in preparation for aggregate analyses. Daily symptom prevalence was calculated as the proportion of children reporting symptoms, where the denominator was the number of children with non-missing diary information on that day. When daily symptom incidence was defined, only subjects free of the symptoms on the previous day and with non-missing diary information on the current day were included in the denominator. This may be expressed as: $\frac{\text{number of events(n)}}{\text{number at risk(N)}}$ (Rothman and Greenland 1998b).

Bronchodilator use

For the bronchodilator use analysis, a daily binary indicator variable (use/no use) was derived. Frequency of use for each child across the study period was categorised as never, less than once a week on average, 1-3 times a week on average, 4-6 times a week on average, and every day.

Daily prevalence of bronchodilator use was calculated using the same method as for symptoms. In the Aggregate model, the outcome was the proportion of children using a bronchodilator (puffer form) on a given area-day. In the non-aggregate model, the outcome was whether the child used a puffer on a given day.

4.4 Statistical methods: descriptive analysis of air quality data

4.4.1 Reliability and validity of air quality data

Several analyses were undertaken to examine the reliability and validity of the air quality data. These included a comparison of the two alternative methods of measuring PM10 (TEOM and SSI), within-area comparisons of both particulate and SO_2 measurement, and repeatability of the pollen counts. Each of these analyses are described below.

Comparison of TEOM and SSI in the measurement of PM10

The EPA provided daily PM10 (measured using TEOM), and 6-daily PM10 (measured using SSI) at Beresfield and Wallsend. These data were used to address how TEOM and SSI compared in measuring PM10. The analyses were conducted separately for each study area. Comparisons involved the plotting of PM10 levels measured using the TEOM against PM10 levels using the SSI, for the 6-daily observations in common. To assess the agreement between the TEOM and SSI in the measurement of PM10, the 95% limits of agreement were calculated (Bland and Altman 1986). To identify systematic departures from agreement the difference between the results of the two devices were plotted against the average of the two methods, forming the Bland-Altman plot (Bland and Altman 1986). The intraclass correlation coefficient (ICC) was calculated using the sum of squares between dates (BMS), and the sum of squares within dates (WMS), and the number of observations per date (n=2) as reported in a one-way analysis of variance.

$$\mathrm{ICC} = \frac{\mathrm{BMS} - \mathrm{WMS}}{\mathrm{BMS} + (\mathrm{n} - 1) \times \mathrm{WMS}}$$

(Bland and Altman 1996)

Within-area comparisons of particulate and sulphur dioxide measurements

The correlation between daily pollution measures from the central monitoring station and those from peripheral stations within the same area were examined. This was possible only for the industrial study areas, where industry are required to set up several monitoring stations in their area. Spearman's rank correlation coefficients were reported since these variables were not normally distributed. Total Suspended Particulates was measured at two stations at Stockton, three stations at Mayfield and five monitoring stations at North Lake Macquarie. Hence, 14 coefficients were computed. Sulphur dioxide was measured at two stations at Mayfield and three at North Lake Macquarie. Nitrogen dioxide was measured at two monitoring stations at Mayfield.

Repeatability of pollen counts

The intra- and inter-observer reliability of pollen counts was assessed using the intraclass correlation coefficient. Agreement was assessed by calculating the 95% limits of agreement.

4.4.2 The relationship between PM10 and TSP

PM10 was measured daily for the duration of the study period at Wallsend and Beresfield. The only particulate measure available every day at Stockton, Mayfield and North Lake Macquarie was TSP. Hence, it was necessary to estimate daily PM10 based on daily TSP measurements at these three sites so that all results could be expressed in terms of the effect of PM10. An analysis was conducted to determine the PM10-to-TSP ratio within each of the study areas using supplementary 6-daily TSP (measured using a high volume sampler) and 6-daily PM10 (measured using a SSI) data obtained from Wallsend, Mayfield and North Lake Macquarie. PM10 was plotted against TSP and a regression line fitted with no intercept. The slope of the regression line was used to estimate the proportion of PM10 in TSP. At Mayfield and North Lake Macquarie, where PM10 data were not obtained directly, these proportions were used to estimate daily PM10 for the whole of the study period. At Stockton, the proportion of PM10 in TSP that was estimated at Mayfield was used due to its close geographical proximity to Stockton. These estimates of the PM10-to-TSP ratio were also used in the analysis of Phase I of the HISAAP study (Lewis *et al.* 1998).

4.4.3 Time of day analysis of particulates and sulphur dioxide

To examine whether pollution levels varied over a given day, the average reading across the year was calculated for each 1-hour period and the 24 values were plotted to determine whether

there was any variation across the time of day. This was done using hourly EPA data provided for Wallsend and Beresfield for the year 1995 for sulphur dioxide, PM10 (measured using TEOM), and PM2.5 (measured using nephelometry).

4.4.4 Descriptive analysis

The analyses were conducted separately for each study area. Summary statistics for each of the air quality variables (particulates, sulphur dioxide, nitrogen dioxide, ozone, pollen grains, and Alternaria) and the meteorological variables were reported. These were also presented as time plots for the duration of the study period. The within-area correlations of the air quality measures were reported using Spearman's rank correlation, due to the skewness of the variables.

4.5 Statistical methods: effect of air quality on health outcomes

4.5.1 Introduction

Various methods of analysis examining the association between environmental and health data have been reported in the literature (as described in Chapter 3). Because there has been no single preferred method of analysis identified, in this thesis various methods were applied and then the results were compared. The aim was to assess the sensitivity of the estimated effect of the air quality measures to model specification. The association of each outcome (evening peak flow, day cough, medication use) with each measure of air quality (PM10, sulphur dioxide, pollen and Alternaria) was evaluated using three approaches.

The *first approach* was an exploratory approach in which daily averages were calculated for all children who provided data on a given day. This was termed Aggregate data analysis. Using aggregated data allowed investigation of confounding and effect modification, examination of scaling of covariates, and examination of model fit, without the inconvenience of handling huge quantities of data. The models that were fitted were:

- Mean standardised evening peak flow deviation on each day was regressed on air quality that day (using aggregated data)
- The proportion of children with day cough symptoms on each day was regressed on air quality that day (using aggregated data)
- The proportion of children using inhaled bronchodilators on each day was regressed on air quality that day (using aggregated data)

In the *second approach*, non-aggregated data were modelled using the Korn-Whittemore approach. In the *third approach*, marginal models were fitted using generalised estimating equations (GEEs). The following models were fitted using the non-aggregated data:

- The child's evening peak flow deviation on each day was regressed on air quality that day (using non-aggregated data)
- The child's day cough symptoms on each day was regressed on air quality that day (using non-aggregated data)
- The child's use of inhaled bronchodilator on each day was regressed on air quality that day (using non-aggregated data)

The measures of air quality that were considered in this modelling process were PM10, sulphur dioxide, pollen and Alternaria. In the modelling, air pollution measures were only used if 80% or more of the hourly records were available. The 15-hourly (6 am to 9 pm) means were taken as daily data if there were at least 12 valid hourly readings each day, and the 24-hourly means were used as daily data if there were at least 19 valid hourly readings. Sulphur dioxide was recorded for a short period only at Beresfield and so limited analysis was undertaken for this study area with this pollutant.

All estimates were adjusted for climate-related covariates which were either statistically significantly associated with the outcome or were confounders. All children observed on the same day were allocated the same climate measures irrespective of study area because the meteorological data were derived from an average of the daily readings at all available weather stations in the region (methodology was described in Section 4.2.4). The weather conditions (temperature and humidity) experienced in each study area were almost the same, as expected because the study areas were less than 20 km apart (see Chapter 6).

Area-specific measures of air quality were sought and used. However, because each area experienced different levels it was desirable to have estimates of effect of air quality on health outcomes for the individual study areas as well as for the Hunter Region as a whole. The study was conducted in two waves because of the limited number of staff and pollen monitors available. Study areas in Wave 1 participated February to October, and study areas in Wave 2 participated September to March. There was one control, or non-industrial study area, in each wave. To provide a quantitative summary across study areas the area-specific regression coefficients were pooled to form a Hunter Region estimate. This was done using a fixed effects approach where the weights were inversely proportional to the area-specific estimate's variance.

If the chi-square test for heterogeneity indicated significant heterogeneity in the area-specific estimates, the between areas variance was estimated from the data using the moment method of Der Simonian and Laird (DerSimonian and Laird 1986), and the coefficients were pooled using a random effects approach.

Both immediate effects and lagged impacts of the air pollutants on health outcomes were considered. It was decided a priori to report results for same day exposure. Suitable exposure lags were determined for PM10, SO_2, and pollens using the following rationale. Initially, unrestricted distributed lag models were fitted using the constrained/unconstrained option in SAS/ETS procedure PROC PDL (SAS Institute Inc 1988) on the aggregated data. However, problems were encountered in the model fitting and so a more simplistic method was used. It was decided a priori to allow different lag structures for the different outcomes, as symptom changes were expected to be more immediate than any lung function changes. It was also decided a priori that aeroallergens (total pollen, grass pollen, weed pollen, tree pollen and Alternaria) would have identical lags as the same biological mechanism was expected to be operating. For SO_2 an immediate physiological response was expected based on previously reported laboratory results. However, it was decided a priori to report the same lag structure in each area. Lags of up to five days were considered, with single day lags of 1 to 5, and moving average lag models of up to five days for the evaluation of the effects of prolonged exposure. Preliminary analyses indicated that the average of the current and previous 4 days had the largest effect estimates in the hypothesised direction. Thus, the lag model chosen for all pollutants was the average of the current and previous 4 days, which is termed the 5-day average. This measure has previously been used in several panel studies including the six-cities study (Pope and Dockery 1992). The fit of the model was not considered when choosing the most appropriate lag structure.

To allow comparison between the sizes of the estimated regression coefficients in continuous models, all reported regression coefficients were rescaled to reflect an increase in the respective air quality measure across the interquartile range. The interquartile range calculation was based on the distribution of daily observations across the five study areas. This resulted in the effect of air quality on respiratory outcomes being extrapolated beyond the range of the air quality measure in some study areas. The association between air quality and EPF was examined in linear regression models, and the regression coefficients were expressed as a percentage change from 300 L/min. The association between air quality and day cough was examined in logistic regression models, and the regression coefficients were expressed as odds ratios. The effect of

the air quality measure (e.g. PM10) in the presence of effect modification was reported using standard methods (Blizzard *et al.* 2004). If the effect modifier was a continuous covariate (for example daily minimum temperature), the effect of PM10 was estimated at the median of the variable (median daily minimum temperature during study period).

Statistical significance was attributed to p-values < 0.05, and all hypothesis tests were two sided. When examining effect modification, p-values<0.05 were also used. No adjustment was made for multiple testing. All findings, both positive and negative, are reported (Rothman and Greenland 1998a). This allows readers who are concerned by the multiple testing to judge the extent of the problem and make formal adjustments if they so desire.

Analyses were performed using SAS version 6.1 software (SAS Institute Inc 1989) and Stata version 8.0 (StataCorp 2003). A listing of the variables considered in statistical modelling is provided in Table 4.4. The methods used in each of these analyses will now be described in detail.

Table 4.4. Variables used in the modelling of respiratory health against air quality

Time-stationary covariates (also known as between-subject covariates)	**Time-varying covariates**			**Outcomes**
	Air quality	**Climate**	**Subject**	
Study Area	Daily PM10	Daily temperature	***Monthly data:***	Daily evening peak
School	(mean, max)	(min, mean, max)	Inhaled corticosteroid use during month	flow
Distance from school to air quality monitoring station*	Daily sulphur dioxide	Daily Humidity	Anti-inflammatory use during month	Daily day cough
Age *	(mean, max)	(mean)		Daily inhaled
Gender *	Daily total pollen	Daily Rainfall	***Daily data:***	bonchodilator use
Any asthma medication use during study *	Daily grass pollen		Inhaled bronchodilator use	
Diagnosed with asthma *	Daily weed pollen	*Seasonal*	Sleeping away from home	
Maternal allergy (hayfever or asthma)*	Daily tree pollen	Month of study	Perceived level of air pollution	
Maternal hayfever	Daily Alternaria	Trend	Runny/stuffy nose	
Adults smoking indoors *				
Indoor cats *			**Other**	
Unflued gas heating *			School term / School holidays	
Gas cooker with no external fan*			Day of week	
Live less than 1km from school *				
Slept less than 5% of nights away from home *				
Completed study *				

*. Putative effect modifiers of the effect of air quality on health outcomes in statistical modelling

4.5.2 Selection of a core set of climate-related covariates

A large array of measures related to climate were collected that were putative predictors of the health outcomes. These included temperature, humidity, rainfall, trend and month of study. Because temperature, humidity and rainfall may have delayed effects on health outcomes, 1-day lag were considered as well as the same-day concentrations. The climate-related variables with longer lags had little predictive power in all models. To adjust for the effects of ageing on lung size, day of study was also included (number of days elapsed since the start of the study). The objective of fitting a term for month of study was to adjust for seasonal variations not captured by other climate variables (such as wind speed, wind direction and thunderstorm activity). For the study areas in Wave 1 (Stockton, Wallsend and Mayfield), binary (0/1) indicator variables were included for the months May, June, July, August and September, with the reference being March to April. For the study areas in Wave 2 (Beresfield and North Lake Macquarie) binary (0/1) indicator variables were included for the months November, December, January, February and March, with the reference being September to October. The 16 variables considered for selection are summarised in Table 4.5.

Table 4.5. Climate-related predictor variables used in the modelling of respiratory health against air quality

Covariate	Lag	Measure
Temperature	Same day, 1 day	Daily maximum, Daily minimum, Daily average Daily temperature range
Humidity	Same day, 1 day	Daily average
Rainfall	Same day, 1 day	≥ 5 versus < 5mm ≥ 1 versus < 1mm
Trend	-	Number of days elapsed since the start of the study
Month	-	Indicator variables for each month of the study

Putative covariates were screened to identify those that were most important in order to provide parsimonious models. This was done using the first modelling approach (the “aggregate analysis”). This core set of climate-related predictors were then used in all modelling approaches (K-W, GEE).

The analysis was conducted for each area separately. The analysis period was limited to those days in which all schools in the same study area were participating. In modelling the outcome evening peak flow, the dependent variable was the average standardised deviation from the mean. In modelling the outcome day cough, the dependent variable was the proportion reporting cough symptoms that day. In modelling the outcome medication use, the dependent variable was prevalence of use of bronchodilators, but the analysis was limited to subjects who took asthma medication at some stage during the study period. This provided a set of time series data for each area. The number of observations was the number of days of the analysis period. In this aggregate level analysis, there were no missing outcome data on any given day because the outcome was calculated from the responses of children who provided data that day. If there were data missing for any explanatory variable, that day was omitted from the analysis.

The method of purposeful selection was used to select the climate-related covariates (Hosmer and Lemeshow 2000). This was undertaken when modelling each of the three outcomes (evening peak flow, day cough and medication), and each of the air quality measures (PM10, sulphur dioxide, total pollen, grass pollen, weed pollen, tree pollen and Alternaria) and in each area separately. To make this task manageable the covariates were selected from the analysis for total pollen and were applied to total pollen, tree pollen, grass pollen and weed pollen. Thus, potentially there were 60 unique sets of climate-related covariates (3 outcomes x 4 air quality measures x 5 areas). Associations between mean standardised evening peak flow deviation and climate-related variables were analysed with linear regression using the SAS procedure PROC REG. Associations between day cough and medication use and climate-related variables were analysed with logistic regression using the SAS procedure PROC LOGISTIC. Autocorrelation was ignored in these models. The selection of the core-set of climate-related predictors specific for each outcome, air quality measure and area involved the following seven-step procedure:

1. In univariable analyses, each of the 16 climate-related variables was modelled against the outcome.
2. Any climate-related variable whose univariable test had a p-value < 0.25 was retained for inclusion in a multivariable model. The air quality measure was included in the multivariable model irrespective of its p-value.
3. The model was simplified by successively deleting the climate-related variable with the least significant coefficient until all the estimated coefficients had a p-value < 0.10. Again, the air quality measure was included in the multivariable model irrespective of its p-value.

4. Excluded variables were added back into the model, one at a time and it was noted if their inclusion produced more than a 20% change in the coefficient of the air quality measure. Any such confounders were retained in the multivariable model. Those variables which were statistically significant (p-value < 0.10) were also retained and entered simultaneously into the model, to form the "preliminary main effects model".
5. Backward stepwise selection was used to verify that the "preliminary main effects model" was appropriate. For the variable selection process, p-values < 0.10 for inclusion and >= 0.10 for exclusion respectively were used for climate-related variables, whilst the air quality measure was forced in.
6. The assumption of linearity was then checked for all continuous variables in the "preliminary main effects model". For the climate-related covariates and PM10, this was done using fractional polynomials (Royston *et al.* 1999). The best power transformation x^P is found, with power P chosen from the set of candidates (-2,-1,-0.5,0,0.5,1,2,3). The set includes the straight line (i.e. no transformation P=1), and the reciprocal (P=-1), logarithmic(P=0), square root (P=0.5) and square transformations (P=2). A test for the need of a fractional polynomial transformation is performed by comparing the difference in model deviances between the polynomial and the straight line with a chi-square distribution with 1 degree of freedom. If the test of P=1 against the best-fitting alternative model was statistically significant the non-linear function was preferred. The air quality variables sulphur dioxide and pollen had many days with zero concentrations, and so the assumption of linearity was checked using a combination of fractional polynomials and binary shift models. This involved including a binary indicator variable (0=no concentration, 1=positive concentration), and a variable defined as the product of the binary term and the actual concentration in the model. If both terms were statistically significant (p-value < 0.10), then both terms were retained when examining the assumption of linearity using fractional polynomials. If only the binary term was statistically significant (p-value < 0.10), then only that term was kept.
7. Variables were then removed if they were neither statistically significant at 0.05 nor an important confounder. This was termed the optimally scaled model.

Hence, the optimally scaled model included the air quality measure and any climate-related predictor which was either statistically significant or an important confounder. It was expected that temperature, days elapsed since the start of the study, and month might be highly correlated and so collinearity was carefully examined.

4.5.3 Aggregate modelling approach

The Aggregate analysis was conducted for each area separately. The dependent variables corresponding to the three outcomes were described in Section 4.5.2. Scatter-plots of the dependent variable versus air quality measure were obtained for each area, and a smoother was plotted using a band width of 0.8. The set of climate-related covariates included in regression models had been previously determined (refer to Section 4.5.2). Given the autocorrelative nature of the data, a time series analysis was undertaken using the Box-Jenkins approach. Lag terms were added until the Durbin-Watson d statistic was sufficiently close to 2, indicating that the residuals were not correlated. A first-order autoregressive model was appropriate for all study areas.

Each climate-related covariate was a putative effect modifier of the association between air quality and the health outcome. This was tested by sequentially adding interaction terms into the main effects model between the air quality measure and each of the other main effect terms that were statistically significant. All interactions that were significant at the 0.05 level were then simultaneously added into the main effects model.

The influence of individual observations on parameter estimates was checked using the Cook's Distance. This diagnostic is formed from leverage and residuals, and measures the effect of deleting an individual observation (date) on the parameter estimates. In addition, the covariate-specific Cook's Distance (also known as DFBETA) was used to identify observations having a large influence on the estimated effect of air quality on the health outcome. Ideally, the questionnaires corresponding to these observations would be examined, and data corrected if data errors are confirmed (Blizzard *et al.* 2003) but this was not possible. The model was checked for stability by repeating the regression after removing high influence observations.

When modelling the dependent variable mean standardised evening peak flow deviation, model assumptions were evaluated using a test for normality of the residuals and a test for homogeneity of error variance. The error variance plot and a test proposed by Cook and Weisberg was used to test the assumption of constant variance. The Shapiro-Francia test for normal data was used to test that the residuals were distributed normally. Residuals of the outcome were plotted against time and temperature to confirm that cyclical and long-term patterns had been removed. Residual plots for the individual pollutants were then examined for potential outliers and heteroscedasticity, using White's test.

Goodness of fit of the linear models was assessed using the coefficient of determination (R^2 values). This is the proportion of variance in the outcome variable explained by the multivariable model. Goodness of fit of the logistic models was assessed using the Hosmer-Lemeshow statistic (Hosmer and Lemeshow 2000). This statistic is not routinely available in SAS for autoregressive models, and so to obtain this statistic the model was fitted with the previous day's outcome as a covariate rather than an autoregressive term.

The models were weighted by the daily numbers of participants in the study area providing outcome data to account for the differences in the number of participants between different days. If the weights are proportional to the reciprocal of the variance for each observation, then the weighted estimate for the exposure (e.g. PM10) is the best linear unbiased estimator.

In models with mean standardised evening peak flow deviation as the dependent variable autoregressive linear models were fitted using the SAS procedure PROC AUTOREG. In models with day cough or bronchodilator use as the dependent variable, autoregressive logistic models were fitted using the SAS procedure PROC NLIN. A correction factor for overdispersion was used for these binary models. Maximum likelihood estimates were reported. The area-specific regression coefficients were pooled to obtain a Hunter Region estimate using a SAS macro (provided by Associate Professor Keith Dear).

4.5.4 Korn-Whittemore modelling approach

The relation between the outcome and air quality (PM10, sulphur dioxide, pollen and Alternaria) was modelled separately for each child using multivariable regression with adjustment for climate-related confounders and allowing for first-order autocorrelation. This gave a regression coefficient between air quality and the dependent variable for each child (Korn and Whittemore 1979). Intercepts for each child were allowed to differ. The set of climate-related covariates included as potential confounders for this analysis had been predetermined in the Aggregate analysis (refer to Section 4.5.2).

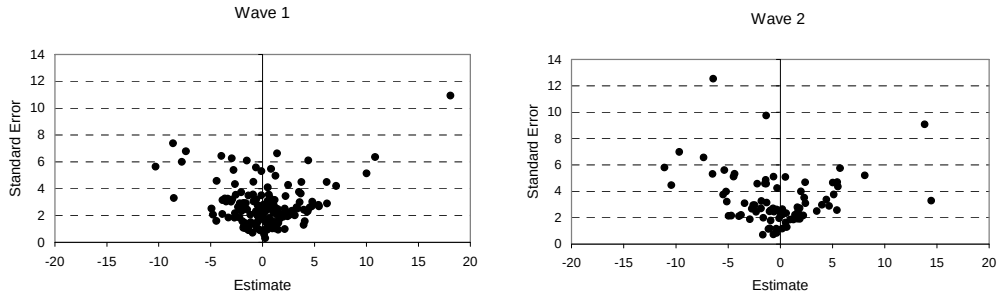
In the K-W analysis, the three outcomes were again modelled. For the outcome evening peak flow, the dependent variable was the daily deviation from mean evening peak flow. For the outcome cough, the dependent variable was a binary term taking the value 1/0 if the child did/did not experience cough symptoms on a given day. Similarly, for the outcome medication use, the dependent variable was a binary term taking the value 1/0 if the child used/did not use a bronchodilator on a given day.

An analysis of the variability of the individual slope coefficients was conducted to detect heterogeneity of response of individual children (Brunekreef *et al.* 1991). In this method, the ratio of observed variance of individual slopes and the expected variance due to random error is compared to an F distribution.

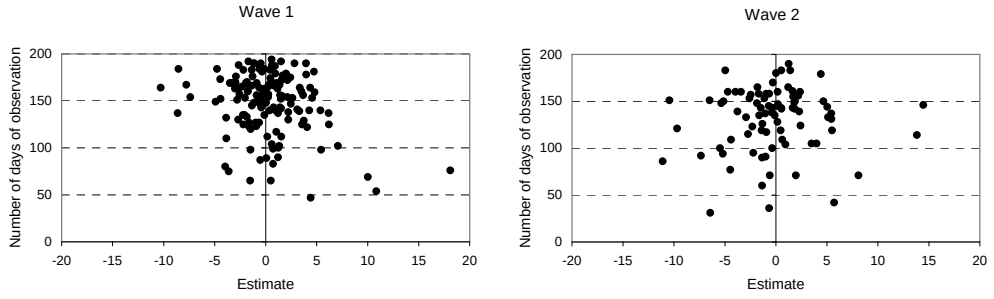
The child-specific maximum likelihood estimates were pooled to obtain area-specific estimates using both a fixed effects and random effects approach. The main purpose in carrying out both analyses was to compare the results of the two approaches. Three alternative weighting schemes were implemented. These were (1) the unweighted or unit weight approach which was simply taking the mean of the estimates; (2) weighting by number of observations contributed by the child; and (3) taking the mean of the regression coefficients, weighted by the reciprocal of their variances. There was some evidence of a relationship between the estimate and the associated standard error with larger estimates having larger standard errors (Figure 4.4). For this reason, pooling was reported using only unit weights and weights based on the number of observations.

Figure 4.4. Scatterplot of precision versus estimate of child-specific regression coefficient, for each wave separately

a) The *standard error* is the measure of precision



b) The *number of days of observation* is the measure of precision



Effect of a 20 μg/m^3 increase in PM10 on same day evening peak flow (L/min); Korn-Whittemore results.

The area-specific estimates were pooled to obtain a Hunter Region estimate using both a fixed and random effects approach as described in Section 4.5.1.

In models where the dependent variable was cough, children reporting cough symptoms on fewer than 5% of days in the study period (10 days) or 95% of days in the study period were excluded to enable the regression models to converge. This left 195 children for the analysis. When the regression model was fitted for individual children, the program gave warnings about model convergence for a few children, and these children had regression coefficients with large standard errors. The analyses were repeated with these children excluded.

In models with evening peak flow as the dependent variable, an autoregressive linear model was fitted for each subject using the SAS procedure PROC AUTOREG. In models with day cough or bronchodilator use as the dependent variable, autoregressive logistic models were fitted using the SAS procedure PROC NLIN. Parameters were estimated using the maximum likelihood method. The child-specific regression coefficients were pooled to obtain area-specific estimates using a SAS macro developed by the candidate.

4.5.5 GEE modelling approach

Generalised estimating equations were fitted for each individual study area. These models were referred to as "area-specific GEE models". The set of climate-related covariates included as potential confounders for this analysis had been predetermined in the Aggregate analysis (refer to Section 4.5.2). The covariance structure chosen was first order autoregressive (AR-1) because it has typically been used in these types of studies and the Aggregate analysis suggested this was appropriate (refer to Section 4.5.3). An AR-1 GEE model addresses serial correlation by assuming a correlation of $\rho^{|r-s|}$ between observations at times r and s. Empirical (or robust) standard errors were reported, which give consistent estimates of parameters even when the assumed covariance structure is incorrect.

In the GEE analysis, the three outcomes were again modelled. For the outcome evening peak flow, the dependent variable was the deviation from mean evening peak flow. This is equivalent to a regression of EPF where each child is allowed to have a different intercept. The measure used for day cough was a binary variable for day cough prevalence (yes/no). The measure used for medication use was also a binary variable. The models for the binary outcome variables were fitted in logistic regression with allowance for overdispersion. Model fit was assessed by

examining case-wise diagnostics including the deviance residual. The area-specific estimates were pooled to obtain an overall estimate using both a fixed and random effects approach as described in Section 4.5.1.

In an analysis combining all study areas, all children were included in the same model. A term for study area or study wave was included irrespective of its p-value. This approach was previously used in the 6-cities study where "city of residence was treated as a categorical explanatory variable to account for differences between communities that were unrelated to the air pollution exposures" (Schwartz *et al.* 1994). The climate-related covariates were chosen using the same 7-step approach described earlier in Section 4.5.2. Interaction terms were sequentially added into the main effects model between the air quality measure and each of the other main effect terms. In addition, interaction terms between wave (or study area) and the climate-related covariates were added. All interaction terms that were significant at the 0.05 level were then simultaneously added into the main effects model. This model was referred to as the "5-day average Hunter Region GEE model".

To assess the robustness of the results to the choice of statistical model, alternative statistical models were fitted. This was done mainly for PM10 as this thesis focuses on estimating the effects of PM10 on respiratory health. The sensitivity analyses are described in Table 4.6. Some analyses are restricted to particular subsets of subjects.

Table 4.6. Sensitivity analyses conducted on the 5-day average Hunter Region GEE model

No.	Outcome	Air quality	Description
1	Each*	All	The covariance structure was specified as independent (the naïve model) and robust standard errors were estimated.
2	Each	All	The differences across study areas in the timing of the measurement of exposures were crudely taken into account in analyses using exposure variables termed the "previous 24-hours".
3	Each	PM10	Several exposure lag structures were fitted to examine the stability of the effect estimate.
4	Each	PM10	The analysis was limited to children eligible for the K-W analysis, so that the results from the two models could be directly compared.

No.	Outcome	Air quality	Description
5	Each	PM10	The PM10 data at Stockton, Mayfield and North Lake Macquarie was estimated from TSP data using a different ratio, namely by PM10=TSP*0.55 which has been used in other studies (Dockery and Pope 1994; Pope and Dockery 1999).
6	Each	PM10	Because missing data may cause regression estimates to be biased, missing data were imputed using two approaches. Firstly, by interpolation assuming a linear function between the closest non-missing values. The missing exposure data were imputed using the SAS procedure PROC EXPAND. Secondly, missing outcome data were imputed with the predicted values from the K-W analysis.
7	Each	PM2.5	The analysis was limited to Mayfield which had the highest level of particulates, to examine the effect of PM2.5 on respiratory health.
8	Each	SO_2	Daytime measures of exposures were used rather than 24-hour measures.
9	EPF	PM10, SO_2	Analysis was limited to children who did not provide suspicious evening peak flow readings. Subjects were excluded if they had at least one reported peak flow greater than 500 L/min, or peak flow was a multiple of 50 on more than 100 days, or peak flow was less than 160 L/min on 10 or more days.
10	EPF	PM10, SO_2	The dependent variable was prevalence of large decrements in peak flow. To investigate associations with large reductions in lung function, the percentage decrement from each child's mean EPF was calculated. The standard approach was followed whereby two binary dependent variables were used to denote decrements greater than 10% and 20% (Hoek *et al.* 1998).
11	Cough	PM10, SO_2	The dependent variable was incidence rather than prevalence.

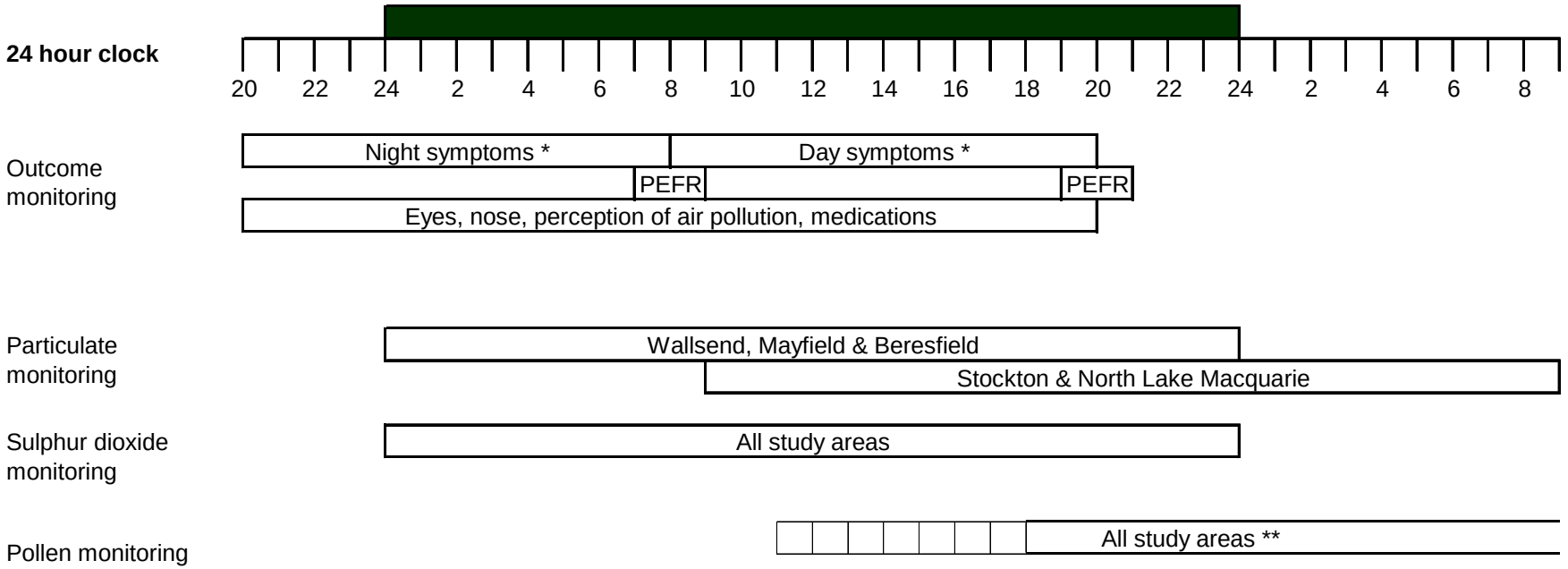
*. The sensitivity analysis was conducted for each of the three outcomes (EPF, day cough, medication).

The second sensitivity analysis, namely the "previous 24-hours" analysis, requires further explanation. For subjects at Wallsend, Mayfield and Beresfield, the measurement of PM10 on the day EPF was measured referred to approximately 20 hours of exposure (from midnight to approximately 8pm) and 4 hours of exposure for the next day EPF was measured (Figure 4.5).

For subjects at Stockton and North Lake Macquarie, however, the measurement of PM10 referred to approximately 11 hours of exposure (from 9 am to approximately 8 pm) on the day EPF was measured and 13 hours of exposure the next day. To address this imbalance, "previous 24-hour" PM10 readings at Stockton and North Lake Macquarie were calculated as the average of the current and previous day, whereas at Wallsend, Mayfield and Beresfield they were calculated as the current day only. Sulphur dioxide monitoring was undertaken from midnight to midnight in each study area and so the measurement of SO_2 on the day EPF was measured referred to approximately 20 hours of exposure. The "previous 24-hour" SO_2 readings were equal to the current day for all study areas. Pollen monitoring was undertaken at various starting times in the range from 10am to 6pm, and so the measurement of pollen referred to anywhere between 2 hours and 9 hours prior to measurement of health outcomes. The "previous 24-hour" pollen counts were calculated as the average of the current and previous day.

The SAS procedure PROC GENMOD was used to fit all GEE models. In models with evening peak flow deviation as the dependent variable, marginal autoregressive linear models were fitted. In models with day cough or bronchodilator usage as the dependent variable, marginal autoregressive logistic regression models were fitted with allowance for dispersion. Overdispersion was accommodated using the "dscale" option. PROC GENMOD uses maximum likelihood estimation to estimate the parameters.

Figure 4.5. Summary of respiratory health and air quality data collection recorded each day during the study period



*. Cough, wheeze, chest tightness and breathlessness.
**. In all study areas the time of measurement varied from day to day; the earliest starting time was 11:00hrs and latest starting time was 18:00hrs.

4.6 Assessment of effect modification by time-stationary covariates (PM10 only)

An analysis was conducted to determine characteristics of children who were more sensitive to PM10. Past research has indicated that symptomatic children not taking asthma medication during the study period may be a more sensitive subgroup. Likewise, children exposed to nitrogen dioxide in the home and/ or passive smoking may be more sensitised to PM10. There are other subject characteristics, which were proxies for the extent of potential exposure misclassification of PM10 as a result of central outdoor monitoring. For example, children who live close to the school may have PM10 measurements that are better proxies for their personal ambient exposure than children who lived more than 10km from their school. Because their exposure is subject to less measurement error the association between PM0 and health outcomes may be stronger for these subjects. In Table 4.4 a list of the thirteen time-stationary variables can be identified with a "*". The rationale for choosing these variables is now given.

Crude estimates of the child's exposure to indoor nitrogen dioxide from gas cooking and heating, and exposure to cigarette smoking inside the home, were recorded during the cross-sectional study (Phase I). Children with long-term exposure to passive smoking will have heightened airways, so it might be expected that children exposed to passive smoking at home may be more affected by pollutants. However, this situation is complex as parents of such children may possibly quit smoking because of their child's condition. Maternal allergy and other time-stationary variables considered important from the earlier cross-sectional study (Phase I) were also examined in this analysis.

In this study PM10 was measured using central outdoor monitoring. Measurement error would arise if there were differences between personal ambient exposure and the readings from central outdoor monitors. It is possible that children with certain characteristics may have had a more accurate measure of PM10. For example, if the child slept less than 5% of the study period out of their home suburb their exposure measurement may be more accurate. Also, children who resided within 1km of their school would have a more accurate measure of exposure, compared to those living more than 1km from the school.

In addition, the association between PM10 and respiratory health for children who completed the study was compared to the association for those who did not complete the study to assess attrition bias.

The search for sensitive subgroups was conducted using all three modelling approaches (Aggregate, Korn-Whittemore and GEE). Each of the 13 time-stationary variables were examined separately. The process of investigating sensitive subgroups is now outlined for the case of the outcome evening peak flow, and the time-stationary covariate, medication use. Now $X_2, X_3, ..., X_Q$ denotes the (Q-1) climate-related covariates.

In *Aggregate analysis*, the analysis was stratified by each of the time-stationary variables of interest. The following two regression models were fitted for each study area:

For the medicated group:

$$Y_t^{(1)} = \beta_0^{(1)} + \beta_{PM10}^{(1)} PM10_t + \beta_2^{(1)} X_{2t} + ... + \beta_Q^{(1)} X_{Qt} + \vartheta_t^{(1)} \qquad (1)$$

For the non-medicated group:

$$Y_t^{(0)} = \beta_0^{(0)} + \beta_{PM10}^{(0)} PM10_t + \beta_2^{(0)} X_{2t} + ... + \beta_Q^{(0)} X_{Qt} + \vartheta_t^{(0)} \qquad (2)$$

where ϑ_t is a latent process allowing autocorrelation in Y_t. The estimates for PM10 were then pooled across study areas using a fixed effects approach as described earlier. The two estimates for PM10 derived from the two sub-populations were then compared. If the estimates were quite different, this indicated that medication use might be an effect modifier in the association between PM10 and the outcome.

In *Korn-Whittemore analysis*, the association between the magnitude of the individual regression coefficients (or slopes) and child characteristics were examined using weighted least squares regression. The number of daily observations from each child determined the weight. The model was fitted with the child-specific regression coefficient as the dependent variable and medication use as an independent variable with terms for study area.

$$\hat{\beta}^{(i)} = \alpha_0 + \alpha_1 med_i + \alpha_S S_i + \alpha_W W_i + \alpha_M M_i + \alpha_B B_i + \varepsilon_i \qquad (3)$$

where $\hat{\beta}^{(i)}$ is the child-specific regression coefficient. In this model, if the medication term was significant at the 0.05 level then it was judged to be an effect modifier. More sophisticated methods have become available since the candidate completed the data analysis, including random variance component analysis which is available using the metareg command in Stata. Estimates for the medicated and non-medicated subgroups were obtained by averaging regression coefficients within the given subgroup under fixed effects.

In *GEE analysis*, the time-stationary covariate was added to the "5-day average area-specific model" as a fixed effect as well as an interaction term with PM10.

$$Y_{it} = \beta_0 + \beta_{PM10} PM10_{it} + ... + \beta_Q X_{itQ} + \beta_{med} med_i + \beta_{\text{int}} PM10_{it} \bullet med_i + \varepsilon_{it} \qquad (4)$$

where the variable "med" takes the value 1 if the subject is medicated at some time during the study and the value 0 if the subject is not medicated. The estimates were then pooled across study areas as previously described.

The analysis was repeated using the "5-day average Hunter Region GEE model". If the interaction term was significant at the 0.05 level then it was judged to be an effect modifier. In this model, to calculate standard errors in the presence of effect modification the following formulas were used:

For non-medicated children: $SE(estimate) = \sqrt{\text{var}(\beta_{PM10})}$ (7)

For medicated children: $SE(estimate) = \sqrt{\text{var}(\beta_{PM10}) + \text{var}(\beta_{\text{int}}) + 2\,\text{cov}(\beta_{PM10}\beta_{\text{int}})}$ (8)

where $\text{var}(\beta_{PM10})$ is the square of the empirical standard error of the β_{PM10} coefficient, and $\text{cov}(\beta_{PM10}\beta_{\text{int}})$ is obtained from the empirical covariance matrix.

4.7 Adjustment for confounding and assessment of effect modification by time-varying covariates using the GEE model (PM10 only)

There were several time-varying covariates that may confound or mediate an association between PM10 and each of the health outcomes. These were controlled for in the analysis. The impact of time-stationary covariates was also examined and this was discussed earlier in Section 4.6. It was not possible to analyse the effect of the time-varying covariates using the Aggregate model, and whilst it is possible to perform the analysis using the Korn-Whittemore modelling approach, it is not straight forward, and so the analysis was limited to GEE. Specifically, the analyses were conducted on the 5-day average area-specific GEE models and the 5-day average Hunter Region GEE model.

Upper respiratory infection (nasal symptoms) may be related to both PM10 and the health outcomes and so was a putative confounder. The eight time-varying covariates examined are listed in Table 4.4. They included the following binary terms: inhaled corticosteroid use during the month, anti-inflammatory use during the month, current day bronchodilator use, and respiratory infection. The remaining covariates were indicators of whether PM10 was subject to

measurement error. For example, in the diary the parents were asked to report on "How much pollution do you think was in the air today?" using the scale 0 (none at all), 1 (a little), 2 (some), or 3 (a lot). Perception of air pollution may be a marker for something that is a confounder, such as avoidance of pollution. In addition, the PM10 measurement should be subject to less measurement error on days during the school term and when the child slept at home, compared to school holidays. Day of the week was also included as a covariate because subjects were expected to spend more time outside on the weekend compared to during the week and so have higher levels of exposure.

All covariates were modelled using binary (0/1) indicators variables. Daily perception of pollution was categorised as yes (did perceive pollution:1-3) and no (did not perceive pollution 0). Day of week was modelled as weekend (Friday to Sunday) or weekday (Monday to Thursday).

Confounding

Confounding was assessed by observing the change in the parameter estimate for the effect of PM10 on health outcome that occurred upon adjustment for the covariate. Covariates were entered one at a time into separate models. A factor was considered to confound the association between PM10 and the outcome if the parameter estimate for PM10 was changed by more than 10% after inclusion of the covariate into the model (Greenland 1989). This was a more conservative approach than used to select the climate-related covariates (Section 4.5.2). Results are presented to show the effect of the inclusion of each of these covariates into the main model.

Daily effect modification

These same covariates were examined for effect modification. Effect modification of the association between PM10 and health outcome was examined by using a GEE model with terms for the possible effect modifier, PM10, climate-related covariates, and interaction term for the possible effect modifier and PM10. Hence, the "hierarchy principle" was always observed (Greenland 1998). The decision as to whether the factor was an effect modifier was based on the p-value associated with the interaction term in the model. Results for statistical tests were regarded as statistically significant if the associated p-values were less than 0.05.

It is important to note that even if a covariate was found to be an effect modifier, the association between PM10 and the outcome within the two strata need not be statistically significant. This was because the variable was not required to be independently associated with the outcome in

the main effects model. The effect of PM10 in the presence of interaction was reported using standard methods such that an estimate and standard error for each strata are reported. This method of testing for interaction has advantages over a stratified or subgroup analysis for two reasons. Firstly, more power is available. Secondly, the primary importance of the analysis is not to assess statistical significance within each strata (as in subgroup analysis) but rather to assess whether the estimated PM10 effects within each strata were statistically significantly different (NHMRC 2000).

4.8 Multi-pollutant analysis using the GEE model

The single-pollutant model was used to determine the effect of each individual air quality measure (PM10, SO_2, pollen and Alternaria) on respiratory health. As described earlier, each air quality measure was separately entered into a model with adjustment for climate-related predictors. The multi-pollutant model was used to estimate the effect of PM10 after controlling for another pollutant or aeroallergen measure. PM10 and alternative air quality measures were simultaneously included in the 5-day average area-specific GEE model. The estimates were then pooled across study areas as previously described. The analysis was repeated using the 5-day average Hunter Region GEE model. In this model, if the effect of both air quality terms on the health outcome were statistically significant, an interaction term was included to assess effect modification.

4.9 Summary

The analysis focused on three health outcomes – evening peak flow, day cough symptoms, and bronchodilator use. The association between air quality and each of these outcomes was assessed using an Aggregate analysis, Korn-Whittemore analysis and Generalised Estimating Equations (GEEs). Each model included adjustment for climate-related covariates. The results from the three different methods were compared. The next chapter gives a brief description of the children recruited into the study and a descriptive analysis of all the health outcomes.

Chapter 5 . Results – Description of study population and health outcomes

This chapter gives a brief description of the children involved in the study (Section 5.1) and reports the results of the initial and final interview (Section 5.2). It also presents a descriptive analysis of all the health outcomes (Section 5.3).

5.1 Participation

In the cross-sectional survey (Phase I), questionnaires were given to 1284 primary school children, and 1284 (82%) were returned (Lewis *et al.* 1998). Three hundred and forty-five (345) children were eligible for enrolment in the longitudinal study (Phase II) based on their previous 12-month symptom reports from the cross-sectional survey. Over three-quarters of the children (78%) were eligible for Phase II because they had experienced a persistent cough in the last 12 months, 26% had experienced 4 or more chest colds, and 30% had experienced 4 or more episodes of wheeze (outcomes not mutually exclusive). Over-half of the children (57%) were eligible for Phase II solely because they had reported a persistent cough in the last 12 months. There was some variability between study areas in the reporting of symptoms, with a larger proportion of eligible children in the industrial study area of North Lake Macquarie (NLM) reporting wheeze compared to eligible children in the other study areas (Table 5.1).

Table 5.1. Symptoms reported amongst the 345 children who were eligible for Phase II, by study area

	Study area				
	S	**W**	**M**	**B**	**NLM**
Symptoms reported *	**N=57**	**N=76**	**N=80**	**N=70**	**N=62**
	n (%)	n (%)	n (%)	n (%)	n (%)
4 or more episodes of wheeze	15 (26%)	22 (29%)	23 (29%)	19 (27%)	26 (42%)
4 or more chest colds	15 (26%)	13 (17%)	25 (31%)	18 (26%)	17 (27%)
Night-time cough without a cold, for more than two weeks	47 (82%)	58 (76%)	63 (79%)	60 (86%)	42 (68%)

***.** Symptoms reported during the previous 12 months, as recorded in the cross-sectional study (Phase I). The categories are not mutually exclusive.

Children eligible for Phase II were more likely, relative to those not eligible for follow-up, to have the following characteristics: have been diagnosed with asthma; taken asthma medication

in the previous 12 months; report suffering from hayfever; or have a mother suffering from hayfever. They were also more likely to live in homes where a cat was kept inside (Table 5.2).

Table 5.2. Characteristics of children who were who were eligible for Phase II compared with characteristics of children who were not eligible for Phase II

Characteristics of children	Eligible N=345	Not eligible N=939	p-value *
Age in yrs as at 30/6/94, mean (sd)	10.3 (0.8)	10.2(0.7)	0.08
Males, %	53%	47%	0.09
Low or intermediate parental education†, %	35%	32%	0.55
Taking bronchodilator medication, %	64%	20%	<0.001
Taking inhaled corticosteroid medication, %	33%	8%	<0.001
Has hayfever, %	29%	14%	<0.001
Diagnosed with asthma, %	58%	22%	<0.001
Maternal hayfever, %	50%	44%	0.03
Adults smoking indoors, %	41%	37%	0.18
Indoor cats, %	24%	19%	0.04
Unflued gas heating, %	21%	22%	0.82

*****. p-values are from chi-squared tests to determine significance of associations between eligibility and child characteristics;
†. Neither parent achieved level of education higher than the school certificate

Amongst the eligible population, there was considerable variation between study areas in child and home environment characteristics (Table 5.3). Children from Stockton and Mayfield were more likely to live in a home with an unflued gas heater, and with a gas cooking appliance without an external fan, compared to children living in the other study areas. Furthermore, very few children at Beresfield and North Lake Macquarie lived in homes where there was a gas cooking appliance without an external fan.

Just over half of the eligible children lived less than 1 km from their school (54%), with only 18 children living more than 5 km from their school (Table 5.3). Most of these children were attending a private school at Mayfield, where no students lived in the immediate area. This has important implications for how representative the child's exposure to air pollution is by the pollution recorded at the nearby ambient monitor. Further results are presented in Appendix A2. Only 39% of the children at Stockton had ever been diagnosed with asthma at the time of the

Phase I questionnaire, compared to over 65% at Beresfield and North Lake Macquarie (Table 5.3).

Table 5.3. Characteristics of the 345 children whom were eligible for Phase II, by study area

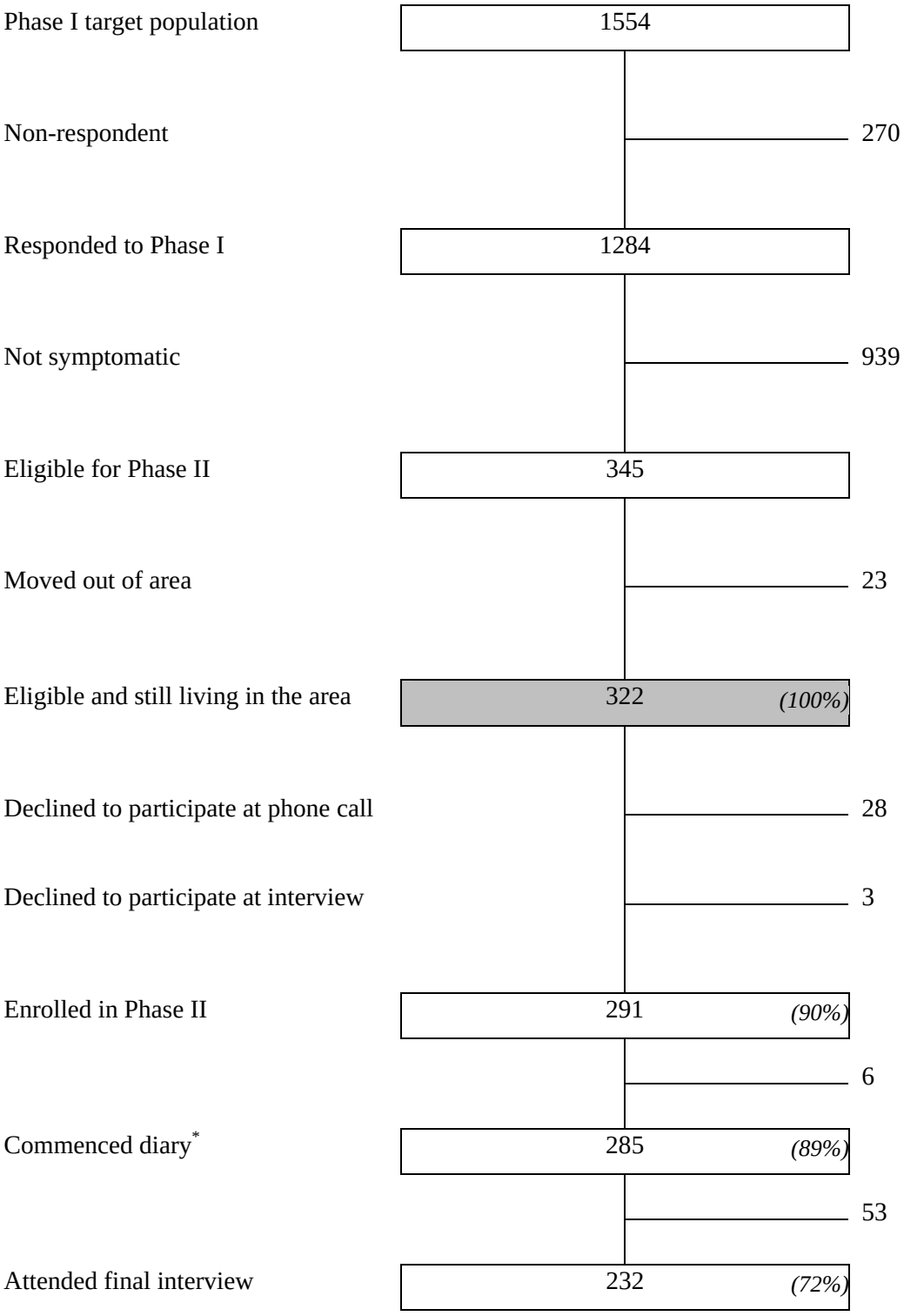
	Study area					p-value*
	S	W	M	B	NLM	
Characteristics of children	N=57	N=76	N=80	N=70	N=62	
Male	44%	58%	46%	57%	56%	0.30
Low / intermediate parental education	35%	29%	34%	42%	35%	0.59
Taking bronchodilator medication	44%	69%	61%	75%	79%	<0.001
Taking inhaled corticosteroid med'n	28%	42%	33%	52%	51%	0.03
Has hayfever	80%	67%	78%	70%	54%	0.01
Diagnosed with asthma	39%	62%	53%	70%	67%	0.003
Maternal allergy	56%	46%	56%	63%	58%	0.35
Maternal hayfever	49%	43%	50%	57%	53%	0.56
Adults smoking indoors	46%	32%	41%	44%	45%	0.40
Indoor cats	30%	24%	21%	24%	23%	0.83
Unflued gas heating	30%	17%	27%	12%	23%	0.069
Gas cooking with no external fan	35%	18%	41%	1%	10%	<0.001
Distance from home to school						0.001‡
<1km	70%	55%	35%	60%	54%	
1-5km	30%	43%	51%	33%	44%	
6-10km	-	1%	4%	3%	2%	
>10km	-	-	10%	4%	-	

Percentages reported as a proportion of all respondents; maternal allergy is defined as asthma or hayfever
*. p-values are from chi-squared tests to determine significance of associations between study area and home environment characteristics; ‡ categories 1-5 km, 6-10km, > 10km were combined to compute the chi-squared test.

Of the 345 children who were eligible to participate in Phase II, 23 had moved out of the area. Beresfield and North Lake Macquarie had a higher rate of movement out of the area, probably as a result of the study commencing six months later than at the other study areas. Of the remaining 322 children, 28 declined to participate when first telephoned and 3 declined at the initial interview. Thus 291 (90%) of eligible children from Phase I who were still living in the region, were enrolled into Phase II. Nine households had more than one child participating in the study. The first diary card, representing the first four-weeks of the study period, was

returned by 285 children. Two hundred and thirty-two (232) children attended the final interview (Figure 5.1).

Figure 5.1. Study participation flowchart



*. Five of these children completed the diary for less than two weeks

The enrolment rate was highest in Stockton (98%) and lowest in North Lake Macquarie (84%). Children enrolled tended to be more likely to have maternal hayfever than those whose parents declined to participate (Odds Ratio 2.85 95% CI: 1.3 to 6.5) but this trend was seen in North Lake Macquarie only. The age of the children enrolled ranged from 8 to 12 years at the time of the initial interview. Children at Beresfield and North Lake Macquarie tended to be older than those from the other study areas because the interview was conducted six months later. North Lake Macquarie had the highest proportion of males enrolled (Table 5.4).

Table 5.4. Response rate, age and sex profiles for all eligible children, by study area and overall

	Study area					Total
	S	**W**	**M**	**B**	**NLM**	
Eligible for Phase II, n	57	76	80	70	62	345
Eligible and still living in the area, n	55	75	75	62	55	322
Enrolled in Phase II, n	54	68	67	56	46	291
Enrolment rate, %	98%	91%	89%	90%	84%	90%
Age yrs* ,mean (sd)	10 (1.0)	9.9 (0.6)	9.9 (0.6)	10.4 (0.6)	10.8 (1.1)	10.2 (0.8)
Males, %	44%	59%	46%	53%	63%	53%

*. Age at time of Phase II initial interview

5.2 Initial and final interview

Clinical data from the initial and final interview are presented in Table 5.5. Lung function results are reported in absolute values and as a percentage of the predicted value based on each child's height and sex. Only one child had marked airflow obstruction at initial interview, as defined by an FEV_1 less than 60% of predicted or an FEV_1/FVC ratio less than 60%. Children grew an average of 3.5 cm during the study and their peak flow reading improved by 28 L/min on average from the initial to the final interview. Children in the second wave (Beresfield and North Lake Macquarie) achieved a larger percent increase in their FEV_1 compared to children in the first wave – mean 9.0% increase versus 5.6%. The peak flow technique at the initial interview was judged to be optimal for 105 children, adequate for 169 children and inadequate for 2 children. The interviewer did not record the technique for the remaining 15 children.

Table 5.5. Clinical measurements obtained at initial and final interview

	Initial interview N=291	Final interview N=232	Absolute change N=232
	Mean (sd)	Mean (sd)	Mean (sd)
Height, cm	140.7 (7.3)	144.1 (7.6)	3.5 (1.2)
Weight, kg	37.1 (8.3)	39.6 (9.2)	2.8 (1.8)
Forced Expiratory Volume in 1sec (FEV_1)			
Measurement, L	2.08 (0.37)	2.20 (0.43)	0.14 (0.18)
% predicted	94 (12)%	n.a.	n.a.
Forced Vital Capacity (FVC)			
Measurement, L	2.40 (0.43)	2.57 (0.51)	0.19 (0.20)
% predicted	98 (12)%	n.a.	n.a.
Peak Flow			
Measurement, L/min	316 (53)	340 (54)	28 (47)
% predicted	156 (29)%	n.a.	n.a.
FEV_1/FVC	0.87 (0.07)	0.86 (0.06)	-0.01(0.06)

At the final interview spirometry measures were obtained from 228 of the 232 children who attended. The absolute change is the within person change for the subjects completing both the initial and final interview.
n.a. Not available as predicted values were not calculated at the final interview, and the candidate could not locate the formulae used to calculate them at the initial interview.

At the initial interview, a total of 51 children were reported to be taking asthma medication regularly. Twenty-five children were taking short-acting bronchodilators ($beta_2$-agonists) regularly, 43 children took inhaled corticosteroids, and 10 children took cromolyns. None of the children reported taking oral corticosteroids. In addition, 9 took corticosteroids for hayfever regularly, and one child took antihistamines regularly, with no children taking antibiotics.

5.3 Diary

5.3.1 Completeness of diary data

A total of 285 children commenced the diary. They contributed a mean of 175 days of observation (range 3 days to 32 weeks, median 207 days) whereby they were requested to complete for 30 weeks. The distribution of completion was similar between the study areas (Table 5.6).

Table 5.6. Number of days diary completed by 285 children, by study area

	Study area				
	S	**W**	**M**	**B**	**NLM**
Number of days diary completed	**N=53**	**N=68**	**N=64**	**N=55**	**N=45**
Minimum	10	3	12	5	28
Maximum	222	224	224	224	222
Median	201	210	199	210	209
Interquartile range	155-209	195-219	124-215	195-211	155-212

A total of 280 children completed the diary during the 28-week diary period. Good compliance was observed with daily diaries obtained for a total of 45,641 child-days of observation from a possible 54,880 child-days (83%). The average diary completion rate was lower in the industrial study areas (Stockton 83%, Mayfield 76%, North Lake Macquarie 80%) than the control areas (Wallsend 89%, Beresfield 87%). The completion rate was over 70% for each of the diary items, with peak flow and perception of air pollution having the lowest rates (Table 5.7). The relatively low peak flow completion-rate may have been due to the measure not being recalled on subsequent days unless it was routinely recorded for an asthma plan. There were no differences in compliance between morning and evening measures.

Table 5.7. Description of completion of individual items in the diary by 280 children over 28-week diary period, by item *

Item	Completion N=54,880 child-days
	n(%)
Any item	45,641 (83%)
Day cough	42,350 (77%)
Night cough	42,569 (78%)
Day breathlessness	42,390 (77%)
Night breathlessness	42,606 (78%)
Day wheeze	42,369 (77%)
Night wheeze	42,572 (78%)
Day chest tightness	42,383 (77%)
Night chest tightness	42,594 (78%)
Runny/stuffy nose	42,373 (77%)
Sore/itchy/red eyes	42,371 (77%)
Evening peak flow	40,091 (73%)
Morning peak flow	40,425 (74%)
Bronchodilator use in inhaled form	44,853 (82%)
Bronchodilator use in nebulised form	44,984 (82%)
Inhaled corticosteroids	45,063 (82%)
Perceive pollution	40,625 (74%)
Time away from school†	25,814 (83%)
Doctor or hospital visit	45,234 (82%)
Sleep at home	44,994 (82%)

*. This represents a total of 54,880 child-days of observation
† Time away from school was limited to 31,123 child-days that fell on a weekday during school term

Of the 280 children, 240 participated for at least 3 months and all but one of these children completed the diary for at least 70% of their participation period. Hence, using the criteria outlined in chapter 4, 239 children were eligible for the non-aggregate analysis. Of these, 229 attended the final interview. This represents an overall participation rate of 74%, with participation poorer in the industrial suburbs of Mayfield and North Lake Macquarie (S 82%, W 79%, M 65%, B 79%, NLM 67%). The characteristics of the children and their home

environment was similar to those not eligible for the non-aggregate analysis except at North Lake Macquarie where participation was better for children with no exposure to passive smoking, with maternal hayfever, with more highly educated parents and living less than 1 km from their school.

5.3.2 Characteristics of children commencing the diary

The characteristics of the 280 children commencing the diary were fairly representative of those 345 eligible for enrolment with only slight variations for children from North Lake Macquarie. Here, there was some evidence that children commencing the diary were less likely to be exposed to passive smoking and more likely to have maternal hayfever, than those children eligible but not commencing the diary. A total of 138 children completed the study, meaning that they completed at least some part of the diary on each day during the 28-week study period. The completion rate was considerably worse in the industrial study areas of Stockton and Mayfield compared to the other study areas (Table 5.8).

Only 44 (16 %) children slept every night at their home. The highest number of study days that were slept away from home was 84, representing 43% of the 28-week study period, or 3 days a week on average. Forty-five children (16%) spent one or more nights away on average per week (range 6% at Wallsend to 31% at North Lake Macquarie). Children from Beresfield and North Lake Macquarie slept away from home more often, probably as a result of their study period including the Christmas holidays. The proportion of days that fell outside public-school term was much higher at Stockton, Wallsend, and Mayfield than for Beresfield and North Lake Macquarie (14-15% versus 32%).

Table 5.8. Characteristics of 280 children commencing the diary

	Study area				
	S	**W**	**M**	**B**	**NLM**
	N=52	**N=66**	**N=63**	**N=54**	**N=45**
Male	23 (44%)	39 (59%)	28 (44%)	30 (56%)	28 (62%)
Low/intermediate parental educn	17 (33%)	19 (29%)	19 (30%)	23 (43%)	14 (31%)
Diagnosed with asthma	19 (37%)	42 (64%)	31 (50%)	38 (70%)	33 (73%)
Maternal allergy	31 (60%)	33 (50%)	36 (57%)	34 (63%)	29 (64%)
Maternal hayfever	27 (52%)	31 (47%)	32 (51%)	30 (56%)	28 (62%)
Adults smoking indoors	24 (46%)	20 (30%)	22 (35%)	25 (46%)	17 (38%)
Indoor cats	17 (33%)	15 (23%)	13 (21%)	13 (24%)	10 (22%)
Unflued gas heating	15 (29%)	11 (17%)	18 (29%)	6 (12%)	7 (16%)
Gas cooking with no external fan	19 (37%)	13 (20%)	25 (40%)	1 (2%)	3 (7%)
Live less than 1km from school	38 (73%)	37 (56%)	22 (35%)	33 (61%)	26 (59%)
Slept away infrequently	29 (56%)	46 (70%)	37 (59%)	12 (22%)	14 (31%)
Completed study	18 (35%)	40 (61%)	22 (35%)	35 (65%)	23 (51%)

Maternal allergy was defined as asthma or hayfever; Slept away infrequently was defined as sleeping away from home for less than 5% of nights in the study period; Completing the study was defined as completing at least some part of the diary on each day during the 28-week study period.

At the initial interview, a total of 51 children were reported to be taking asthma medication regularly. Based on the diary information, 153 (55%) children took some form of asthma medication during the study. During the 28-week study period, 146 children (52%) reported taking a short-acting bronchodilator (beta$_2$-agonist) at least once. Of these, 99 reported using a puffer only, 5 reported using a nebuliser only, and 42 reported using a combination of puffers and nebulised therapy. Eighty-six (86) children took inhaled corticosteroids at least once during the study period, 26 children took cromolyns, and six children took the oral corticosteroid Prednisone.

So of the cohort consisting of 280 children, 127 (45%) required no medication, 53 (19%) required bronchodilators only, and 100 (36%) required a combination of bronchodilators and anti-inflammatory agents. Most children who were diagnosed with asthma were taking medication (77%). Unexpectedly, 22% of children without a diagnosis of asthma took asthma medication during the study period. This could be explained by the asthma diagnosis being recorded during Phase I, up to 11 months prior to the commencement of Phase II. There was considerable variation across study areas in asthma medication use (44%-64%) (Table 5.9).

Table 5.9. Asthma medication taken by 280 children during the 28-week diary period, by study area

	Study area				
	S	**W**	**M**	**B**	**NLM**
Medication	**N=52**	**N=66**	**N=63**	**N=54**	**N=45**
	n (%)	n (%)	n (%)	n (%)	n (%)
Any asthma medication	23 (44%)	35 (53%)	35 (56%)	31 (57%)	29 (64%)
Bronchodilator (inhaled form)	20 (38%)	33 (50%)	33 (52%)	30 (56%)	25 (56%)
Bronchodilator (nebuliser form)	9 (17%)	10 (15%)	12 (19%)	5 (9%)	11 (24%)
Inhaled corticosteroids	11 (21%)	19 (29%)	17 (27%)	20 (37%)	19 (42%)
Cromolyns *	4 (8%)	7 (11%)	9 (14%)	3 (6%)	3 (7%)
Oral corticosteroids	1 (2%)	1 (2%)	1 (2%)	1 (2%)	2 (4%)

* Sodium Cromoglycate

The types of medications reported at the initial interview and during the study are shown in Table 5.10. The most frequently used bronchodilator medication was salbutamol. Most children took only one (88%) or two (10%) varieties of bronchodilators. Of the children using a puffer, 67 (48%) used it less than once a week, 42 (30%) used it 1-3 times a week and 32 (23%) used it more than four times a week on average, with 12 children requiring it every day. Of the children using a nebuliser, 37 used it less than once a week, 8 used it 1-3 times a week and 2 used it more than 4 times a week on average. The number of times a child used a nebuliser on a single day ranged from 1 to 16 (median 2). The number of puffs of bronchodilator medication taken by a child on a single day ranged from 1 to 39 (median 4).

Eighty-six children (31%) took inhaled corticosteroids at least once during the study period, with 83 taking the same generic drug for the whole time. Only 19 children consistently took inhaled corticosteroids each month during the 7-month study period, with 16 taking it daily. The remaining children were on short courses of this medication. The frequency of use of corticosteroids on a given day ranged from 1 to 12 puffs (median 2). A total of 26 children (9%) took cromolyns at least once during the study period, with 20 children using it during at least 3 months. Six children (2%) required the oral corticosteroid Prednisone during the study period. Five of these children took it for one month only, with one child requiring it for four months.

Table 5.10. Asthma medications recorded in the initial interview (as being regularly taken), and in the diary card (as being taken at least once during the 28-week study period)

Drug class / Generic drug name	Initial interview N=291	Diary N=280
	n (%)	n (%)
Bronchodilators	***25 (9%)***	***146 (52%)***
Salbutamol	16 (5%)	103 (37%)
Terbutaline Sulfate	9 (3%)	50 (18%)
Fenoterol Hydronomide	Nil	2 (1%)
Orciprenaline Sulfate	Nil	1 (0%)
Inhaled Corticosteroids	***43 (15%)***	***87 (31%)***
Beclomethasone Dipropionate	16 (5%)	43 (15%)
Budesonide	29 (10%)	52 (19%)
Cromolyns		
Sodium Cromoglycate	10 (3%)	26 (9%)
Oral Corticosteroids		
Prednisone	Nil	6 (2%)

Eighty-four children (30%) took antihistamines and /or decongestants during the study period. Only 24 children required them during three or more months. Twenty-four children took nasal preparations for hayfever. The respective number of children taking the medication during at least three months was 12 (Table 5.11).

Table 5.11. Non asthma medications recorded in the initial interview (as being regularly taken), and in the diary card (as being taken at least once during the study period)

Medication	Initial interview N=291	Diary N=280
	n (%)	n (%)
Preparations for upper respiratory tract symptoms		
Antihistamines and/or Decongestants	1 (0%)	84 (30%)
Nasal preparations for hayfever	***9 (3%)***	***24(9%)***
Beclomethasone Dipropionate	4 (1%)	15 (5%)
Budesonide	4 (1%)	8 (3%)
Sodium Cromoglycate	1 (0%)	3 (1%)

Eight-nine children (32%) took antibiotics for respiratory tract infections during the study period. Eight of these children required antibiotics at some stage during at least three separate months, indicating repeated infections.

A total of 265 (96%) of children perceived a high level of pollution on at least one day during the study period. The percentage of children reporting high pollution at least 4 times a week on average, ranged from 20% in the control study area Beresfield to 71% in the industrial study area Mayfield (S 67% W 50% M 71% B 20% NLM 48%).

5.3.3 Health outcomes

One hundred and twenty-eight children (46%) had time away from school due to lung symptoms or hayfever, totalling 424 days during the study period. Seventy-three of these children (57%) were absent for only one or two days. During Phase II, 106 children (38%) visited a doctor or hospital for lung symptoms or hayfever. The total number of hospital visits was 6, whilst 192 visits to the doctor were reported.

On 29,030 child-days (69%) cough was reported to be absent. There was slight variation across the study areas in the reporting (S 65%, W 78%, M 54%, B 77%, NLM 64%). A score of one (hardly any discomfort), was reported on 16% of child-days, score 2 on 8%, score 3 on 4%, score 4 on 2%, score 5 or 6 (most severe discomfort ever) on 1% (Figure 5.2). The distributions were similar for night cough. For the remainder of the analysis symptoms were analysed on a binary scale of presence/ absence.

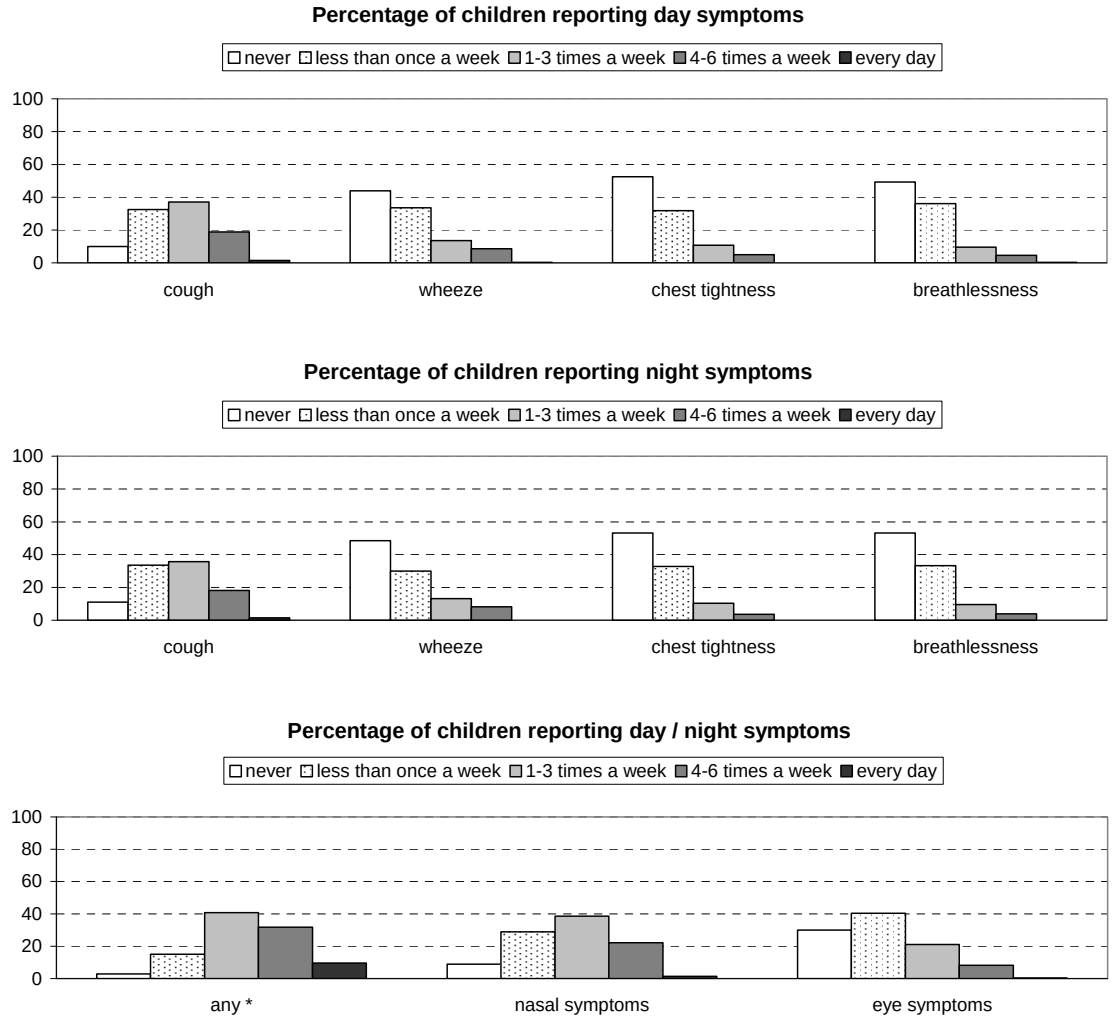
Figure 5.2. Distribution of day cough symptoms amongst 280 children during the 28-week diary period, all study areas combined. N=54,880 child days *

*. The "day cough" item in the diary was completed on 42,350 child-days.

The children reported a day cough on 13,320 child-days. On 8,245 of these child-days (62%) the child also reported nasal symptoms including a runny or stuffy nose.

Only four children reported no symptoms during the 28-week study period. Day and night cough, and runny/stuffy nose were the most frequently reported symptoms. Fifty-seven children (20%) reported day cough symptoms four or more times a week on average (range 9% at W to 35% at M). In general, children were slightly more likely to report a day rather than night symptom (Figure 5.3).

Figure 5.3. Percentage of children reporting each symptom during 28-week study period: never, less than once a week, 1-3 times a week on average, 4-6 times a week on average, every day. Total of 280 children.



*. Cough, breathlessness, chest tightness, wheeze during the day or night (excludes nasal symptoms and eye irritation)

Of the 285 children participating in Phase II, 264 reported experiencing cough symptoms on at least one day. The symptoms lasted for a median 2 days (range 1 to 114 days).

The evening PEF recorded during the study period across the 54,880 child-days ranged from 70 to 700 Litres/min (mean 310 L/min, sd: 56.2 L/min). The mean PEF for individual children ranged from 162 to 541 L/min (mean: 321 L/min; sd: 51 L/min). Children in the industrial areas of Stockton and North Lake Macquarie had higher peak flows on average than the other areas. North Lake Macquarie had the largest between-subject variation in mean evening peak flow. The within-subject variation in evening peak flow (as determined by the coefficient of variation) was on average 8.0%, with Wallsend children having slightly less variation at 7.5%. The morning peak flow tended to be slightly lower than the evening peak flow, and it had slightly greater within-subject variation with an average of 9.0%. The average of each child's mean diurnal peak flow (absolute difference between same day morning and evening peak flow measurements) was 19 L/min. The average of each child's evening peak flow change (absolute difference between evening peak flow measurements on successive dates) was 18 L/min (Table 5.12).

Table 5.12. Characteristics of the 280 children during the 28-week diary period, by study area

	Study area				
	S	**W**	**M**	**B**	**NLM**
Child characteristic	**N=52**	**N=66**	**N=63**	**N=54**	**N=45**
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Mean morning PEF, L/min	330(48)	316(49)	310(46)	308(46)	328(62)
Mean evening PEF, L/min	335(48)	318(48)	315(47)	309(46)	332(64)
Evening PEF variability, %	8.5 (4.6)	7.5 (4.1)	8.7 (4.0)	8.3 (3.8)	8.3 (3.9)
Morning PEF variability, %	8.6 (4.6)	7.9 (4.6)	9.1 (3.9)	9.0 (4.0)	8.8 (4.3)
Mean diurnal PEF variability, L/min	21 (16)	18 (13)	22 (11)	19 (11)	20 (14)
Mean day-to-day evening PEF variability, L/min	19 (11)	17 (12)	21 (12)	17 (10)	19 (10)

PEF. Peak Expiratory Flow

5.3.4 Aggregate analysis

Univariate results from the aggregate analysis for the main outcomes will now be described. In these analyses the unit of observation is area-day. There were 274 children contributing data to

the aggregate analysis. The daily proportion of children (n=280 children) completing at least one item of the diary during the aggregate analysis period ranged from 62% to 98%, with average 83% (Table 5.13).

Table 5.13. Percentage of children completing the diary during the study period. Total of 280 children; Mean (sd) of daily percentage reported

	Study area				
	S	**W**	**M**	**B**	**NLM**
Aggregate outcome	**175 days**	**175 days**	**175 days**	**182 days**	**189 days**
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Completion, %	85(8)	89(5)	76(7)	87(4)	80(6)

Evening peak flow

The mean deviation in evening PEF ranged from –20 L/min to 18 L/min (mean: 0.1 L/min; sd: 5.4 L/min) across the study period (Table 5.14). It was normally distributed across time. The distribution of mean standardised evening PEF deviation was very similar with range –19 L/min to 17 L/min (mean: 0.1 L/min; sd: 5.1).

Table 5.14. Daily peak flow measures during the study period. Total of 280 children; Mean (sd) of daily measure reported

	Study area				
	S	**W**	**M**	**B**	**NLM**
Aggregate outcome	**175 days**	**175 days**	**175 days**	**182 days**	**189 days**
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Evening PEF, L/min	334 (6)	316 (5)	309 (6)	312 (7)	326 (8)
Morning PEF, L/min	329 (6)	313 (5)	304 (7)	310 (7)	323 (8)
Mean standardised evening PEF deviation, L/min	-0.08(4.60)	+0.03(4.14)	-0.14 (4.58)	+0.18(5.51)	+0.40(6.41)
Mean standardised morning PEF deviation, L/min	-0.06 (5.04)	+0.04 (4.43)	-0.06 (5.15)	+0.20 (6.06)	+0.33 (6.44)

PEF. Peak Expiratory Flow

A timeplot showing mean evening peak flow deviation across time for each of the study areas is shown in Figure 5.4. In the first wave, Stockton and Mayfield showed no trend over time, and

Wallsend had a slight upward trend. In the second wave, both areas exhibited a strong upward trend over time. This is quite common in these types of studies and is a reflection of the growth of children over time. Seasonal differences in measurement may explain why the trend was seen amongst children in the second wave and not the first. The correlation between the mean evening PEF on the current day, with the mean evening PEF on the previous day, was higher in the second wave (Beresfield 0.75, North Lake Macquarie 0.72) than the first wave (Stockton 0.50, Wallsend 0.60, Mayfield 0.33).

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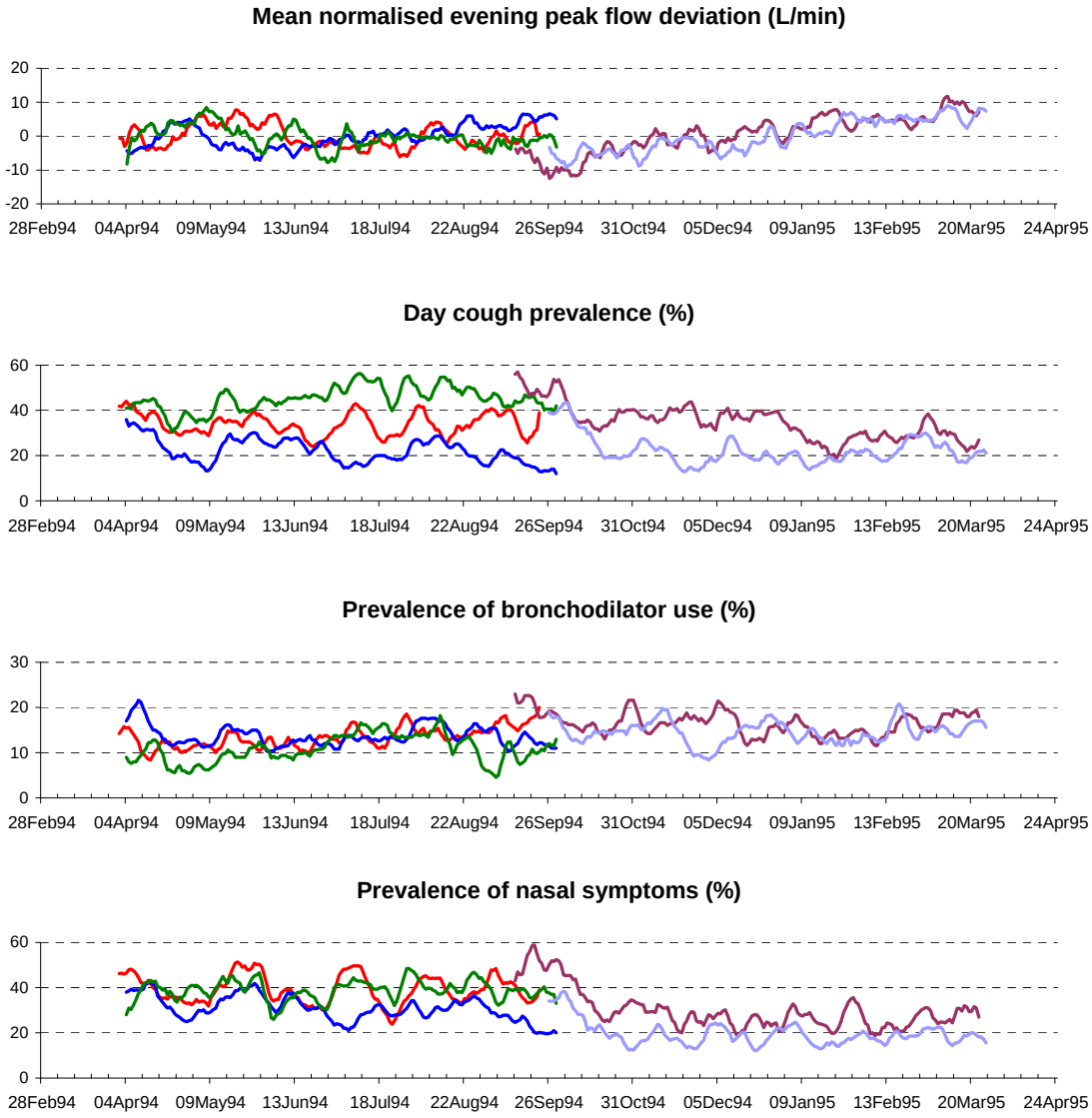
Figure 5.4. Timeplot of health outcomes, by study area



5-day moving average of daily health outcomes for children in Wave 1: Stockton; Wallsend; Mayfield
for children in Wave 2: Beresfield; North Lake Macquarie

The study period for the second wave began at the end of winter. At both Beresfield and North Lake Macquarie there was a flu epidemic during September and October of that year and children's' peak flow readings were lower than usual during this period of sickness. Other studies have stressed the importance of recording the presence of cough or cold symptoms for this reason (Neukirch *et al.* 1985). Further evidence of the effect of flu-like symptoms on lung function tests is provided with the FEV_1 data obtained in interviews at the start and end of the study period. FEV_1 increased more for children enrolled in the second wave as discussed earlier

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in Section 5.2. It is unlikely to have resulted from differences in lung growth, as the changes in weight and height were similar between the first and second wave (Table 5.5).

The results for Stockton, Wallsend, Mayfield, Beresfield, and North Lake Macquarie are presented in Figures 5.5, 5.6, 5.7, 5.8, and 5.9 respectively. The timeplots shown are for completion, day cough prevalence, day cough incidence, mean standardised evening peak flow deviation, bronchodilator use, and nasal symptoms prevalence.

Day cough

The proportion of children with reported cough symptoms on a given day ranged from 11% to 60% over the study period with mean 32% (sd 11%). The prevalence of breathlessness, chest tightness, and wheeze were considerably lower (Table 5.15). Daily cough prevalence over time was normally distributed and so the mean and standard deviation are reported. The average daily prevalence of eye symptoms (including sore, itchy or red eyes) observed in the industrial areas Mayfield and North Lake Macquarie, was approximately double that observed in the other study areas.

Table 5.15. Daily prevalence of symptoms during the study period; Mean (sd) reported

	Study area				
	S	**W**	**M**	**B**	**NLM**
Aggregate outcome	**175 days**	**175 days**	**175 days**	**182 days**	**189 days**
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Day cough, %	34 (6)	22 (6)	46 (7)	23 (7)	35 (9)
Night cough, %	32 (7)	21 (6)	42 (7)	22 (6)	33 (8)
Day breathlessness, %	9 (3)	4 (3)	12 (4)	3 (2)	15 (5)
Night breathlessness, %	8 (3)	4 (2)	10 (4)	3 (2)	12 (5)
Day chest tightness, %	8 (3)	5 (3)	13 (4)	3 (2)	14 (5)
Night chest tightness, %	8 (3)	4 (3)	12 (4)	3 (2)	12 (4)
Day wheeze, %	14 (4)	9 (3)	20 (6)	6 (3)	17 (5)
Night wheeze, %	12 (3)	9 (3)	18 (6)	6 (3)	16 (5)
Any symptom*, %	46 (6)	32 (6)	55 (6)	30 (7)	47 (9)
Nasal symptoms, %	40 (7)	31 (6)	39 (6)	20 (6)	30 (10)
Eye symptoms, %	12 (4)	8 (4)	22 (5)	9 (4)	20 (6)

*. Cough, breathlessness, chest tightness, wheeze, nasal symptoms, or eye irritation during the day or night

The incidence of day cough on a given day, i.e. proportion of children having cough symptoms amongst those symptom free the previous day, ranged from 0% to 48% with mean 9% (sd 7%). The distribution of incidence of all symptoms was right skewed, with the natural logarithm transformation making them normally distributed. The log-transformed values were used in the statistical modelling analysis, but not reported in Table 5.16.

Table 5.16. Daily incidence of symptoms during the study period; Mean (sd) reported

	Study area				
	S	**W**	**M**	**B**	**NLM**
Aggregate outcome	**175 days**	**175 days**	**175 days**	**182 days**	**189 days**
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Day cough incidence, %	8(5)	6(4)	9(6)	6(4)	9(7)

Timeplots showing cough prevalence and day cough incidence are also included in Figures 5.5-5.9. Day cough prevalence was higher in the industrial study areas of Stockton, Mayfield, and North Lake Macquarie, than the two control areas. The prevalence peaked in the second group in September and October 1995, and this corresponds to when evening peak flow levels were lower than average. Day cough incidence was also highest in the industrial areas, with North Lake Macquarie showing much greater variation.

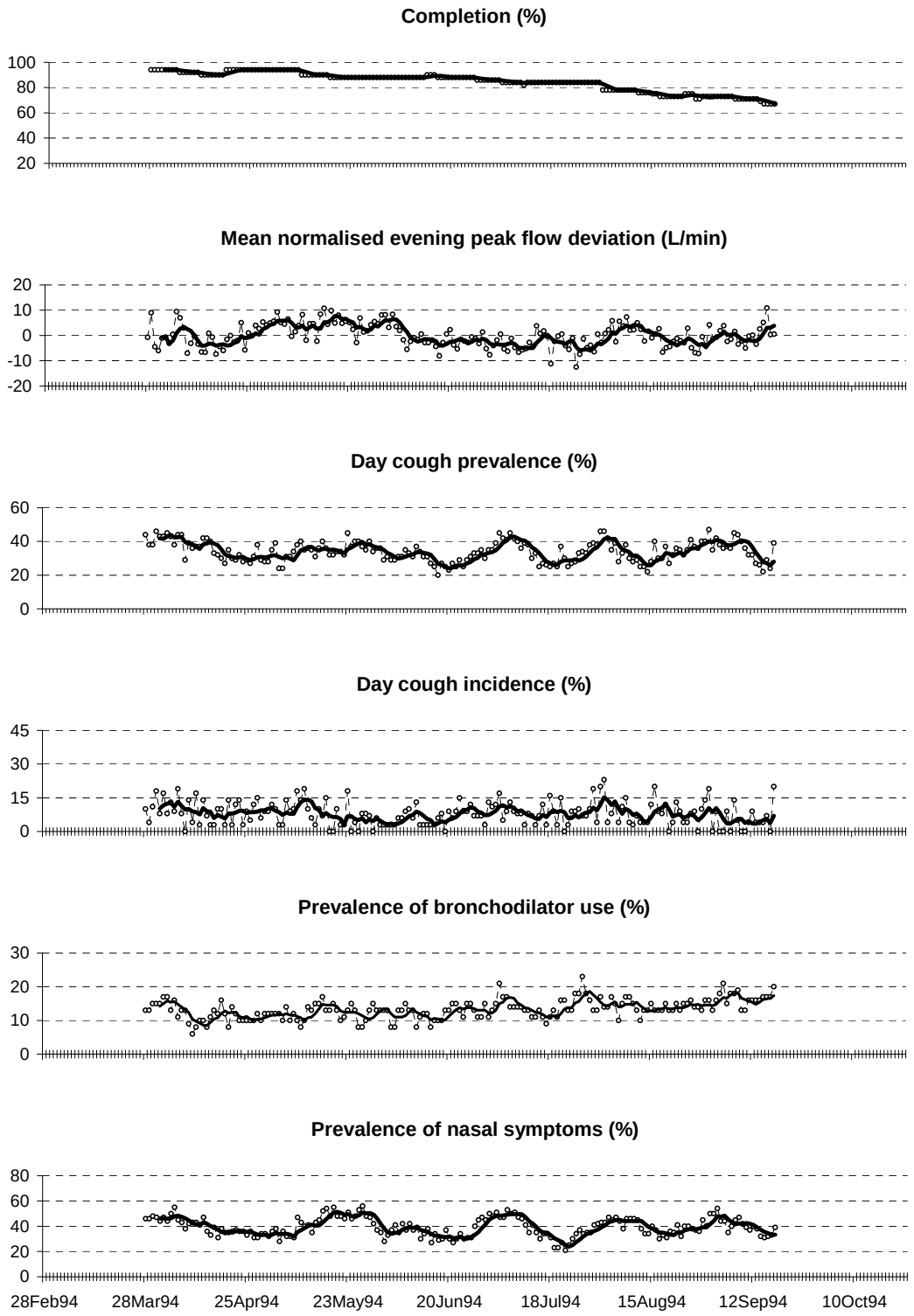
Bronchodilator usage

Use of a bronchodilator (puffer) on a given day ranged from 2% of children to 28% with mean 14% (sd 4%), and was normally distributed across time. A timeplot showing the prevalence of bronchodilator use among study subjects is included in Figures 5.5-5.9. There was a high use of medications at the start of the study at North Lake Macquarie, again following the same type of pattern observed for evening peak flow and day cough.

Table 5.17. Daily prevalence of bronchodilator use during the study period; Mean (sd) reported

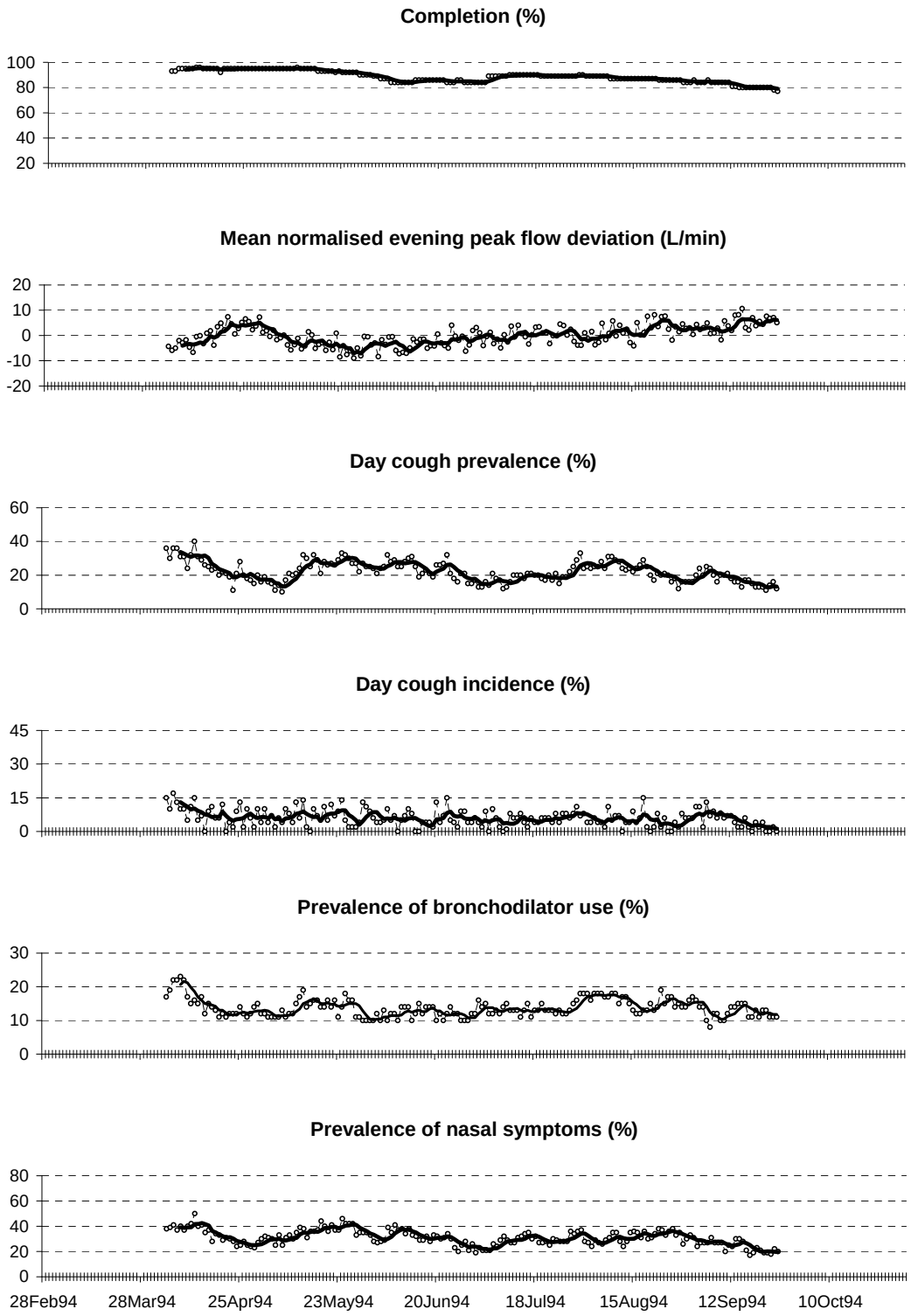
	Study area				
	S	**W**	**M**	**B**	**NLM**
Aggregate outcome	**175 days**	**175 days**	**175 days**	**182 days**	**189 days**
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Prevalence of bronchodilator use, %	14 (3)	14(3)	11(4)	15(3)	17(3)

Figure 5.5. Percentage of subjects completing some of the diary, and prevalence of key health outcomes, for each day in the study period: Stockton *



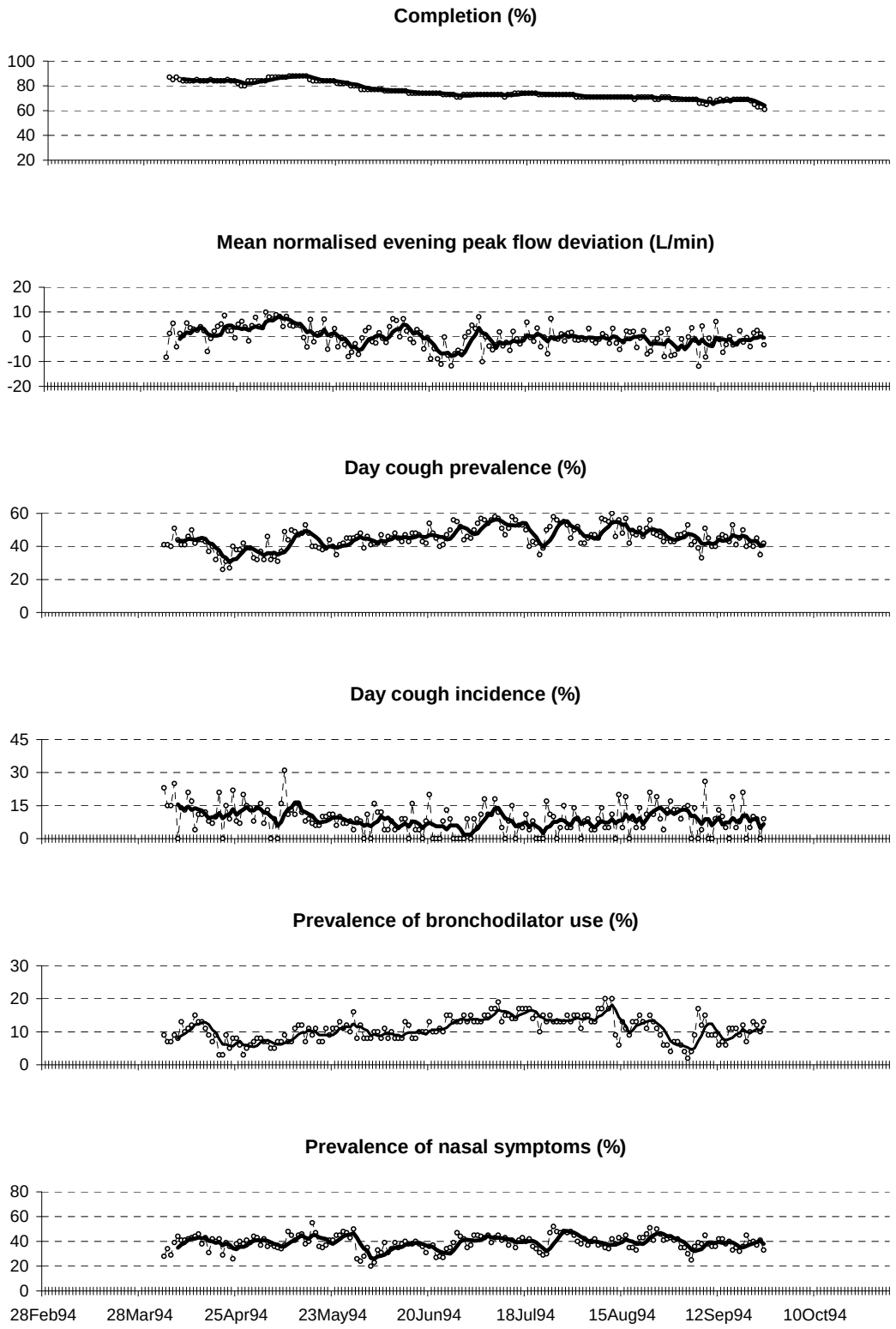
*. Time scale restricted to the 25-week aggregate analysis period. Completion refers to the proportion of subjects completing at least one item of the diary, where the denominator is the total number of subjects commencing the diary, 52. All other percentages are based on the proportion of respondents: ····o··· Observed value ——— Smoothed function (5-day moving average)

Figure 5.6. Percentage of subjects completing some of the diary, and prevalence of key health outcomes, for each day in the study period: Wallsend *



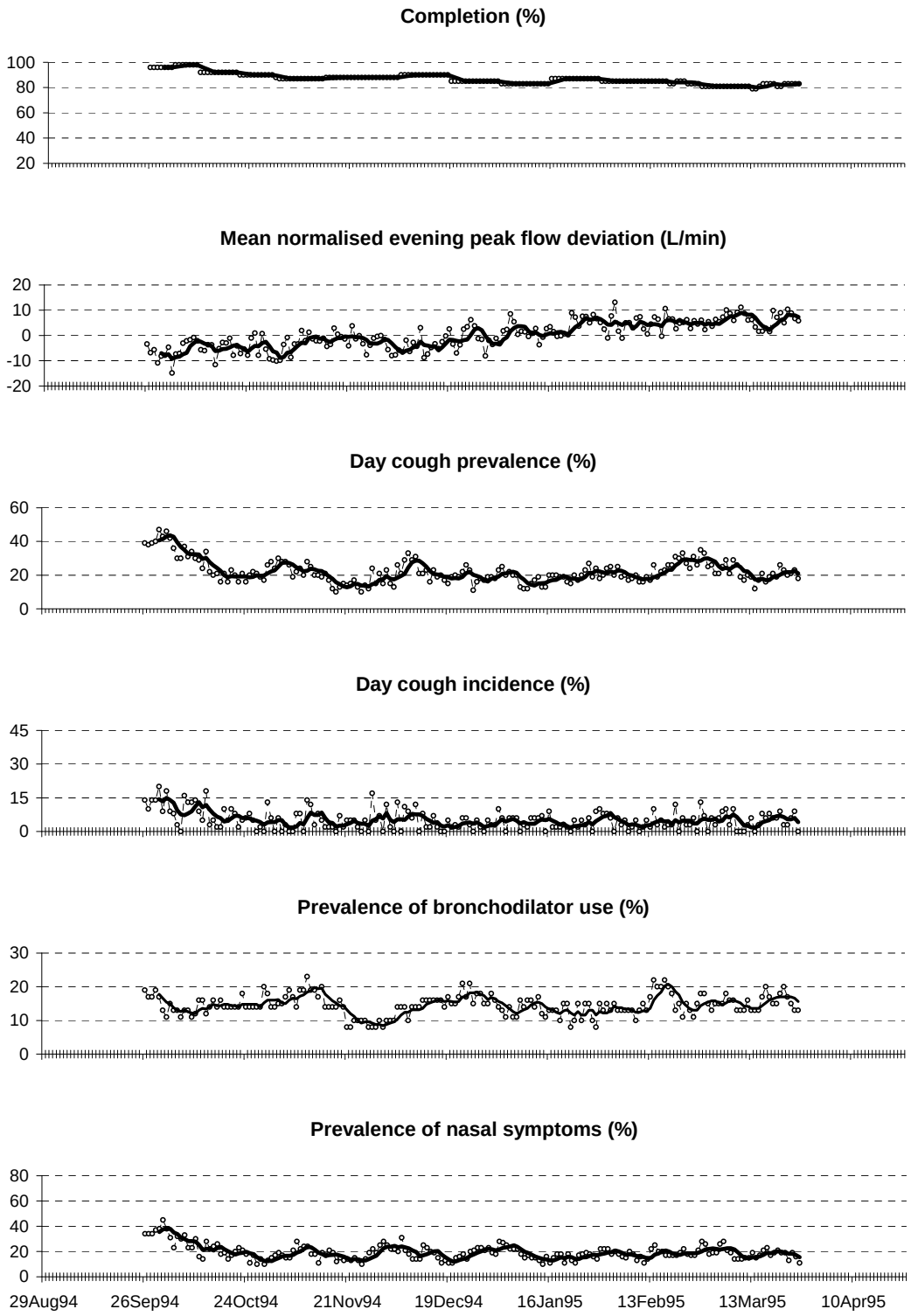
*. Time scale restricted to the 25-week aggregate analysis period. Completion refers to the proportion of subjects completing at least one item of the diary, where the denominator is the total number of subjects commencing the diary, 66. All other percentages are based on the proportion of respondents: ····o··· Observed value ——— Smoothed function (5-day moving average)

Figure 5.7. Percentage of subjects completing some of the diary, and prevalence of key health outcomes, for each day in the study period: Mayfield *



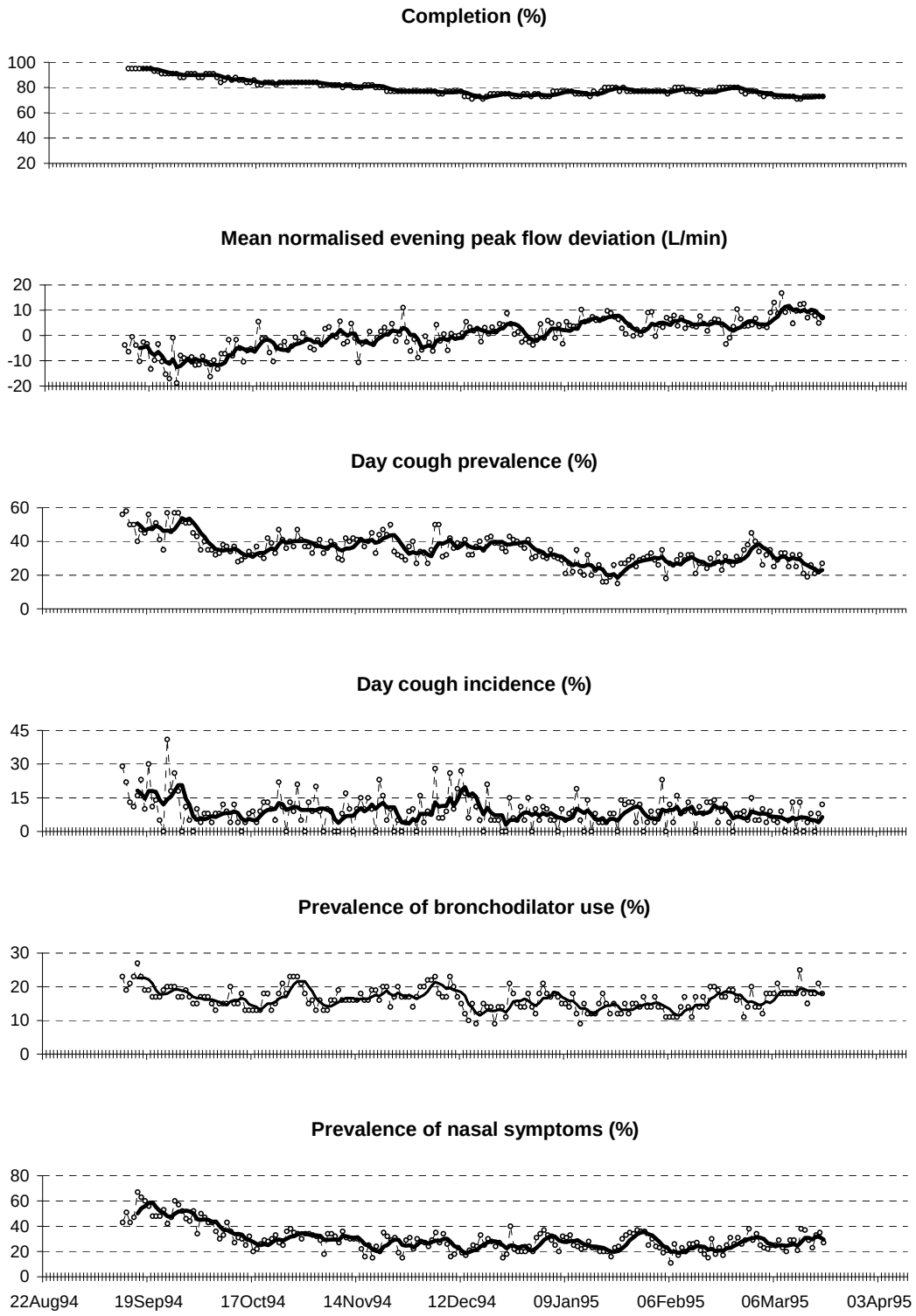
*. Time scale restricted to the 25-week aggregate analysis period. Completion refers to the proportion of subjects completing at least one item of the diary, where the denominator is the total number of subjects commencing the diary, 63. All other percentages are based on the proportion of respondents: ····o·· Observed value ——— Smoothed function (5-day moving average)

Figure 5.8. Percentage of subjects completing some of the diary, and prevalence of key health outcomes, for each day in the study period: Beresfield *



*. Time scale restricted to the 26-week aggregate analysis period. Completion refers to the proportion of subjects completing at least one item of the diary, where the denominator is the total number of subjects commencing the diary, 54. All other percentages are based on the proportion of respondents: ····o··· Observed value ——— Smoothed function (5-day moving average)

Figure 5.9. Percentage of subjects completing some of the diary, and prevalence of key health outcomes, for each day in the study period: North Lake Macquarie *



*. Time scale restricted to the 27-week aggregate analysis period. Completion refers to the proportion of subjects completing at least one item of the diary, where the denominator is the total number of subjects commencing the diary, 45. All other percentages are based on the proportion of respondents: ····o·· Observed value ——— Smoothed function (5-day moving average)

5.4 Summary

Three hundred and forty-five (345) children were eligible for the study based on their previous 12 months symptom data from the cross-sectional study. Of the 322 children still living in the area at the time of Phase II recruitment, 285 (89%) children commenced the diary. They contributed a mean 175 days of observation out of a possible 196 days. The completion rate was considerably worse in the industrial study areas Stockton and Mayfield. The children in the second wave reported spending more time away from home compared to children in the first wave, probably as a direct result of this wave including the Christmas holidays.

Health effects of pollution are primarily observed in the most susceptible populations. The children in this study were selected because of their past history of respiratory problems. Of the 280 children in this study, 58% were diagnosed with asthma, and 54% used asthma medication. During the 28-week diary period, 258 children (92%) experienced cough symptoms during the day or night, 168 (60%) experienced wheeze, 160 (57%) experienced breathlessness, and 146 (52%) experienced chest-tightness. In summary, at least half of the cohort experienced symptoms that were not cough-related, with only three children reporting no daytime symptoms during the diary period. However, at the initial and final interview during spirometry assessment, only one child had marked air flow obstruction as defined by an FEV_1<60% of predicted or an FEV_1/FVC ratio less than 60%. Only 6 children were admitted to hospital for lung symptoms during the study period. Overall the subjects were symptomatic although they did not have objective evidence of severe respiratory disease.

One hundred and twenty seven (127) or 45% used no asthma medication during the study period, 53 (19%) used bronchodilators only, and 105 (38%) used a combination of bronchodilators and preventer medication.

There were 239 children whom provided sufficient data for the non-aggregate analysis including the Korn-Whittemore and GEE methods. These children had similar characteristics to the symptomatic group as a whole (n=345) except for those children from North Lake Macquarie. It was found that in this study area, the analysis group comprised a disproportionately higher percentage of children without exposure to passive smoking, with maternal hayfever, and higher educated parents.

A coefficient of variation (CV) was calculated so that the daily variation in peak flow measurements for each child could be characterised. The average CV was 8%. This was quite low compared to another study of mild asthmatic children in Mexico city which reported an average CV of 13% (Romieu *et al.* 1997) but similar to a study in western Sydney (Jalaludin *et al.* 2000).

The next chapter gives a descriptive analysis of the air pollution, aeroallergen and meteorological data.

Chapter 6 . Results – Description of air pollution, aeroallergen and meteorological data

This chapter provides an overview of the completeness of the daily air quality and meterological data collected (Section 6.1). In Section 6.2 a univariate analysis of the daily air pollutant data in each of the study areas is provided. This is followed by a univariate analysis of the daily pollen and fungi data in Section 6.3. A summary of the meteorological data across all study areas is given in Section 6.4. The correlations between the various air quality measures are provided in Section 6.5. Further details of the analyses are provided in Appendix D.

6.1 Completeness of air quality and meteorological data

There was incomplete air quality and/or meteorological data on about 13% of the days in each study area. The data were missing because of technical difficulties or due to public holidays. No sulphur dioxide measurements were recorded at Beresfield until midway through the study period (5 January 1995), as the EPA station did not commence monitoring this pollutant until this time. Nitrogen dioxide was recorded at four of the five areas. Ozone was only recorded at Wallsend and Beresfield. Meteorological data were available on over 90% of the days in the study period.

Data from the continuously measured pollutants were flagged for deletion if there was not at least 80% of the hourly data available as this is standard practice in Australian studies (Jalaludin *et al.* 2000). Table 6.1 shows the proportion of days that measurements were recorded for each of the pollutants, and the proportion of days the data met the eligibility criteria. The study areas at which the EPA was responsible for collecting data (Wallsend, Beresfield) had poorer capture rates than study areas for which industry was responsible (Stockton, Mayfield, and North Lake Macquarie).

Table 6.1. Completeness of air quality and meteorological data, by study area

	Study area				
	S	**W**	**M**	**B**	**NLM**
Period of diary study	**Feb-Oct**	**Feb-Oct**	**Feb-Oct**	**Aug-Apr**	**Aug-Apr**
Days in study period †	238	245	245	238	231
PM10					
Data available	224 (94%)	238 (97%)*	242 (99%)	216 (91%)	206 (89%)
Capture rate >=80%	n.a.	219 (89%)	n.a.	179 (75%)	n.a.
Sulphur dioxide					
Data available	238 (100%)	227 (93%)	235 (96%)	90 (38%)	231 (100%)
Capture rate >=80%	238 (100%)	217 (89%)	224 (91%)	63 (26%)	231 (100%)
Nitrogen dioxide					
Data available	238 (100%)	232 (95%)	240 (98%)	183 (77%)	0
Capture rate >=80%	229 (96%)	219 (89%)	236 (96%)	168 (71%)	0
Ozone					
Data available	0	245 (100%)	0	217 (91%)	0
Capture rate >=80%	0	239 (98%)	0	209 (88%)	0
Pollen and fungi					
Data available	234 (98%)	207 (84%)	229 (93%)	187 (79%)	183 (79%)
Temperature					
Mean, Max					
Data available	238 (100%)	245 (100%)	245 (100%)	237 (99%)	230 (99%)
Capture rate >=80%	235 (99%)	242 (99%)	242 (99%)	236 (99%)	228 (99%)
Minimum					
Data available	238 (100%)	245 (100%)	245 (100%)	214 (90%)	222 (96%)
Humidity					
Data available	238 (100%)	245 (100%)	245 (100%)	237 (99%)	231 (100%)
Capture rate >=80%	234 (98%)	241 (98%)	241 (98%)	235 (99%)	228 (99%)
Rainfall					
Data available	237 (99%)	244 (99%)	244 (99%)	211 (89%)	219 (95%)

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.
n.a. Not applicable as PM10 was estimated from TSP in this study area which only records daily averages
PM10. particulate mass concentration < 10μm.
*. After two outliers removed, 236 observations
†. Stockton's study period was 28/2/1994 to 23/10/1994 a total of 238 days or 34 weeks. Refer to Chapter 4 Figure 1a for the study periods corresponding to the other areas.

The pollen and fungi measurement record at Stockton, Wallsend and Mayfield began on 2 March 1994 and ceased on 24 October 1994, thereby covering the whole of the study period. At Stockton there were no breaks in the measurements. At Wallsend the machine was broken and no measurements made during the four-week period 13 September 1994 to 10 October 1994. This coincided with the spring pollen season. At Mayfield the machine was removed one week early (no measurements for the period 18 October 1994 to 24 October 1994) due to renovations at the club where the spore trap was located.

The pollen and fungi measurement record at Beresfield began on 13 September 1994 and ceased on 30 March 1995. The measurement record at North Lake Macquarie began on 26 August 1994 and ceased on 23 March 1995. No measurements were made during the Christmas period (27 December 1994 to 2 January 1995) at both Beresfield and North Lake Macquarie. At North Lake Macquarie the machine was broken and no measurements were made during the two-week period 20 September 1994 to 3 October 1994. This also coincided with the spring pollen season.

The pollen tapes were changed every 7 days between 11am and 5pm. The tape was over-run at Stockton on 2 days (31/5/94, 7/6/94) and at Wallsend on 2 days (31/5/94, 7/6/94) but the tape was not over-run at any time at Mayfield. The tape was over-run or no trace was recorded on 5 days at Beresfield and 5 days at North Lake Macquarie resulting in no measurements. At Mayfield identification and counting was sometimes very difficult due to the heavy deposition of particulate material.

6.2 Descriptive analysis of air pollutants

Levels of PM10 and sulphur dioxide differed in the five study areas. The highest PM10 concentrations were in Mayfield as expected. The air quality data of the pollutants PM10, sulphur dioxide, nitrogen dioxide, and ozone are summarised in Table 6.2. The distribution of PM10 was symmetric whereas the distribution of other air quality data was rather skewed and so medians and interquartile ranges are reported. The statistical measures of skewness for mean sulphur dioxide ranged between one and two, and maximum sulphur dioxide ranged between one and three. Had the skewness been larger, the results of the regression analysis (outlined in Chapters 7,8 and 9) might have been dominated by a few outliers and would thus have been unstable. In such situations, it is necessary to transform the skewed variable to get more stable results. Given the moderate amount of skewness, transformations were not applied.

Table 6.2. Ambient air quality measures during study period, by study area

	Study area				
	S	**W**	**M**	**B**	**NLM**
Period of diary study	**Feb-Oct**	**Feb-Oct**	**Feb-Oct**	**Aug-Apr**	**Aug-Apr**
Daily mean PM10 (μg/m³)*					
Mean (sd)	31.0 (16.1)	19.7 (9.6)	37.6 (25.5)	25.1 (13.9)	25.5 (11.7)
Minimum, Maximum	1.9, 91.9	3.4, 74.3	5.9, 143.6	1.9, 82.2	1.2, 73.8
Median (IQR)	29 (19-41)	19 (13-24)	30 (18-49)	22 (15-32)	23 (17-32)
No. of exceedences > 150 (50)	Nil (28)	Nil (4)	Nil (57)	Nil (11)	Nil (6)
Daily max SO_2 (pphm)					
Prop'n of days zero level	1%	1%	1%	1%	29%
Mean (sd)	1.85 (1.06)	1.48 (1.36)	1.18 (0.99)	0.43 (0.35)	1.89 (2.74)
Minimum, Maximum	0.0, 5.8	0.0, 7.3	0.0, 9.0	0.0, 1.8	0.0, 15.9
Median (IQR)	1.5 (1.3-2.3)	1.1 (0.5-2.1)	0.9 (0.5-1.5)	0.4 (0.2-0.7)	0.6 (0.0-2.7)
No. of exceedences > 12.5 (20)	Nil (Nil)	Nil (Nil)	Nil (Nil)	Nil (Nil)	2 (Nil)
Daily mean SO_2 (pphm)					
Mean (sd)	0.97 (0.57)	0.34 (0.30)	0.37 (0.25)	0.16 (0.17)	0.26 (0.37)
Minimum, Maximum	0.00, 2.90	0.00, 1.85	0.00, 1.97	0.00, 0.87	0.00, 1.86
Median (IQR)	0.95 (0.6-1.3)	0.25 (0.1-0.5)	0.33 (0.2-0.5)	0.11 (0.0-0.2)	0.09 (0.0-0.4)
No. of exceedences > 12.5 (8)	Nil (Nil)	Nil (Nil)	Nil (Nil)	Nil (Nil)	Nil (Nil)
Daily max NO_2 (pphm)					
Mean (sd)	2.81 (1.07)	2.34 (1.07)	2.61 (0.76)	1.91 (0.79)	n.a.
Minimum, Maximum	0.0, 5.9	0.2, 11.2	0.8, 5.1	0.0, 4.1	n.a.
Median (IQR)	2.9 (2.2-3.6)	2.2 (1.6-2.9)	2.5 (2.1-3.1)	1.9 (1.4-2.4)	n.a.
No. of exceedences > 16 (12)	Nil (Nil)	Nil (Nil)	Nil (Nil)	Nil (Nil)	n.a.
Daily mean NO_2 (pphm)					
Mean (sd)	1.54 (0.82)	1.05 (0.48)	1.48 (0.48)	0.91 (0.39)	n.a.
Minimum, Maximum	0.00, 3.62	0.03, 2.99	0.18, 2.77	0.00, 2.27	n.a.
Median (IQR)	1.43 (0.9-2.2)	1.01 (0.7-1.3)	1.47 (1.2-1.8)	0.88 (0.6-1.1)	n.a.
No. of exceedences > 16	Nil	Nil	Nil	Nil	n.a.
Daily max Ozone (pphm)					
Mean (sd)	n.a.	2.20 (0.75)	n.a.	2.36 (0.96)	n.a.
Minimum, Maximum	n.a.	0.6, 4.9	n.a.	0.1, 6.5	n.a.
Median (IQR)	n.a.	2.1 (1.6-2.6)	n.a.	2.3 (1.6-3.0)	n.a.
No. of exceedences > 12 (10)	n.a.	Nil (Nil)	n.a.	Nil (Nil)	n.a.
Daily mean Ozone (pphm)					
Mean (sd)	n.a.	0.90 (0.47)	n.a.	1.19 (0.49)	n.a.
Minimum, Maximum	n.a.	0.06, 2.33	n.a.	0.03, 3.50	n.a.
Median (IQR)	n.a.	0.82 (0.6-1.2)	n.a.	1.13 (0.9-1.5)	n.a.
No. of exceedences > 4	n.a.	Nil	n.a.	Nil	n.a.

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.

The exceedences reported in this table were against NHMRC guidelines, which were revoked in 1998. Where applicable, the exceedences against the NEPM standard levels developed in 1998 are also reported in brackets.

n.a. Data not collected at this area

IQR. interquartile range

*. Mean PM10 was measured directly at Wallsend and Beresfield using TEOM, mean PM10 was estimated from TSP measured using high volume sampler at Stockton, Mayfield and North Lake Macquarie (S: 45% of TSP, M: 45% of TSP, NLM: 60% of TSP)

The timeplots of each of the pollutants are shown in Figures 6.1 (Stockton), 6.2 (Wallsend), 6.3 (Mayfield), 6.4 (Beresfield), and 6.5 (North Lake Macquarie). Both the raw data and 5-day moving averages are shown for mean PM10, maximum sulphur dioxide, maximum nitrogen dioxide, and maximum ozone. Seasonal patterns were observed for PM10 and sulphur dioxide, probably due to prevailing wind directions. For example, the point source of PM10 at BHP is approximately N/NE of the Mayfield monitoring station and E/SE of the Stockton monitoring station. During late summer and early autumn, the prevailing North East wind direction contributes to high PM10 levels at Mayfield and lower than average levels at Stockton.

6.2.1 Particulates including PM10

The average levels of particulates observed during the Phase II study period were considerably lower than the annual means recorded during Phase I of the HISAAP study, especially at Stockton and Mayfield. At Stockton during Phase I the mean PM10 recorded was 42.0 $\mu g/m^3$, compared to 31.0 $\mu g/m^3$ in Phase II. At Mayfield during Phase I the mean PM10 was 43.7 $\mu g/m^3$, compared to 37.6 $\mu g/m^3$ in Phase II. The levels in the control areas were similar to that observed in Western Sydney at 22.8 $\mu g/m^3$ (Jalaludin *et al.* 2000).

PM10 was measured directly at the EPA monitoring stations of Wallsend and Mayfield using a TEOM. Whereas, the industrial areas of Stockton, Mayfield, and North Lake Macquarie recorded daily TSP using a high volume sampler for the duration of the study period. The sampling period generally began between 9am and 10am and with very few exceptions, the operation of the high volume air sampler was for a 24-hour period or close to it.

Using 6-daily PM10 data that were also provided, measured using a high volume sampler with a size-selective inlet (SSI) attached, the ratio of PM10 to TSP was estimated. The ratio of PM10 to TSP was estimated as 45% at Mayfield, and 60% at North Lake Macquarie. No ratio could be calculated for Stockton and so it was assumed to be the same as Mayfield as the two study areas were in close geographical proximity. Refer to Appendix D for further details on these calculations. Where PM10 data were not obtained directly using TEOM these proportions were used to estimate PM10 for the whole of the study period based on daily TSP measurements.

One explanation of small particles making up a larger component of all particles at North Lake Macquarie, is that a larger component of the total suspended particulates is from sea salt from Lake Macquarie. The only other estimates of the ratio of PM10 to TSP available in Australia are

from a study conducted in Sydney where it was unclear whether it was 25% or 40% (Ismail 1996). In the United States the ratio has been estimated to be 55% (Dockery and Pope 1994).

Using 6-daily PM10 data also provided by the EPA, the intracluster correlation coefficient between TEOM and SSI was estimated to be 0.92 at Wallsend and 0.85 at Beresfield. Again, further information on these calculations is provided in Appendix D.

A limitation of the present study is reliance on outdoor central site exposures to represent individual exposures. To better understand the spatial variation of outdoor PM10 concentrations, the correlation between the PM10 concentrations measured at the central monitor with each of the peripheral monitors in the same study area was calculated. Note that the correlation coefficients measure association, and not agreement (Zeger *et al.* 2000). The correlation across time for particulate measurements at different stations within the same area was 0.37 (Stockton 6-daily TSP), 0.67 to 0.91 (Mayfield 6-daily TSP), 0.41 to 0.81 (North Lake Macquarie 6-daily TSP), and 0.57 to 0.66 (North Lake Macquarie daily TSP).

The industrial area of Mayfield exceeded the United States EPA goal for total suspended particulates of 260 $\mu g/m^3$ on three occasions during the study period (6/10/94, 7/10/94 and 17/10/94). The highest reading at the main station was 319 $\mu g/m^3$. The goal was also exceeded one occasion at Stockton (29/8/94) at a peripheral monitor. None of the study areas exceeded the PM10 goal of 150 $\mu g/m^3$.

6.2.2 Sulphur dioxide

The daily maximum sulphur dioxide levels were also considerable lower during phase II at North Lake Macquarie and Mayfield, compared to Phase I. At North Lake Macquarie the mean daily maximum sulphur dioxide was 3.17 pphm in Phase I and only 1.89 pphm in Phase II. There is concern however in the accuracy of the North Lake Macquarie Phase II data as 27% of the dates had zero concentrations recorded. At Mayfield the mean daily maximum sulphur dioxide was 2.79 pphm in Phase I and only 1.18 pphm in Phase II. The level of sulphur dioxide was surprisingly high at the control area Wallsend, although comparable to Phase I (Phase I mean 2.24 pphm, Phase II mean 2.08 pphm). This may be a result of Wallsend picking up some sulphur dioxide from the industrial plant, Pasminco Metals-Sulphide, at North Lake Macquarie.

The industrial area of North Lake Macquarie exceeded the WHO goal of 12.5 pphm for maximum hourly SO_2 on two occasions (11/9/94, 22/3/95) and was equal to the goal on one

occasion (3/9/94). The correlation coefficients for sulphur dioxide measurements at different stations within the same area were 0.54 (Mayfield) and 0.43 (North Lake Macquarie).

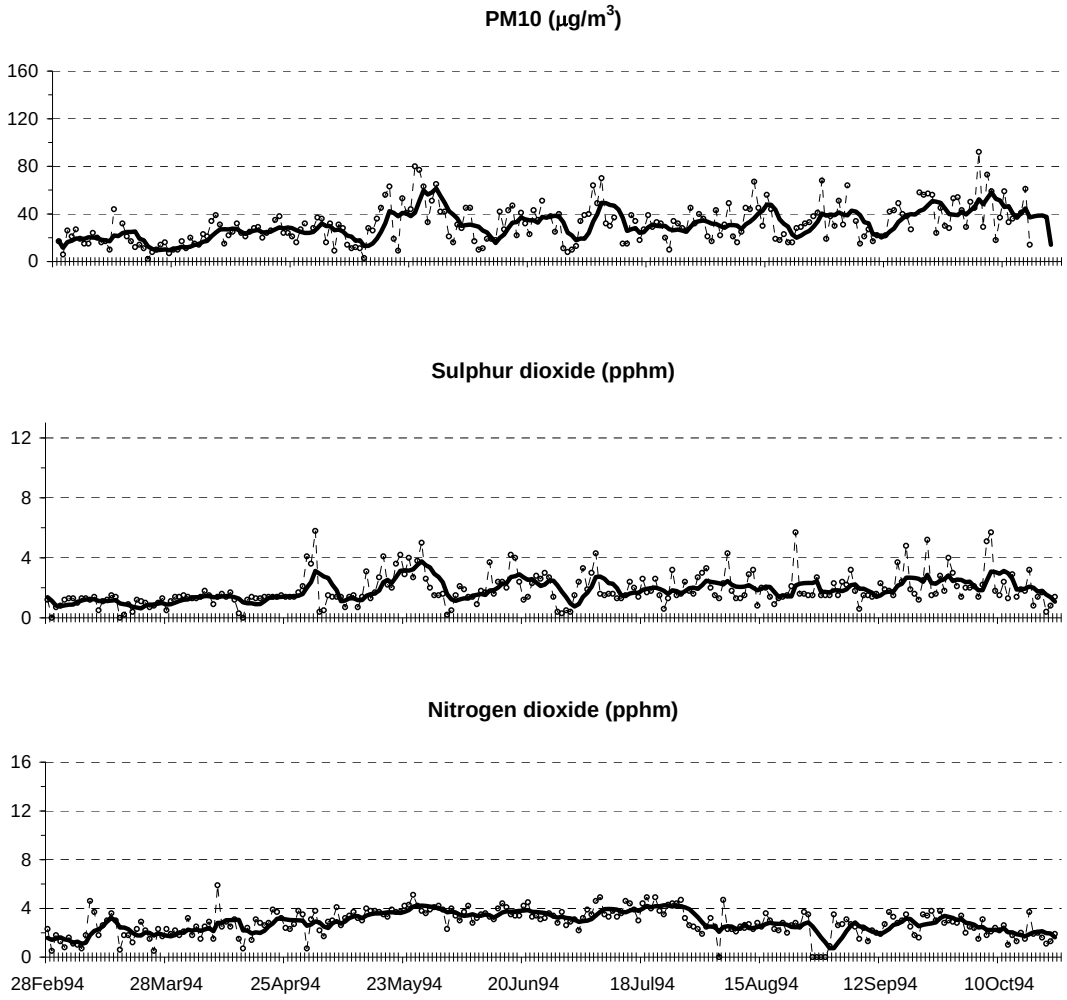
6.2.3 Nitrogen dioxide

The maximum hourly readings were well below the NHMRC goal of 16 pphm. The highest values observed during the study were 5.9 pphm, which occurred at Stockton during winter, and there were isolated peaks at Wallsend (11.2 pphm) and Mayfield (5.1 pphm). The average of daily maximum nitrogen dioxide levels (mean 2.4 pphm) were slightly lower than that observed at both Illawarra (mean 2.1 pphm in 1994) (NSW EPA 2005) but comparable to Western Sydney (mean 2.9 pphm in 1994) (NSW EPA 2005). The correlation coefficients for nitrogen dioxide measurements at different stations within the same area were 0.41 (Mayfield).

6.2.4 Ozone

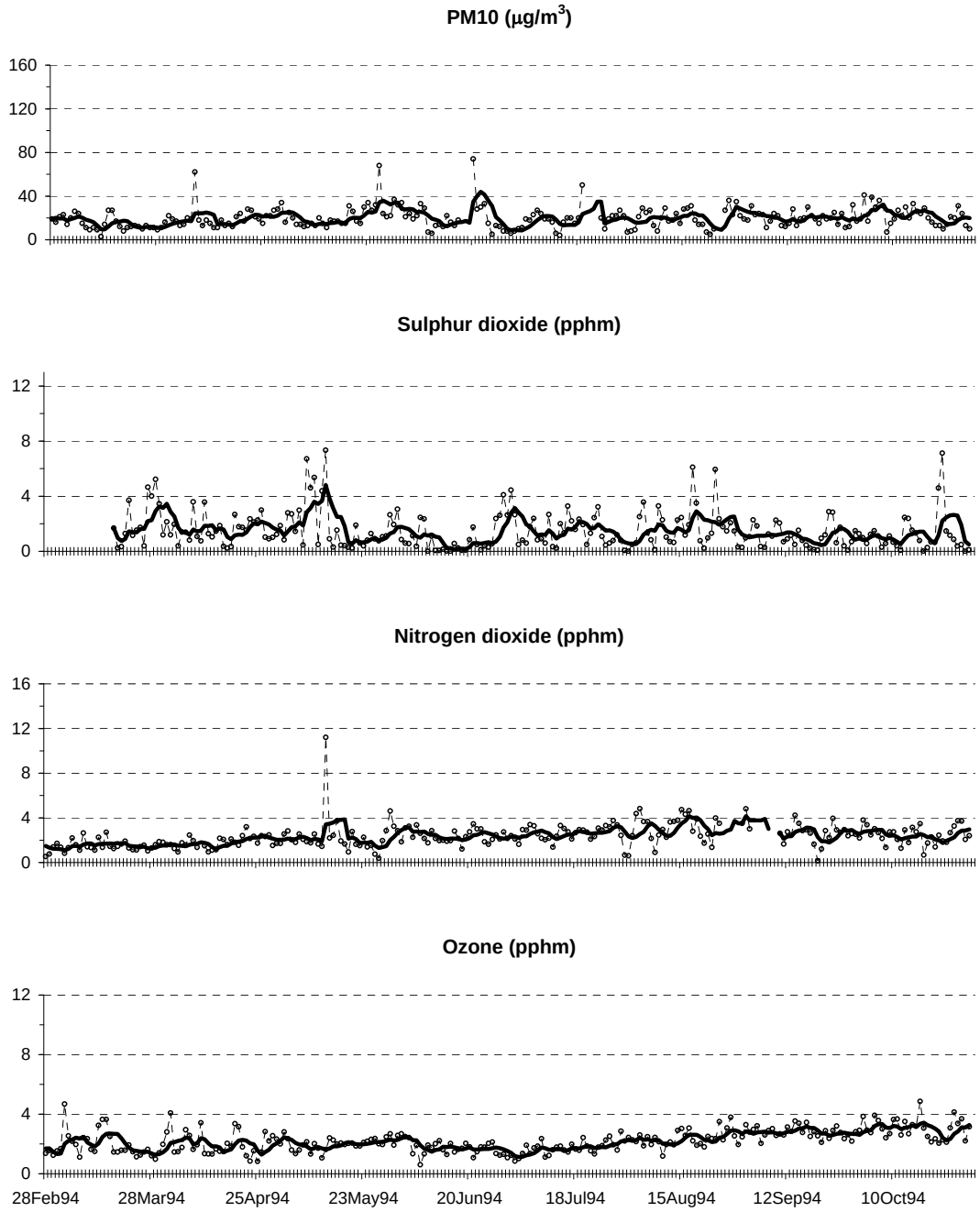
The maximum hourly readings were well below the NHMRC goal of 12 pphm, with the highest level recorded being 6.5 pphm at Beresfield. The average of daily maximum ozone levels observed (mean 2.3 pphm) was slightly lower than that observed at both Illawarra (mean 2.6 pphm in 1994) (NSW EPA 2005) and Western Sydney (mean 3.1 pphm in 1994) (NSW EPA 2005).

Figure 6.1. Daily pollutant concentrations during study period at Stockton



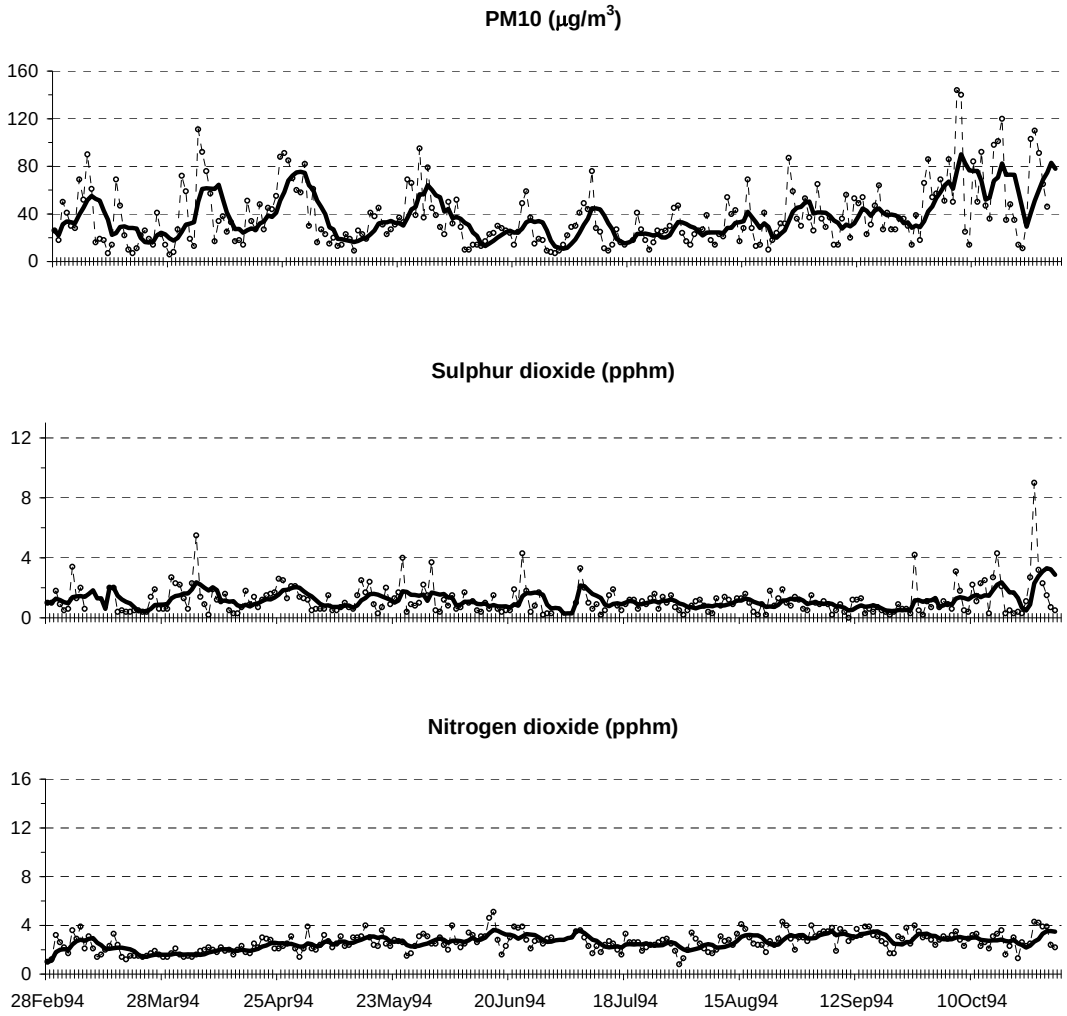
Time scale restricted to the study period 28 February 1994 to 23 October 1994.
PM10: particle mass concentration < 10µm was estimated as 45% of TSP at Stockton.
Ozone was not measured at Stockton.
Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.2. Daily pollutant concentrations during study period at Wallsend



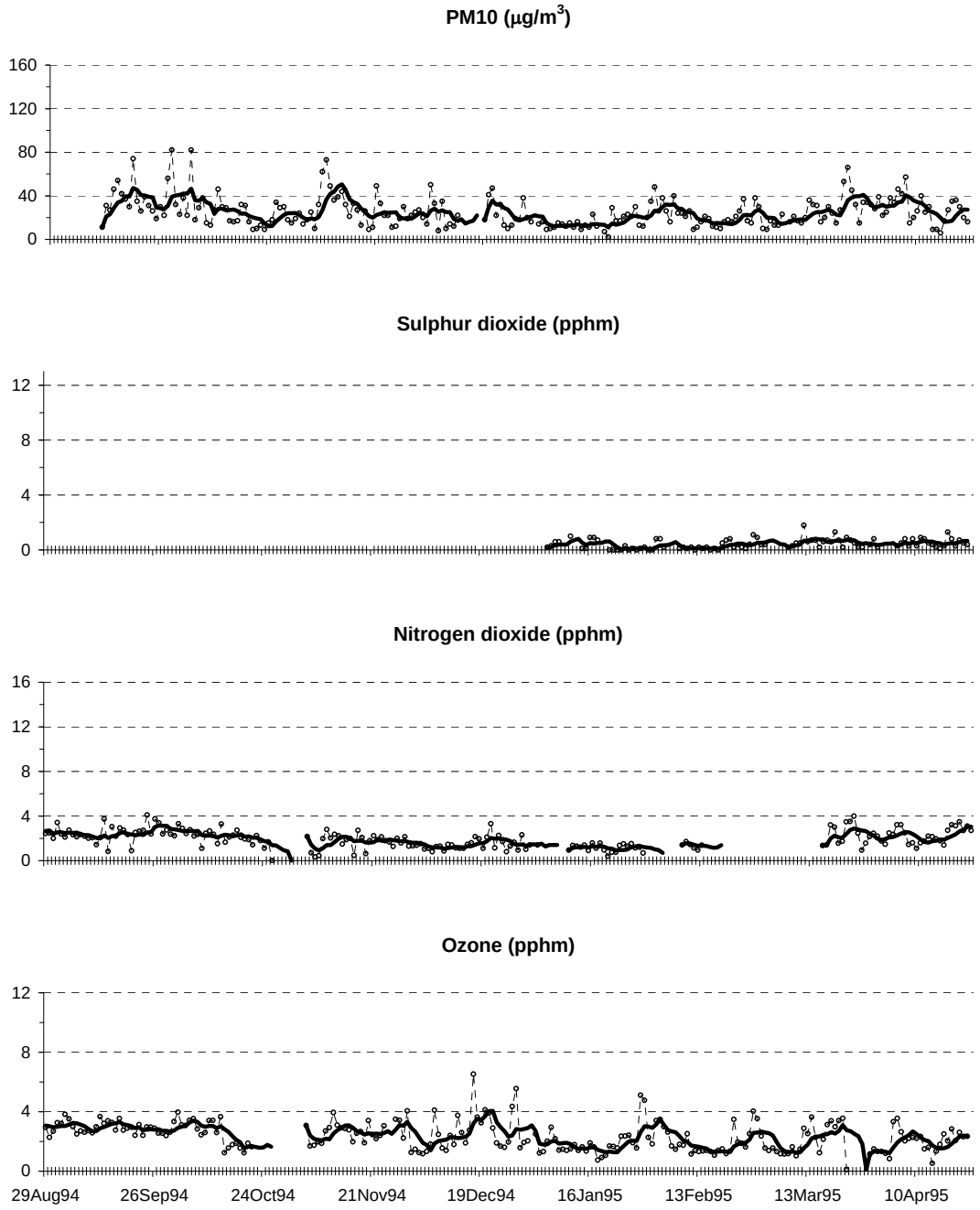
Time scale restricted to the study period 28 February 1994 to 30 October 1994.
PM10: particle mass concentration < 10µm was obtained directly using TEOM.
O Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.3. Daily pollutant concentrations during study period at Mayfield



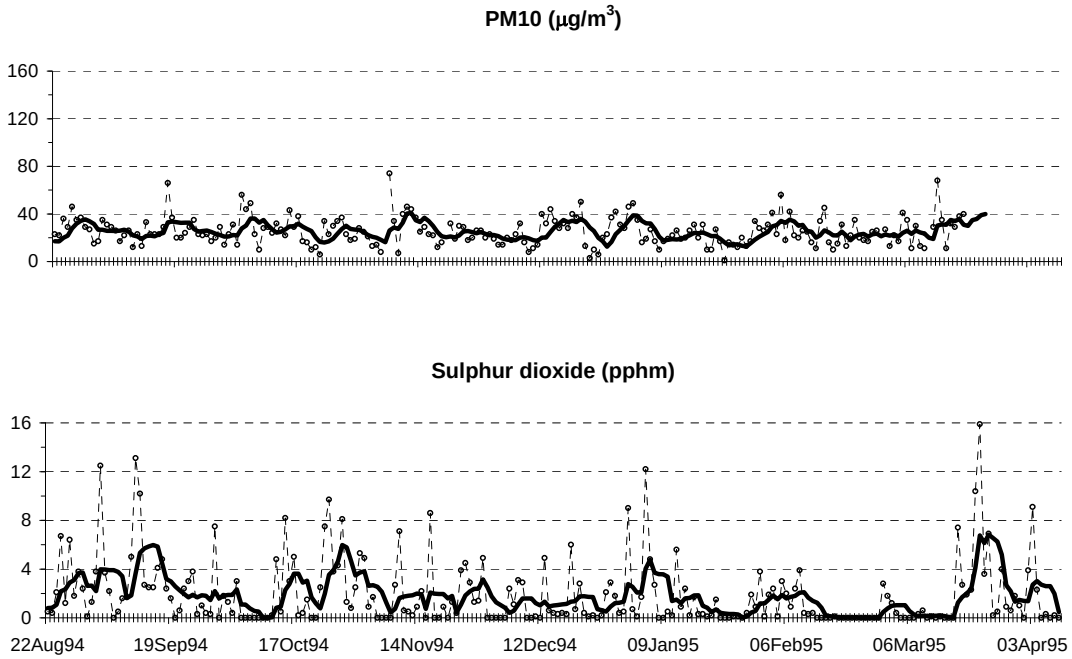
Time scale restricted to the study period 28 February 1994 to 30 October 1994.
PM10: particle mass concentration < 10µm was estimated as 45% of TSP at Mayfield
Ozone was not measured at Mayfield
Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.4. Daily pollutant concentrations during study period at Beresfield



Time scale restricted to the study period 29 August 1994 to 23 April 1995.
PM10: particle mass concentration < 10µm was obtained directly using TEOM.
Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.5. Daily pollutant concentrations during study period at North Lake Macquarie



Time scale restricted to the study period 22 August 1994 to 9 April 1995.
PM10: particle mass concentration < 10µm was estimated as 60% of TSP at North Lake Macquarie.
Nitrogen dioxide and ozone were not measured at North Lake Macquarie.
Observed value — Smoothed function (average of current and previous 5 days)

6.3 Descriptive analysis of aeroallergens

Pollen counts were very low as a direct result of drought conditions. The concentrations were similar to that observed in Sydney over the same time period (Bass 1995; Jalaludin *et al.* 2000). The Alternaria levels observed in the Hunter were much lower than that reported in Sydney at the same time (Jalaludin *et al.* 2000). The pollen and fungi data are summarised in Table 6.3.

Table 6.3. Aeroallergen counts per cubic metre of air, by study area

	Study area				
	S	**W**	**M**	**B**	**NLM**
Period of diary study	**Feb-Oct**	**Feb-Oct**	**Feb-Oct**	**Aug-Apr**	**Aug-Apr**
Total pollen (grains/m^3)					
Proportion of days zero level	9%	10%	4%	2%	9%
Minimum, Maximum	0, 106	0, 483	0, 179	0, 1970	0, 234
Median (IQR)	7 (2-18)	6 (2-15)	9 (4-21)	41(23-80)	27 (7-61)
Grass pollen (grains/m^3)					
Proportion of days zero level	55%	58%	52%	16%	25%
Minimum, Maximum	0, 61	0, 16	0, 37	0, 37	0, 36
Median (IQR)	0 (0-2)	0 (0-2)	1 (0-2)	4 (2-8)	2 (0-5)
Weed pollen (grains/m^3)					
Proportion of days zero level	64%	64%	55%	15%	32%
Minimum, Maximum	0, 16	0, 14	0, 11	0, 27	0, 44
Median (IQR)	0 (0-1)	0 (0-1)	0 (0-2)	3 (1-6)	1 (0-4)
Tree pollen (grains/m^3)					
Proportion of days zero level	37%	39%	37%	9%	24%
Minimum, Maximum	0, 56	0, 478	0, 167	0, 1952	0, 131
Median (IQR)	1 (0-5)	1 (0-4)	2 (0-6)	10 (2-24)	5 (1-22)
Misc. pollen (grains/m^3)					
Proportion of days zero level	19%	20%	9%	5%	14%
Minimum, Maximum	0, 73	0, 38	0, 66	0, 106	0, 223
Median (IQR)	3 (1-8)	3 (1-6)	4 (2-10)	16 (8-23)	9 (2-20)
Alternaria (spores/m^3)					
Proportion of days zero level	42%	44%	31%	12%	25%
Minimum, Maximum	0, 56	0, 55	0, 49	0, 97	0, 162
Median (IQR)	1 (0-3)	1 (0-4)	1 (0-3)	7 (3-14)	2 (1-9)

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.

The pollen data have been published (McShane and Cripps 1997). The intra-rater and inter-rater agreement was assessed based on a recounting undertaken on a sample taken from North Lake Macquarie. The intra-cluster correlation coefficients were over 0.80 for total, weed, tree, and Alternaria but were poor (0.45) for grass pollen where the original counts were much higher.

The timeplots of the various pollens are shown in Figures 6.6-6.7 (Stockton), 6.8-6.9 (Wallsend), 6.10-6.11 (Mayfield), 6.12-6.13 (Beresfield), and 6.14-6.15 (North Lake Macquarie). Seasonal patterns were observed for the pollens and Alternaria, due to germinating seasons.

Pollen grains

The daily pollen totals at Stockton, Wallsend and Mayfield peaked in early to mid-autumn and then there was a downward trend to winter, before rising again to reach peaks at various times throughout late winter and spring. Daily pollen totals at Beresfield and North Lake Macquarie also peaked in spring. Beresfield showed various peaks in early, mid and late summer before declining into autumn. North Lake Macquarie encountered total daily pollen peaks in early summer before declining and rising again in autumn. The largest daily total pollen counts across all areas occurred during late winter and early spring, with the highest levels observed at Beresfield.

At Stockton, Wallsend and Mayfield, grass and unclassified pollens, and to a lesser extent weed pollens contributed to the peaks in early to mid autumn. The high pollen counts in late winter and spring for these areas was a result of significant amounts of tree pollen.

The pollen peaks observed in spring at Beresfield and North Lake Macquarie were mainly as a result of tree pollen, with unclassified pollen also contributing at North Lake Macquarie. The tree pollen levels observed at Beresfield were up to 6 times those experienced in North Lake Macquarie, and 13 times higher than those experienced in the other areas. Rising levels of pollen during the summer months and autumn in Beresfield and North Lake Macquarie resulted mainly from unclassified sources, with grass and weed contributing to a lesser extent.

Six varieties of weed pollen were identified. The weed pollen contributing to the autumn peaks observed was asteracea (at Stockton), asteracea, polygona and plantagi (Wallsend), polygona and chenpad (Mayfield). Asteracea has been identified as the most allergic plant in NSW, and is considered the pollen most responsible for hayfever. The weed pollen contributing to high spring levels was plantagi (Mayfield, Beresfield and North Lake Macquarie). Five varieties of tree pollen were identified. The most common tree pollen in the late winter/ early spring was curpressus (Stockton, Wallsend and Mayfield), and the most common tree pollen in mid-spring was Mytrtacea (North Lake Macquarie).

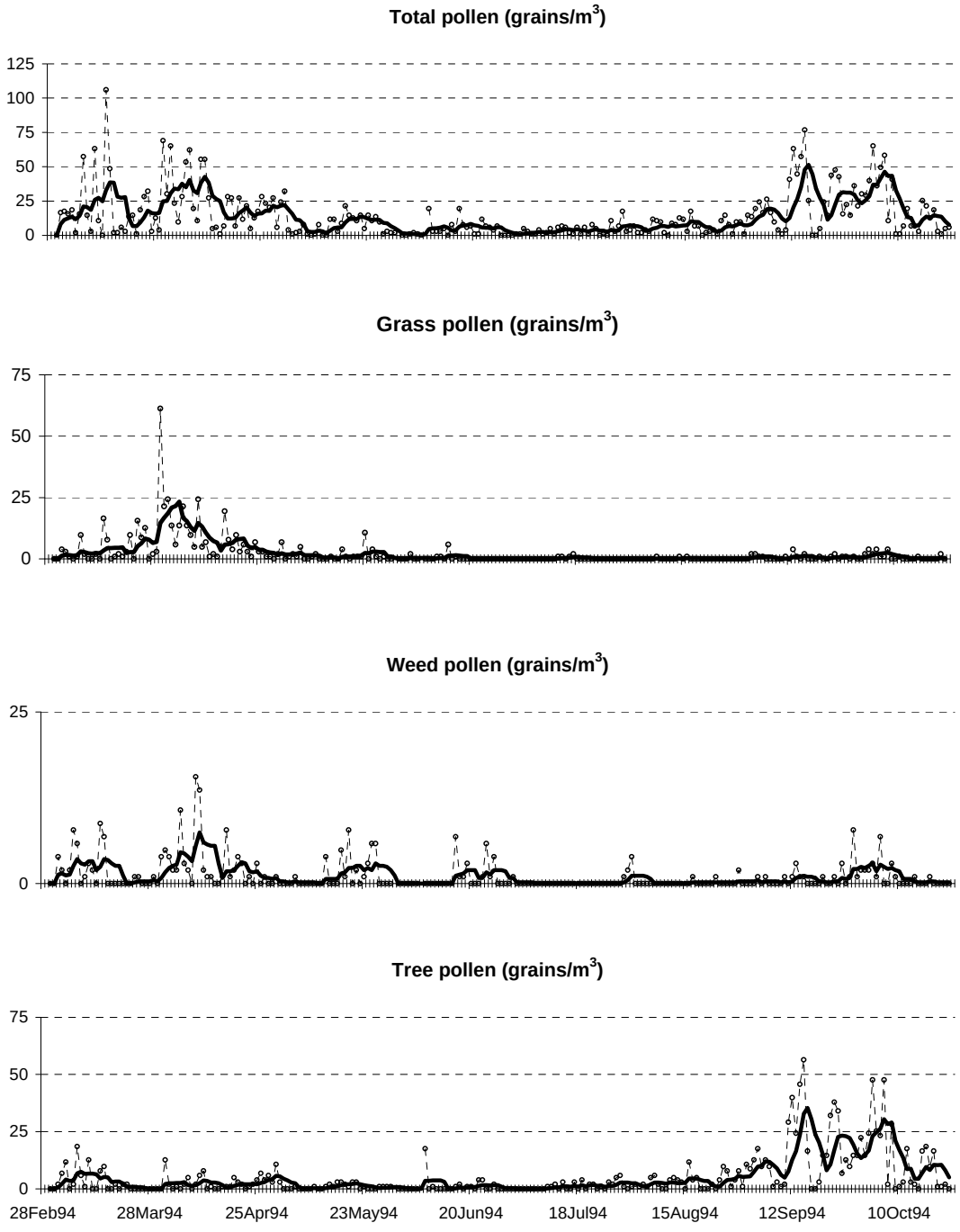
Fungal spores

Stockton, Wallsend, and Mayfield had peaks of Alternaria spores in late summer and again during late Autumn/early winter with May having the highest spore count at all these areas. Spore levels appeared to subside throughout the rest of winter and early spring.

At Beresfield and North Lake Macquarie, Alternaria spores were quite high during late spring and summer, and then declined over late spring and summer into autumn. The levels in the summer period at these two areas were many times that of the levels found at Stockton, Wallsend, and Mayfield during the peak episodes of early winter.

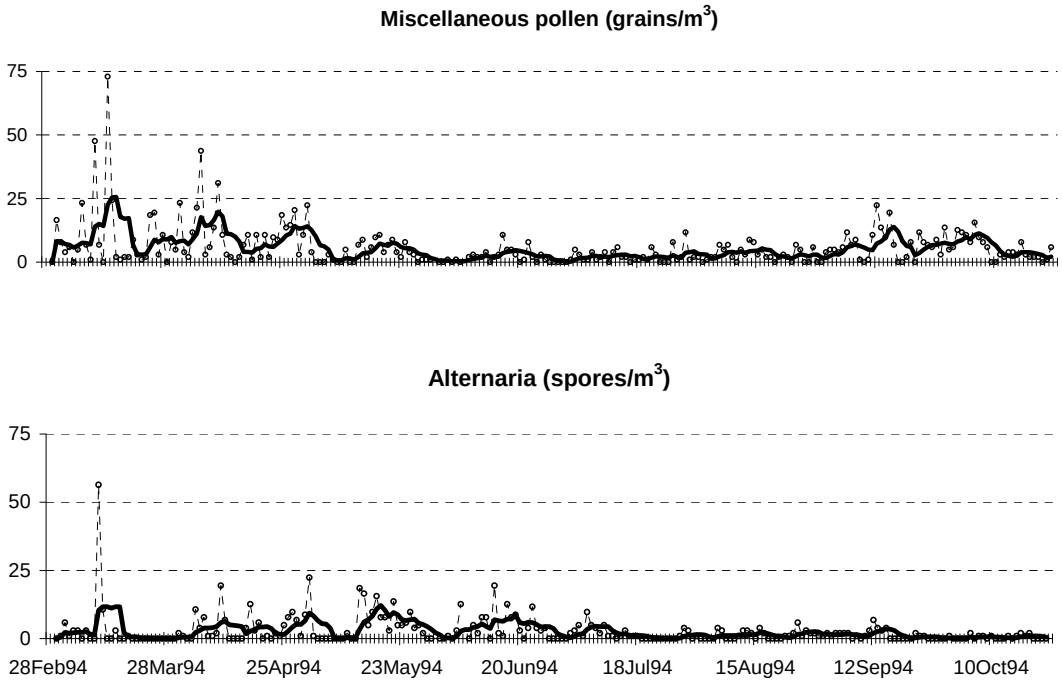
The upward trend approaching winter for Alternaria spores was opposite to that for pollen, which had a downward trend towards and throughout winter. The reverse was the case for the spring months where daily pollen counts were at their highest and Alternaria spore counts at their lowest.

Figure 6.6. Daily pollen concentrations during study period at Stockton



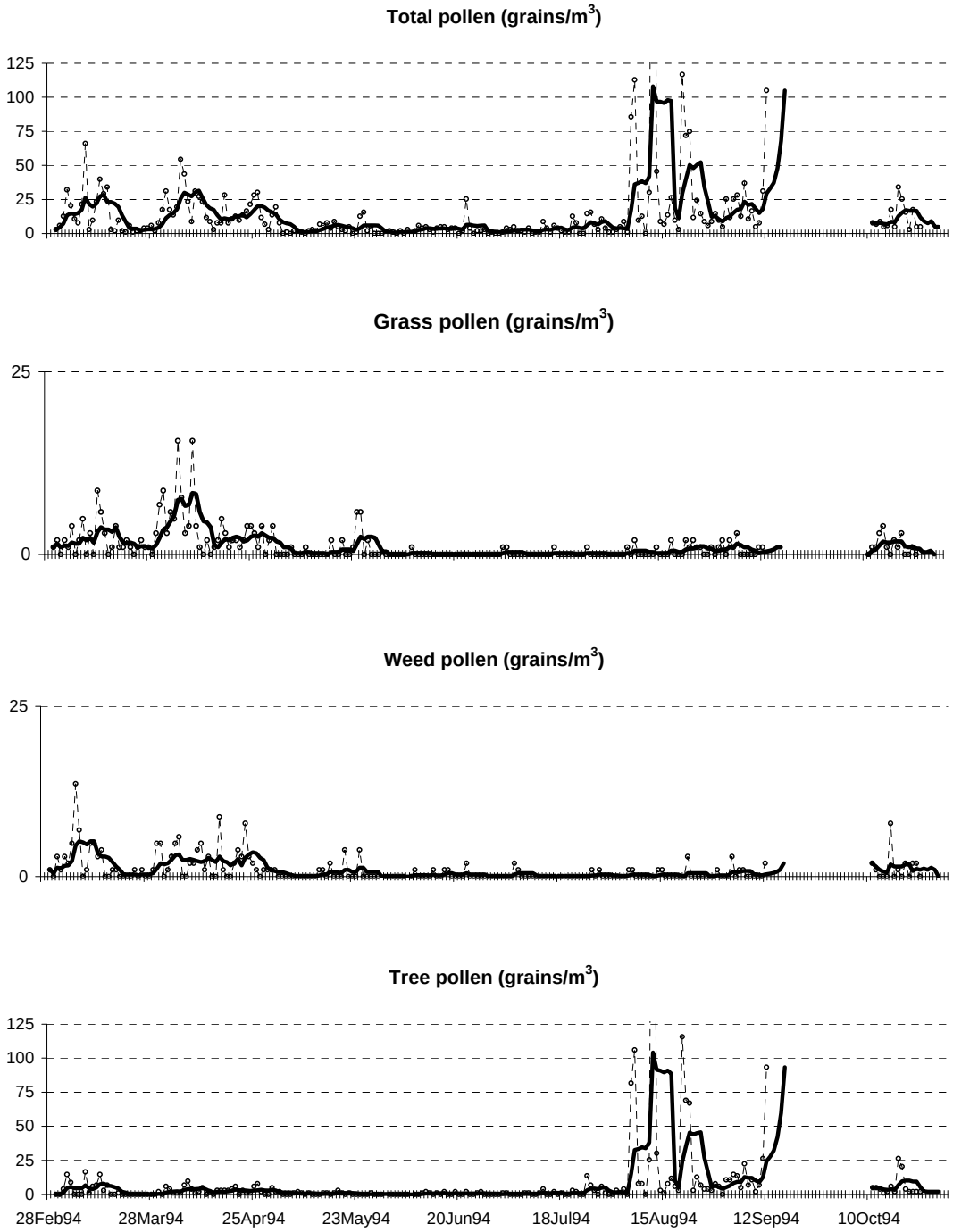
Time scale restricted to the study period 28 February 1994 to 23 October 1994.
Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.7. Daily unclassified pollen and Alternaria concentrations during study period at Stockton



Time scale restricted to the study period 28 February 1994 to 23 October 1994.
Observed value — Smoothed function (average of current and previous 5 days)

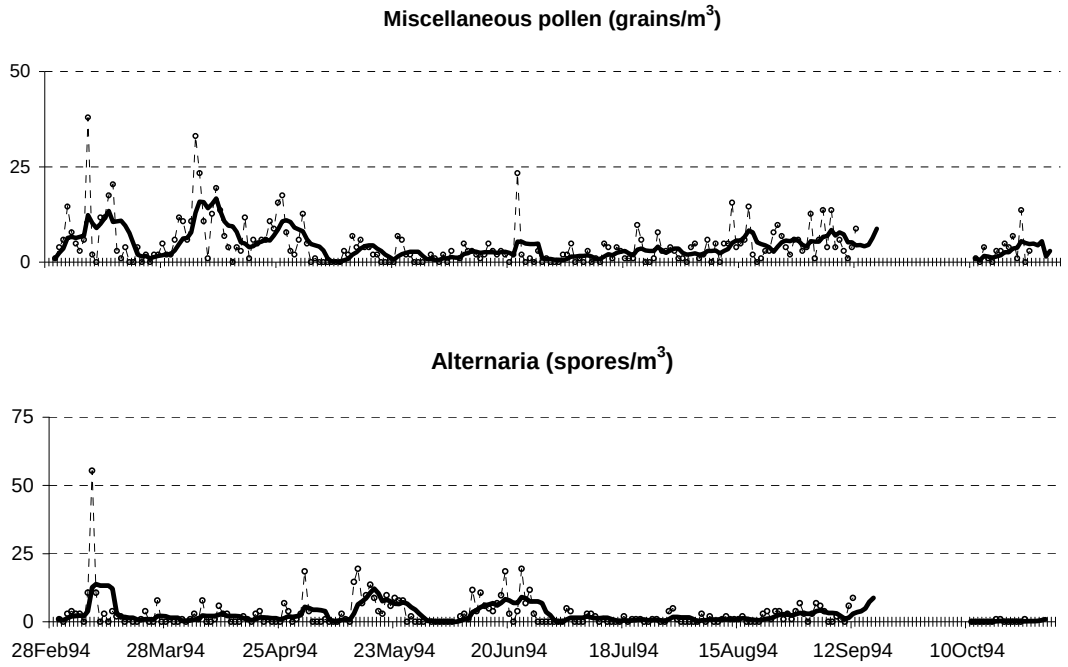
Figure 6.8. Daily pollen concentrations during study period at Wallsend



Time scale restricted to the study period 28 February 1994 to 30 October 1994. On 12 August 1994, tree pollen was 478 grains/m^3 and total pollen was 483 grains/m^3. This observation was removed from the graph for display purposes.

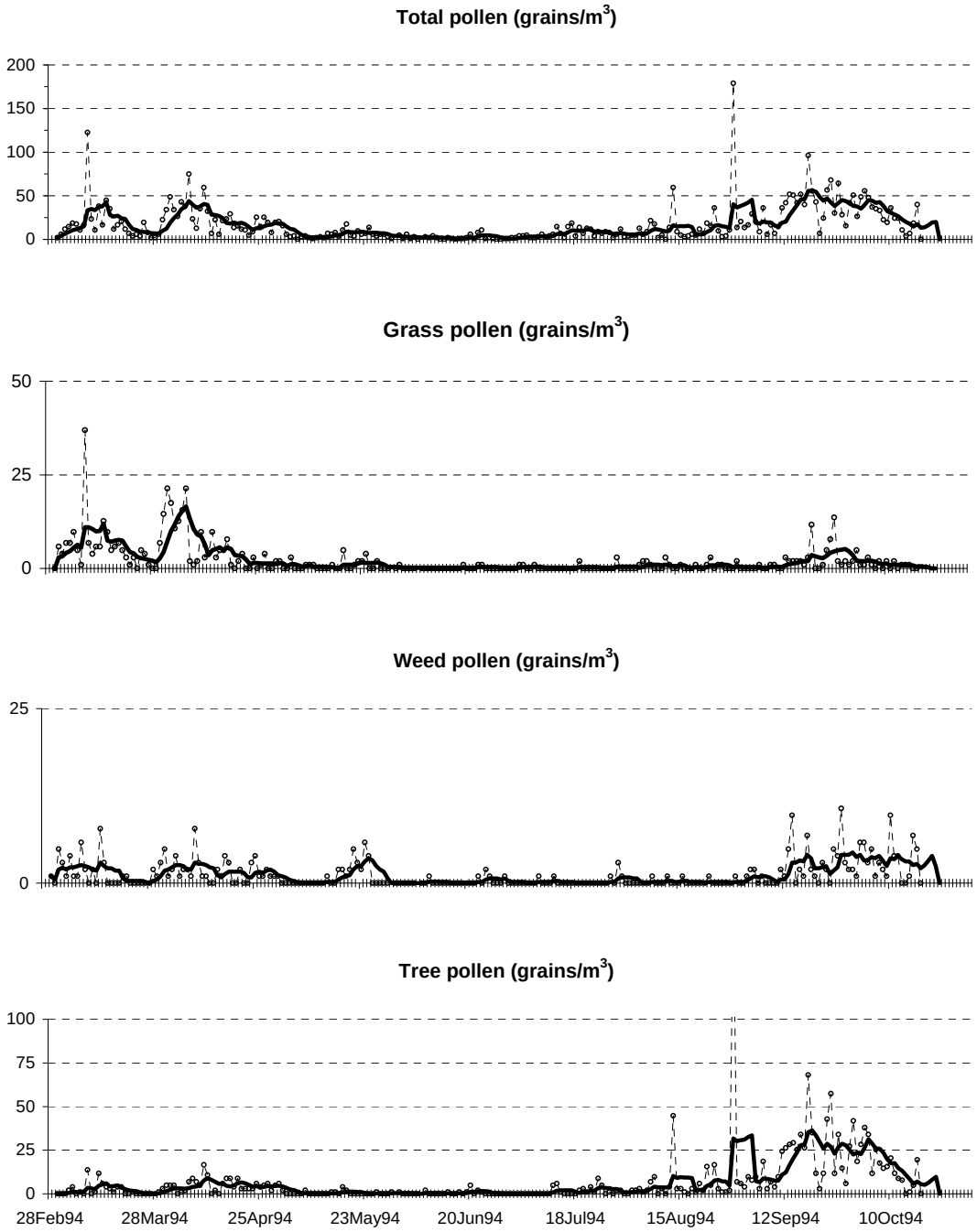
O Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.9. Daily unclassified pollen and Alternaria concentrations during study period at Wallsend



Time scale restricted to the study period 28 February 1994 to 30 October 1994.
O Observed value — Smoothed function (average of current and previous 5 days)

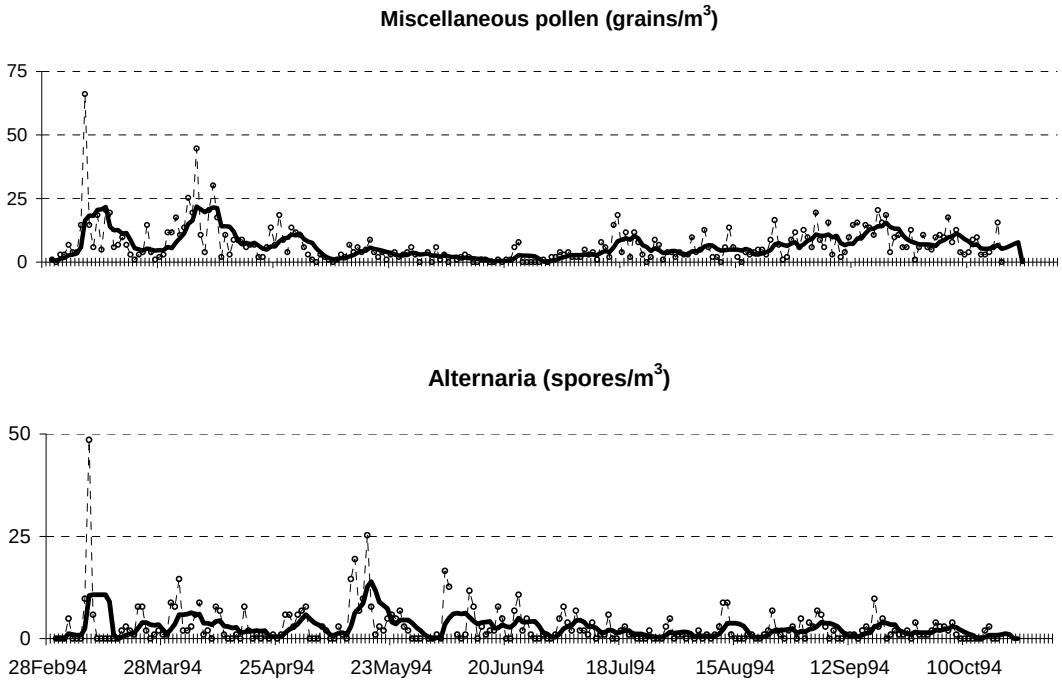
Figure 6.10. Daily pollen concentrations during study period at Mayfield



Time scale restricted to the study period 28 February 1994 to 30 October 1994. On 29 August 1994, tree pollen was 167 grains/m^3. This observation was removed from the graph for display purposes

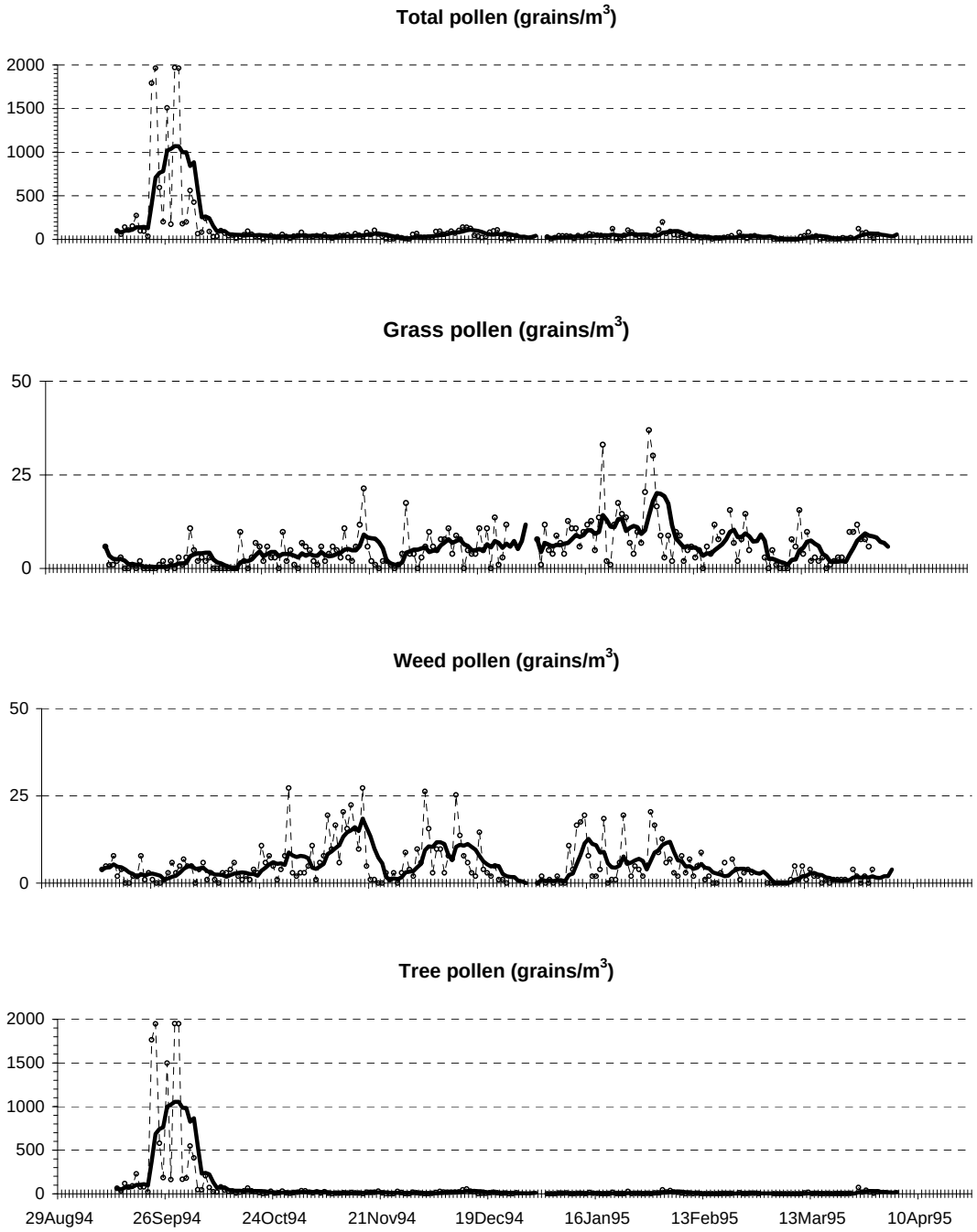
O Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.11. Daily unclassified pollen and Alternaria concentrations during study period at Mayfield



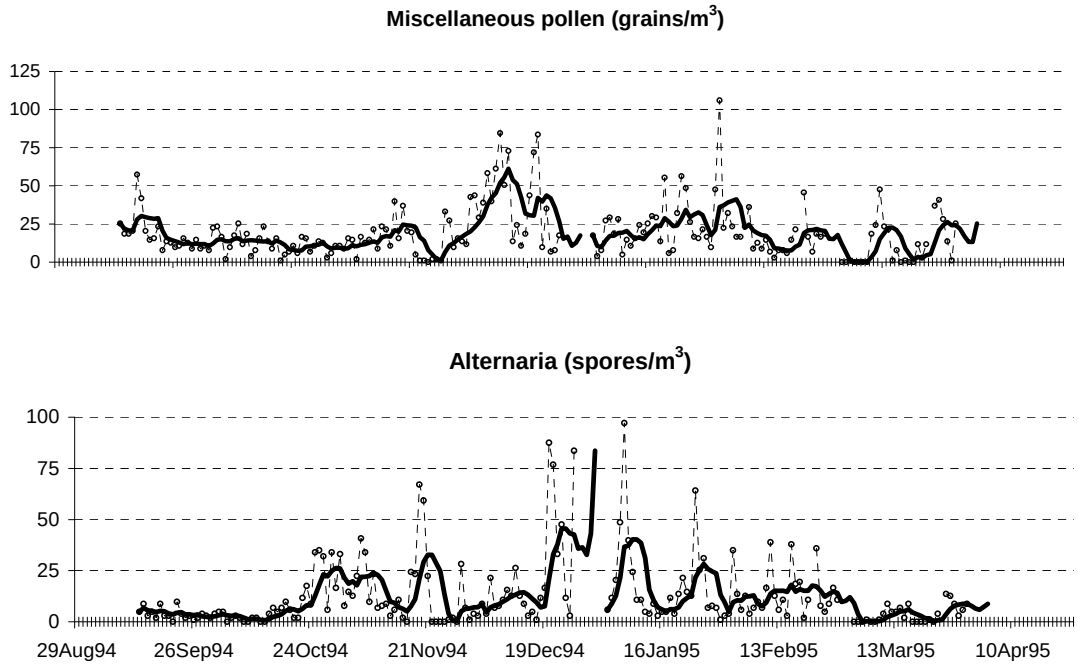
Time scale restricted to the study period 28 February 1994 to 30 October 1994.
O Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.12. Daily pollen concentrations during study period at Beresfield



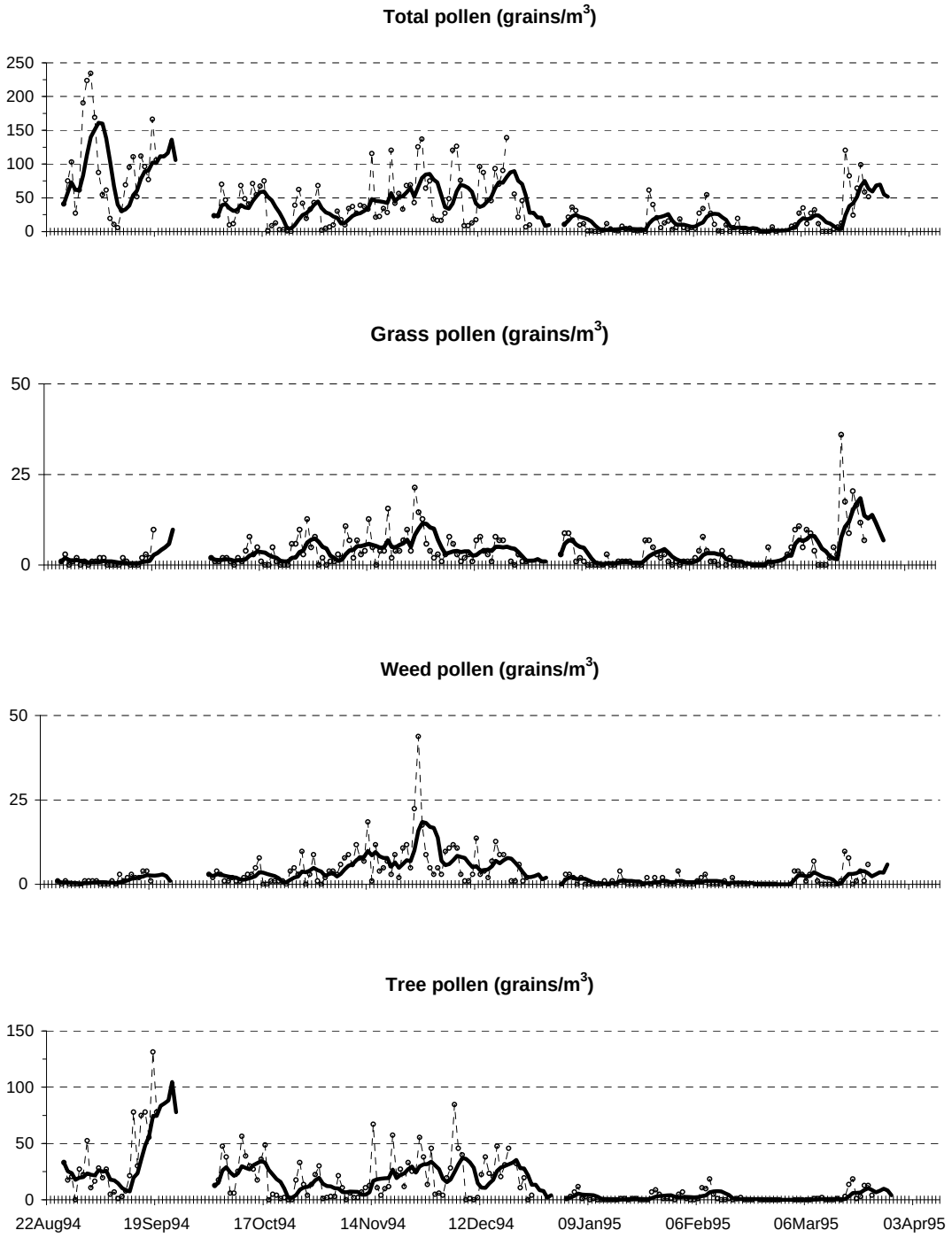
Time scale restricted to the study period 29 August 1994 to 23 April 1995.
Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.13. Daily unclassified pollen and Alternaria concentrations during study period at Beresfield



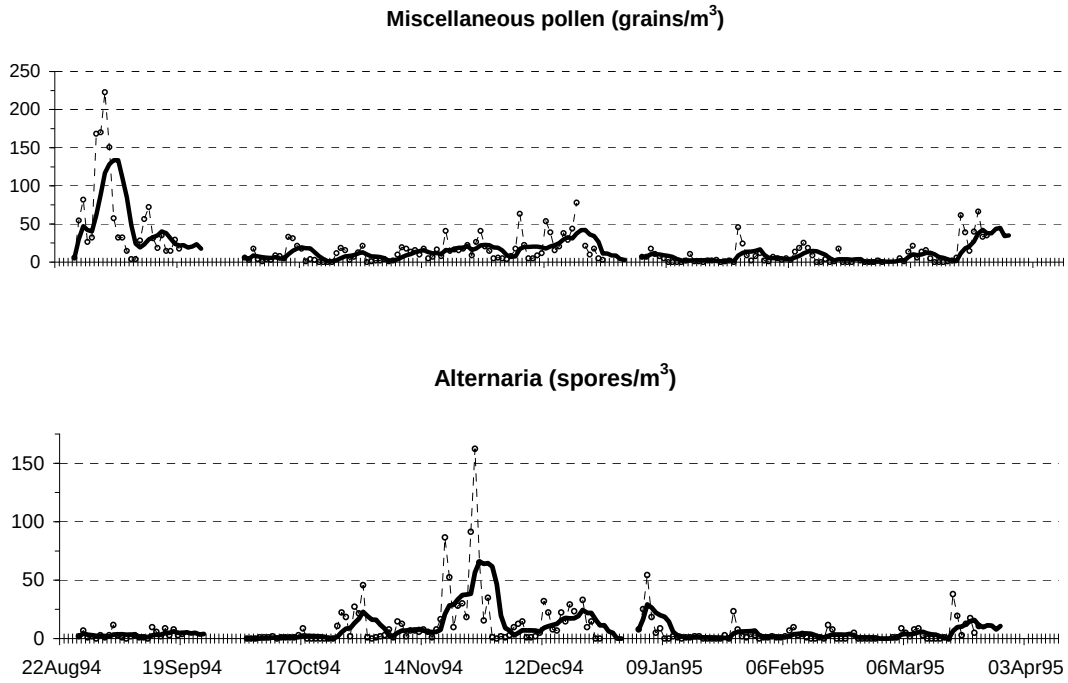
Time scale restricted to the study period 29 August 1994 to 23 April 1995.
Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.14. Daily pollen concentrations during study period at North Lake Macquarie



Time scale restricted to the study period 22 August 1994 to 9 April 1995.
Observed value — Smoothed function (average of current and previous 5 days)

Figure 6.15. Daily unclassified pollen and Alternaria concentrations during study period at North Lake Macquarie



Time scale restricted to the study period 22 August 1994 to 9 April 1995.
O Observed value — Smoothed function (average of current and previous 5 days)

6.4 Descriptive analysis of meteorological data

The meteorological measures were averaged across available sites to reflect the entire community's exposure. The descriptive statistics of temperature, humidity and rainfall are shown in Table 6.4. During the monitoring of the first wave at Stockton, Wallsend and Mayfield the daily maximum temperature ranged from 12 to 34 ^{o}C. During the monitoring of the second wave, daily maximum temperature ranged from 15 to 40 ^{o}C. The correlation between maximum temperature and mean temperature was 0.82 in Wave 1 (Stockton, Wallsend and Mayfield) and 0.73 in Wave 2 (Beresfield and North Lake Macquarie).

Rainfall was recorded at only two study areas. The total rainfall at Mayfield during the monitoring of the first group was 481 mm. The total rainfall at Lake Macquarie during the monitoring of the second group was 694 mm. There were substantial falls between March 1 and 7, 1995.

The timeplots of temperature and rainfall are shown in Figure 6.16 for the two separate waves.

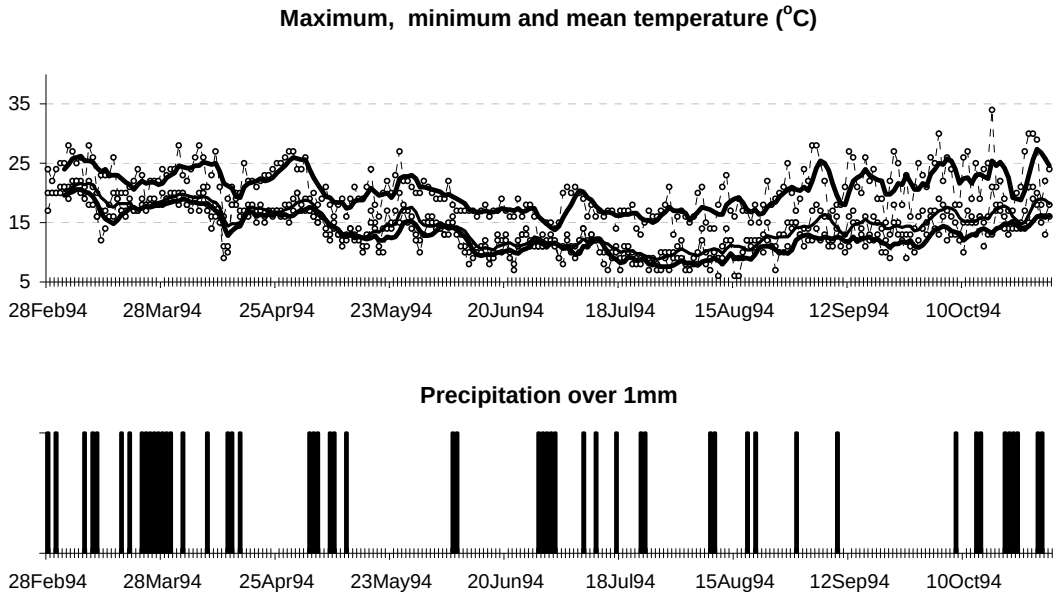
Table 6.4. Meteorological measures by study area

	Study area	
	S, W, M	**B, NLM**
Period of diary study	**Feb-Oct**	**Aug-Apr**
Maximum temperature (°C)		
Mean (sd)	20 (4)	24 (4)
Minimum, maximum	12, 34	15, 41
Median (interquartile range)	20 (17-23)	24 (22-27)
Mean temperature (°C)		
Mean (sd)	15 (4)	19 (3)
Minimum, maximum	8, 22	12, 30
Median (interquartile range)	15 (12-17)	19 (16-21)
Minimum temperature (°C)		
Mean (sd)	13 (4)	17 (3)
Minimum, maximum	6, 22	7, 22
Median (interquartile range)	13 (10-16)	18 (14-20)
Mean humidity (°C)		
Mean (sd)	80 (15)	81 (14)
Minimum, maximum	37, 99	37, 100
Median (interquartile range)	85 (71-91)	85 (74-91)
Rainfall		
No. of days with rainfall >1mm; n (%)	53 (22%)	50 (24%)
No. of days with rainfall >20mm; n (%)	7 (3%)	12 (6%)

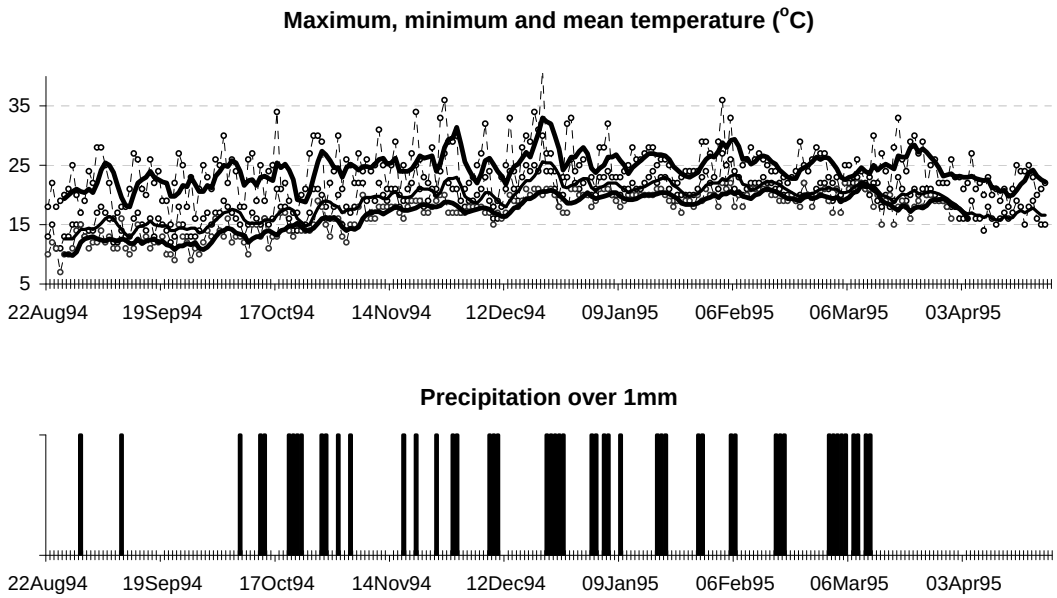
The meteorological data were derived from an average of the daily readings at the available measure stations; all areas were assumed to have the same temperature reading and rainfall on a given day.

Figure 6.16. Daily temperature and rainfall during study period

Wave 1 (Stockton, Wallsend and Mayfield):



Wave 2 (Beresfield and North Lake Macquarie):



O Observed value — Smoothed function (5-day moving average)

6.5 Correlations

There was strong correlation between the daily air quality and meteorological measures. The Spearman correlation coefficients are reported separately for each study area in Table 6.5 to Table 6.9. The following associations were found based on an observed correlation coefficient of at least 0.40. There was a positive association between PM10 and sulphur dioxide in the industrial areas Stockton and Mayfield, and a positive association between sulphur dioxide and total pollen in the industrial study area of North Lake Macquarie. Associations were found between Alternaria and pollen concentrations in the two study areas making up Wave 2, namely Beresfield and North Lake Macquarie. In particular, there was a strong positive association between Alternaria and total pollen (at North Lake Macquarie), between Alternaria and grass pollen (at both Beresfield and North Lake Macquarie), and between Alternaria and weed pollen (North Lake Macquarie).

Maximum temperature was positively correlated with PM10 at Mayfield, and minimum temperature was negatively correlated with maximum sulphur dioxide at Stockton. The various forms of temperature were also positively correlated with several pollen measures in the study areas making up the first wave but not the second wave - total pollen (Stockton, Wallsend and Mayfield), grass pollen (Stockton, Wallsend and Mayfield), and weed pollen (Wallsend and Mayfield only). Humidity was negatively correlated with PM10 at both Stockton and Beresfield. It was also negatively correlated with sulphur dioxide at Stockton. On days with rainfall, PM10, sulphur dioxide, and Alternaria concentrations tended to be lower at Stockton.

In summary, there was substantial correlation among the explanatory variables. Explanatory variables that are highly correlated might be nearly collinear, i.e., one of the explanatory variables might be nearly a linear combination of some of the others. In such cases, the regression model might not be estimable or might be ill-conditioned, and the estimated results would be unstable. Most of the pollution measures are indeed significantly correlated, but the magnitudes of the simple correlations are all moderate; the largest ones are under 0.6. Thus, collinearity among the explanatory variables is not a major concern.

Table 6.5. Matrix of Spearman's rank correlation coefficients between daily concentrations of ambient air quality measures and meteorological measures, at Stockton

	PM10	SO_2 (max)	SO_2 (mean)	Pollen (total)	Pollen (grass)	Pollen (weed)	Alternaria
PM10	1.00						
Sulphur dioxide							
Maximum	0.59	1.00					
Mean	0.56	0.90	1.00				
Pollen & fungi							
Total pollen	0.10	0.14	0.19	1.00			
Grass pollen	-0.17	-0.15	-0.09	0.59	1.00		
Weed pollen	0.03	0.07	0.13	0.52	0.40	1.00	
Alternaria	0.22	0.36	0.47	0.33	0.11	0.29	1.00
Temperature							
Maximum	0.13	0.12	0.16	0.52	0.45	0.30	0.21
Mean	-0.18	-0.23	-0.19	0.44	0.54	0.37	0.06
Minimum	-0.32	-0.41	-0.38	0.29	0.51	0.32	0.00
Humidity							
Mean	-0.43	-0.56	-0.49	-0.25	0.08	-0.18	-0.14
Rainfall (>1mm)	-0.43	-0.48	-0.50	-0.23	0.01	-0.12	-0.37

The study period at Stockton was 28 February 1994 to 23 October 1994 (238 days, or 34 weeks)
All correlations above 0.13 or below –0.13 were statistically significant at α=0.05
Correlations between total pollen and its constituents (grass pollen and weed pollen) are not very informative but are provided for completeness.
PM10: particle mass concentration < 10μm.

Table 6.6. Matrix of Spearman's rank correlation coefficients between daily concentrations of ambient air quality measures and meteorological measures, at Wallsend

	PM10	SO_2 (max)	SO_2 (mean)	Pollen (total)	Pollen (grass)	Pollen (weed)	Alternaria
PM10	1.00						
Sulphur dioxide							
Maximum	0.06	1.00					
Mean	0.12	0.88	1.00				
Pollen & fungi							
Total pollen	0.07	-0.08	-0.12	1.00			
Grass pollen	0.01	0.07	0.01	0.53	1.00		
Weed pollen	-0.00	-0.05	-0.06	0.50	0.44	1.00	
Alternaria	0.05	-0.35	-0.35	0.25	0.09	0.16	1.00
Temperature							
Maximum	0.32	-0.01	-0.04	0.44	0.55	0.46	0.18
Mean	0.10	0.02	-0.06	0.28	0.56	0.43	0.08
Minimum	0.01	0.11	0.04	0.14	0.49	0.35	-0.02
Humidity							
Mean	-0.16	0.36	0.37	-0.20	0.03	-0.05	-0.30
Rainfall (>1mm)	-0.33	0.32	0.26	-0.28	-0.01	-0.12	-0.33

The study period at Wallsend was from 28 February 1994 to 30 October 1994 (245 days, or 35 weeks)
All correlations above 0.13 or below –0.13 were statistically significant at α=0.05
Correlations between total pollen and its constituents (grass pollen and weed pollen) are not very informative but are provided for completeness.
PM10: particle mass concentration < 10μm.

Table 6.7. Matrix of Spearman's rank correlation coefficients between daily concentrations of ambient air quality measures and meteorological measures, at Mayfield

	PM10	SO_2 (max)	SO_2 (mean)	Pollen (total)	Pollen (grass)	Pollen (weed)	Alternaria
PM10	1.00						
Sulphur dioxide							
Maximum	0.57	1.00					
Mean	0.46	0.76	1.00				
Pollen & fungi							
Total pollen	0.33	0.13	0.08	1.00			
Grass pollen	0.20	0.03	0.25	0.58	1.00		
Weed pollen	0.38	0.19	0.21	0.61	0.45	1.00	
Alternaria	0.18	0.15	0.19	0.17	0.14	0.20	1.00
Temperature							
Maximum	0.58	0.38	0.49	0.57	0.48	0.56	0.30
Mean	0.33	0.12	0.41	0.46	0.53	0.49	0.15
Minimum	0.18	0.01	0.36	0.28	0.47	-0.31	0.07
Humidity							
Mean	-0.14	-0.04	0.17	-0.36	-0.08	-0.34	-0.15
Rainfall (>1mm)	-0.34	-0.28	-0.10	-0.19	-0.00	-0.22	-0.26

The study period at Mayfield was from 28 February 1994 to 30 October 1994 (245 days, or 35 weeks)
All correlations above 0.13 or below –0.13 were statistically significant at α=0.05
Correlations between total pollen and its constituents (grass pollen and weed pollen) are not very informative but are provided for completeness.
PM10: particle mass concentration < 10μm.

Table 6.8. Matrix of Spearman's rank correlation coefficients between daily concentrations of ambient air quality measures and meteorological measures, at Beresfield

	PM10	SO_2 (max)	SO_2 (mean)	Pollen (total)	Pollen (grass)	Pollen (weed)	Altern aria
PM10	1.00						
Sulphur dioxide							
Maximum	0.29	1.00					
Mean	0.26	0.88	1.00				
Pollen & fungi							
Total pollen	0.28	0.05	0.06	1.00			
Grass pollen	-0.19	-0.03	-0.02	0.26	1.00		
Weed pollen	0.03	-0.03	-0.15	0.47	0.39	1.00	
Alternaria	-0.20	-0.27	-0.26	0.22	0.48	0.29	1.00
Temperature							
Maximum	0.12	-0.01	-0.03	0.03	0.20	0.17	0.16
Mean	-0.15	-0.19	-0.16	-0.24	0.36	0.10	0.23
Minimum	-0.21	-0.09	-0.04	-0.37	0.35	-0.01	0.20
Humidity							
Mean	-0.49	-0.12	-0.07	-0.42	0.25	-0.13	0.15
Rainfall (>1mm)	-0.42	-0.21	-0.11	-0.20	0.06	-0.18	0.10

The study period at Beresfield was from 29 August 1994 to 23 April 1995 (238 days, or 34 weeks). However, sulphur dioxide measurement was undertaken on only 90 days.

All correlations above 0.13 or below –0.13 were statistically significant at α=0.05

Correlations between total pollen and its constituents (grass pollen and weed pollen) are not very informative but are provided for completeness.

PM10: particle mass concentration < 10μm.

Table 6.9. Matrix of Spearman's rank correlation coefficients between daily concentrations of ambient air quality measures and meteorological measures, at North Lake Macquarie

	PM10	SO_2 (max)	SO_2 (mean)	Pollen (total)	Pollen (grass)	Pollen (weed)	Alternaria
PM10	1.00						
Sulphur dioxide							
Maximum	0.32	1.00					
Mean	0.32	0.97	1.00				
Pollen & fungi							
Total pollen	0.29	0.42	0.42	1.00			
Grass pollen	0.13	0.19	0.19	0.56	1.00		
Weed pollen	0.18	0.18	0.19	0.63	0.58	1.00	
Alternaria	0.16	0.35	0.33	0.66	0.62	0.59	1.00
Temperature							
Maximum	0.33	0.27	0.28	0.18	0.25	0.26	0.33
Mean	0.11	-0.06	-0.05	-0.15	0.22	0.11	0.25
Minimum	-0.01	-0.21	-0.22	-0.37	0.11	-0.12	0.05
Humidity							
Mean	-0.24	-0.13	-0.13	-0.30	0.03	-0.19	-0.07
Rainfall (>1mm)	-0.33	-0.06	-0.06	-0.25	-0.01	-0.05	-0.10

The study period at North Lake Macquarie was from 22 August 1994 to 9 April 1995 (231 days, or 33 weeks)
All correlations above 0.13 or below –0.13 were statistically significant at α=0.05
Correlations between total pollen and its constituents (grass pollen and weed pollen) are not very informative but are provided for completeness.
PM10: particle mass concentration < 10μm.

6.6 Summary

Concentrations of the pollutants in the industrial areas were lower during this study than was anticipated from concentrations measured in previous years. Mean daily PM10 was well below the national recommended level of 150 μg/m^3. Similarly, sulphur dioxide levels were mostly below 12.5pphm, with exceedences on only 2 days. The concentrations of ozone and nitrogen dioxide were slightly lower than those reported in two studies in Sydney which found an association between pollutants and respiratory health (Morgan *et al.* 1998a; Jalaludin *et al.* 2000). However, the focus of this thesis was on industrial pollutants, and so ozone and nitrogen dioxide were not used in statistical modelling.

Concentrations of the pollutants in the control areas were unexpectantly high. PM10 concentrations at the control area Beresfield were similar to that in the industrial area North Lake Macquarie. Sulphur dioxide concentrations at Wallsend were also unexpectantly high.

The mean daily pollen count across all study areas for the 14 months of 37 grains/m^3 was comparable to that reported in Western Sydney during the same period (Jalaludin *et al.* 2000). However, the Alternaria levels in this present study, mean 7 spores/m^3, were approximately one-fifth the size experienced in Western Sydney during the same year. A panel study conducted in America which reported associations between Alternaria and respiratory health, reported mean daily Alternaria of 99 spores/m^3 (Delfino *et al.* 1997). Hence, it was not expected that associations between Alternaria and respiratory health would be found in this present study. The Melbourne pollen group classifies grass pollen counts into three groups: low (less than 20 grains), moderate (20-49 grains), high (50-99) and extreme (greater than 100). Using this classification, high grass pollen was only experienced at Stockton, and this occurred for one day only.

There was concern regarding the quality of the sulphur dioxide data provided for three of the five study areas. Of particular concern was the data provided for North Lake Macquarie, which was chosen because of its high sulphur dioxide, in fact the highest in the state. The pollen data were missing during several periods for three of the study areas due to machine breakdowns. Unfortunately, these lapses in data tended to coincide with the spring pollen season. All industrial study areas had substantial within-area variation in air pollutant concentration. Such measurement error is likely to result in estimates of the effect of air quality on health to be biased toward the null.

Particulates were positively correlated with sulphur dioxide in two areas and temperature at Mayfield. It was negatively correlated with humidity in two study areas. Such correlation will be taken into account during the modelling phase of the analysis. The next chapter reports on the effect of air quality on evening peak flow, after adjustment for these climate-related covariates.

Chapter 7 . Results – Effect of air quality on evening peak flow

An analysis of evening peak flow (EPF) was performed for each of the air quality measures individually, in what are termed individual exposure models (Section 7.1). The air quality measures examined included particulates, sulphur dioxide, total pollen, grass pollen, weed pollen, tree pollen and Alternaria. Complete analyses are presented for particulates, given the focus of this thesis was on estimating the effects of particulates on respiratory health. Summaries only are provided for the other measures. The results in Section 7.1 are presented in order of complexity of the modelling approaches used. Firstly, results from the Aggregate models are presented, and then those from non-aggregate models where both the Korn-Whittemore (K-W) analysis and generalised estimating equations (GEEs) were used. All models relate the levels of EPF with the air quality levels measured on the same day, and the average air quality over the current and previous four days (so called 5-day average models). All analyses were adjusted for climate-related predictors and confounders.

Analyses of subgroups that were considered likely to be more susceptible to the effects of particulates are included in Section 7.2. Section 7.3 examines whether there was any confounding from non-climate-related time-varying covariates such as the perception of pollution in the estimated association between particulates and EPF. These covariates were also investigated as potential effect modifiers. Results from the multi-pollutant models are presented in Section 7.4, and a summary and brief discussion of the results is provided in Section 7.5.

7.1 Individual exposure models

7.1.1 Particulates (PM10)

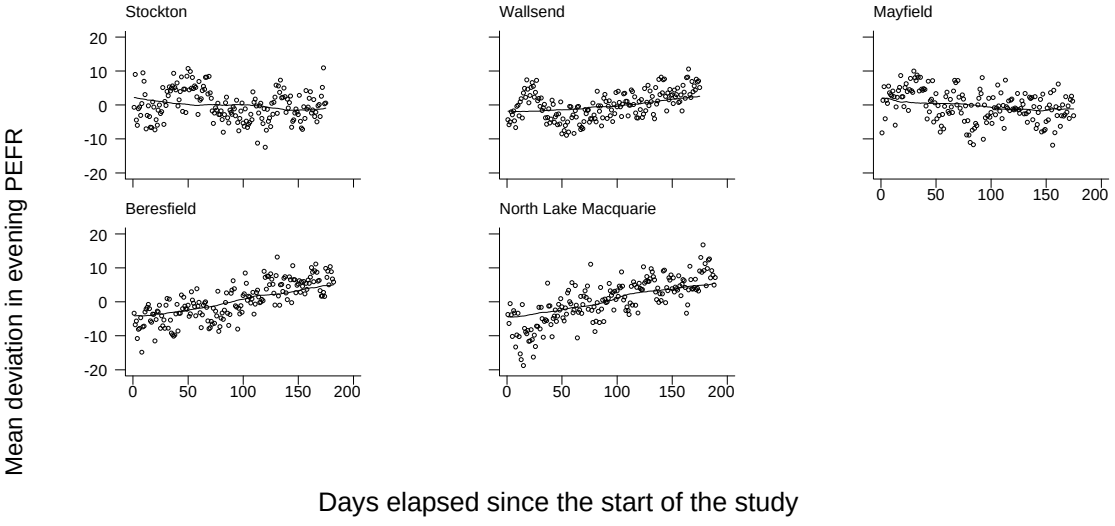
Selection of climate-related covariates

A large array of climate-related measures were collected that were potential predictors of EPF. To restrict the range of factors that would be considered for inclusion in each modelling approach (Aggregate, K-W, GEE), this large group of potential covariates were screened to identify those that were most important. This was done using the first modelling approach (the "Aggregate analysis"). Model selection was made using ordinary least squares regression of aggregated data. Each subject's EPF on each day was expressed as the deviation from their mean EPF over the study and adjusted to a standard of 300 L/min. The mean standardised deviation in EPF was then calculated across all subjects recording EPF each day, and this was

used as the daily outcome in the Aggregate analysis. The variables considered for selection included temperature, humidity, rainfall, trend and month of study.

There were 280 subjects for whom there was an adequate amount of data for inclusion in this analysis, using the criteria described in Section 4.1.3. Figure 7.1 presents scatter plots of mean standardised EPF deviation against days elapsed, and a smoothed function curve. The Aggregate analysis period for study areas in Wave 1 (Stockton, Wallsend and Mayfield) was from late March to September. Each was 25 weeks duration. The Aggregate analysis period for Wave 2 (Beresfield and North Lake Macquarie) was from September to March. Beresfield was 26 weeks duration and North Lake Macquarie was 27 weeks duration. In the first wave there was no evidence of a drop in peak flow corresponding to the winter period. A cyclical pattern was observed at Stockton and to some extent at Wallsend, but not at Mayfield. However, lung function showed a steady improvement over the course of the study period in the second wave.

Figure 7.1. Mean standardised deviation in evening peak flow (L/min) on any one day against number of days elapsed since the start of the study

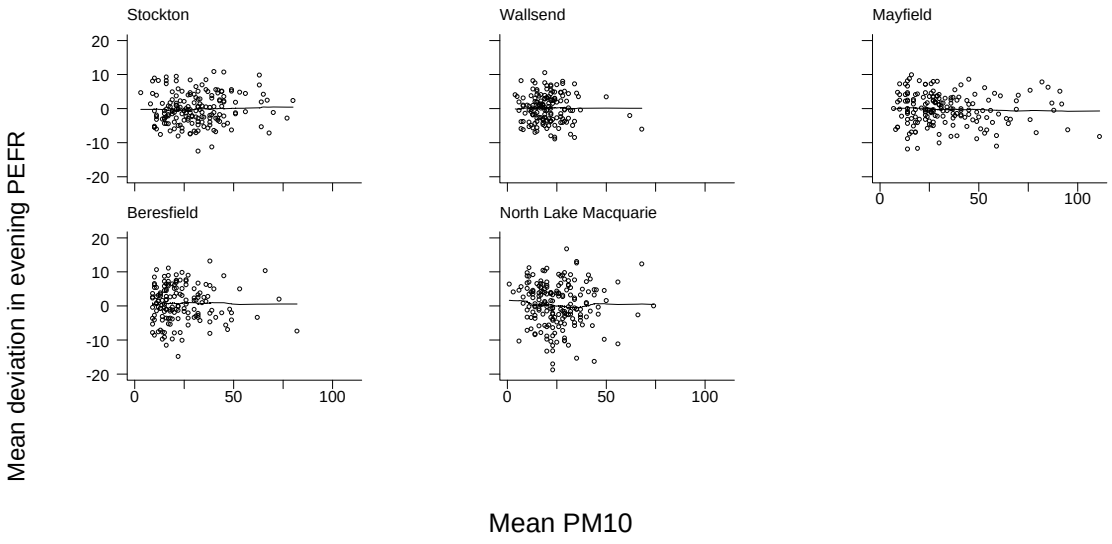


Definition of abbreviations: PEFR= peak expiratory flow rate.
Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994 (Stockton commenced one week earlier than the other two study areas). Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995 (North Lake Macquarie commenced two weeks prior to Beresfield).

In the industrial study areas of Stockton, Mayfield and North Lake Macquarie total suspended particulates (TSP) were measured providing 24-hour average measures. In the control study areas of Wallsend and Beresfield, PM10 was directly measured using a Tapered Element

Oscillating Microbalance (TEOM) providing both hourly and 24-hour average measures. To ensure comparability of the results, TSP were scaled to equivalent PM10 measures using a locally derived conversion factor as outlined in Section 6.2.1. The industrial study areas Stockton, Mayfield and North Lake Macquarie each had less than 5 days with missing PM10 data. The control areas Wallsend and Beresfield had 26 and 35 days with missing PM10 data respectively. Figure 7.2 shows scatter plots of mean standardised EPF deviation against mean daily PM10 concentrations, and a smoothed function curve. There was little evidence of an association between PM10 and EPF.

Figure 7.2. Mean standardised deviation in evening peak flow (L/min) on any one day against mean PM10 (μg/m^3) recorded that day



Definition of abbreviations: PEFR= peak expiratory flow rate.
Children in Wave 1 that was comprised of Stockton, Wallsend and Mayfield completed diaries from March 1994 to September 1994. Children in Wave 2 that was comprised of Beresfield and North Lake Macquarie completed diaries from September 1994 to March 1995.

For demonstration purposes complete analyses are presented in this section for the Mayfield study area only. The results of fitting the univariable linear regression models to the Mayfield data are given in Table 7.1. In this table, for each variable listed in the first column, the following information is presented: (1) The estimated slope coefficient for the univariable linear regression model containing only this variable, (2) the estimated standard error of the estimated slope coefficient, (3) the p-value for the hypothesis that the slope coefficient was zero.

Table 7.1. Results of fitting univariable linear regression models containing PM10 and climate-related variables. The dependent variable in all models was mean standardised evening peak flow deviation (L/min). Mayfield only

Variable	Estimate (SE)	p-value
PM10	-0.017 (0.017)	0.31
Same day climate-related		
Daily maximum temperature	0.12 (0.10)	0.21
Daily minimum temperature	0.22 (0.11)	0.04
Daily average temperature	0.19 (0.11)	0.11
Daily temperature range	-0.07 (0.11)	0.53
Daily average humidity	0.06 (0.02)	0.007
Rainfall ≥ 20 versus < 20 mm	4.42 (2.06)	0.03
Rainfall ≥ 1 versus < 1 mm	1.13 (0.94)	0.23
Previous day climate-related		
Daily maximum temperature	0.09 (0.10)	0.37
Daily minimum temperature	0.29 (0.11)	0.007
Daily average temperature	0.23 (0.11)	0.04
Daily temperature range	-0.22 (0.11)	0.05
Daily average humidity	0.08 (0.02)	0.001
Rainfall ≥ 20 versus < 20 mm	3.20 (2.07)	0.12
Rainfall ≥ 1 versus < 1 mm	2.42 (0.93)	0.01
Days elapsed since the start of the study	-0.03 (0.006)	<0.0001
Month		
March/April 1994	Reference	0.0004
May 1994	-0.41 (1.14)	
June 1994	-3.84 (1.15)	
July 1994	-2.66 (1.14)	
August 1994	-3.84 (1.14)	
Sept /Oct 1994	-3.68 (1.21)	

Any variable whose univariable test had a p-value less than 0.25 was retained for inclusion in a multivariable model. There was a problem with collinearity between month and days elapsed as evidenced by the dramatic change in the standard errors of their estimates. But it seemed important to include both in the model as otherwise there would be residual confounding of the estimate of PM10. The model was simplified by successively deleting the covariate with the least significant coefficient until all the estimated coefficients had a p-value less than 0.10. Excluded variables were added back into the model and if they were either an important confounder or statistically significant (p-value less than 0.10) then they were retained and entered simultaneously into the model. This preliminary main effects model is shown in Table 7.2.

Table 7.2. Results of fitting a multivariable linear regression model containing PM10 and climate-related variables. The dependent variable was mean standardised evening peak flow deviation (L/min). Mayfield Only

Variable	Estimate (SE)	p-value
PM10	-0.042 (0.017)	0.01
Previous day's daily average humidity	-0.06 (0.02)	0.03
Days elapsed since the start of the study	-0.099 (0.039)	0.01
Month		
March/April 1994	Reference	0.001
May 1994	2.28 (1.58)	
June 1994	1.07 (2.65)	
July 1994	5.09 (3.74)	
August 1994	7.94 (4.81)	
Sept /Oct 1994	11.37 (5.83)	

The next step in the modelling process was to check the scale of the three continuous covariates in the model. A first-order fractional polynomial was fitted to the data. At Mayfield, the best-fitting power for PM10 was P=3, indicating a cubic transform. This model had a deviance 0.861 lower than a straight line so the hypothesis that P=1 was accepted (p-value > 0.05). Similarly, when average humidity and days elapsed was tested with fractional polynomials the best model was the linear model. Variables were then removed if they were neither statistically significant at 0.05 nor an important confounder. At Mayfield this resulted in the removal of no terms. This was the main effects model. There was no evidence of an interaction between PM10 and the other terms at Mayfield (Table 7.3).

Table 7.3. Log-likelihood, likelihood ratio test statistic, degree of freedom (df) and p-value for interactions of interest when added to the main effects model. Mayfield Only

Interaction	Log-likelihood	Likelihood ratio test statistic chi-square	df	p-value
Main effects model	-486.38			n.a.
PM10 X humidity	-486.32	0.12	1	0.74
PM10 X days elapsed	-485.42	1.91	1	0.18
PM10 X month	-482.99	6.75	5	0.24

The climate-related covariates for each study area are shown in Table 7.4. Mean humidity and minimum temperature were important predictors in at least one study area, but it was still necessary to include terms for month to capture important (possibly climatic) sources of variation. There was a significant positive trend in EPF with days elapsed for Wallsend, Mayfield and Beresfield (where a positive trend was expected as the study progressed into

summer). All subsequent regression models included adjustment for these climate-related covariates.

Table 7.4. Climate-related covariates which were included in all PM10 regression models because they were confounders or were independently associated with mean standardised evening peak flow deviation (L/min).

	Study area				
	S	**W**	**M**	**B**	**NLM**
Same day climate-related					
Daily maximum temperature	Y	-	-	-	Y
Daily minimum temperature	-	Y	-	-	-
Daily average temperature	Y	-	-	-	-
Daily temperature range	Y§	-	-	-	Y§
Daily average humidity	-	Y	-	Y	Y
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	Y
Rainfall ≥ 1 versus < 1 mm	Y	Y	-	Y§	-
Previous day climate-related					
Daily maximum temperature	-	-	-	Y§	-
Daily minimum temperature	-	Y	-	-	Y§
Daily average temperature	-	-	-	-	-
Daily temperature range	-	-	-	-	-
Daily average humidity	Y	Y	Y§	Y	Y
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	-
Rainfall ≥ 1 versus < 1 mm	-	-	-	-	-
Days elapsed since the start of the study	Y§	Y§	Y§	Y§	Y
Month	Y§	Y§	Y§	Y§	Y§

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.
§. p-value <0.05.

Aggregate analysis

There was no evidence of an association between EPF and same-day PM10 in any study area in a univariable analysis. However, when adjustment was made for climate-related covariates there was evidence of an association at Mayfield. Here, a mean decrease of 0.85 L/min per interquartile range increase (20 $\mu g/m^3$) in PM10 was observed with a standard error of 0.35 (Mayfield: -0.85(0.35) L/min). This represents a 0.28% reduction in the mean peak flow of 300 L/min. There was heterogeneity between study areas (χ^2=10.60, df=4, p-value=0.03) and results were pooled across study areas using a random effects approach. The Hunter Region estimate was –0.13 (0.37) L/min. Refer to Table 7.5 for the results of this analysis.

Table 7.5. The effect of a 20 μg/m^3 increase in mean PM10 on evening peak flow (L/min): Aggregate analysis

	PM10 measured same day	
	Unadjusted	Adjusted†
By study area		
Stockton	+0.43 (0.48)	-0.29 (0.53)
Wallsend	-0.63 (0.77)	-0.66 (0.69)
Mayfield	-0.35 (0.34)	-0.85 (0.34)§
Beresfield	-0.13 (0.69)	+1.25 (0.58)§
NLM	-0.55 (0.79)	+0.11 (0.55)
Pooled ‡		
Wave 1	-0.15 (0.26)	-0.68 (0.26)§
Wave 2	-0.31 (0.52)	+0.66 (0.41)§
Hunter Region	-0.18 (0.23)	-0.13 (0.37)

Estimates and standard errors (in parentheses) are reported. The pollutant was fitted as a linear term on the same day of peak flow measurement.
In the Aggregate analysis, the data points were daily averages and the dependent variable was mean standardised EPF deviation.
†. In the adjusted analysis each estimate of effect of PM10 has been adjusted by climate-related covariates but not autocorrelation.
‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.
§. p-value <0.05.

Separate autoregressive models were fitted for each study area. Table 7.6 shows the coefficient of determination (R^2 values) and AR-1 coefficients for each of the study areas, where PM10 was fitted as a linear term using the same day of peak flow measurement. Similar coefficients of determination and AR-1 coefficients were found for pollution modelled using the 5-day average and so are not included here.

Table 7.6. Coefficient of determination from multivariable models fitting mean daily PM10 as a function of mean standardised evening peak flow deviation: Aggregate analysis

	S	W	M	B	NLM
Coefficient of determination (R^2)	40%	52%	27%	69%	70%
AR-1 term	0.24§	0.27§	0.11	0.29§	0.18§

The R^2 was obtained from a model containing same day PM10 , climate-related covariates and an autocorrelation term.
§. p-value <0.05.

Table 7.7 shows the effect of a 20 μg/m^3 increase in PM10 on EPF after adjusting for the climate-related covariates and autocorrelation in the Aggregate analysis. The only significant association between PM10 and EPF occurred at Beresfield. Here, an increase of 1.09 L/min per 20 μg/m^3 increase in same day PM10 was observed. Different sample sizes were taken into account by weighting the data from each day by the number of children reporting an EPF. This had little impact on the estimates. When the 5-day average model was used the effect of PM10 on EPF was stronger (-1.31 L/min) than for same day (-0.77 L/min) but the standard errors had doubled.

Table 7.7. The effect of a 20 μg/m^3 increase in mean PM10 on evening peak flow (L/min): Aggregate analysis

	PM10 measured same day		Average PM10 measured on current and previous 4 days (5-day average)	
	Unweighted	Weighted †	Unweighted	Weighted †
By study area				
Stockton	-0.37 (0.52)	-0.40 (0.52)	-0.75 (0.75)	-0.75 (0.76)
Wallsend	-0.46 (0.67)	-0.43 (0.66)	-1.71 (0.92)	-1.73 (0.92)
Mayfield	-0.51 (0.35)	-0.48 (0.35)§	-0.86 (0.50)	-0.75 (0.49)
Beresfield	+1.09 (0.56)§	+1.04 (0.56)	+0.94 (0.64)	+0.96 (0.64)
NLM	+0.13 (0.54)	+0.15 (0.55)	+0.29 (0.97)	+0.24 (0.99)
Pooled ‡				
Wave 1	-0.46 (0.27)§	-0.45 (0.27)§	-0.98 (0.38)§	-0.91 (0.37)§
Wave 2	+0.60 (0.39)	+0.59 (0.39)	+0.75 (0.53)	+0.75 (0.54)
Hunter Region	-0.07 (0.29)	-0.08 (0.28)	-0.39 (0.44)	-0.37 (0.44)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted by climate-related covariates and autocorrelation as required. The pollutant was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

In the Aggregate analysis, the data points were daily averages and the dependent variable was mean standardised EPF deviation.

†. In the weighted analyses, the data were weighted by the number of children reporting EPF.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05.

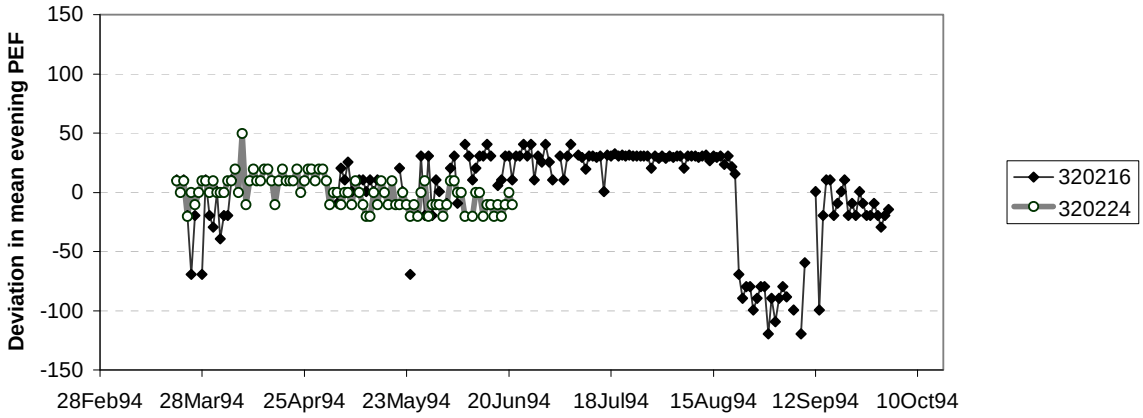
The deviance residuals for each study area were approximately normally distributed and showed no non-random trends or patterns, indicating that the models were correctly specified. Residual

plots revealed that the cyclical behaviour apparent in the plots for Stockton and Wallsend had been explained by the models. The Durbin Watson test was between 2.0 and 2.1 in all study areas indicating that there was no residual autocorrelation in the errors. Values with high leverage or large residuals as determined by the Cook's Distance were removed in one analysis, and the regression coefficients were stable.

Korn-Whittemore analysis

Two hundred and thirty-nine subjects were eligible for the non-aggregate analysis because they completed the diary on a sufficient number of days. However, four children were omitted due to an insufficient number of EPF measurements. Hence the Korn-Whittemore and GEE analysis was restricted to 235 children. The number of days that EPF was recorded per subject ranged from 67 to the maximum possible 196 days, with a median of 177 days. The number of person-days for analysis was 38810 (84%). In the non-aggregate analysis, the outcome variable was EPF deviation. The data for two children from the Mayfield study area are shown in Figure 7.5.

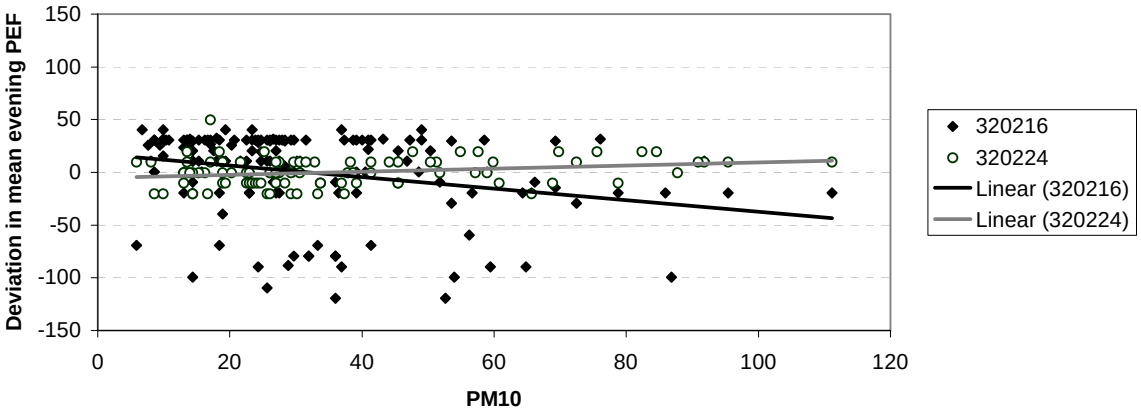
Figure 7.3. Timeplot of evening peak flow deviation (L/min) for two children from the Mayfield study area



The timeplot is for two children with study number 320224 and 320216. The two lines join the children's data on successive days.

Regression models were obtained for each child for same-day exposure with adjustment for the previously identified climate-related covariates and autocorrelation. Figure 7.6 shows a plot of EPF deviation versus PM10 concentration for the same two children.

Figure 7.4. Child-specific regressions of evening peak flow (L/min) against same day PM10 for two children from the Mayfield study area. Results from the Korn-Whittemore analysis



The coefficient (i.e. slope) for study number 320216 was estimated to be –5.23 L/min per 20 μg/m^3 increase in PM10. The coefficient for study number 320224 was estimated to be +2.22 L/min per 20 μg/m^3 increase in PM10.

PM10 had an inconsistent influence upon the EPF of individual children. At Mayfield, the subject-specific coefficients ranged from –5.30 L/min to +6.65 L/min per 20 μg/m^3 increase in PM10. Two children had a statistically significant decrease in peak flow in response to an increase in PM10, and one child showed a statistically significant improvement of their peak flow in response to PM10, and the remaining 43 children showed no significant change. The estimates from each child were pooled across study areas using two approaches, an unweighted analysis, and an analysis weighted by the number of observations. They were not pooled using the standard errors because a relationship was found between the subject-specific estimates and their standard errors (refer to Figure 4.4). The results of the Korn-Whittemore analysis are presented in Table 7.8. In the unweighted analysis of same-day PM10 there were no significant associations in any study area, and the Hunter Region estimate was –0.02 (0.23) L/min per 20 μg/m^3 increase in PM10. When the estimates were pooled with weights determined by the number of observations contributed by the child the results were very similar. Using the 5-day average model and weighting there was a significant reduction in peak flow, and the Hunter Region estimate was –0.89 (0.48) L/min.

Table 7.8. The effect of a 20 μg/m^3 increase in mean PM10 on evening peak flow (L/min): Korn-Whittemore analysis

	Same day		5-day average	
	Unweighted	Weighted†	Unweighted	Weighted†
By study area				
Stockton	+0.07 (0.54)	+0.13 (0.54)	-1.43 (1.14)	-1.29 (1.14)
Wallsend	-0.26 (0.58)	-0.23 (0.58)	-1.69 (0.97)	-1.98 (0.97)§
Mayfield	-0.09 (0.35)	-0.15 (0.35)	-0.23 (0.82)	-0.32 (0.82)
Beresfield	+0.96 (0.73)	+0.89 (0.73)	+0.91 (1.30)	+0.27 (1.30)
NLM	-0.31 (0.60)	-0.41 (0.60)	-0.84 (1.59)	-1.04 (1.59)
Pooled ‡				
Wave 1	-0.09 (0.26)	-0.10 (0.26)	-0.98 (0.55)§	-1.08 (0.55)§
Wave 2	+0.21 (0.48)	+0.13 (0.50)	-0.20 (1.01)	-0.26 (1.01)
Hunter Region	-0.02 (0.23)	-0.05 (0.23)	-0.71 (0.48)	-0.89 (0.48)§

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted for climate-related covariates and autocorrelation as required. The pollutant was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

In the Korn-Whittemore analysis child specific regressions were fitted with the dependent variable evening peak flow deviation. The child specific regression coefficients were then pooled across children using a fixed effect approach. The analysis was based on 235 children.

†. In the weighted analyses, the child specific regression coefficients were weighted by the number of observations contributed for each child.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05.

Generalised Estimating Equations analysis

Linear regression analysis using GEE was used to model EPF (outcome variable) on PM10 and the climate-related covariates. The level of clustering for this analysis was the child. In response to a 20 μg/m^3 increase in same day PM10, the children had an increase in EPF of 0.10 (0.23) L/min, and using the 5-day average a decrease of 0.25 (0.41) L/min. The results from the GEE analysis are shown in Table 7.9. A model was fitted which included all children, termed the 5-day average Hunter Region model. It included terms for month of study, daily average humidity, days elapsed since the start of the study, study wave, and an interaction between wave and days elapsed. Similar estimates were obtained using this model though the standard errors were smaller (–0.04 (0.38) L/min).

Table 7.9. The effect of a 20 μg/m^3 increase in mean PM10 on evening peak flow (L/min): marginal (GEE) analysis

	Same day	5-day average
By study area		
Stockton	-0.05 (0.64)	-1.17 (1.08)
Wallsend	+0.29 (0.52)	-0.53 (0.93)
Mayfield	-0.09 (0.32)	-0.14 (0.62)
Beresfield	+0.94 (0.77)	+0.63 (1.13)
NLM	+0.12 (0.68)	-0.03 (1.41)
Pooled ‡		
Wave 1	+0.01 (0.25)	-0.43 (0.47)
Wave 2	+0.48 (0.51)	+0.38 (0.88)
Hunter Region	+0.10 (0.23)	-0.25 (0.41)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted for climate-related covariates and autocorrelation as required. The pollutant was fitted as a linear term on the same day as peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

In the GEE analysis, the dependent variable was evening peak flow deviation. The analysis was based on 235 children.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§ p-value <0.05

The results were reasonably robust to different model specifications. For example, when missing PM10 data were imputed using PROC EXPAND similar results were obtained for the 5-day average model. The 5-day average Hunter Region GEE model was refitted after removing children with unusual EPF measurements. In this analysis, nine subjects with at least one reported peak flow greater than 500 L/min were excluded as well as 18 subjects who had a peak flow as a multiple of 50 on more than 100 days, and 5 subjects who had peak flow less than 160 L/min on 10 or more days. The results were very similar with a 20 μg/m^3 increase in PM10 associated with an increase of 0.18 (0.43) L/min for the overall group.

A naïve model was fitted which ignored the correlations between repeated measures on subjects. This resulted in similar estimates, but much smaller standard errors than the GEE as expected (Hunter Region: -0.29 (0.39)). A GEE model with robust standard error estimates was also fitted using the 5-day average PM10 (Hunter Region: -0.30 (0.45)). Due to site variation in the timing of particulate measurements, previous 24-hour models of PM10 use the average of current and previous days at Stockton and North Lake Macquarie, and measures taken on the same day for

the other study areas. No association was found between PM10 and EPF for the previous 24-hour period (Hunter Region: +0.04 (0.23)). In a further analysis, EPF was analysed as a dichotomous variable (deviations more than 20% below the median) rather than a continuous variable. An increase of 20 $\mu g/m^3$ in 5-day average PM10 was not associated with a corresponding increase in the prevalence of large decrements in EPF (Odds Ratio 0.93 95% CI: 0.78 to 1.12).

In general, there are many measurements of particulates available. In this study the measurements included TSP, mean daily PM10, max daily PM10, mean daily PM2.5, mean daily daytime PM10, and max daily daytime PM10. The results above were based on using TSP and mean daily PM10. PM2.5 was recorded at Mayfield and Wallsend only by Australian Nuclear Science and Technology Organisation (ANSTO) using a size-selective inlet. The GEE analysis was repeated for mean PM2.5 at Mayfield but no significant associations were observed (same day: +0.18 (0.88) L/min, 5-day average: +1.11 (2.25) L/min).

There was a tendency for those subjects with a high proportion of incomplete data to have above average EPF. The subjects were stratified by the amount of missing data during the study period into five equal sized groups. The mean EPF for the group with the largest amount of missing data was 331 L/min, compared to 314 L/min for the group with very few missing data, but the test for trend was not statistically significant (Means: 331, 312, 323, 317, 314 respectively; p-value=0.21). Multiple imputation was used to determine the likely size of the bias due to missing data. On repeating the GEE analysis with missing EPF data imputed with the predicted values generated in the K-W analysis, the results remained similar for the overall group, with +0.13 (0.24) L/min for same-day PM10 and –0.07 (0.46) L/min for 5-day average PM10.

The model was refitted for various lag structures. The results from these models are presented in Table 7.10. The largest estimates were observed in the lag 4 and the 5-day average models.

Table 7.10. The effect of a 20 μg/m^3 increase in mean PM10 on evening peak flow (L/min). Results of various lag models using GEE analysis

	Wave 1	Wave 2	Hunter Region
Single day lags			
Lag 0	+0.01 (0.25)	+0.48 (0.51)	+0.10 (0.23)
Lag 1	-0.13 (0.25)	-0.08 (0.37)	-0.11 (0.21)
Lag 2	+0.15 (0.24)	+0.28 (0.46)	+0.18 (0.21)
Lag 3	-0.12 (0.22)	-0.17 (0.38)	-0.13 (0.19)
Lag 4	-0.51 (0.25)§	+0.14 (0.32)	-0.26 (0.20)
Lag 5	+0.24 (0.28)	+0.10 (0.37)	+0.19 (0.22)
Averages			
2-day average	-0.16 (0.34)	+0.32 (0.54)	-0.02 (0.29)
3-day average	-0.08 (0.40)	+0.46 (0.69)	+0.06 (0.34)
4-day average	-0.06 (0.44)	+0.58 (0.69)	+0.12 (0.37)
5-day average	-0.43 (0.47)	+0.38 (0.88)	-0.25 (0.41)
6-day average	-0.46 (0.58)	+0.34 (1.01)	-0.26 (0.50)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted for climate-related covariates and autocorrelation as required.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

Summary of PM10 results so far

In the univariable Aggregate analysis there was no evidence of an association between same-day PM10 and EPF in any study area. After adjustment for climate-related confounders (but not autocorrelation), there was a significant association between PM10 and EPF at Mayfield only (a reduction of 0.85 L/min per 20 μg/m^3 increase in PM10). This represents a 0.28% reduction in EPF from the average of 300 L/min. In the Aggregate analysis upon adjustment for both the climate-related confounders and autocorrelation the association was no longer statistically significant. Various lags were fitted into the models and they yielded similar results. The strongest association was seen using a 5-day average model but the results remained non-significant at Mayfield (-0.75 L/min). The Wave 1 estimate was –0.91 (0.37) L/min and the Wave 2 estimate was +0.75 (0.54) L/min, with the former being statistically significant. In the Korn-Whittemore analysis, where subject-specific estimates were pooled using fixed effects and weighted by the number of days of observation for the child, the Wave 1 estimate under the 5-

day average model was –1.08 (0.55) L/min and the Wave 2 estimate was –0.26 (1.01) L/min, with the former again being statistically significant. In the GEE analysis the Wave 1 estimate under the 5-day average model was –0.43 (0.47) L/min and the Wave 2 estimate was +0.38 (0.88) L/min; neither were statistically significant. The results from the Aggregate, Korn-Whittemore and GEE approaches are summarised in Table 7.11.

Table 7.11. The effect of a 20 μg/m^3 increase in mean PM10 on evening peak flow (L/min): Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	-0.40 (0.52)	-0.75 (0.76)	-0.13 (0.54)	-1.29 (1.14)	-0.05 (0.64)	-1.17 (1.08)
Wallsend	-0.43 (0.66)	-1.73 (0.92)	-0.23 (0.58)	-1.98 (0.97)	+0.29 (0.52)	-0.53 (0.93)
Mayfield	-0.48 (0.35)	-0.75 (0.49)	-0.15 (0.35)	-0.32 (0.82)	-0.09 (0.32)	-0.14 (0.62)
Beresfield	+1.04 (0.56)	+0.96 (0.64)	-0.89 (0.73)	+0.27 (1.30)	+0.94 (0.77)	+0.63 (1.13)
NLM	+0.15 (0.55)	+0.24 (0.99)	-0.41 (0.60)	-1.04 (1.59)	+0.12 (0.68)	-0.03 (1.41)
Pooled‡						
Wave 1	-0.45 (0.27)§	-0.91 (0.37)§	-0.10 (0.26)	-1.08 (0.55)§	+0.01 (0.25)	-0.43 (0.47)
Wave 2	+0.59 (0.39)	+0.75 (0.54)	-0.13 (0.50)	-0.26 (1.01)	+0.48 (0.51)	+0.38 (0.88)
Hunter Region	-0.08 (0.28)	-0.37 (0.44)	+0.05 (0.23)	-0.89 (0.48)§	+0.10 (0.23)	-0.25 (0.41)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted by climate-related covariates and autocorrelation as required. PM10 was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate model where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

The analysis of these data has produced a number of interesting findings with respect to the best exposure lag model, the comparison of statistical techniques and the differences between the two waves. Using the criteria provided by a number of researchers, the best model was the 5-day average because it provided the largest negative coefficient. It was intriguing to find differences between the two waves that were not changed by the intensive multivariable

adjustment for climate-related covariates. The small effect sizes and the differences in effect sizes between the two waves leads to the conclusion that there was no effect of PM10 on EPF for the group as a whole.

These preceding analyses were adjusted for climate-related predictors and confounders. In Sections 7.2 to 7.4 analyses have been further adjusted for non climate-related predictors and confounders including medication use.

7.1.2 Sulphur dioxide (SO_2)

Sulphur dioxide monitoring did not commence at Beresfield until half-way through the study resulting in 136 days with missing data (69% of the study period). Hence this analysis excluded all children from Beresfield. There were less than 12 days with missing sulphur dioxide data in each of the remaining four areas.

Maximum daily sulphur dioxide was the primary measurement used in this analysis. The climate-related covariates used in regression models are listed in Table 7.12. The assumption of linearity was checked using a combination of fractional polynomials and binary shift models. It was determined that sulphur dioxide on the linear scale was appropriate in all study areas.

Table 7.12. Climate-related covariates which were included in all sulphur dioxide regression models because they were confounders or were independently associated with mean standardised evening peak flow deviation (L/min)

	Study area				
	S	**W**	**M**	**B**[†]	**NLM**
Same day climate-related					
Daily maximum temperature	Y	-	-	-	-
Daily minimum temperature	Y[§]	-	Y[§]	-	-
Daily average temperature	-	-	-	-	-
Daily temperature range	-	-	-	-	Y[§]
Daily average humidity	-	-	-	-	Y
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	-
Rainfall ≥ 1 versus < 1 mm	Y[§]	Y	-	-	-
Previous day climate-related					
Daily maximum temperature	Y	-	Y[§]	-	Y
Daily minimum temperature	-	Y[§]	-	-	-
Daily average temperature	Y[§]	-	-	-	Y[§]
Daily temperature range	-	-	-	-	-
Daily average humidity	Y[§]	Y[§]	Y[§]	-	-
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	-
Rainfall ≥ 1 versus < 1 mm	-	-	Y	-	-
Days elapsed since the start of the study	Y[§]	Y[§]	Y[§]	-	Y
Month	Y[§]	Y[§]	Y[§]	-	Y[§]

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.
†. Beresfield was excluded from this analysis due to an insufficient number of sulphur dioxide measurements.
§. p-value <0.05.

In the industrial area of North Lake Macquarie a significant association was observed between sulphur dioxide and EPF in the univariable Aggregate analysis (-0.66 (0.30) L/min per 1.5 pphm increase in SO_2). The coefficient changed direction and was no longer significant when adjusted for climate-related covariates (+0.32 (0.21) L/min). At Stockton and Mayfield there was some evidence of an association between maximum daily sulphur dioxide and EPF (-1.20 (0.59) and –1.65 (0.73) respectively). In both these areas there was evidence of effect modification by climate with greater reductions in peak flow observed during the cooler months. These effects were no longer significant upon adjustment for autocorrelation. The estimates were Wave 1: -0.58 (0.42) L/min, Wave 2: +0.23 (0.21) L/min, and overall: –0.24 (0.30) L/min. The K-W analysis gave an overall result of –0.03 (0.16). The GEE analysis reported overall –0.26 (0.25) but within Stockton there was a significant association. A summary of the main results is presented in Table 7.13.

Table 7.13. The effect of a 1.5 pphm increase in maximum sulphur dioxide on evening peak flow (L/min): Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	-1.23 (0.57)§	-1.05 (1.10)	-1.03 (0.58)	-0.84 (1.59)	-1.17 (0.53)§	-0.40 (1.57)
Wallsend	+0.06 (0.29)	+0.47 (0.58)	+0.04 (0.25)	+0.62 (0.70)	+0.02 (0.23)	+0.40 (0.74)
Mayfield	-1.14 (0.72)	-1.98 (1.28)	-0.42 (0.58)	-0.05 (1.63)	-1.00 (0.54)	-0.31 (1.66)
Beresfield	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
NLM	+0.23 (0.21)	+0.85 (0.39)§	+0.11 (0.15)	+0.55 (0.47)	+0.16 (0.15)	+0.65 (0.42)
Pooled ‡						
Wave 1	-0.58 (0.42)	-0.16 (0.48)	-0.28 (0.30)	+0.33 (0.60)	-0.56 (0.37)	+0.18 (0.62)
Wave 2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hunter Region	-0.24 (0.30)	+0.13 (0.48)	-0.03 (0.16)	+0.47 (0.37)	-0.26 (0.25)	+0.50 (0.35)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of sulphur dioxide has been adjusted by climate-related covariates and autocorrelation as required. Sulphur dioxide was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

n.a. Beresfield was excluded from this analysis due to an insufficient number of sulphur dioxide measurements.

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

When the GEE analysis was repeated for 5-day average maximum daily SO_2 but limited to the 165 children who provided non-suspicious data, the estimates were very similar but now statistically significant (Hunter Region: +0.85 (0.34) L/min). Problems with the sulphur dioxide data at both Wallsend and North Lake Macquarie have been outlined earlier (Section 4.2.2). The EPA provided a revised dataset and when these data were used at Wallsend similar results were obtained. When North Lake Macquarie concentrations were set to missing if zero concentrations were recorded, similar results were obtained for both same day (+0.05 (0.19) L/min) and 5-day average models (+0.71 (0.43) L/min).

All study areas were able to provide both hourly values and 24-hour averages SO_2. A sensitivity analysis was conducted whereby alternative measures of sulphur dioxide were modelled and the

results compared to those obtain using maximum daily SO_2. When daytime maximum was used similar results were obtained for same-day models (Wave 1: -0.53 (0.32), Wave 2: +0.09 (0.19), Hunter Region: -0.26 (0.22)). When mean daily or mean daytime sulphur dioxide was used, stronger effects were seen and there was a trend towards statistical significance (Hunter Region: -1.13 (0.75) and –0.99 (0.64) respectively).

7.1.3 Aeroallergens

Aeroallergens (that is pollens and Alternaria) were measured in each area using a Burkhard spore trap. Aeroallergen data were missing for only 2 days at Stockton and Mayfield. At Wallsend and Lake Macquarie the machine was temporarily broken, resulting in 15 days and 27 days respectively, with no aeroallergens measured. There was some evidence that aeroallergen data were not missing at random in these two study areas. At Wallsend, mean EPF was significantly higher on days with no pollen measurement (4.25 L/min), compared to other days in the study period. At North Lake Macquarie mean EPF was significantly lower (3.57 L/min) on days with no pollen measurement, compared to other days in the study period. Beresfield had 12 days with missing data when the building at which measurements were made was closed over the Christmas period, and the data was missing at random.

The climate-related covariates that were included in all pollen analyses are listed in Table 7.14. Their selection was based on the regression models for total pollen.

Table 7.14. Climate-related covariates which were included in all pollen regression models because they were confounders or were independently associated with mean standardised evening peak flow deviation (L/min)

	Study area				
	S	**W**	**M**	**B**	**NLM**
Same day climate-related					
Daily maximum temperature	-	-	-	-	-
Daily minimum temperature	-	-	Y§	-	-
Daily average temperature	-	-	-	-	-
Daily temperature range	-	-	-	Y	-
Daily average humidity	-	-	-	Y	-
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	-
Rainfall ≥ 1 versus < 1 mm	Y	-	-	Y	Y
Previous day climate-related					
Daily maximum temperature	Y	Y§	-	Y	-
Daily minimum temperature	-	Y§	-	-	Y§
Daily average temperature	-	-	-	-	-
Daily temperature range	-	Y§	-	-	-
Daily average humidity	-	Y§	Y§	Y§	-
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	-
Rainfall ≥ 1 versus < 1 mm	-	-	-	-	-
Days elapsed since the start of the study	Y§	Y§	Y§	Y§	Y§
Month	Y§	Y§	Y§	Y§	Y§

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.
§. p-value <0.05.

The climate-related covariates that were included in all Alternaria analyses are listed in Table 7.15.

Table 7.15. Climate-related covariates which were included in all Alternaria regression models because they were confounders or were independently associated with mean standardised evening peak flow deviation (L/min)

	Study area				
	S	**W**	**M**	**B**	**NLM**
Same day climate-related					
Daily maximum temperature	Y	-	-	Y	-
Daily minimum temperature	-	-	Y§	-	-
Daily average temperature	-	-	-	-	-
Daily temperature range	-	-	-	-	-
Daily average humidity	-	-	-	-	-
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	-
Rainfall ≥ 1 versus < 1 mm	Y	-	-	Y§	-
Previous day climate-related					
Daily maximum temperature	-	Y§	-	-	Y§
Daily minimum temperature	-	Y§	-	-	-
Daily average temperature	-	-	-	-	Y§
Daily temperature range	-	Y§	Y§	Y	-
Daily average humidity	-	Y§	Y§	Y§	-
Rainfall ≥ 20 versus < 20 mm	-	-	-	-	-
Rainfall ≥ 1 versus < 1 mm	-	-	Y§	Y	-
Days elapsed since the start of the study	Y§	Y§	Y§	Y§	Y
Month	Y§	Y§	Y§	Y§	Y§

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.
§. p-value <0.05.

Total pollen

Prior to adjustment for climate-related covariates a significant association between total pollen and EPF was seen in Wave 2 (-0.18 L/min per 30 grain/m^3 increase). A summary of the results after adjustment for climate-related covariates and autocorrelation is shown in Table 7.16. The effect of a 30 grain/m^3 increase in 5-day average total pollen was –0.07 (0.05) L/min from the Aggregate analysis, -0.10 (0.11) from the K-W analysis, and –0.02 (0.08) L/min from the GEE analysis. The effect of the "previous 24-hours" was examined by taking an average of measures taken on the current and previous days. Again, there was no association and the result from the GEE analysis was –0.03 (0.05) L/min.

Table 7.16. The effect of a 30 grains/m^3 increase in total pollen on evening peak flow (L/min): Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	+0.37 (0.73)	+1.17 (1.27)	+1.29 (0.68)	+2.43 (1.92)	+0.78 (0.61)	+2.28 (1.75)
Wallsend	-0.17 (0.18)	+0.05 (0.40)	-0.26 (0.16)	-0.28 (0.53)	-0.13 (0.13)	+0.04 (0.52)
Mayfield	-0.28 (0.54)	-0.27 (1.09)	-0.91 (0.66)	-2.58 (1.76)	-0.48 (0.61)	-1.63 (2.10)
Beresfield	-0.05 (0.04)	-0.07 (0.05)	+0.03 (0.05)	-0.04 (0.08)	+0.01 (0.03)	-0.01 (0.08)
NLM	-0.32 (0.29)	-0.44 (0.38)	-0.64 (0.36)	-1.18 (0.47)	-0.30 (0.44)	-0.54 (0.55)
Pooled ‡						
Wave 1	-0.15 (0.17)	+0.11 (0.36)	-0.05 (0.45)	-0.28 (0.49)	-0.09 (0.17)	+0.12 (0.49)
Wave 2	-0.05 (0.04)	-0.07 (0.05)	+0.02 (0.05)	-0.06 (0.08)	+0.01 (0.03)	-0.02 (0.08)
Hunter Region	-0.05 (0.04)	-0.07 (0.05)	-0.14 (0.15)	-0.10 (0.11)	-0.00 (0.03)	-0.02 (0.08)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of total pollen has been adjusted by climate-related covariates and autocorrelation as required. Total pollen was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

Grass pollen

In the univariable analysis Beresfield was the only study area where a significant association was observed between EPF and grass pollen (+0.90 (0.27) L/min per 4 grains/m^3 increase). After adjusting for the climate-related covariates, statistically significant associations were observed at Stockton, Wallsend and North Lake Macquarie in some though not all models. In all areas the most appropriate scale for grass pollen was linear. The pooled Hunter Region estimate per 4 grain/m^3 increase in 5-day average grass pollen was –0.87 (0.36) in the Aggregate analysis, -0.60 (0.36) in the K-W analysis, and –0.55 (0.33) in the GEE analysis. The results are summarised in Table 7.17.

Table 7.17. The effect of a 4 grains/m^3 increase in grass pollen on evening peak flow (L/min): Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - Weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	-0.44 (0.21)§	-0.92 (0.40)§	+0.14 (0.24)	-0.10 (0.71)	-0.09 (0.18)	-0.47 (0.75)
Wallsend	-1.19 (0.52)§	-2.80 (0.94)§	-0.55 (0.60)	-3.05 (1.75)	-0.25 (0.45)	-1.88 (1.48)
Mayfield	-0.00 (0.51)	-0.91 (0.72)	-0.37 (0.58)	-0.76 (1.24)	+0.03 (0.43)	-0.65 (0.89)
Beresfield	+0.10 (0.18)	+0.03 (0.32)	+0.12 (0.21)	+0.15 (0.66)	+0.12 (0.19)	-0.02 (0.54)
NLM	-0.31 (0.27)	-1.02 (0.46)§	-0.36 (0.31)	-1.35 (0.63)§	-0.16 (0.35)	-1.04 (0.63)
Pooled ‡						
Wave 1	-0.48 (0.18)§	-1.29 (0.49)§	-0.01 (0.21)	-0.69 (0.69)	-0.09 (0.15)	-0.72 (0.54)
Wave 2	-0.02 (0.15)	-0.34(0.29)	-0.03(0.17)	-0.62(0.54)	+0.06(0.17)	-0.45(0.41)
Hunter Region	-0.28 (0.18)	-0.87 (0.36)§	-0.02 (0.13)	-0.60 (0.36)§	-0.02 (0.11)	-0.55 (0.33)§

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of grass pollen has been adjusted by climate-related covariates and autocorrelation as required. Grass pollen was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

Weed pollen

In the univariable Aggregate analysis, there was a significant association between weed pollen and EPF at the two study areas in Wave 2. A 3 grain/m^3 increase in weed pollen was associated with a decrease in EPF of 0.51 (0.20) L/min at Beresfield and 0.60 (0.26) L/min at North Lake Macquarie. After adjusting for the climate-related covariates and autocorrelation significant associations were observed at Wallsend and North Lake Macquarie in the Aggregate analysis, and at Wallsend and Mayfield in the GEE analysis. Using a combination of binary shift models and fractional polynomials it was determined that the most appropriate scale for weed pollen was linear at Wallsend, and binary at Beresfield and North Lake Macquarie. The pooled Hunter Region estimate per 3 grain/m^3 increase in 5-day average weed pollen was -0.32 (0.26) L/min in

the GEE model. Weed pollen was also modelled as a binary term and presence of weed pollen on the current or previous 4 days resulted in –0.57 (0.29) L/min in the GEE model. The results are summarised in Table 7.18.

Table 7.18. The effect of a 3 grains/m^3 increase in weed pollen on evening peak flow (L/min): Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	-0.09 (0.41)	-0.67 (0.76)	+0.40 (0.42)	-0.70 (1.20)	+0.25 (0.31)	-0.53 (1.14)
Wallsend	-1.64 (0.56)§	-1.30 (1.80)	-1.37 (0.59)§	-1.44 (2.17)	-1.34 (0.61)§	-1.39 (2.16)
Mayfield	-0.56 (0.68)	-0.12 (1.40)	-1.31 (0.69)	-0.95 (1.22)	-1.53 (0.78)§	-0.73 (1.45)
Beresfield	-0.07 (0.13)	+0.03 (0.21)	-0.06 (0.16)	+0.06 (0.37)	+0.02 (0.14)	+0.04 (0.32)
NLM	-0.41 (0.21)§	-0.94 (0.32)§	-0.48 (0.23)§	-1.52 (0.60)§	-0.31 (0.26)	-1.17 (0.55)§
Pooled ‡						
Wave 1	-0.72 (0.49)	-0.63 (0.62)	-0.66 (0.58)	-0.91 (0.79)	-0.68 (0.54)	-0.72 (0.83)
Wave 2	-0.17 (0.11)	-0.35 (0.26)	-0.19 (0.13)	-0.48 (0.40)	-0.05 (0.12)	-0.27 (0.28)
Hunter Region	-0.36 (0.19)§	-0.28 (0.17)§	-0.36 (0.23)	-0.46 (0.29)	-0.26 (0.22)	-0.32 (0.26)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of weed pollen has been adjusted by climate-related covariates and autocorrelation as required. Weed pollen was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

Tree pollen

In the univariable Aggregate analysis there was a significant association between tree pollen and EPF at the two study areas of Wave 2. At Beresfield, -0.05 (0.02) L/min per 10 grains/m^3 increase and North Lake Macquarie –1.12 (0.19) L/min per 10 grains/m^3 increase. When adjusted for climate-related covariates these associations were no longer evident. The pooled Hunter Region estimate per 10 grains/m^3 increase in 5-day average tree pollen was –

0.01 (0.09) L/min in the Aggregate analysis, -0.01 (0.03) L/min in the K-W analysis and +0.001 (0.03) L/min in the GEE analysis. The results are summarised in Table 7.19.

Table 7.19. The effect of a 10 grains/m^3 increase in tree pollen on evening peak flow (L/min): Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	+0.91 (0.53)	+2.09 (0.86)§	+0.41 (0.59)	+1.44 (1.30)	+0.43 (0.53)	+1.90 (1.20)
Wallsend	-0.03 (0.06)	+0.07 (0.14)	+0.12 (0.34)	+0.15 (0.25)	-0.04 (0.05)	+0.06 (0.18)
Mayfield	-0.09 (0.22)	-0.02 (0.52)	-0.20 (0.31)	-0.64 (0.86)	-0.16 (0.27)	-0.97 (0.83)
Beresfield	-0.01 (0.01)	-0.02 (0.02)	+0.02 (0.02)	-0.01 (0.03)	+0.01 (0.01)	+0.00 (0.03)
NLM	-0.11 (0.18)	-0.26 (0.21)	-0.38 (0.24)	-0.81 (0.33)§	-0.24 (0.30)	-0.62 (0.37)
Pooled ‡						
Wave 1	+0.01 (0.14)	+0.40 (0.44)	+0.00 (0.21)	+0.14 (0.24)	-0.04 (0.04)	+0.05 (0.32)
Wave 2	-0.02 (0.01)	-0.02 (0.02)	+0.01 (0.02)	-0.02 (0.03)	+0.01 (0.01)	-0.01 (0.03)
Hunter Region	-0.02 (0.01)	-0.01 (0.09)	+0.01 (0.02)	-0.01 (0.03)	+0.00 (0.01)	+0.00 (0.03)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of tree pollen has been adjusted by climate-related covariates and autocorrelation as required. Tree pollen was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

Alternaria

Alternaria was largely unrelated to peak flow in both the univariable and multivariable analyses. After adjusting for the climate-related covariates the pooled Hunter Region estimate per 6 spores/m^3 increase in 5-day average Alternaria was +0.001 (0.10) in the Aggregate analysis, -0.04 (0.17) in the K-W analysis, and +0.06 (0.17) in the GEE analysis. The results are summarised in Table 7.20.

Table 7.20. The effect of a 6 spores/m^3 increase in Alternaria on evening peak flow (L/min): Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	-0.42 (0.44)	-0.23 (0.77)	-0.48 (0.36)	-1.10 (1.01)	-0.50 (0.37)	-1.01 (1.09)
Wallsend	+0.18 (0.37)	+0.26 (0.70)	+0.27 (0.46)	+0.75 (0.85)	+0.00 (0.45)	+0.73 (0.68)
Mayfield	-0.52 (0.48)	-0.82 (0.85)	-0.40 (0.73)	-0.48 (1.21)	-0.39 (0.68)	-1.29 (1.21)
Beresfield	-0.06 (0.10)	+0.10 (0.14)	-0.03 (0.11)	+0.07 (0.21)	-0.15 (0.12)	+0.10 (0.21)
NLM	+0.22 (0.10)§	-0.11 (0.16)	+0.03 (0.15)	-0.24 (0.31)	+0.24 (0.14)	+0.01 (0.30)
Pooled ‡						
Wave 1	-0.19(0.24)	-0.20(0.44)	-0.22(0.27)	-0.12(0.57)	-0.32(0.26)	-0.07(0.54)
Wave 2	+0.08(0.10)	+0.01(0.10)	-0.01(0.09)	-0.03(0.18)	+0.03(0.13)	+0.07(0.17)
Hunter Region	+0.05 (0.07)	+0.00 (0.10)	-0.03 (0.08)	-0.04 (0.17)	-0.02 (0.09)	+0.06 (0.17)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of Alternaria has been adjusted by climate-related covariates and autocorrelation as required. Alternaria was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

7.2 Assessment of effect modification by time-stationary covariates (PM10)

Characteristics of children who were more sensitive to PM10 were explored in the Aggregate, Korn-Whittemore and GEE analysis. This was completed using the 5-day average of PM10, which was identified as the most promising in preliminary analyses (refer to Section 4.5.1). A characteristic was judged to potentiate the association between PM10 and EPF if those with the characteristic had a more negative coefficient for effect of PM10 on EPF than those without the characteristic. Specifically, it was of interest if PM10 was significantly associated with EPF for those with the characteristic, or if the difference in effect was statistically significant across subcategories of the characteristic.

To examine whether PM10 was significantly associated with EPF for those with the characteristic, a stratified analysis was conducted. In the Aggregate analysis, for example, this involved fitting separate area-specific regression models for each of the 26 strata corresponding to the 13 characteristics and then pooling the estimates across study areas. The results by subject characteristics are shown in Table 7.21. Children who lived more than 1km from school were significantly affected by 5-day average PM10 across all three modelling approaches. However, there was considerably heterogeneity in the area-specific estimates and the result seemed to be mainly driven by Stockton. It is noteworthy that in all three modelling approaches, children not on asthma medication were more sensitive to PM10 than children on asthma medication. In the GEE analysis, children not on asthma medication had a reduction in peak flow of 0.91 (0.63) L/min in response to a 20 $\mu g/m^3$ increase in 5-day average PM10 and children on asthma medication had an increase in peak flow of 0.22 (0.52) L/min. A child was medicated if they used asthma medication during the study period (bronchodilators and/or anti-inflammatory agents).

In the Korn-Whittemore and GEE analyses it was also possible to test if the difference in effect was statistically significant across subcategories of the characteristic. In the Korn-Whittemore analysis, a weighted regression model was fitted with the subject's regression coefficient for the PM10/EPF association as the dependent variable, and the putative effect modifier as the independent variable as well as study area terms, with weights according to the number of days of observation for each child. In the GEE analysis, the test for difference across subgroups was completed by including main-effect terms for PM10 and for the putative effect modifier in the 5-day average Hunter Region model, along with an interaction term for the putative effect modifier and PM10. If the interaction term was significant then there was effect modification. There was no evidence of effect modification by subject characteristics in the K-W analysis. However, in the GEE analysis there was evidence that children with no smokers inside the home had a larger decrease in EPF in response to an increase in PM10 than children with smokers inside the home (p-value=0.05). The difference in effect between medicated and non-medicated children was not statistically significant in either of these modelling approaches.

Table 7.21. The effect of a 20 μg/m^3 increase in 5-day average PM10 on evening peak flow (L/min), by subject characteristics. Results from the Aggregate, Korn-Whittemore and GEE analysis

Subject characteristic	Number of children *	Aggregate – weighted †	K-W – weighted †	GEE †
Gender				
Female	132 (47%)	-0.27 (0.45)	-0.76 (0.76)	-0.33 (0.61)
Male	148 (53%)	-0.48 (0.64)	-1.07 (0.73)	-0.43 (0.59)
Age				
8, 9	127 (45%)	n.a.	-0.45 (0.67)	+0.30 (0.54)
10	107 (38%)	n.a.	-1.65 (0.76)§	-1.14 (0.66)
11, 12	46 (16%)	n.a.	-1.02 (2.15)	+0.42 (1.46)
Asthma medication use				
No	127 (45%)	-0.80 (0.46)	-0.92 (0.59)	-0.91 (0.63)
Yes	153 (55%)	-0.29 (0.72)	-0.56 (0.75)	+0.22 (0.52)
Diagnosed with asthma				
No	117 (42%)	-0.79 (0.44)	-1.24 (0.71)	-0.83 (0.63)
Yes	163 (58%)	-0.13 (0.41)	-0.58 (0.65)	+0.12 (0.52)
Maternal allergy				
No	117 (42%)	-0.16 (0.49)	-0.55 (0.74)	+0.21 (0.58)
Yes	163 (58%)	-0.56 (0.76)	-0.62 (0.68)	-0.16 (0.53)
Smokers inside the home				
No	172 (61%)	-0.64 (0.39)	-0.90 (0.54)	-0.39 (0.51)£
Yes	108 (39%)	+0.15 (0.59)	-0.71 (0.82)	+0.22 (0.67)
Cats inside the home				
No	212 (76%)	-0.27 (0.35)	-0.53 (0.54)	-0.07 (0.46)
Yes	68 (24%)	-0.45 (0.68)	-1.94 (1.02)	-0.98 (0.83)
Gas heating without flue				
No	223 (80%)	+0.31 (0.85)	-1.12 (0.51)§	-0.45 (0.45)
Yes	57 (20%)	-0.65 (0.54)	-1.14 (1.37)	-0.93 (1.11)
Gas cooking without fan				
No	219 (78%)	-0.73 (0.68)	-1.49 (0.53)§	-0.88 (0.47)§
Yes	61 (22%)	+0.06 (0.61)	+1.61 (1.87)	+0.70 (1.93)
Live close to school				
No	124 (44%)	-1.53 (0.65)§	-1.64 (0.75)§	-1.26 (0.62)§
Yes	156 (56%)	+0.08 (0.40)	-0.25 (0.61)	+0.42 (0.54)
Slept away infrequently				
No	142 (51%)	-0.24 (0.58)	-1.08 (0.72)	-0.52 (0.66)
Yes	138 (49%)	-0.56 (0.41)	-0.67 (0.61)	-0.25 (0.59)
Completed study				
No	142 (51%)	-0.51 (0.70)	-0.41 (1.06)	-0.02 (0.75)
Yes	138 (49%)	-0.10 (0.39)	-0.68 (0.55)	-0.30 (0.54)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted by climate-related covariates and autocorrelation as required.

*. Based on sample of 280 children in the Aggregate analysis. Note that only 235 children were eligible for the K-W and GEE analysis

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations. Pooled estimates were derived by pooling results across study areas using a random effects approach.

§. p-value <0.05 for subgroup

£. p-value <0.05 for interaction effect.

n.a. This analysis was not completed

It was of interest to see if non-medicated children were also more affected by sulphur dioxide and aeroallergens than medicated children. The effect of each of the pollutants and aeroallergens on EPF is shown separately for medicated and non-medicated children in Table 7.22. The analysis was limited to grass and weed pollen as the other aeroallergens were not associated with EPF. These estimates were obtained from the GEE model. There was some evidence that non-medicated children were more affected by grass pollen than medicated children.

Table 7.22. The effect of an increase in 5-day average pollutants on evening peak flow (L/min) among non-medicated and medicated children: GEE analysis

	Wave 1‡	Wave 2‡	Hunter Region‡
PM10 (per 20 μg/m^3 increase)			
Non-medicated	-0.98 (0.70)	-0.65 (1.43)	-0.91 (0.63)
Medicated	-0.13 (0.61)	+1.26 (1.03)	+0.22 (0.52)
Sulphur dioxide (per 1.5 pphm increase)			
Non-medicated	+0.63 (0.96)	+0.94 (0.56)	+0.86 (0.48)
Medicated	-0.32 (0.80)	+0.52 (0.56)	+0.24 (0.46)
Grass pollen (per 4 grains/m^3 increase)			
Non-medicated	-0.68 (0.84)	-1.69 (0.78)§	-1.30 (0.53)§
Medicated	-1.08 (0.81)	+0.05 (0.44)	-0.48 (0.51)
Weed pollen (per 3 grains/m^3 increase)			
Non-medicated	-0.45 (1.20)	-0.42 (0.54)	-0.42 (0.49)
Medicated	-1.06 (1.13)	-0.21 (0.29)	-0.26 (0.28)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of exposure has been adjusted by climate-related covariates and autocorrelation as required. PM10 was fitted as a linear term on the same day of peak flow measurement, and 5-day average (average concentration over the current and previous 4 days).

GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

7.3 Adjustment for potential confounding and assessment of effect modification by time-varying covariates using the GEE model (PM10)

Confounding

A 20 μg/m^3 increase in 5-day average PM10 was associated with a 0.43 (0.47) L/min decrease in EPF for children in Wave 1, and a 0.38 (0.88) L/min increase for children in Wave 2, and a 0.25 (0.41) L/min decrease overall. All of these estimates had been adjusted for climate-related predictors and confounders. The analysis was repeated after adding in several time-varying terms one at a time to the area-specific GEE models and examining the change in the pooled PM10 coefficient.

Several of the time-varying terms were significantly associated with EPF. Corticosteroid use during the month of measurement of EPF was associated with a mean EPF reduction of 0.95 L/min (p-value=0.04). Same day puffer use and same day nasal symptoms were associated with a mean EPF reduction of 2.48 L/min (p-value<0.001) and 3.63 L/min (p-value<0.001) respectively. School term also proved to be an important predictor of EPF at the two industrial areas on Mayfield and North Lake Macquarie where it was protective of EPF. The effect of PM10 on EPF was little changed by control of these terms, as the estimates changed by less than 15%, indicating that these terms were independent of PM10. However, the effect of PM10 on EPF was substantially changed by control of perception of pollution as its inclusion strengthened the Wave 1 estimate from a decrease of 0.43 L/min to a decrease of 0.60 L/min, per 20 μg/m^3 increase in PM10. This result was not replicated in Wave 2. Similar conclusions were reached when fitting the 5-day average Hunter Region model.

Table 7.23. The effect of a 20 μg/m^3 increase in 5-day average PM10 on evening peak flow (L/min) after adjustment for potential confounders: GEE analysis

	Wave 1	Wave 2	Hunter Region
No adjustment	-0.43 (0.47)	+0.38 (0.88)	-0.25 (0.41)
After adjustment			
Inhaled corticosteroid use during the month	-0.44 (0.47)	+0.38 (0.88)	-0.26 (0.41)
Inhaled bronchodilator usage during the day	-0.37 (0.47)	+0.37 (0.89)	-0.21 (0.42)
Nasal symptoms recorded that day	-0.42 (0.48)	+0.39 (0.88)	-0.24 (0.42)
Perceived pollution that day	-0.60 (0.48)	+0.32 (0.92)	-0.40 (0.42)
Slept at home the previous night & that night	-0.41 (0.47)	+0.37 (0.89)	-0.24 (0.42)
School term	-0.44 (0.47)	+0.37 (0.85)	-0.25 (0.41)
Weekday	-0.40 (0.46)	+0.31 (0.89)	-0.25 (0.41)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted by climate-related covariates and autocorrelation as required. PM10 was fitted as a linear term of the 5-day average (average concentration over the current and previous 4 days).

Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

Effect modification

To examine whether any of the time-varying covariates were effect modifiers the putative effect modifier was added into the GEE 5-day average area-specific model as well as its interaction term with PM10 and the estimates were then pooled across study areas. This allowed estimation of the effect of PM10 of EPF when the putative effect modifier was present and when it was absent. All time-varying covariates were examined regardless of whether they were statistically significant in the main effects model. The results for Wave 1, Wave 2 and overall are presented in Table 7.24.

There were two results of note. Firstly, it is interesting that in Wave 1, on days when pollution was not perceived, there was a statistically significant reduction in EPF in response to an increase in PM10. Secondly, if nasal symptoms were not present there was a greater reduction in EPF in response to an increase in PM10, relative to days when they had nasal symptoms. However, because these results were not replicated in Wave 2 there is only weak evidence of

effect modification. Similar conclusions were reached when fitting the 5-day average Hunter Region model.

Table 7.24. The effect of 20 μg/m^3 increase in 5-day average PM10 on evening peak flow (L/min): GEE analysis. Stratification by various time-varying covariates

	Wave 1	Wave 2	Hunter Region
Inhaled corticosteroid use that month			
No	-0.64 (0.51)	-0.29 (0.97)	-0.57 (0.45)
Yes	+0.53 (1.21)	+2.66 (1.80)	+1.11 (1.05)
Inhaled Bronchodilator use that day			
No	-0.39 (0.49)	+0.11 (0.96)	-0.29 (0.44)
Yes	+0.03 (1.14)	+1.74 (1.74)	+0.54 (0.95)
Nasal symptoms recorded that day			
No	-0.69 (0.54)	+0.03 (0.88)	-0.49 (0.46)
Yes	+0.09 (0.65)	+1.54 (1.75)	+0.26 (0.61)
Perceived air pollution that day			
No	-1.91 (0.75)§	+1.09 (1.18)	-1.03 (0.65)
Yes	-0.16 (0.56)	-0.36 (1.24)	-0.19 (0.51)
Slept at home the previous night and that night			
No	-0.33 (0.50)	+0.36 (0.89)	-0.16 (0.44)
Yes	-2.08 (2.08)	+0.71 (1.92)	-0.90 (1.42)
During school term			
Yes	-0.63 (1.04)	+0.26 (1.13)	-0.23 (0.77)
No	-0.44 (0.48)	+0.39 (0.97)	-0.28 (0.43)
Weekday			
No	+0.12 (0.66)	+0.53 (0.99)	+0.32 (0.49)
Yes	-0.83 (0.57)	+0.20 (1.06)	-0.60 (0.50)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted by climate-related covariates and autocorrelation as required. PM10 was fitted as a linear term of the 5-day average (average concentration over the current and previous 4 days).

Main effect and interaction terms were included for PM10 and each time-varying covariate. The regression coefficients and their standard errors, incorporate both main effects and interaction terms. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. The effect of the pollutant was significant at this level of the time-varying covariate (p-value <0.05).

£. The effect of the pollutant was statistically significantly different across subcategories of the time-varying covariate (p-value <0.05 for interaction term).

7.4 Multi-pollutant analysis using the GEE model

No significant associations were found between EPF and PM10 in the single-pollutant analysis. This result may have been confounded by other pollutants and so multi-pollutant models were next fitted. In this analysis, PM10 and another pollutant were simultaneously included into the

area-specific models as linear terms, and the PM10 coefficient was pooled across study areas. This was completed using the GEE model with the 5-day average of the pollutants.

The inclusion of sulphur dioxide resulted in a large change in the PM10 coefficient in Wave 1. However, because sulphur dioxide was not independently related to the outcome there was a corresponding increase in its standard error. The inclusion of aeroallergens made little change to the PM10 coefficient (Table 7.25). Similar results were observed when fitting the 5-day average Hunter Region GEE model, which included all children in the one model. In conclusion, there was no evidence that the association between PM10 and EPF was confounded by another pollutant.

Table 7.25. The effect of a 20 μg/m^3 increase in 5-day average PM10 on evening peak flow (L/min) in single-pollutant and multi-pollutant models: GEE analysis

	Wave 1	Wave 2	Hunter Region
Single-pollutant	-0.43 (0.47)	+0.38 (0.88)	-0.25 (0.41)
Multi-pollutant			
Sulphur dioxide	-0.62 (0.57)	-0.45 (1.45)*	-0.60 (0.53)*
Grass pollen	-0.37 (0.46)	+0.52 (0.91)	-0.19 (0.41)
Weed pollen	-0.47 (0.48)	+0.58 (0.94)	-0.26 (0.43)

Estimates and standard errors (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted for climate-related covariates and autocorrelation as required. All air quality measures were fitted as a linear term of the 5-day average (average concentration over the current and previous 4 days).

Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

*. Data from Beresfield were excluded from this model due to incomplete sulphur dioxide measurement at this study area.

§. p-value <0.05.

7.5 Summary

No significant association was found between PM10 and EPF when the results were averaged across all five study areas (0.03% increase from mean 300 L/min; 95% CI –0.11% to +0.18%; per 20 μg/m^3 increase in same-day PM10). However, for the subgroup of children not on asthma medication, a 20 μg/m^3 increase in PM10 was associated with a 0.15% decrease in EPF and for the subgroup of children on asthma medication it was associated with a 0.18% increase in EPF.

Stronger effects were observed for EPF when the 5-day average PM10 was modelled (0.08% decrease). The estimated effect of PM10 on EPF differed across the two waves of children

(Wave 1: 0.14% decrease, Wave 2: 0.13% increase per 20 $\mu g/m^3$ increase in 5-day average PM10). Wave 1 (Stockton, Wallsend and Mayfield) was conducted between Autumn and early Spring whilst Wave 2 (Beresfield, North Lake Macquarie) was conducted between Spring and early Autumn. The most likely explanation for the observed differences in estimates is seasonal variation. However random variation cannot be ruled out, as the estimates across study areas were not heterogeneous (χ^2=1.49, df=4, p-value=0.83).

There was no evidence of an association between maximum sulphur dioxide and EPF except at Stockton. It is noteworthy that no association was observed between sulphur dioxide and EPF at North Lake Macquarie in any models. This may be a result of the study being conducted over the warmer months, as the analyses in Wave 1 suggested that the effect of sulphur dioxide was stronger during the cooler months. There was some evidence of association between the exposures - grass pollen and weed pollen – and EPF. There was no evidence of an association between the other exposures - total pollen, tree pollen and Alternaria – and EPF. When multi-pollutant models were fitted the estimated effect of PM10 did not change indicating that there was no confounding by these other pollutants.

The next chapter reports on the effect of air quality on the binary outcome variable - day cough.

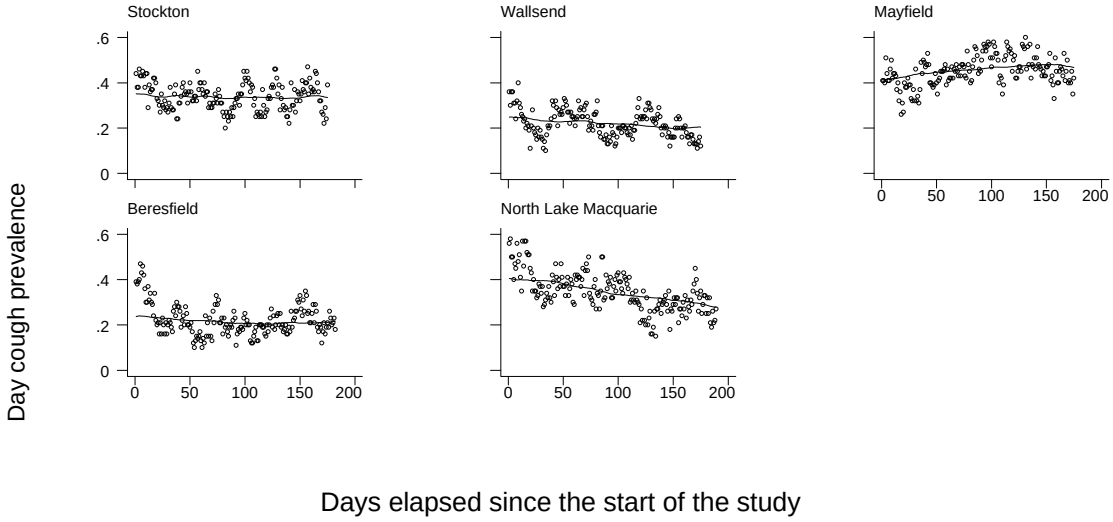
Chapter 8 . Results – Effect of air quality on prevalence of day cough

This chapter presents the results of analyses undertaken evaluating the association between air pollution and the second health outcome – day cough. A summary and brief discussion of the results is provided at the end of the chapter.

8.1 Introduction

Figure 8.1 presents scatter plots of day cough prevalence against days elapsed, and a smoothed function curve. A cyclical pattern was observed in all areas except Mayfield. The prevalence of day cough significantly decreased over the course of the study period at Wallsend, Beresfield and North Lake Macquarie, and significantly increased over the study period at Mayfield.

Figure 8.1. Day cough prevalence (fraction) on any one day against number of days elapsed since the start of the study



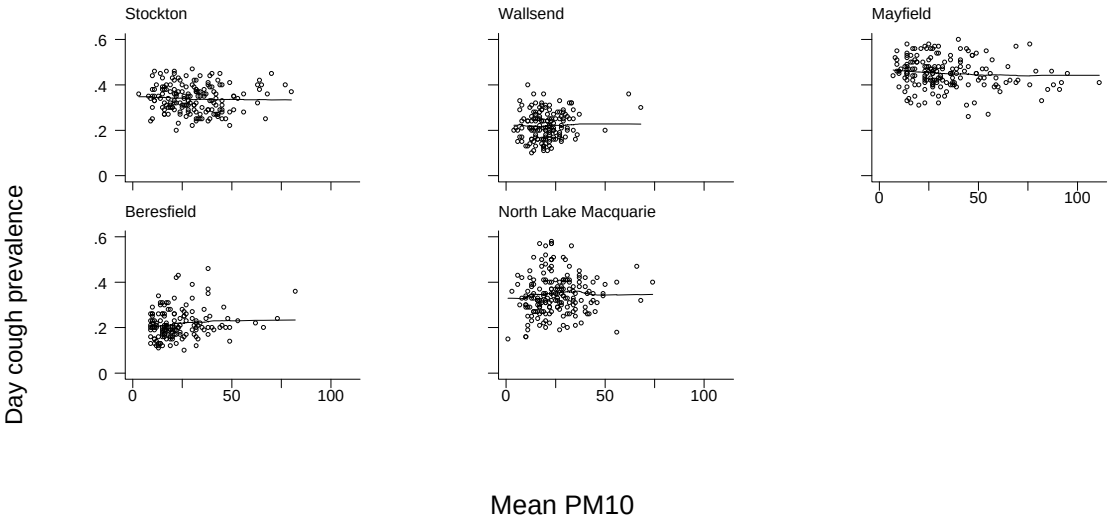
Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994 (Stockton commenced one week earlier than the other two study areas). Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995 (North Lake Macquarie commenced two weeks prior to Beresfield).

Two hundred and thirty-seven children were eligible for the GEE analysis because they completed the diary on a sufficient number of days. In the Korn-Whittemore analysis it was necessary to also exclude children who had low variability in their reporting of cough symptoms. This excluded 38 asymptomatic children (less than 5% of days with symptoms) and 7 symptomatic children (more than 95% of days with symptoms), leaving 192 children eligible for the K-W analysis.

8.2 Particulates (PM10)

Figure 8.2 shows scatter plots of day cough prevalence against mean daily PM10 concentrations, and a smoothed function curve. There was little evidence of an association between PM10 and day cough prevalence.

Figure 8.2. Day cough prevalence (fraction) on any one day against mean PM10 (μg/m^3) recorded that day



Children in Wave 1 that was comprised of Stockton, Wallsend and Mayfield completed diaries from March 1994 to September 1994. Children in Wave 2 that was comprised of Beresfield and North Lake Macquarie completed diaries from September 1994 to March 1995.

In the univariable Aggregate analysis there was a small but statistically significant association between PM10 and day cough at the control areas Wallsend and Beresfield. In the Aggregate analysis, after adjusting for the climate-related predictors and confounders significant associations were observed at Wallsend only but there was no evidence of heterogeneity in the estimates across study areas (χ^2=3.73, df=4, p-value=0.44). The results from the Aggregate, Korn-Whittemore and GEE analysis are summarised in Table 8.1. In the GEE analysis, a 20 μg/m^3 increase in PM10 was associated with a non-significant 1% increase in the odds of day cough (Hunter Region: Odds Ratio (OR) 1.01 95% CI 0.99 to 1.03). This represents a 1% increase in the relative prevalence of day cough using the approximation (1-OR). When modelling incidence of day cough in the Aggregate analysis the odds ratio for same-day PM10 at Wave 2 was now statistically significant (Wave 2: OR 1.20 95% CI 1.02 to 1.42) but was still

non-significant overall (Hunter Region: OR 1.09 95% CI 0.91 to 1.29) with significant heterogeneity of the estimates across study areas (χ^2=15.58, df=4, p-value=0.004).

Table 8.1. The effect of a 20 μg/m^3 increase in mean PM10 on day cough prevalence: Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	1.00 (0.92, 1.10)	1.04 (0.92, 1.19)	0.80 (0.55, 1.17)	1.75 (0.13, 24.5)	0.98 (0.95, 1.02)	0.95 (0.84, 1.08)
Wallsend	1.14§ (1.00, 1.30)	1.30 (1.07, 1.57)	0.39 (0.05, 2.97)	0.51 (0.04, 6.20)	1.04 (0.95, 1.15)	1.08 (0.92, 1.27)
Mayfield	1.01 (0.96, 1.06)	0.98 (0.91, 1.05)	0.88 (0.65, 1.19)	1.45 (0.46, 4.51)	1.01 (0.99, 1.04)	0.97 (0.90, 1.06)
Beresfield	1.08 (0.95, 1.22)	1.06 (0.92, 1.21)	3.04 (0.27, 34.8)	0.13 (0.01, 13.2)	1.02 (0.95, 1.10)	1.09 (0.94, 1.25)
NLM	1.01 (0.91, 1.12)	0.86 (0.71, 1.03)	1.47 (0.79, 2.76)	0.07 (0.01, 5.24)	1.06§ (1.01, 1.12)	0.98 (0.85, 1.13)
Pooled‡						
Wave 1	1.03 (0.97, 1.09)	1.07 (0.94, 1.21)	0.84 (0.67, 1.06)	1.27 (0.48, 3.33)	1.00 (0.98, 1.02)	0.98 (0.92, 1.05)
Wave 2	1.04 (0.96, 1.12)	0.98 (0.87, 1.10)	1.54 (0.84, 2.83)	0.09 (0.01, 2.17)	1.05§ (1.00, 1.09)	1.03 (0.94, 1.14)
Hunter Region	1.02 (0.99, 1.06)	1.03 (0.94, 1.12)	0.91 (0.73, 1.13)	1.02 (0.40, 2.56)	1.01 (0.99, 1.03)	1.00 (0.95, 1.05)

Estimates of odds ratios and 95% confidence intervals (in parentheses) are reported. Each estimate of effect of exposure has been adjusted by climate-related covariates and autocorrelation as required. PM10 was fitted as a linear term on the same day of reporting of day cough, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

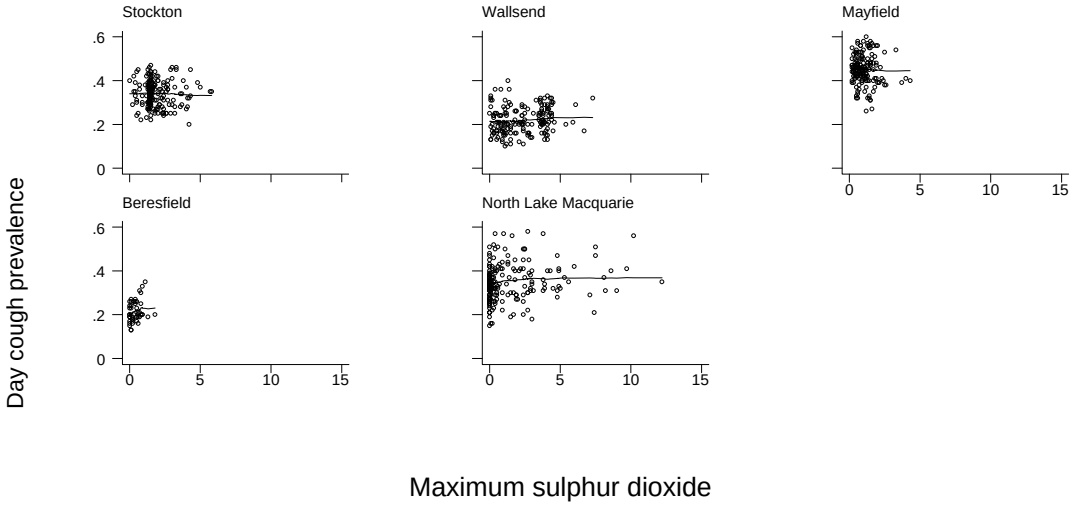
When the Aggregate analysis was restricted to children with maternal allergy the same-day PM10 was statistically significantly associated with day cough (Hunter Region: OR 1.06 95% CI 1.00 to 1.12) but not 5-day average PM10. When examining whether there were any predictors to the subject-specific coefficients in the Korn-Whittemore analysis it was found that

non-medicated children were more affected by increases in 5-day average PM10 than medicated children (odds ratios were 10 times greater, p-value=0.09) and children living close to their school were more affected than children living further away (odds ratios were 5 times greater, p-value=0.10). However, these results were not replicated in the GEE analysis. The estimated effect of 5-day average PM10 on day cough prevalence was not confounded by any of the subject-related covariates.

8.3 Sulphur dioxide (SO_2)

Figure 8.3 shows scatter plots of day cough prevalence against maximum daily SO_2 concentrations, and a smoothed function curve. Beresfield was excluded from this analysis due to an insufficient number of sulphur dioxide measurements.

Figure 8.3. Day cough prevalence (fraction) on any one day against maximum sulphur dioxide (pphm) recorded that day



Children in Wave 1 that was comprised of Stockton, Wallsend and Mayfield completed diaries from March 1994 to September 1994. Children in Wave 2 that was comprised of Beresfield and North Lake Macquarie completed diaries from September 1994 to March 1995.

In the univariable Aggregate analysis there was an association between maximum SO_2 and day cough prevalence at North Lake Macquarie only. The results for sulphur dioxide from the Aggregate, Korn-Whittemore and GEE analysis are shown in Table 8.2. In the Aggregate analysis there was no evidence of an association between maximum SO_2 and day cough prevalence, but when day cough incidence was modelled on same-day maximum SO_2 there was a significant association (Hunter Region: OR 1.06 95% CI: 1.00 to 1.12). In the GEE analysis there was evidence of an association between maximum SO_2 and day cough prevalence at North

Lake Macquarie only (OR 1.06 95% CI: 1.01 to 1.11). In the GEE analysis when same-day mean daily or mean daytime SO_2 was used, similar estimates to that from maximum SO_2 were found, and remained non-significant.

Table 8.2. The effect of a 1.5 pphm increase in maximum sulphur dioxide on day cough prevalence: Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	0.97 (0.88, 1.07)	1.08 (0.89, 1.30)	0.59 (0.14, 2.46)	0.56 (0.08, 4.19)	1.00 (0.96, 1.05)	1.12 (0.95, 1.32)
Wallsend	1.00 (0.94, 1.07)	1.00 (0.88, 1.13)	0.96 (0.78, 1.18)	1.15 (0.59, 2.24)	1.01 (0.96, 1.05)	0.98 (0.89, 1.09)
Mayfield	1.00 (0.90, 1.12)	1.13 (0.93, 1.38)	0.54 (0.14, 2.08)	0.59 (0.04, 9.05)	0.96 (0.90, 1.02)	0.96 (0.85, 1.08)
Beresfield	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
NLM	1.01 (0.98, 1.05)	1.05 (0.98, 1.13)	0.87 (0.69, 1.10)	0.90 (0.43, 1.92)	1.01 (0.99, 1.03)	1.07§ (1.01, 1.13)
Pooled‡						
Wave 1	0.99 (0.95, 1.04)	1.05 (0.95, 1.14)	0.94 (0.77, 1.15)	1.04 (0.56, 1.93)	0.99 (0.97, 1.02)	1.00 (0.93, 1.07)
Wave 2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hunter Region	1.01 (0.98, 1.04)	1.05 (0.99, 1.11)	0.91 (0.78, 1.06)	0.98 (0.61, 1.58)	1.01 (0.99, 1.02)	1.03 (0.98, 1.09)

Estimates of odds ratios and 95% confidence intervals (in parentheses) are reported. Each estimate of effect of exposure has been adjusted by climate-related covariates and autocorrelation as required. Sulphur dioxide was fitted as a linear term on the same day of reporting of day cough, and 5-day average (average concentration over the current and previous 4 days).

n.a. Beresfield was excluded from this analysis due to an insufficient number of sulphur dioxide measurements.

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

8.4 Summary

No association was found between PM10 and the prevalence of day cough when the results were averaged across all five study areas (1.18% increase in odds; 95% CI –0.70% to +3.00% per 20 $\mu g/m^3$ increase in same-day PM10). Within study areas and within subgroups there were some statistically significant associations but all estimates were small: less than 5.00% increase in odds of day cough.

A small but statistically significant association was observed between SO_2 and the prevalence of day cough at North Lake Macquarie only (6.74% increase in odds; 95% CI 0.68% to 13.00% per 1.5 pphm increase in 5-day average SO_2). It is noteworthy that there was no evidence of an association between SO_2 and EPF at North Lake Macquarie (refer to Chapter 7). One explanation for this apparent inconsistency is that EPF may be less affected by increases in SO_2 than day cough, however, the associations observed in the GEE analysis were not replicated in the Aggregate and Korn-Whittemore analyses and so caution needs to be applied when interpreting these results.

Bronchodilator use did not confound the association between PM10 and day cough. The analysis reported in Chapter 7 also found that bronchodilator use did not confound the association between PM10 and EPF. This suggests that there was no association between PM10 and bronchodilator use and this was explored further in the next chapter.

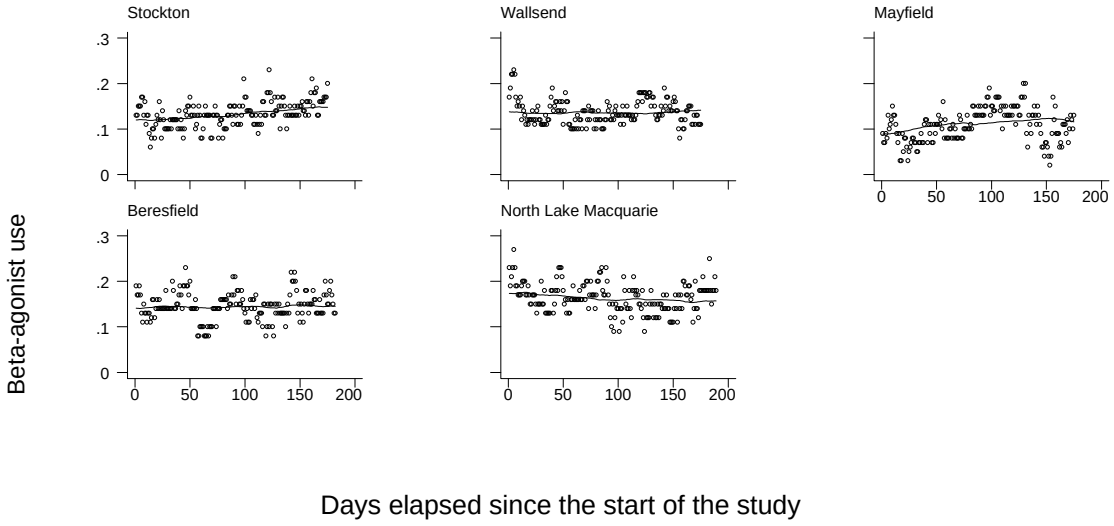
Chapter 9 . Results – Effect of air quality on prevalence of bronchodilator use

This chapter presents the results of the analyses undertaken evaluating the association between air pollution and the third (and final) health outcome – bronchodilator use. It was hypothesised that increases in air pollution would be associated with increases in the prevalence of bronchodilator use. A summary and brief discussion of the results is provided at the end of the chapter.

9.1 Introduction

Bronchodilators can be in either inhaled or nebulised form, however, only the inhaled form was considered in this analysis. Figure 9.1 presents scatter plots of the prevalence of bronchodilator ($beta_2$-agonist) use against days elapsed, and a smoothed function curve. A cyclical pattern was observed in all areas. The prevalence of use significantly increased over the course of the study period at Stockton and Mayfield.

Figure 9.1. Prevalence of bronchodilator use (fraction) on any one day against number of days elapsed since the start of the study



Definition of abbreviations: Beta-agonist=$Beta_2$-agonist or bronchodilator

Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994 (Stockton commenced one week earlier than the other two study areas). Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995 (North Lake Macquarie commenced two weeks prior to Beresfield).

Two hundred and thirty-nine subjects were eligible for the non-aggregate analysis because they completed the diary on a sufficient number of days. Of these, 136 children took asthma medication during the study. Asthma medication included bronchodilators (inhaled and/or nebulised form), corticosteroids (inhaled and/or oral form) or cromolyns. At Mayfield, there were 29 medicated children and the number of children using a puffer on a given day ranged from 0 to 9. Table 9.1 contains the data for Mayfield and the other study areas. The GEE analysis included these 136 medicated children. In the Korn-Whittemore analysis it was necessary to exclude children who had low variability in their reporting of puffer usage. This excluded 17 children who did not use a puffer at all during the study, 40 infrequent users (used a puffer on less than 5% of days) and 17 regular users (used a puffer on at least 95% of days), leaving 62 children eligible for the Korn-Whittemore analysis.

Table 9.1. Description of asthma medication use by the 239 children eligible for the non-aggregate analysis

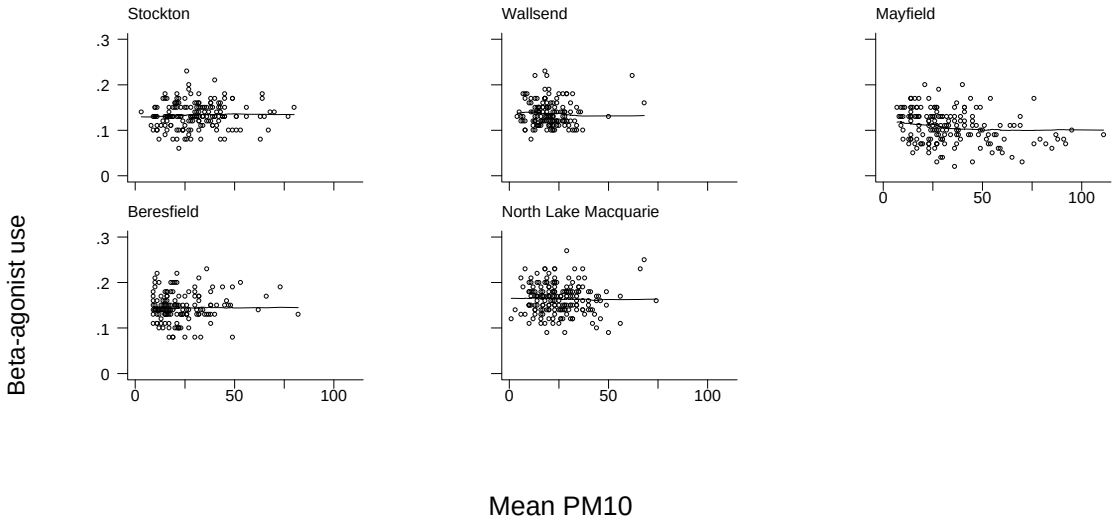
	Study area				
	S	W	M	B	NLM
Number of children	45	59	49	49	37
Number of medicated children	21	32	29	29	25
Number of children using a bronchodilator on a given day (minimum, maximum)	1, 10	0, 14	0, 9	2, 11	2, 12

S denotes Stockton; W Wallsend; M Mayfield; B Beresfield; and NLM North Lake Macquarie.

9.2 Particulates (PM10)

Figure 9.2 shows scatter plots of prevalence of bronchodilator use against mean daily PM10 concentrations, and a smoothed function curve. There was little evidence of an association between PM10 and prevalence of bronchodilator use.

Figure 9.2. Prevalence of bronchodilator use (fraction) on any one day against mean PM10 (μg/m^3) recorded that day



Definition of abbreviations: Beta-agonist=$Beta_2$-agonist or bronchodilator
Children in Wave 1 that was comprised of Stockton, Wallsend and Mayfield completed diaries from March 1994 to September 1994. Children in Wave 2 that was comprised of Beresfield and North Lake Macquarie completed diaries from September 1994 to March 1995.

Prior to adjustment for potential confounders and autocorrelation, a significant association between mean PM10 and prevalence of bronchodilator use was observed at Mayfield. However, the estimate of effect was in the opposite direction to that hypothesised as the prevalence of bronchodilator use decreased as PM10 increased (OR: 0.90 per 20 μg/m^3 increase in same-day PM10). A summary of the results after adjustment for the climate-related covariates and autocorrelation is shown in Table 9.2.

Table 9.2. The effect of a 20 μg/m^3 increase in mean PM10 on prevalence of bronchodilator use: Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	1.00 (0.89, 1.13)	0.94 (0.78, 1.12)	1.77 (0.27, 11.7)	0.15 (0.02, 0.96)	1.01 (0.95, 1.07)	0.99 (0.93, 1.05)
Wallsend	1.04 (0.89, 1.21)	0.97 (0.77, 1.21)	0.04 (0.00, 4.43)	0.42 (0.08, 2.28)	1.00 (0.92, 1.08)	0.90 (0.76, 1.08)
Mayfield	0.95 (0.87, 1.02)	0.87§ (0.78, 0.98)	0.67 (0.43, 1.04)	1.26 (0.51, 3.09)	0.98 (0.93, 1.04)	0.90 (0.77, 1.03)
Beresfield	1.09 (0.95, 1.26)	1.08 (0.92, 1.26)	3.73 (0.07, 192)	4.72 (0.47, 47.5)	0.98 (0.92, 1.04)	1.02 (0.89, 1.17)
NLM	1.01 (0.89, 1.14)	0.92 (0.73, 1.16)	0.81 (0.43, 1.52)	0.29 (0.05, 1.55)	1.01 (0.96, 1.05)	0.95 (0.82, 1.10)
Pooled‡						
Wave 1	0.97 (0.92, 1.03)	0.90§ (0.83, 0.99)	0.72 (0.33, 1.60)	0.58 (0.21, 1.63)	0.99 (0.96, 1.03)	0.97 (0.92, 1.02)
Wave 2	1.04 (0.95, 1.15)	1.02 (0.90, 1.17)	0.84 (0.45, 1.57)	0.98 (0.11, 8.76)	1.00 (0.96, 1.03)	0.99 (0.89, 1.09)
Hunter Region	0.99 (0.94, 1.05)	0.94 (0.87, 1.02)	0.73 (0.52, 1.04)	0.64 (0.25, 1.63)	1.00 (0.97, 1.02)	0.97 (0.93, 1.02)

Estimates of odds ratios and 95% confidence intervals (in parentheses) are reported. Each estimate of effect of exposure has been adjusted by climate-related covariates and autocorrelation as required. PM10 was fitted as a linear term on the same day of reporting of medication use, and 5-day average (average concentration over the current and previous 4 days).

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

9.3 Sulphur dioxide (SO_2)

In the univariable Aggregate analysis there was no evidence of an association between maximum daily SO_2 and prevalence of bronchodilator use. This persisted in the multivariable analysis. A summary of the results after adjustment for the climate-related covariates and autocorrelation is shown in Table 9.3. In the GEE analysis when same-day mean daily or mean daytime SO_2 was used, similar estimates to that from maximum SO_2 were found, and remained non-significant.

Table 9.3. The effect of a 1.5 pphm increase in maximum sulphur dioxide on prevalence of bronchodilator use: Results from Aggregate, Korn-Whittemore and GEE analysis

	Aggregate - weighted†		K-W - weighted†		GEE†	
	Same day	5-day average	Same day	5-day average	Same day	5-day average
By study area						
Stockton	0.98 (0.85, 1.12)	0.99 (0.77, 1.28)	0.45 (0.11, 1.85)	0.07 (0.00, 1.76)	1.00 (0.95, 1.06)	1.03 (0.87, 1.21)
Wallsend	0.98 (0.91, 1.06)	1.01 (0.87, 1.16)	0.79 (0.53, 1.18)	0.78 (0.41, 1.51)	1.00 (0.96, 1.04)	0.96 (0.87, 1.06)
Mayfield	1.00 (0.85, 1.19)	1.11 (0.83, 1.47)	0.81 (0.37, 1.75)	1.18 (0.23, 5.90)	0.94 (0.82, 1.07)	0.95 (0.79, 1.14)
Beresfield	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
NLM	1.01 (0.97, 1.06)	1.05 (0.97, 1.15)	0.86 (0.65, 1.14)	1.02 (0.78, 1.32)	1.00 (0.98, 1.02)	1.00 (0.97, 1.03)
Pooled‡						
Wave 1	0.98 (0.93, 1.04)	1.02 (0.91, 1.14)	0.77 (0.54, 1.09)	0.76 (0.39, 1.45)	1.00 (0.96, 1.03)	0.97 (0.90, 1.05)
Wave 2	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Hunter Region	1.00 (0.97, 1.04)	1.04 (0.97, 1.12)	0.82 (0.66, 1.02)	0.97 (0.76, 1.24)	1.00 (0.98, 1.01)	1.00 (0.97, 1.03)

Estimates of odds ratios and 95% confidence intervals (in parentheses) are reported. Each estimate of effect of exposure has been adjusted by climate-related covariates and autocorrelation as required. Sulphur dioxide was fitted as a linear term on the same day of reporting of medication use, and 5-day average (average concentration over the current and previous 4 days).

n.a. Beresfield was excluded from this analysis due to an insufficient number of sulphur dioxide measurements.

†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations.

‡. Pooled estimates were derived by pooling results across study areas using a random effects approach. Children in Wave 1, which comprised Stockton, Wallsend and Mayfield, completed diaries from March 1994 to September 1994. Children in Wave 2, which comprised Beresfield and North Lake Macquarie, completed diaries from September 1994 to March 1995. The Hunter Region estimate was obtained by pooling results across all five study areas.

§. p-value <0.05

9.4 Summary

No association was found between PM10 and the prevalence of bronchodilator use when the results were averaged across all five study areas. Within Mayfield there was a statistically significant association in the Aggregate analysis when modelling 5-day average PM10. However, because the estimate of effect was in the opposite direction to that hypothesised and the association observed was not replicated in the GEE analysis caution needs to be applied when interpreting this result.

No association was found between sulphur dioxide and the prevalence of bronchodilator use. This result was consistent across all three modelling approaches and the two lag intervals.

The next (and final) chapter discusses the findings of the study.

Chapter 10 . Discussion

The first section of this chapter presents an overview of the results of the study (Section 10.1). A comparison of the study results with previous research, and possible reasons for inconsistencies are discussed in Section 10.2. A review of the study design, and a discussion of possible biases or errors arising from the study design are contained in Section 10.3. The statistical methods used in the analysis are reviewed in Section 10.4. The final section of this chapter discusses the implications of the research (Section 10.5). Throughout this chapter the results are expressed as percentage changes so that they can be directly compared to that reported in the major review undertaken by Dockery and Pope (Dockery and Pope 1994).

10.1 Summary of main results

In this section results are presented for the main exposure, PM10. Results for the other exposures (sulphur dioxide, pollen and fungi) are presented later in this chapter. No significant association was found between PM10 and evening peak flow (EPF) when the results were averaged across all five study areas (0.03% increase from mean 300 L/min; 95% CI -0.11% to +0.18%; per 20 $\mu g/m^3$ increase in same-day PM10). However, for the subgroup of children not on asthma medication, a 20 $\mu g/m^3$ increase in PM10 was associated with a 0.15% decrease in EPF and for the subgroup of children on asthma medication it was associated with a 0.18% increase in EPF. The results were not confounded by sulphur dioxide or aeroallergen concentrations. Stronger effects were observed for EPF when the 5-day average PM10 was modelled. A summary of the main results from the GEE analysis is presented in Table 10.1. In Section 10.4 the estimate of association and its standard error are compared for the three modelling approaches (Aggregate, K-W and GEE). Within study areas, there were some statistically significant associations but all estimates were small: less than 0.40% decrease in EPF and less than 5.00% increase in the odds of day cough.

Table 10.1. The effect of a 20 μg/m^3 increase in PM10 on respiratory outcomes, overall and among non-medicated and medicated children

	Overall	Non-medicated	Medicated
Same-day			
Change in EPF	+0.03%	-0.15%	+0.18%§
	(-0.11, +0.18)	(-0.40, +0.10)	(+0.01, +0.35)
Day cough	+1.18%	+1.38%	+1.80%
	(-0.70, +3.00)	(-2.43, +5.00)	(-0.83, +4.00)
Bronchodilator use	-0.47%	n.a.	-0.47%
	(-3.01, +2.00)		(-3.01, +2.00)
5-day average			
Change in EPF	-0.08%	-0.30%	+0.07%
	(-0.35, +0.19)	(-0.71, +0.10)	(-0.27, +0.42)
Day cough	-0.30%	+2.62%	-1.30%
	(-5.43, +5.00)	(-10.29, +17.00)	(-7.86, +6.00)
Bronchodilator use	-2.87%	n.a.	-2.87%
	(-7.44, +2.00)		(-7.44, +2.00)

Values are percentage change with 95% confidence interval in parentheses. Percentage changes for the outcome EPF were calculated as 100 X (Change/300). Percentage changes for the outcomes day cough and medication were calculated as 100 X (odds ratio - 1).
Each estimate of effect of exposure has been adjusted by climate-related covariates and autocorrelation as required. The pollutant was fitted as a linear term on the same day as the outcome measurement, and 5-day average (average concentration over the current and previous 4 days). Area-specific GEE models were fitted. The Hunter Region estimate was obtained by pooling results across all five study areas using a random effects approach.
§. p-value <0.05.

10.2 Consistency with previous findings

Many diary studies have estimated the effect of air quality on respiratory outcomes. In this section, the results of this study are compared with previous research, and possible reasons for any inconsistencies are discussed. The main focus of this comparison is on the effect of PM10, but sulphur dioxide, pollen and Alternaria are also briefly mentioned.

10.2.1 PM10

In the cross-sectional survey (Phase I) an association was found between particulate concentrations and the outcomes chest colds and night-time cough, but not wheeze (Lewis *et al.* 1998). In this longitudinal study, no association was found for the outcomes examined: EPF, day cough and

bronchodilator use. There are at least two explanations for this apparent inconsistency. Firstly, different outcomes were examined between the two studies and so it remains to be seen whether there are statistically significant associations for chest colds and night-time cough in the longitudinal study. Secondly, it may indicate that pollution has long-term effects on respiratory health, but no short-term effects. A study in Lake Munmorah, an industrial suburb in the Lower Hunter Region, also found air pollution had long-term effects on respiratory health in the cross-sectional survey, but there was no evidence of short-term effects in the longitudinal study (Henry *et al.* 1991b).

For the overall cohort, no association was observed between PM10 and respiratory health. A 0.03% increase in EPF and a 1% increase in odds of day cough were observed per 20 $\mu g/m^3$ increase in same-day PM10. A slightly larger decrease in EPF (0.08% decrease) was observed for 5-day average PM10, but none of the results were statistically significant. Several panel studies have been conducted in a number of cities in the United States and Europe and have been summarised by several researchers (Dockery and Pope 1997; Desqueyroux and Momas 1999; Pope and Dockery 1999). In a meta-analysis of diary studies, the combined effect estimates was a 0.16% decrease of EPF and a 5% increase in odds of day cough per 20 $\mu g/m^3$ increase in PM10 (Dockery and Pope 1994).

The estimated effect on EPF and day cough are considerably lower than that observed in other panel studies. However, the results obtained from the subgroup of non-asthma medicated children are consistent (0.15% decrease in EPF) with those obtained from other panel studies. In this study, the medicated group included people taking any asthma medication during the study period. These medications included both anti-inflammatory medications (inhaled corticosteroids, sodium cromoglycate) and bronchodilators. In this study, 153 children (55%) took asthma medication during the study, with 112 of these taking anti-inflammatory medications.

There have been several diary studies which have found results similar to this study (Silverman *et al.* 1992; Ostro *et al.* 1994; Peters *et al.* 1996; Delfino *et al.* 1998; Roemer *et al.* 1998; Segala *et al.* 1998; Roemer *et al.* 1999; Ostro *et al.* 2001; Delfino *et al.* 2002). In Delfino *et al.* associations were notably stronger in 12 asthmatic children who were not taking anti-inflammatory medications versus 10 subjects who were (Delfino *et al.* 2002). This was also observed in their earlier asthma

panel (Delfino *et al.* 1998). Persons on oral corticosteroids were less susceptible to indoor pollutants in a panel study of adult asthmatics (Ostro *et al.* 1994). In a small diary study of 36 asthmatic subjects, persons on oral corticosteroids had increases in peak flow in response to PM10 (Silverman *et al.* 1992). A French study concluded that increased PM13 was associated with a fall in PEF in mild but not severe asthmatics, where severity was assessed by the inhaled corticosteroid dose (Segala *et al.* 1998). In the PEACE study, no consistent pattern between air pollution and respiratory health was found when analysing the complete panel of asthmatic children (Roemer *et al.* 1999). However, in a stratified analysis, the association between air pollution and EPF was positive in children who used respiratory medication whereas the associations tended to be negative in children who did not use respiratory medication. The association between concentrations of air pollution and daily prevalence of symptoms was not different between these subgroups (Roemer *et al.* 1999). Associations between PM10 and respiratory health were stronger in school children whose selection was based on respiratory symptoms in the preceding year than in subjects selected on the basis of diagnosed asthma (Pope *et al.* 1991). It was hypothesised that this difference was due to a higher proportion of subjects in the second group using asthma medication, compared to the first group (Pope *et al.* 1991). In addition, most panel studies that excluded children on asthma medication from their study found significant associations between PM10 and respiratory outcomes. It is also consistent with toxicological studies. Chamber studies have indicated that medication use attenuates or reverses the effects of pollutants on heath outcomes in asthmatic volunteers (Linn *et al.* 1988; Linn *et al.* 1990; Koenig *et al.* 1992).

Three diary studies found associations in the opposite direction to that found in this study (Gielen *et al.* 1997; Peters *et al.* 1997a; Mortimer *et al.* 2000). In Amsterdam, subjects using bronchodilators during the study period had more severe changes in respiratory health in response to increases in Black Smoke than subjects not using bronchodilators (Gielen *et al.* 1997). In a large cohort of 846 asthmatic children in the NCICAS study the association between ozone and respiratory health (morning peak flow, cough) was examined for various subgroups including medication use, and birthweight (Mortimer *et al.* 2000). Children taking cromolyn experienced greater ozone effects than children in the groups reporting use of inhaled bronchodilators or xanthines only, of corticosteroids, or of no medications. However, when the analysis was limited to the 127 children of low birthweight or premature birth, children who had no medication were most sensitive to ozone (Mortimer *et al.* 2000). In a diary study conducted in the Czech Republic, larger decreases in peak flow in response to increases in sulphate were observed for the 31 medicated children, compared to

the 51 non-medicated children (Peters *et al.* 1997a). There are several explanations for this apparent finding. Firstly, most children were treated with theophylline (an oral bronchodilator), which is not first-line treatment in Australia. Secondly, the assessment of medication use was done at baseline rather than during the study and studies using baseline data are more prone to exposure misclassification. Thirdly, the medications may not have been taken appropriately but this is difficult to assess.

In comparing the results of this study with those in the literature, several issues need to be considered. Firstly, although most studies reviewed reported a significant relationship with at least one of the pollutants examined, this may partly be influenced by publication bias. This is the phenomenon whereby a study with negative results is less likely to get published either as a result of the journal review process or because the researchers themselves hold back on submitting these results (Begg and Berlin 1989). A recent review of panel studies concluded there was some evidence of publication bias (Anderson *et al.* 2004). There are several other possible reasons for the observed lack of association between outdoor air pollution and lung function for the overall panel in this study. These include *the outcomes examined, low levels of pollutants, the size of the particulates measured, and the chemical properties of the pollutants.* Each of these will now be discussed. Other issues relating to bias will be discussed in Section 10.3.

Outcomes examined

This study looked at measures that are conveniently recorded in the evening by the participants, namely daytime cough and EPF. This is consistent with the Western Sydney panel study, where EPF was associated with ozone (Jalaludin *et al.* 2000). However, there is some evidence that night-time cough and morning peak flow are better indicators of asthma control. For instance, a recently reported diary study found that the effects on peak flow and symptoms were limited primarily to morning measures (Mortimer *et al.* 2002). Also, peak flow monitoring has been found to be not as sensitive as symptom diary for revealing acute exacerbations in adults (Chan-Yeung *et al.* 1996).

Low level of particulates

One explanation for the absence of associations seen in this study is the relatively low levels of air pollution. Daily PM10 did not exceed the National Health and Medical Research Council (NHMRC) guideline, and total suspended particulates at both Stockton and Mayfield were found to exceed the NHMRC guideline of 90 $\mu g/m^3$ on less than four days during the study period. The

largest annual average of PM10 was observed in the Mayfield study area, at 37.6 μg/m^3 with the lowest at Wallsend at 19.7 μg/m^3. These levels of air pollution are relatively low compared to international studies of air pollution and health where annual averages of PM10 have ranged from 35 to 48 μg/m^3 (Dockery and Pope 1994). In fact, Australia had the lowest annual average of PM10 in a recent review by Stieb (refer to Table 10.2). However, previous studies have indicated that the dose-response relationship between morbidity and particulate pollution was linear, with no evidence of a "safe" threshold level below which particulate matter has no effect on health (Brunekreef and Holgate 2002; Kjellstrom *et al.* 2002; World Health Organization 2003).

Table 10.2. Annual average PM10 in various cities, from time series mortality studies published 1985 to 2000

Region	PM10
Eastern Europe	123.2 μg/m^3
Asia	89.5 μg/m^3
South America, Mexico	84.5 μg/m^3
Western Europe	57.4 μg/m^3
United States	34.3 μg/m^3
Canada	26.9 μg/m^3
Australia and New Zealand	23.0 μg/m^3

Source: (Stieb *et al.* 2002)

Size of particulates measured

In this study, PM10 was not directly measured in the three industrial areas. Instead, it was calculated as a fixed percentage of TSP. Studies have found that fine particles (PM10) are more strongly associated than coarse (PM10+) particles with acute respiratory health effects in children (Schwartz and Neas 2000). In addition, it is generally recognised that PM2.5 or even smaller particles may be more harmful than PM10 because they can penetrate deeper into the lungs. There have been few epidemiological studies focusing on the effect of PM2.5. In this study, there was the opportunity to examine the effect of PM2.5 in the industrial area of Mayfield and the effect on peak flow was not statistically significant.

Chemical content of particulates

The sources of particulate pollution in the three industrial areas (Stockton, Mayfield and North Lake Macquarie) are similar to other industrial areas in Australia and overseas. There is some evidence that particulates must be combustion related to affect symptoms and that particulates consisting of soil / dust and sea-spray do not have a significant effect on respiratory health (Brunekreef and Holgate 2002). In a study conducted at six sites across Newcastle in 1995 it was found that particulate levels in sites closest to industrial activities were influenced by high levels of iron and manganese, and non-industrial suburbs were influenced by bare soil and surface disturbance, indicated by higher concentrations of calcium, magnesium, and potassium (Hobson 1995). This suggests that for any concentration it is likely that particulate air pollution in an industrial area is more likely to cause health problems than in a non-industrial area. Particulate matter includes sulphur dioxide and sulphates, which are discussed in the next section (Section 10.2.2).

10.2.2 Sulphur dioxide

There was no significant association between sulphur dioxide and EPF when the results were averaged across all five study areas (0.09% decrease in EPF per 1.5 pphm increase in same-day maximum SO_2 from GEE analysis; 95% CI -0.25% to +0.08%). There are at least two explanations for the absence of associations between sulphur dioxide and respiratory health seen in this study. Firstly, the levels of sulphur dioxide were quite low. Table 10.3 compares annual SO_2 concentrations at Newcastle with other cities. Despite Newcastle's predominance of heavy industries, mean annual SO_2 emissions lie well within NSW EPA guidelines of 2.3 pphm. Secondly, other studies have indicated that aerosol sulphates may be more strongly associated with respiratory health than sulphur dioxide (Dockery *et al.* 1993; Hoek and Brunekreef 1994). Aerosol sulphates (SO_4) are water-soluble derivatives of sulphur dioxide, and may be important because of their chemical nature and small size. The average daily sulphate component of the particulates at North Lake Macquarie during the study period was 1.56 $\mu g/m^3$ (Luck 1997), which is quite low compared to the Harvard Six Cities Study where the city with the lowest levels of sulphate reported an average daily concentration of 4.8 $\mu g/m^3$ (Health Effects Institute 2000). It is interesting that associations between SO_2 and EPF were seen in Stockton and Mayfield but not at North Lake Macquarie, where the latter is the site of a lead smelter and fertilizer plant and experienced several short-term exceedences. One explanation may be that Stockton and Mayfield had higher aerosol sulphate concentrations than North Lake Macquarie because they are coastal (Bridgman *et al.*

1992). Another is that the study at North Lake Macquarie was conducted over summer and the analysis conducted at Stockton and Mayfield indicated that the effect of SO_2 on EPF may be stronger in winter.

Table 10.3. Annual average sulphur dioxide concentrations in various cities compared to Newcastle. From the Global Environment Monitoring System network

City	Country	Year	Sulphur dioxide
Tehran	Iran	1988-89	5.69 pphm
Athens	Greece	1986-1987	1.34 pphm
Auckland	New Zealand	1988-1989	0.11 pphm
Sydney	Australia	1984-1985	0.50 pphm
Newcastle	Australia	1990	0.65 pphm

Source: (Bridgman *et al.* 1992)

10.2.3 Pollen

In this study pollen was analysed as all pollens combined, tree pollen, grass pollen and weed pollen. No association was observed between the exposures - total pollen and tree pollen – and EPF. There was a small but significant association between grass pollen and EPF when the results were averaged across all five study areas (0.18% decrease in EPF per 4 grains/m^3 increase in 5-day average grass pollen from GEE analysis; 95% CI -0.40% to -0.00%). This result was robust to choice of modelling approach but not to choice of lag, as no significant associations were observed for same-day grass pollen. For weed pollen, small but statistically significant associations were observed in the Aggregate analysis 0.12% decrease in EPF per 3 grains/m^3 increase in same-day weed pollen; 95% CI –0.24% to –0.00%) but not in the K-W and /or GEE analysis.

Other studies have not been able to demonstrate an association between pollen counts and lung function (Neas *et al.* 1996; Scarlett *et al.* 1996; Jalaludin *et al.* 2000). Possible reasons for this have included daily pollen counts being too low to effect respiratory health, or not enough variation in daily concentrations of pollen counts (Delfino *et al.* 1997). In this study, the level of pollens and fungi were extremely low in the Hunter Region compared to previous years because of an unusually dry climate (L McShane, NSW Health Pollen Study, pers. com., 1997). Using the classification of

grass pollen developed by the Melbourne pollen group (E Newbigin, Melbourne Pollen Group, pers. com., 2003) of low (<20 grains/m^3), moderate (20-50 grains/m^3) and high (>50 grains/m^3), Stockton was the only study area with high concentrations of pollen recorded during the study period. Although grass pollen was not speciated in this study, it was anticipated that it was mainly Rye grass because of its phenomenal pollen production in Australia (Bhalla *et al.* 1999).

10.2.4 Fungi including Alternaria

The only fungus measured in this study was Alternaria. There was no significant association between Alternaria and EPF when the results were averaged across all five study areas (0.01% decrease in EPF per 6 spores/m^3 increase in same-day Alternaria from GEE analysis; 95% CI – 0.07% to +0.05%). There are at least two explanations for the absence of associations between Alternaria and respiratory health seen in this study. Firstly, concentrations were extremely low with zero levels were recorded on more than 30% of days for areas in Wave 1 (Stockton: 42%, Wallsend: 44%, Mayfield: 31%), and more than 10% of days for areas in Wave 2 (Beresfield: 12%, North Lake Macquarie: 25%). The maximum level on any day was 162 spores/m^3. Recent panel studies conducted in Australia have reported similar levels of Alternaria to this study (Jalaludin *et al.* 2000; Rutherford *et al.* 2000; Downs *et al.* 2001). Two diary studies conducted in the United States have reported an association between fungi and respiratory health (Neas *et al.* 1996; Delfino *et al.* 1997). Concentrations of fungi in these studies were considerably higher, with average daily Cladosporium spore concentrations of over 1000 spores/m^3. Secondly, there may have been very few children whom were sensitive to Alternaria. One panel study examining the association of daily Alternaria spore counts with respiratory outcomes (symptom prevalence, level of peak expiratory flow) in children, found stronger associations amongst children sensitised to Alternaria (Downs *et al.* 2001). In a study conducted in inland NSW (Wagga Wagga and Moree), it was found that 15% of children were sensitive to Alternaria (Peat *et al.* 1995). It was also found that among Alternaria-sensitised individuals, the risk of hospital attendance for an exacerbation of asthma was higher on days with higher ambient Alternaria spore counts (Peat *et al.* 1995).

10.3 Strengths and weaknesses of the study design

The strengths of this study included its longitudinal design, which allowed for the prospective assessment of the effects of air pollution on the respiratory health of symptomatic children. In assessing the strengths and weaknesses of the study design, it is important to consider both the

external validity and internal validity of the study. The limitations of this study can be considered at all levels of the study including the subjects, the exposure measures, the outcome measures and confounders.

10.3.1 Strengths of the study

Purposive sampling of study areas

An important feature of HISAAP was its use of multiple study areas, with three high exposure areas and two control areas, providing a gradient of exposure intensity (Lewis *et al.* 1995). This allowed the study to have considerable heterogeneity of air pollutant exposure.

Enriched sample

The subjects in this study were selected from a cross-sectional survey of all school children in years 3 and 4 attending school in the five study areas. Their selection was based on the occurrence of any of the following symptoms within the preceding 12 months: a night-time cough, without a cold, for more than 2 weeks; four or more episodes of wheeze; four or more chest colds. Hence, there are a greater proportion of symptomatic children than would be the case in a random sample, allowing a good distribution of the outcome factors. Neas *et al.* found that only children with a history of respiratory symptoms were sensitive to the pollution recorded during their panel study (Neas *et al.* 1995).

Reduced potential for Selection Bias

The proportion participating in Phase I was high (83%) and the enrolment rate into Phase II was very high (90%; n=291). Therefore, selection bias attributable to non-response is unlikely to be a major problem. Selection bias occurs in an analytical study if the association between a study factor (PM10 in this study) and an outcome factor (EPF, day cough and medication use in this study) depends on factors that effect participation (Rothman and Greenland 1998a). In the Phase I cross-sectional survey factors that might affect participation were measured. The Phase II study sample was similar to the source population of symptomatic children identified from the Phase I cross-sectional survey in terms of demographics, household characteristics and asthma severity (as determined by prevalence of asthma diagnosis and asthma medication use). A problem with studies such as this is the potential for selection bias due to a “healthy child” effect. The children who were most affected by pollution may have left the area and so become ineligible for this study. It is not

possible to estimate the size of this effect, but the expected impact is small and likely to bias the estimated exposure-response relationships toward the null.

Ability to adjust for potential confounders and effect modifiers

A wide range of putative confounders and effect modifiers were measured and this enabled investigation of the causal pathways involved in a more comprehensive fashion than any previous study.

Climate-related putative confounders such as temperature could not be controlled for in the design, but were measured, and so controlled for in the analysis. Daily measurements were made on a wide range of potential confounders including temperature, humidity and rainfall and the analysis adjusted for these confounders. The ambient pollutants monitored during the study-period included particulates, sulphur dioxide, nitrogen dioxide and ozone. No formal analysis was conducted on nitrogen dioxide and ozone as their levels were low (mean of daily maximum NO_2 during study: 1.9 pphm to 2.8 pphm across study areas; mean of daily maximum ozone during study: 2.2 pphm to 2.4 pphm across study areas), and these pollutants were not monitored in all the study areas.

This study was also able to examine whether there was effect modification by various subject factors. For example, nitrogen dioxide exposure may result in an enhanced bronchoconstrictor response to inhaled house dust mite and pollen antigens, thereby making people exposed to nitrogen dioxide a more sensitive subgroup. This was examined in the present study by stratifying analyses by whether the child was exposed to indoor sources of pollution. Importantly, there was also a good distribution of medication use, which was one of the putative effect modifiers. Approximately half the subjects were taking asthma medication and so the effect of medication use could be examined.

10.3.2 Limitations of the study

Non-representative sampling

Purposive sampling of the study areas in Phase I may not have produced a representative sample of symptomatic children. However, this is not an issue in an analytical (association) study, where prevalence estimates are not required and the purpose is to estimate the association between a study factor (PM10 in this study) and an outcome factor (EPF, day cough and medication use in this

study) (Miettinen 1985; Rothman and Greenland 1998a). Key concerns with regard to study base are (a) definition of eligible participants, (b) a proper distribution of study factors, modifiers and confounders and (c) sample size (Miettinen 1985). This study meets criteria (a) and (b), as previously discussed in Section 10.3.1. This study also fulfils criteria (c) as discussed below.

The statistical power of a longitudinal study depends on the number of subjects, the variation in outcomes reported and the variation of the exposure of interest. A post hoc analysis was undertaken using the estimate and standard error observed in the GEE analysis for a 20 $\mu g/m^3$ increase in same-day PM10. This post hoc analysis revealed that the study only had 71% power to detect a 0.16% decrease in EPF, where 0.16% had been previously estimated in a major review (Dockery and Pope 1994). However, the present study did have 86% power to detect a 0.20% decrease in EPF, which was a more clinically important change. Hence it is unlikely that the power was not adequate to detect a clinically important relationship for the overall group (point c).

In conclusion, this study will have external validity to symptomatic children, but will be less generalisable to asymptomatic children.

Eligibility criteria differed between study areas

All children enrolled in years three and four at each of the primary schools within the five study areas were eligible to participate. Year 5 students in two study areas were also enrolled in order to achieve adequate sample size. However, whilst the age criteria differed between the study areas no evidence of effect modification by age was found and so the estimates are appropriate for students in years 3,4 and 5.

Loss to follow-up

There was considerable loss to follow-up in this cohort, with only 231 of the original 345 participants attending the final interview. In addition, many children did not complete the diary each day, with only 239 children (69%) providing sufficient data for the non-aggregate analysis. However, this group had similar characteristics to the symptomatic group as a whole (n=345). There was one minor exception - children in the analysis group from North Lake Macquarie comprised a disproportionately higher percentage of children without exposure to passive smoking, with maternal allergy, and with higher educated parents compared to those children not eligible for the non-aggregate analysis. Attrition bias was evaluated using information from 138 (40%) subjects

who completed the diary each day for the entire study period. Similar estimates were found for the association between PM10 and the outcomes EPF and day cough for this subgroup.

The outcome measurements were subject to measurement error

Outcome misclassification in diary studies is always a potential source of error due to a lack of verifiable subject data. Several steps were taken to reduce measurement error. The interviewers were well trained, and the first two-weeks of data from each subject was discarded to avoid any learning effect, particularly in relation to recording of peak flow measurement. A high standard of data quality was maintained throughout the study by fortnightly contact with the parents, which aided motivation and encouraged completion of the diary. It has been acknowledged that missing outcome data can bias estimates and so this frequent contact was important.

Anecdotal reports provided by the study interviewers suggested that some children completed the diary rather than parents, as was requested. This raises concerns about the reliability of the data, given the subjects' young age. However, it is understood that this occurred in less than 20% of cases. The study team checked the diary records from each child every fortnight in order to detect any unusual patterns of response. During data analysis outliers were investigated. In addition, when subjects with suspicious EPF data were removed similar results were obtained.

The outcomes examined in this study were EPF, day cough and bronchodilator use. Measurement issues relating to each of these outcomes will now be discussed.

Peak flow is widely regarded as an objective measure of lung function (Quanjer *et al.* 1997). The daily peak flow measurements in this study were supported by complete spirometry conducted on each subject at the initial and final interview. The child-specific mean peak flow observed over the study period correlated well with the average of their FEV_1 values at the initial and final interview (r=0.61). The peak flow meters were not calibrated during monthly school visits, however this should not have resulted in any systematic error. Adequacy of peak flow technique was recorded at each monthly interview at the school, however, because this information was not recorded in the database it was not possible to perform a separate analysis of subjects based on the quality of their technique. Subjects were carefully instructed and there was no reason to suspect systematic bias such as would occur if on high pollution days they did not blow hard enough. If the use of an incorrect EPF technique resulted in random error then this would result in a bias towards the null. A

previous study of children aged 5 to 9 years found that compliance with peak flow monitoring was quite poor and that manual records considerably overestimated actual use (Redline *et al.* 1996). In this study some children reported little variation in EPF measurement or appeared to only report EPF at even multiples of 50 L/min. Nonetheless, the exclusion of such subjects did not alter the results substantially. This study did not provide instructions to participants regarding when to take medication in relation to obtaining their peak flow reading. If medication reduced the variability in peak flow measurements, this would have introduced a bias toward the null for the medicated group.

The symptom modelled was day cough, which may be a result of an upper or lower respiratory tract infection, and not necessarily asthma. Questionnaire surveys are widely used to study respiratory symptoms in children, and have been shown to yield reproducible answers (Brunekreef *et al.* 1992). However, the reporting of symptoms is subjective, and can be influenced by a number of factors including perceived air pollution concentrations (Schwartz *et al.* 1994). This was a particular concern in this present study because the distribution of the principal exposure, PM10, was well known to all participants. The NSW Environmental Protection Agency in 1993 and 1994 found that air quality complaints from the NSW public were highest among Newcastle and Lake Macquarie residents. Complaints about air pollution focused on odour (68%), dust particles (14%) and smoke (13%). If reporting varied with perceived air pollution concentrations, this would introduce a bias away from the null assuming the perceptions were positively correlated with actual pollution measures (Schwartz *et al.* 1994). The possible misclassification of respiratory symptoms could not be assessed because the subjects' parents were the sole source of symptom information.

Amongst the subgroup of children who used bronchodilators at some stage during the study, the daily prevalence of bronchodilator use did not increase with increasing air pollution levels. However, it is possible that these children increased their dose or frequency of use of bronchodilators. This was not assessed because the doses of medication were not recorded accurately. Some studies have used automatic recording of as-needed bronchodilator usage (Perry *et al.* 1983), but these devices are costly and so are rarely used. In summary, daily prevalence of use may have been too crude a measure, and daily dosage may have revealed a relationship with the exposures of interest (PM10, sulphur dioxide and aeroallergens).

The exposure measurements were subject to measurement error

All exposures (PM10, sulphur dioxide and aeroallergens) were measured using central outdoor monitoring. This is an indirect measure of personal ambient exposure. Personal exposure can be measured by attaching filtering devices to the child's clothing. These devices are costly, and it has been shown that it is difficult to obtain reliable measurements for children because of high sample losses (Alm *et al.* 1998). Moreover, it is not generally feasible to routinely measure exposure in this way and hence the type of monitoring used in this study has relevance for public health surveillance.

Measurement error would arise if there were differences between personal ambient exposure and the results of central outdoor monitoring. These differences could be due to spatial location. Additionally individual behaviour may influence individual exposure to ambient sources. The actual dose to the lung would be affected by several factors including indoor level of pollutants, trigger avoidance, location of the child's home, whether the child attended school, time spent outdoors, and level of exertion during outdoor exercise. Proxy data were available for some of these factors, and in some analyses techniques were used to minimise this bias, but one cannot be sure that these techniques solved the problem. Indoor level of pollutants is not relevant to measurement error, but was a potential confounder and this will be discussed later.

This study used exposure data provided by the EPA and industry. This avoided the need to collect new data specific to the study's purpose. The principle advantages of using an existing database are that the substantial costs of data collection are eliminated, and the study's results will be available much sooner. There are also limitations, however and these are discussed later in this section.

Trigger avoidance

It is likely that some individuals, particularly those most susceptible to air pollution effects, modify their exposure on high air pollution days. For example, the children in this study may have reduced their exposure to ambient air pollution in order to avoid triggers that instigate their asthma attacks. This is likely because information regarding awareness and avoidance of asthma triggers is provided as part of asthma management plans that are recommended for children with an asthma diagnosis. The extent to which the child follows these guidelines will influence the validity of the measurements of personal ambient exposure made by a fixed monitoring device. In this study, the effect of PM10 on EPF was stronger when the child did not perceive pollution to be present. A

possible explanation of this finding is that they avoided going outside on high pollution days. A strength of this study is that information on perceptions of pollution were obtained, and this was taken into account in analysis. No other study has done this.

Spatial differences

An additional issue in the use of central outdoor monitoring as a proxy for personal ambient exposure is that it ignores local spatial variation. However, the study areas were small in geographical size and all schools were less than 1 km from the central monitoring device. Further, a single monitoring site was found to be sufficient for defining average outdoor concentration of fine particles (PM2.5) in several demarcated residential areas within the United States where the monitoring stations were up to 5 km from residences (Kotchmar *et al.* 1987). Four of the areas in this study were similarly isolated but this was not the case of Stockton which, given usual wind conditions is exposed to pollution originating in Mayfield. In this study, the correlation coefficients between daily pollution measures from the central monitoring station and those from peripheral stations within the same area were calculated for three of the study areas and were reasonably high apart from Stockton (Stockton: 0.37, Mayfield: 0.65, North Lake Macquarie: 0.63). This suggests that misclassification of ambient exposure is unlikely to be substantial and should be random.

The misclassification would be greatest on non school days for children who live outside the area. During weekends, children will typically spend more time outdoors, but those living outside the area are less likely to be in the vicinity of the outdoor monitor. This issue was addressed in two different ways. Firstly, a binary indicator term was included for weekday versus weekend but this was found to be neither an effect modifier nor confounder of the association between PM10 and EPF. Secondly, additional analysis was undertaken and limited to approximately half the sample that lived within 1km of their school, and found that doing so had no material impact on the estimated coefficient of PM10.

There was also potential for misclassification during school holidays for all children. In this study, daily measurements of ambient exposure and health outcomes were obtained for a period of seven months, which included weekends and school holidays. Daily information was obtained on whether the child slept in their home, and it was found that approximately 77% (209/271) did not sleep every night in their home during school holidays. Since some areas were chosen specifically because of proximity to industrial sources of pollution, it is likely that children would holiday in an

area less polluted than where they live. To the extent that this reduced their "real" exposure, it would do so particularly on days of high pollution, and this might result in a bias towards the null. However, in this study no evidence of this was found. The approach typically used in other studies has been to exclude days where the child was not in the area. In this study, this issue was addressed in two different ways. In some analyses, a binary indicator term was included to indicate if they slept at home and it was found the PM10 coefficient was unchanged but the standard error was reduced (more precise estimate). Secondly, a binary indicator term was included for school term. There was no evidence of effect modification or confounding on the association between PM10 and EPF. In conclusion, there was no systematic error due to misclassification of exposure.

Inability to adequately control for exposure bias

The diary was not as detailed as those used in some other studies. For instance, there were no measures of the amount of indoor and outdoor exercise, the amount of time spent indoors, and the time the child usually rose and went to bed. Such information would have been useful to examine the validity of the ambient pollutant measures as estimates of personal ambient exposure, and to better define each subject's actual exposure.

Issues related to the measurement of sulphur dioxide

Unlike PM10, sulphur dioxide does not penetrate well indoors (Schwartz 2004). Exposure to ambient sulphur dioxide in outdoor air could be very different from indoor air implying that individual behaviour could substantially influence individual exposure to ambient source levels. If individuals modify their exposure on high pollution days, for example by staying indoors when levels are high, this might result in a bias towards the null. This study did not examine whether effect modification existed by perception of air pollution for sulphur dioxide, but did examine it for PM10 (see earlier section titled trigger avoidance).

Issues related to the measurement of aeroallergens

Ambient pollen and fungi concentrations were measured in each area using a central outdoor monitor. The monitor collected aeroallergens at weekly intervals from which a technician manually counted the number of spores. In this study, the repeatability of these daily aeroallergen counts was assessed whereby the intra-observer and inter-observer agreement was computed based on a recount of the collected aeroallergens on two week-long samples taken from North Lake Macquarie. The intra-observer and inter-observer correlation coefficients were over 0.80 for total pollen, weed

pollen, tree pollen and Alternaria, but were poorer (intra-observer = 0.73, inter-observer=0.45) for grass pollen where the counts used in the analysis were much higher.

There have been very few studies examining the influence of spatial location and individual behaviour on aeroallergen concentrations. Mitakakis *et al.* studied personal ambient concentrations in 9 families using two devices (nasal air samplers and passive air samplers) over 4 days in November in Moree, NSW (Mitakakis *et al.* 2000). They found that exposure to pollen and fungi can be highly variable between individuals. The within-family correlation of personal outdoor concentrations measured using passive air samplers during inactivity was only 0.38 for Alternaria and 0.47 for total particles (spore counts plus pollen counts), and the within-family correlation for nasal air samplers was considerably worse (0.04 and –0.03 respectively). Additionally, they found that personal ambient concentrations were higher during periods of moderate activity, compared to periods of inactivity. This suggests that in this present study, the ambient pollen and fungi concentrations recorded by the central monitor (measured using Burkhard Spore trap) were poor proxies for personal ambient pollen and fungi concentrations. In conclusion, misclassification of ambient exposure to pollen and Alternaria is likely to be substantial. Unless subjects chose to stay indoors during peak pollen periods, the error is likely to be random. Thus, any bias in the results is likely to be towards the null. For this reason, this study should not be reporting significant associations, where none exist.

There has been debate about whether pollen antigen should be measured in preference to pollen counts in epidemiological studies (Beggs 1998). Symptoms of hayfever may result from pollens landing on the surface of the upper respiratory system and eyes. However, allergic asthma is triggered by pollen antigen which are smaller granules that gain access to the airways of the lower respiratory system (Suphioglu *et al.* 1992; Marks *et al.* 2001). These allergen-containing starch granules are released as a result of airflow patterns during a thunderstorm sweeping up grass pollen grains that have been ruptured by the rain (Suphioglu *et al.* 1992; Marks *et al.* 2001). This explains why, in time series studies of emergency room visits for asthma attacks, that the numbers of visits increase after a thunderstorm. In a study of six towns in south-eastern Australia, it was found thunderstorms were present on 33 percent of the days when emergency-room attendance by asthmatics soared (Marks *et al.* 2001) . In a recent review, pollen antigen was found to be correlated with outcomes of the lower respiratory system, and on balance to correlate well with pollen count except at the beginning and end of the pollen season (Beggs 1998). Hence, in this present study,

pollen counts are expected to be a good proxy to pollen antigen levels for most days during the study period. It would have been useful to collect data on thunderstorm activity to allow examination of whether it was an effect modifier of the association between pollen count and respiratory health.

Missing exposure data and unexpected exposure data

The exposure data were missing for some contaminants at some sites due to equipment failure, or because monitoring was not done on public holidays. When missing PM10 data were imputed, similar estimates of effect were found. There were also some concerns regarding the validity of the data provided, especially the sulphur dioxide measurements at the industrial study area North Lake Macquarie which were considerably lower than expected based on the previous year's data. Because the daily amount of measurement error is not expected to be correlated with the daily respiratory outcomes, this misclassification of exposure is most likely non-differential and as a result, the estimate of effect would be biased toward the null (Armstrong *et al.* 1992).

Different devices were used to measure PM10

A weakness of this study was that particulate measurement was obtained using two different instruments. In the industrial areas of Stockton, Mayfield, and North Lake Macquarie, total suspended particulates were recorded using a high volume sampler and a scale correction was applied to estimate approximate PM10 levels. In the control areas of Wallsend and Beresfield, PM10 was directly measured using a TEOM. One of the very few studies comparing the measurement of PM10 using these two devices was conducted in England. They found the PM10 concentration is most likely underestimated using the TEOM because of it operating at 50 degrees Celsius, thereby losing volatile compounds (Smith 1997). Hence, in this present study, PM10 may have been consistently underestimated at the study areas using the TEOM. The same device was used for the whole study period within each area, but the estimated PM10 health effect would be biased if there was daily variation in the amount of volatile compounds making up PM10. No evidence of systematic error was found, however. In this study, it was possible to assess the agreement in the daily concentrations of PM10 between the TEOM and high volume sampler with size-selective inlet (SSI) for a number of days in the study period for the two control areas. There was no evidence of underestimation, with the mean difference between SSI and TEOM in the measurement of PM10 being 0 $\mu g/m^3$ in Beresfield and 1 $\mu g/m^3$ at Wallsend.

Bias due to influence of other causal factors

Additional sources of bias include the possibility of inadequate control for confounding variables. Confounders such as smoking and diet, which tend to remain constant and do not vary over time, are less of a potential problem in panel studies. More of a problem are factors such as climatic conditions if they influence outcome and co-vary with exposure. For a longitudinal study of daily responses to PM10, it is necessary to have data on such factors on a daily basis in order to attempt to avoid biases caused by unmeasured changes over time. In longitudinal diary studies, the principal confounders are likely to be weather factors that have not been adequately controlled.

Weather

In this study, regression estimates were adjusted for several climate variables including temperature. Season and weather are important potential confounders because they are causally related to the outcome measures and may be related to the level of exposure. Ideally, in the design, studies such as this would give attention to controlling for seasonal influences, perhaps by restricting the study period to one season. This was not the case here, and hence it was necessary to control for these factors in the analysis. This may have resulted in an underestimation of the PM10 coefficient because temperature is also correlated with meteorological conditions that cause PM10 build up.

Multi-pollutant model

The main purpose of this study was to estimate the effect of PM10 on respiratory health. An attempt was also made to isolate the effect of PM10 by fitting a multi-pollutant model whereby PM10 and alternative air quality measures (sulphur dioxide, pollen and Alternaria) were entered simultaneously into the regression model. For a 20 $\mu g/m^3$ increase in PM10 the estimated effect on EPF was –0.08% (95% CI: -0.35% to +0.18%) in single-pollutant models, and –0.20% (95% CI: -0.55% to +0.15%) in multi-pollutant models. However, it is difficult to isolate the health effects of individual pollutants within the PM10 mixture (Kjellstrom *et al.* 2002) and so the appropriateness of fitting this model is not clear. The fact that PM10 is not a chemically specific pollution index makes the issue of confounding even more complicated. For example, PM10 may include sulphates, which are formed from sulphur dioxide. Then, sulphur dioxide becomes part of the causal pathway of PM10 effects, and so is no longer a confounder. Similarly, it was expected that PM10 would include some pollen matter.

Indoor pollution

One limitation of this study was that indoor air quality may have been a confounding factor in the association between ambient air quality and respiratory health. In general, children are estimated to spend 90% of their time indoors during the day (Godar 2001). The main sources of indoor pollution are gas appliances and passive smoking. For daily indoor pollution levels to affect the effect estimates they must be associated with the outcome as well as the study factor (ambient PM10, sulphur dioxide and pollen in this study). It has been demonstrated that there is an association between daily record of gas appliance use and daily record of symptoms (Ostro *et al.* 1994), and a study of children living in Western Sydney provided evidence that short-term exposure to the peak levels of nitrogen dioxide produced by unflued gas appliances affects respiratory health (Pilotto *et al.* 1997). Indoor pollution would be a confounder if this exposure varied over time and was correlated with ambient PM10. For example, passive smoking may be a confounder if the windows of the home were closed during periods of high ambient PM10 concentrations but this is unlikely to happen. In this study, 50% of children were exposed to indoor sources of pollution in the home (passive smoking, unflued gas heating, gas cooker with no external fan).

It was not possible to adjust for daily exposure to indoor pollutants, as daily records were not kept of the use of indoor sources of pollution. However, it was possible to take indoor air pollution into account indirectly. Indicator terms were included in the model for presence of indoor sources, and separate estimates of the effect of PM10 on respiratory outcomes were reported when tests of statistical interaction showed that the effect differed between subjects with exposure to indoor sources and those without.

Lack of information on key putative effect modifiers

There was limited information on the atopic status of the participants, as allergy testing was not performed in this study. Had it been available, it would have allowed examination of the effect of pollutants on subgroups of children defined by atopic status, including those allergic to grass pollen, weed pollen, or Alternaria, as a history of allergic skin reactions has been shown to be a marker of individual susceptibility of the respiratory tract to air pollutants in children (Jedrychowski *et al.* 1996). Similarly, the children's airway hyper-responsiveness or bronchial reactivity was not measured in this study. Other studies have found that pollution has a stronger effect on peak flow among children with bronchial hyperresponsivity (Jalaludin *et al.* 2000). One area that has not been explored at all in the literature is the role of genetic differences in mediating the effects of pollution.

10.4 Statistical issues

Many approaches can be taken to analyse longitudinal data. These include data reduction methods, mixed model methods and marginal methods (Hardin and Hilbe 2003). One of the strengths of this study is in the number of approaches used. Three general approaches were used. This included a representative of data reduction methods (Aggregate analysis), subject-specific or mixed model methods (Korn-Whittemore analysis) and marginal methods (Generalised estimating equations analysis). There are other methods, but these were considered the most appropriate in terms of understandability and interpretability, consistency with analysis of similar studies, and availability of software and practical application. This section discusses some of the statistical issues in analysis of the data, and areas of future research.

10.4.1 Modelling approaches

It is well recognised that the analysis of longitudinal studies must account for the correlation of residuals. Several modelling approaches were used in the analysis of this study. They included an Aggregate analysis, Korn-Whittemore analysis and generalised estimating equations (GEEs) analysis.

The strength of the *Aggregate analysis* was that few computer resources were required, however, it was tedious to examine whether there was any effect modification by the time-stationary covariates (e.g. medication use: yes/no). In the *Korn-Whittemore* analysis a separate model was fitted for each child thereby allowing each subject to have a different slope and different intercept. The subject-specific regression estimates for the pollutant were then pooled. The Korn-Whittemore approach may be considered the simplest form of a mixed model and it was developed before the introduction of more sophisticated random effects models and so is quite dated now. However, it was very useful to examine the distribution of the coefficients both overall, and by various time-stationary covariates. One limitation of the K-W modelling approach is that, empirically, the logistic model cannot be applied to people who are healthy almost all the time or to people who are sick almost all the time. The *GEE approach* to modelling longitudinal data is attractive for two reasons. Firstly, there is convenient software that is readily available to produce parameter estimates and their associated standard errors. Secondly, they tend to give valid parameter estimates even if the

specified correlation structure is not correct. One potential disadvantage of GEE is that the robust variance adjustment may not work well in settings like this panel study where there are few subjects and many observations per subject. Also, GEE give biased effect estimates when the exposure affects a confounder or is affected by the study outcome (Greenland 1998).

The association between PM10 and the respiratory outcomes, for each of the three modelling approaches is shown in Table 10.4. None of the analyses suggest that there is a strong association between PM10 and respiratory health. An interesting feature when comparing the results across the different methods is the variation in the parameter estimates. One possible explanation is random variation. The three methods can lead to very different parameter estimates because each is estimating the parameters in a slightly different way. However, they are all addressing the induced correlation structure, which makes them valid approaches. The magnitude and degree of association differs for each of the fitted models, but in general the associations are in the same direction. Hence, while the three sets of results are not identical, they do not contradict each other. There are no instances in which one approach gave a statistically significant positive result, and the other method gave a statistically significant negative result. For the dichotomous outcome cough, similar regression parameter estimates were found from the GEE and mixed model methods (K-W), although theoretically, they should be estimating different population parameters as the GEE estimates population effects and the K-W estimates individual effects. The standard errors from the K-W analysis were larger than those from the other two methods for all three outcomes, particularly for the dichotomous outcomes.

Table 10.4. The effect of a 20 μg/m^3 increase in 5-day average PM10 on respiratory outcomes: Results from Aggregate, Korn-Whittemore and GEE analysis

Model †	Evening Peak Flow Mean (95% CI)	Day cough OR (95% CI)	Medication Use OR (95% CI)
Aggregate - weighted	-0.37 (-1.23, +0.49)	1.03 (0.94, 1.12)	0.94 (0.87, 1.02)
K-W - weighted	-0.89 (-1.83,-0.00)§	1.02 (0.40, 2.56)	0.64 (0.25, 1.63)
GEE	-0.25 (-1.05, +0.55)	1.00 (0.95, 1.05)	0.97 (0.93, 1.02)

Estimates and 95% confidence intervals (in parentheses) are reported. Each estimate of effect of PM10 has been adjusted by climate-related covariates and autocorrelation as required. PM10 was fitted as a linear term on the 5-day average (average concentration over the current and previous 4 days).
Mean=Mean change in evening peak flow, L/min.
OR=Odds ratio
†. Various models were fitted: Aggregate - weighted= Aggregate analysis where the daily group mean was weighted by the number of children providing data; K-W - weighted=Korn-Whittemore modelling approach where subject-specific regression coefficients were pooled across study subjects using a fixed effects approach and with weighting determined by the number of observations from the subject; GEE=Generalised Estimating Equations. Pooled estimates were derived by pooling results across study areas using a random effects approach.
§. p-value <0.05

In a recent review of panel studies, larger PM10 effect estimates were obtained from studies using GEE or K-W methods to model autocorrelation, than in studies using Aggregate methods (Ward and Ayres 2004). This evidence was based on a between-study comparison. In this study it was possible to compare the PM10 effect estimates across the three modelling approaches using a within-study comparison and the findings do not support this result.

10.4.2 Assessment of effect modification by time-stationary covariates

Several analyses were undertaken to examine whether children with certain characteristics were more affected by air pollution than those without these characteristics. For example, it was hypothesised that children exposed to indoor air pollution in the home by gas cooking, gas heating or passive smoking may be more sensitive to ambient pollutants than unexposed children. To test for this, an interaction term was included in the statistical model. In these analyses, 0.05 was used as the critical significance level. Tests of interaction are less sensitive than tests of main effects, and so an argument could be made that a critical value of 0.10 or 0.15 may have been more appropriate. However, a large number of tests were undertaken which might introduce spurious significant results (Bland 2000) and so it seemed necessary to maintain tighter control of nominal type I error. On balance, a critical p-value of 0.05 seemed a prudent choice.

10.4.3 Adjustment for climate-related covariates

In this study, seasonal affects such as temperature and humidity were taken into account during the analysis using linear terms. Statistical techniques are now available for the extension of GEEs to generalised additive models (GAMs), so called generalised additive mixed models, which allow greater flexibility to model non-linearities. However, the appropriate scale of the covariates was routinely assessed by using fractional polynomials and so it seems unlikely that the use of more sophisticated techniques, such as GAMs would have altered the estimated coefficients substantially.

In this study, data were collected in three areas simultaneously in the first wave, and two areas simultaneously in the second wave. The areas in this study were all less than 20 km apart and it was confirmed that they experience practically the same daily weather conditions (temperature and relative humidity). There are statistical methods available that enable control for putative confounders that occur simultaneously in the study areas. Peters *et al*. also examined two study areas which were in close proximity, and regressed the daily differences in the outcome between the two areas against the daily difference in pollutants (Peters *et al.* 1996). A similar technique could have been used in this study but it was judged unlikely that there would be any benefit in doing so given the limitations of this method. That is, the technique is straightforward when only two study areas are being examined but it is not clear how to proceed when there are three study areas completing the diary simultaneously as in this present study.

It is noteworthy that in the Aggregate analysis, climate-related predictors explained some 30% of the variation in EPF amongst children in Wave 1, but 60% of the variation amongst children in Wave 2. One explanation for these differences is that children in Wave 1 completed their diary during winter and so may have been exposed to higher levels of indoor pollution, than children in Wave 2. Because there was no daily information on exposure to indoor pollutants the proportion of variance explained was smaller for children in Wave 1. Interestingly, the standard errors of the PM10 effect estimates were smaller in models restricted to children in Wave 1 than that for Wave 2.

10.4.4 Pooling results across study areas

The estimates of effect from individual study areas were pooled to obtain a Hunter Region estimate. This was done in a crude way by precision-weighting the estimates. The application of more sophisticated analytic methods would have the advantage of both gaining a unified estimate more

easily, and allowing a more precise estimate of the effect of pollution on health. Hierarchical or multilevel models may be appropriate for this. Such techniques have recently been implemented in time series studies of mortality but the techniques have not yet been applied to panel studies such as this one.

There has been a recent trend away from fitting GEE models in panel studies, and instead fitting generalised linear mixed models with a random effect for the intercept and a fixed effect for the pollutant. For a model with a linear link and normal errors (EPF in this study), the estimates are not expected to be appreciably different (apart from minor differences due to the maximum likelihood estimation algorithm differing from the GEE algorithm). However, for a model with a logit link and binomial errors (day cough and medication use in this study) there may be appreciable differences. Exploration of such models is an area of future research, and beyond the scope of this thesis.

10.4.5 Lags for the pollutant

Various lags for the pollutant variables were modelled for the outcome EPF. These included same day, lags of 1 to 5 days, and averages of between 2 to 6 days. The overall effect did not vary with the selection of the lag interval. Consequently, estimates are shown that correspond to changes in respiratory health associated with an increase in the 5-day average pollution concentration. Other studies have also reported larger estimates from models regressing on moving day average exposures than those regressing on single-day exposures (Hoek *et al.* 1998).

10.4.6 Missing outcome data

It has been acknowledged that missing outcome data can bias estimates especially if the reason for missing data is related to the outcome (Schafer 1997). The Aggregate analysis and the Korn-Whittemore analysis assume that the outcome data are missing at random (MAR). The GEE analysis assumes that the outcome data are missing completely at random (MCAR). Three approaches were taken to examine whether the data were missing completely at random for the outcome EPF and these are described in the next paragraph.

Firstly, the correlation between the daily proportion of subjects with EPF data and the corresponding daily air quality measure was examined. The daily proportion of subjects that reported EPF ranged from 51% to 94%. There was no correlation with daily sulphur dioxide in any

of the study areas but it was correlated with PM10 at Wallsend (r=0.24), implying that for this study area the MAR assumption may not have been valid. Secondly, the subjects were stratified by the amount of non-missing data during the study period into five equal sized groups. There was some evidence that subjects with a lot of missing data had larger mean EPF than subjects with few missing data (mean EPF for the five groups were 331, 312, 323, 317, 314 respectively), but the test for trend was not statistically significant (p-value=0.21). Thirdly, the GEE analysis for the outcome EPF was repeated using two alternative methods of imputation. When predicted values from the K-W analysis were used, the pooled estimate was a 0.02% decrease in EPF per 20 $\mu g/m^3$ increase in PM10. Linear interpolation was also used between the non-missing values. Both estimates were similar to the pooled estimate of 0.08% decrease in EPF per 20 $\mu g/m^3$ increase in PM10. These models perform well under MCAR but more sophisticated imputation methods such as multiple imputation would result in more precise estimates under MAR (Pfeffermann and Natham 2001). However, this is beyond the scope of this thesis.

During the 28-week study period among the 280 children, EPF was reported on 73% of child-days, day cough on 77% of child-days, and inhaled bronchodilator use on 82% of child-days. One limitation of the GEE model is that when the outcome is normally distributed (EPF in this study), estimates tend to be biased if there is more than 20% missing data (Rijcken *et al.* 1997). However, in this study the GEE analysis was restricted to the 235 children with a high rate of completion. This group of children were similar to the overall sample of 291 in terms of demographics, household characteristics, and asthma severity (as determined by prevalence of asthma diagnosis and asthma medication use) and so the estimates are generalisable to the entire cohort.

10.4.7 Measures of effect

Panel studies generally reported associations using the odds ratio, rather than the relative risk. Odds ratios are estimated using the logistic regression model (a generalised linear model with a logit link and binomial errors). However, in panel studies of symptomatic children, the respiratory outcomes are not rare, and so the odds ratio over-estimates the relative risk substantially (Zhang and Yu 1998). Relative risks can be estimated using the log binomial regression model (a generalised linear model with a log link and binomial errors). However, the performance of this model in real data situations is not well established. There are problems with non-convergence and inadmissible

solutions (e.g. fitted probabilities exceeding unity) when the marginal probability is not small (Blizzard and Hosmer, Menzies Research Institute, pers. com., 2004).

10.4.8 Adjustment for exposure-measurement error

Recent advances in the area of exposure-measurement error offer new approaches for evaluating the consequences of measurement error and adjusting the estimates of effect of the environmental exposures (Committee on Environmental Epidemiology 1997). There are two general approaches. The first approach is to estimate personal ambient exposure, and to model this. For example, one study obtained exposure measurements from various sources including outside near the home, indoor measurements in the home and school, and use spatial statistic methods to estimate personal exposure (Delfino *et al.* 1996). Another study weighted ambient monitor data by the amount of time spent outside (Neas *et al.* 1995). In a further study, exposure was estimated using outdoor monitoring data, time spent outdoors and crude estimates of indoor/outdoor ratios of pollutants (Ostro *et al.* 1991). The second approach is to fit the regression model using the ambient concentration and then rescale the coefficient using study-specific information collected on the agreement between ambient and personal monitors. Most studies that have attempted to adjust for measurement error have reported stronger associations between pollutants and health outcomes. In fact, Zeger *et al.* developed a theoretical model illustrating that regression models that use ambient particulate measurements to predict mortality would always give smaller estimates of pollution relative risks than would be obtained if average personal exposure were available (Zeger *et al.* 2000). In mixed model methods, the interest is in estimating the individual-level (as opposed to group-level) effects of exposure on respiratory health. This suggests individual level data should be used, but further research is necessary to understand the impact of incorporating a spatio-temporal personal exposure model (Sheppard and Damian 2000). In this study, it was not possible to adjust for exposure-measurement error because the information required to implement either of the two methods was not collected.

10.5 Significance and implications of the findings

This population-based study was conducted in response to community concerns that poor environmental air quality was a major trigger for childhood asthma in industrial areas. In the cross-sectional survey, various indicators of asthma were more common in industrial areas compared to

control areas. The present study assessed whether current levels of air pollution might be causing exacerbations of asthma-type symptoms.

In this study, no association was found between pollution and respiratory health. This study was conducted during 1994-1995 and so it is important to consider whether this null association would remain if the study were repeated now. Particulate pollution levels have reduced since the study was conducted in the Mayfield study area as a direct result of BHP closing down in December 1999. In 2001, the annual average of TSP recorded was 45 $\mu g/m^3$, compared to 84 $\mu g/m^3$ in the year of the study (Newcastle City Council 2001). Similarly, SO_2 concentrations in North Lake Macquarie have reduced as a result of Pasminco Metals-Sulphide closing down in 2003 (Lake Macquarie City Council 2001). The association between pollution and respiratory health is expected to have remained the same, but the daily prevalence of symptoms may be lower because the exposure is lower.

The findings of this study are consistent with previous research in the Newcastle area, which found only limited association between air pollution and asthma-type symptoms. This study represents the Hunter component of the Hunter-Illawarra Study of Airways and Air Pollution (HISAAP). The Illawarra Region is similar to the Hunter Region in that it is exposed to high levels of industrial air pollution. The Illawarra component of the study was conducted in four study areas, and particulate measurement was limited to TSP and PM10. Consent rates were poor (approximately 54%) and so limited gains would result from an analysis of these data.

These data should contribute to the evidence about air pollution and health thereby having direct implications for air pollution policy in NSW. Finally, because effects can be expected to be quite different between medicated and non-medicated children, future studies should ensure that there is adequate statistical power to examine effects in non-medicated children and to ensure that daily medication use is recorded accurately for the medicated children.

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