THE NATURAL HISTORY OF PRE-SCHOOL RESPIRATORY SYMPTOMS AND THEIR VALUE IN PREDICTING ASTHMA IN THE EARLY SCHOOL YEARS

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AUTHOR: ADRIAN M BROOKE

ABSTRACT

To test whether wheeze and cough in pre-school children would predict the presence of asthma later in childhood, a population whose symptoms had been ascertained during the first five years of life were re-sampled when 4-7 years old to measure current symptoms, lung function, atopy, bronchial responsiveness, airway lability and night cough.

Symptoms were re-assessed by questionnaire, whilst ventilatory function, bronchial responsiveness (BR) and atopy were measured using spirometry, methacholine bronchial challenge and skin prick testing respectively. A peak-flow diary was completed to estimate airway lability and overnight recordings made to assess nocturnal cough.

Of the pre-school groups, 37.9% of wheezers continued to wheeze. Although 36.8% of the coughers continued to cough, only 7.2% had started wheezing, a similar proportion to that seen in the asymptomatic group (6.7%). Wheezers showed the greatest BR (geometric mean 1.91mg/ml) and the highest atopic prevalence (AP) (43.6%) when compared with the asymptomatic (BR: 3.39mg/ml; AP 23.8%) and cough groups (BR: 2.62mg/ml; AP 26.7%) (p=0.0001 and p=0.006 respectively). Children whose wheeze persisted demonstrated the highest level of bronchial responsiveness, the poorest lung function and a high prevalence of atopy compared to normals. A subgroup analysis of the cohort originally aged < 3 years showed that compared to those who had outgrown their wheeze, persistent symptoms appeared more likely if children were premature, wheezed without having colds (Odds ratio (OR)=7.25, p=0.001), had mothers who smoked (OR=6.18, p=0.003), had frequent wheezing episodes (OR=19.50, p=0.001), or had nocturnal worsening of wheeze (OR=4.14, p=0.015). Night cough was associated with colder bedrooms in wheezy children (17.7°C Vs 21.56°C, p=0.0159).

The study showed that fewer than half of pre-school wheezy children continued to wheeze in the early school years but those with persisting wheeze displayed many clinical characteristics consistent with a diagnosis of asthma. Reassuringly few with pre-school cough progressed to develop asthma characterised by wheeze. Patterns of wheeze and other factors easily identified in pre-school children may help to determine the risk of continuing symptoms. The sleeping environment merits further study.
ACKNOWLEDGEMENTS

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I thank the National Asthma Campaign for providing the financial backing to allow the follow-up study to be realised and thank the parents and children from participating families for their efforts.

Finally I would like to thank my wife for her continued support and gentle encouragement to complete this thesis.
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<thead>
<tr>
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<td>ANOVA</td>
<td>one way analysis of variance</td>
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<tr>
<td>ATS</td>
<td>American Thoracic Society</td>
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<tr>
<td>BHR</td>
<td>bronchial hyperresponsiveness</td>
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<tr>
<td>CI</td>
<td>confidence interval</td>
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<td>CVA</td>
<td>cough variant asthma</td>
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<td>DDA</td>
<td>doctor diagnosed asthma</td>
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<tr>
<td>FEF&lt;sub&gt;25-75&lt;/sub&gt;/MEF&lt;sub&gt;25-75&lt;/sub&gt;</td>
<td>flow over the middle 50% of a forced expiratory manoeuvre</td>
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<td>FEV&lt;sub&gt;1&lt;/sub&gt;</td>
<td>forced expiratory volume in 1 second</td>
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<td>FRC</td>
<td>functional residual capacity</td>
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<td>FVC</td>
<td>forced vital capacity</td>
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<td>ICC</td>
<td>intra-class correlation coefficient</td>
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<td>IgE</td>
<td>immunoglobulin E</td>
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<td>k</td>
<td>Cohen's kappa</td>
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<td>n</td>
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<td>OR</td>
<td>odds ratios</td>
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<td>P</td>
<td>pressure</td>
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<td>partial pressure of oxygen</td>
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<td>PC&lt;sub&gt;20&lt;/sub&gt;</td>
<td>provoking concentration of methacholine/histamine required to produce a 20% decrease in lung function from baseline values</td>
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<tr>
<td>PC&lt;sub&gt;20tc-pO&lt;sub&gt;2&lt;/sub&gt;&lt;/sub&gt;</td>
<td>provoking concentration of methacholine that produced a 20% decrease from baseline values of transcutaneous oxygen tension</td>
</tr>
<tr>
<td>PD&lt;sub&gt;20&lt;/sub&gt;</td>
<td>provoking dose of methacholine/histamine required to produce a 20% decrease in lung function from baseline values</td>
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<td>PEFR</td>
<td>peak expiratory flow rate</td>
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<td>PEFV</td>
<td>peak expiratory flow variability</td>
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<td>Raw</td>
<td>airways resistance</td>
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<td>RTI</td>
<td>respiratory tract infection</td>
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<td>SaO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>arterial oxygen saturation</td>
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<td>SAS</td>
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<td>standard deviation of the mean</td>
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<tr>
<td>tc-pO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>transcutaneous oxygen tension</td>
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<td>TLC</td>
<td>total lung capacity</td>
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<tr>
<td>( \dot{V} )</td>
<td>flow</td>
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<tr>
<td>( \dot{V}_{\text{max}} )</td>
<td>maximal airflow</td>
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<tr>
<td>( \chi^2 )</td>
<td>Chi squared</td>
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CHAPTER ONE

BACKGROUND AND INTRODUCTION
1.1 BACKGROUND

Childhood asthma is the most common chronic disease of childhood (Morrison-Smith, Harding and Cumming 1971) and is estimated to affect between 10 and 20 percent of the population in the industrialised world (Strachan, Anderson, Limb et al 1994, Anderson, Butland and Strachan 1994, Peak Van den Berg, Green et al 1994). The symptoms of this disorder may start at any time during childhood and the time course of the disease is also equally variable, with some children experiencing the symptoms of the disorder for a short time. It is known that most asthmatic suffer the onset of symptoms during the first five years of life (Williams and McNichol 1969). However most of the subjects scrutinised in published studies of childhood asthma are recruited in mid childhood. Although this is an age sufficient to allow the investigators to assess objective measures of lung function, for example by using forced expiratory manoeuvres, important insights into the onset of the condition may be lost due to poor recall of symptoms early in childhood (Strachan 1985). Furthermore, children with nascent early symptoms who are asymptomatic by mid childhood would be unlikely to be recruited thus leading to a spurious estimation of the prognosis. Furthermore this early period may be critical into providing insights into the development of the condition.

It is therefore preferable to gain information prospectively about asthma symptoms in young children to avoid recall bias. Follow up of the impact of these early symptoms upon those which occur subsequently can be assessed in the early school years and objective physiological measures can be gleaned by appropriate use of methods which require minimal co-operation or are effort independent.
INTRODUCTION
1.2.1 THE SCOPE OF THE PROBLEM

1.2.1.1 PREVALENCE OF ASTHMA IN CHILDHOOD

Asthma is a common problem in childhood, although the ascertainment of accurate data regarding its prevalence are difficult because of the lack of an agreed definition of the condition (see below). Current prevalence in the UK is estimated (depending on age of children sampled and methods used) to vary between 10-33%, and these current estimates represent an increase in prevalence over recent years, as outlined below.

In a recent national survey of over 27,000 school children aged 12 to 14 years who completed self questionnaires, 33% reported wheeze within the last year (often used epidemiologically as measure of current asthma), 20.9% reported a diagnosis of asthma ever and 19.8% reported receiving current treatment with anti-asthma medications. This used a large cohort with good geographic spread around the UK. Validated questions were used, developed from the International study of asthma and allergies in childhood (ISAAC). A high response rate was obtained allowing robust estimates to be made (Kaur, Anderson, Austin, Burr, Harkins, Strachan, Warner, 1998). A similar age group of children from the Scottish Highlands reported a prevalence of wheeze within the last year of 17%. This was a smaller study that obtained a similar response rate, but used a smaller range of validated respiratory questions (Austin and Russell, 1997). A study of primary school children in Nottingham found the prevalence of self reported current wheeze to be 15.1%. Data were based on a large (22,968 children) cohort, but questionnaires were answered by the parents of this younger age group. (Venn, Lewis, Cooper, Hill, Britton, 1998). Another recent national survey of asthma set out to look at the prevalence, severity and treatment of
the condition. Parents of 5472 subjects were aged 5-17 years and were interviewed in a nation-wide household survey. The prevalence of wheeze within the last year was 15.0%. Of this group 13.1% had doctor-diagnosed asthma and 13.6% were prescribed antiasthmatic drugs. This study used ISAAC questions across a large age-range but accrued information via face-to-face interviews rather than by self completed questionnaire. The term ‘doctor diagnosed asthma’ was not defined. (Strachan, Anderson, Limb, et al 1994). The same group looked specifically at over 3000 7 to 8 year old children in Croydon, South London in 1991 to assess prevalence and found that 12.8% had experienced wheezing in the past year. This was compared to the results from an identical questionnaire carried out in the same geographic area in 1978. The prevalence of wheeze within the last year from this previous survey was found to be 11.1%, and the difference between these two figures (16%) represented a significant rise in prevalence. The large populations sampled and the selection of populations of identical age range, geographic location and method of ascertainment strengthened the evidence for an increase in wheeze prevalence. (Anderson, Butland, and Strachan 1994). A similar exercise reported in 1989 used data from two surveys conducted upon school children from South Wales in 1973 and 1988. In addition to estimating the prevalence of respiratory complaints and asthma, corroborative evidence was gleaned from performing exercise provocation tests on the populations under study. They also found that the prevalence of asthma, current asthma and wheeze within the past year had all increased significantly in the interim by 5.5% to 12.0%, 4.2% to 9.1% and 9.8% to 15.2% respectively. The prevalence of ever having wheezed also increased from 17.0% to 22.3%, in addition to a rise in the prevalence of atopic disorders. The use of exercise provocation testing obvious strengthened the finding of an increase in symptoms; the age group under study was slightly older (12 year olds) and the sample size was somewhat smaller at under a thousand children.
Further evidence comes from the results of a large longitudinal study of nearly 30,000 primary school children. By multiple sampling over the study period of 1973 to 1986 and analysis of parental reporting of symptoms in the children, the authors showed an average year on year increase in asthma prevalence of 6.9% in boys and 12.8% in girls, and an concomitant increase in the prevalence of wheezing on most days/nights of 4.3% for boys and 6.1% for girls. The large sample size and use of a geographically representative population selected from primary schools in 22 different areas enhance the plausibility of the increase. (Burney, Chinn, and Rona 1990). An increase was also observed by comparing the prevalence rates obtained from two surveys of Aberdeen school children conducted in 1964 and 1989. Although these were relatively large populations of primary school children (over 2500 and 3400 in 1964 and 1988 respectively), precise changes in prevalence were harder to interpret in this study because questions concerning wheeze asked about occurrence over different time periods in the two phases of the study (Ninan and Russell, 1992). In another study using the administration of an identical questionnaire separated by a period of 24 years to 6-7 year old children in towns in Northern and Southern England and South Wales, an increase in the rate of wheezing ever or wheezing on most days or nights was found to have increased from 18.3% to 21.8% and 3.9% to 6.1% respectively from 1966 to 1990. The large populations sampled (over 1500 and 2000 in 1966 and 1990 respectively) and good geographic spread of respondents, lend credence to the increase reported (Whincup, Cook, Strachan, et al 1993).

The increase in the prevalence of asthma and its cardinal underlying symptom, wheeze, have also been observed outside the UK. Striking increases have been observed in Australia. In a recent questionnaire-based study the rate of wheeze in the
last year for 6-7 year olds was 24.6%. These data were based upon large samples (over 10000 children) using well validated (ISAAC) questions representative and geographic locations around Australia (Robertson, Dalton, Peat, Haby, Bauman, Kennedy, and Landau, 1998). In a serial cross-sectional study of 8-10 year old children in two towns over a ten-year interval, the prevalence of wheeze within the past 12 months was shown to increase from an average of 12.95% in 1982 to 25.35% in 1992. Although the populations sampled were smaller, corroborative data were gleaned by testing airway hyperresponsiveness; increases in reported symptoms were reflected by increases in the prevalence of bronchial hyperresponsiveness. (Peat, van den Berg, Green, et al 1994). A recent analysis of data pooled from 17 population-based studies undertaken in Australia on children aged between 5 and 12 since 1969 were reviewed and results showed that on average, prevalence rates for asthma and wheeze had increased by nearly 1% per year over the 20 year period reviewed. For instance, in the period from 1983 to 1989 the rate of recent asthma increased from 3.3% in 1983 to 8.3% in 1989. The observation of increasing prevalence seemed plausible, as the analysis was restricted to population-based studies within the specified age group where standardised symptom questionnaires had been used and acceptable response rates had been obtained. (Bauman 1993). A similar trend has been reported more recently by workers from the United States (Farber, Wattigney, and Berenson, 1997). These researchers used data from a question concerning ‘asthma’ rather than wheeze on ages ranging from 5 to 17 years. Analysis was weakened by relying on diagnostic recall rather than current symptoms and the population, though large, was restricted to one semi-rural part of the United States. Increases have also been reported in Israel. This study used repeated and identical, validated methodologies. The increase in reported asthma was corroborated by concomitant increases in wheeze. (Goren and Helman, 1997). These data from the latter study were corroborated by objective

evidence from pulmonary function testing. The evidence of the increasing prevalence of asthma has however been questioned by others who feel that repeat surveys which report subjective symptoms without any objective outcomes being reported may be systematically biased and therefore unsound. Critical appraisal of repeated cross-sectional surveys using strict inclusion criteria showed that whilst increases in both current asthma and current wheezing were reported, changes in labelling of wheezing illnesses and recall of wheeze may have incurred systematic bias, weakening the assertion that there had been any true increase in the prevalence of these disorders. (Magnus and Jaakkola, 1997).

All these prevalence estimates are based upon surveys of children of school age. The prevalence of wheeze in younger children is thought to be higher. In Strachan’s survey of the general practice records of 437 seven year olds, 31% were found to have ever wheezed, and over half of these had started prior to their third birthday (Strachan 1985). Whilst the sample size was small, the use of general practice records to look at early history avoided incurring recall bias and greatly enhanced the accuracy of these data. An American group looking at the level of lung function and its relation to wheezing lower respiratory tract illness found that out 97 infants studied, 59 (61%) had experienced wheeze in the first year of life (Tager, Hanrahan, Tosteson, et al 1993). The high prevalence must be viewed with caution in light of the small sample size; the onerous nature of the study was also likely to incur further sources of bias. In Luyt’s 1990 epidemiological survey which specifically looked at wheeze and doctor diagnosed asthma in the under 5 year old population of Leicestershire, England (the cohort upon which this follow-up study is based), it was found that 15.6% reported ever having wheezed whilst 13.0% reported wheeze within the year of survey and 11.0% were formally diagnosed by their doctor as having asthma. These data were based upon an
acceptable response (86%) from a demonstrably representative, relatively large (over 1600) sample of pre-school children. Questions concerning wheeze were adapted from questions used previously for school-aged populations and were therefore presumed to be a valid instrument for this age group. (Luyt, Burton, and Simpson 1993). There is therefore evidence that wheeze in early childhood is at least as common, if not more so, than wheeze later on in childhood.

1.2.1.2 ASTHMA MORBIDITY IN CHILDHOOD

The impact of asthma in childhood in terms of ill health is considerable; given the high prevalence of the condition this is not a surprising observation. One of the crudest measures of morbidity are hospital admission rates for asthma and these were noted to have increased threefold in the period from 1959 to 1973. Examination of these data showed that this change was not due to diagnostic transfer. Rather it was speculated that such change could be produced by changes in admission criteria or therapeutic regimens or possibly because of changes in the morbidity of the illness, i.e. asthma was becoming more severe. These data did not permit identification of the main cause of the rise, however (Anderson 1978). A seminal work on the under diagnosis and under treatment of asthma in children in 1983 showed that half of a group of Tyneside children who wheezed more than four times per year had lost more than 50 days of school because of wheeze. Despite the small size of the study (less than 200 children aged 7), the authors hypothesised that similar morbidity trends existed elsewhere. (Speight, Lee and Hey 1983). In the same year a report into the morbidity caused by asthma and wheeze in schoolchildren in Croydon revealed that in 58% of wheezy children, days had been lost from school during the previous year, and 12% of children
had lost at least 30 days of school. These data were based on interviews with a small sample drawn from a larger population-based pool enrolled via questionnaire. Severity bias was counteracted by interviewing parents of children with varying severity of wheeze. (Anderson, Bailey and Cooper et al 1983). In 1985 Mitchell confirmed the earlier findings of Anderson regarding increasing trends in hospitalisation for asthma. He collected admission data from several different developed countries from dates between 1952 to 1981. He found a tenfold increase in New Zealand, a six fold increase in England and Wales and a threefold increase in the USA. His analysis suggested that not all of the increase was due to increases in the prevalence of asthma and that only a small increase could be attributed to increased readmission of the same cases. Little change in admission criteria were observed which led to the suggestion that the frequency and/or severity of asthma had increased. The rise in admissions for young children appeared paradoxical, as antiasthma treatment in this age group was thought to have undergone recent improvement (Mitchell 1985). These international trends were found to be echoed by local observers. For instance an eight-fold increase in hospital admissions was observed in Brighton over a 15 year period from 1971 to 1985. Again this was found to be a result of increased numbers of children rather than increased re-admissions of the same children. This was based upon admissions to a single hospital so may have reflected local practice, weakening the ability of the results to be generalised to the rest of the UK (Storr, Barrell and Lenney 1988). Although there is some debate about exactly what morbidity hospital admissions actually represent, there is little doubt that admissions are a marker for morbidity and that there have been increases in this measure over recent years. (see table 1.1). Mortality in childhood from asthma over a similar period has however decreased, probably reflecting better management of the condition (Campbell, Cogman, Holgate and Johnston, 1997).
Table 1.1 - rates (per 10 000) for admission to hospital for asthma for England and Wales from 1976 to 1985 (Hyndman, Williams, Merrill, et al 1994)

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1.2.2 DEFINITIONS AND RELATIONSHIPS IN CHILDHOOD ASTHMA
Central to any study of any illness is a precise set of diagnostic criteria by which the presence of the disease may be defined. There is unfortunately no accepted definition of what asthma precisely represents, but rather several nebulous working definitions which allow a constellation of clinical and physiological abnormalities to be equated to the condition. The word itself is of Greek origin meaning "breathless", or "to breath with an open mouth" and hence the term is purely descriptive of the observed clinical abnormality resulting from increased work of breathing. The word itself does not define the various causes of this observed abnormality. In a recent book on childhood asthma by Milner, the diagnosis of asthma was used for "all children up to 16 years old who have symptoms secondary to bronchoconstriction which, either in the short term or the long term, respond to anti-asthma therapy" (Milner 1993). In a standard British textbook of paediatrics, asthma is defined by Silverman as "a condition characterised by variation in intrathoracic airway obstruction, occurring spontaneously or as the result of treatment and in young children persistent or episodic wheeze, usually accompanied by cough, in a clinical setting where asthma is likely and other conditions have been excluded" (Campbell and McIntosh 1992). A standard text on asthma carries the following definition: "A disease characterised by wide variations over short periods of time in resistance to flow in intrapulmonary airways. This leads to increase in resistance to flow and may be related to exposure to environmental factors, especially inhaled substances in concentrations that do not effect the majority of persons, or may occur without apparent external cause. Detectable factors include hyperresponsiveness of the airways to physical and chemical stimuli, specific antigen-antibody reactions, usually inhaled antigens and exercise. Diminution of increased
airways resistance in response to bronchodilator drugs or to corticosteroid treatment is usually demonstrable." (Clark, Godfrey and Lee 1992) This last definition encompasses the most widely accepted definitions of Scadding "asthma is a disease characterised by wide variations over short periods of time in resistance to flow in intrapulmonary airways" and of the American Thoracic Society "asthma is a disease characterised by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy."(American Thoracic Society 1962)

It can therefore be seen that any study of, or about childhood asthma, will require measurement of the clinical and physiological abnormalities that are consistent with this diagnosis. Furthermore, the measurement of these markers must be carried out in a manner appropriate to the age-group under study.

Wheeze, cough (including nocturnal cough) and breathlessness are the subjective symptomatic markers of asthma. Objective evidence of current symptoms may be measured by use of a tape recorder to store and replay respiratory noises (usually cough). The physiological measures of peak expiratory flow rate and maximum flow rates achieved during forced expiratory manoeuvres are often taken as markers of ventilatory function; abnormalities of these indices may demonstrate airways obstruction, which is in turn a defining abnormality of asthma (see above). Inhalational tests using bronchoconstricting agents may demonstrate the presence and degree of airway hyperresponsiveness, which is again present in many asthmatics. Another aspect of increased airway responsiveness is increased lability of the airway and this may be analysed by looking at the variability of a frequently repeated ventilatory
measure over a period of time (most often peak expiratory flow). Finally, subjective symptoms of atopic conditions can be recorded and objective evidence can be provided by performing skin tests to assess the presence of an atopic diathesis. The relationship between these measures and asthma is discussed below.

The symptoms of wheeze, cough and breathlessness often accompany attacks of asthma and are therefore the mainstay of measurement when attempting to register the symptoms of asthma. However the precise relationship of wheeze, particularly wheeze in early life and asthma is incompletely understood, not least because there is continuing debate about the exact nature of the term “asthma” (Silverman and Wilson, 1997).

1.2.2.2 STUDIES ON THE NATURAL HISTORY OF WHEEZE

In an attempt to delineate the relationship between wheeze in childhood and subsequent asthma many studies have identified subjects with asthma and examined the relationship with past factors pertaining to early symptoms and the effect of familial and environmental/social conditions. The populations of children studied and the design of such studies effect the observations seen and therefore have an impact on the inferences drawn. The ideal study design would be a population based sample followed prospectively. Studies have indeed been carried out in this manner but other designs have also been reported as detailed below.

One of the first people to attempt to address the issue of what happened to children presenting with acute wheeze in childhood was John Fry, a general practitioner
operating in a suburban area of South East London. Over a period of ten years from 1948 to 1958 he looked at the outcome of children presenting with wheeze. Out of a total population of 1402 children, 126 were identified and followed. Wheezing occurred in 87% of this group before 6 years of age and 10% of the group were diagnosed as asthmatic. By the end of the ten-year period, 87% were said to be free of wheeze (Fry 1961). A similar study was undertaken by Blair, who followed 267 childhood asthmatics attending his East London practice. They were enrolled between 1948 and 1952 and followed for twenty years. An impressive follow-up rate of 94% was achieved. Careful data collection enabled an examination of the impact of age of onset of wheeze, severity of wheeze (defined as the number of attacks per year), gender, personal and family history of atopy, effect of breast-feeding and length of follow-up on outcome. Data from objective tests (skin prick tests, blood counts and chest X-rays) were also collected. The population from which the sample was drawn was demonstrated to be broadly representative of the general population and asthma was defined as recurrent (three or more) attacks of paroxysmal dyspnoea with wheezing. In this series, 84% presented by age five and at the end of follow-up 52% had become free of wheeze. A sizeable proportion (27%) had enjoyed a period of remission before symptoms relapsed whilst the remaining 21% had never been symptom free for longer than 6 months. He identified a personal/family history of atopy and early severity as poor prognostic indicators. Age at onset, sex and the results of skin prick testing had no effect on prognosis whilst breast feeding had a positive prognostic effect (Blair 1977).

An influential study was conducted in Melbourne, Australia when a population of 3000 school children aged 7 years were sampled in 1964 to obtain 3 groups of children with symptoms of wheeze and 1 asymptomatic group (approximately 100 in each group). Children with wheeze were selected for each of the groups on the basis of symptom
profile. Those who reported wheezing on less than 5 occasions and only with respiratory tract infection (RTI's) formed the mild wheezy bronchitis group; children with wheeze on at least 5 occasions but only with RTI's were assigned to the moderate wheezy bronchitis group and children who wheezed on at least one occasion in the absence of a RTI were designated as 'asthmatic'. The study looked at various clinical and physiological features of these groups and then examined the natural history of all three wheezing groups combined. The conclusions of the initial phase of the study was that the differences in symptoms, family history, and atopy that existed between the four groups were only systematically different between the control group and all 3 of the symptomatic groups. Furthermore they observed that features of a RTI did not always precede later episodes of wheeze even in children with mild wheezy bronchitis. On the basis of this work, they concluded that asthma and wheezy bronchitis were both manifestations of the same underlying disorder and that the different conditions of 'asthma' and 'wheezy bronchitis' merely represented a spectrum of symptom severity seen in response to the same basic condition. When analysing the natural history of wheeze they considered outcome (wheezing at 10 years old) in relation to age of onset of symptoms and frequency of attacks. They found that early onset and a high frequency of wheeze during the first year of symptoms was associated with a poor prognosis. At initial follow-up (at 10 years old) about two thirds of children had been free of wheeze for the last 2 years. Most of the severe group (those with persistent symptoms) were found to have commenced wheezing in the first 3 years of life (McNichol and Williams 1969). Although these groups were well selected in order to provide an accurate answer to the question of prevalence of childhood wheezing disorders (approximately 11%), the study was retrospective with respect to recall of early symptoms and their frequency, and would have incurred some bias. The sample was reassessed when aged 14 to track the clinical and physiological profile of those
identified and to monitor the natural history of the condition. Over 300 wheezy children were re-examined, including 82 additional severe asthmatics recruited to the study when aged 10 years. The children were subdivided into 4 groups, depending on present symptoms and past wheeze frequency. It was found that in the mildest group (defined as having no more than 5 attacks up to age 14), all but 11% had ceased wheezing by age 10. Approximately two thirds of the second mildest group were also free of symptom after 10 years of age. Persisting abnormalities of lung function were found in the two severe groups and analysis of past symptoms revealed that severe asthma was characterised by early onset and frequent episodes of wheeze in the first year of symptoms. This contrasted to the situation found in the mild group where onset of wheeze was later and infrequent in nature. The enrichment of the population with subjects with severe symptoms limited the generalisability of these natural history data. (McNichol and Williams 1973). Further follow-up of this cohort has been reported as the population is now 38 years old. A high follow-up rate has been achieved (86%) and the population was classified according to the presence or absence of recent wheeze (within the last three years) and its current frequency. They found that approximately two thirds of children who were classified at age 7 as having wheezy bronchitis were free of recent wheeze. For those children from the cohort who were classified as asthmatic at age 7, about one third were free of recent wheeze, one third reported persistent wheeze whilst the remaining third reported an intermediate frequency of recent wheeze (wheezed in the last three years but not in the last 3 months and wheezed in the last three months but not more than once a week). Two thirds of the severe asthmatics who had been enrolled at 10 years still reported persistent symptoms. The severity-bias incurred during the early phase of the study may have limited the validity of these observations and the authors acknowledged that some parents of the children enrolled may have forgotten early transient wheeze in the pre-
school era, causing an overestimation in the proportion of children with wheeze who continued to have symptoms in adulthood. (Oswald, Phelan, Lanigan, et al 1994). Another long-term follow-up study from Australia has also been recently reported in which a cohort of Tasmanian children, again recruited at 7 years were followed over 25 years. In this study, all children born in 1961 who were attending school in Tasmania were recruited onto the cohort. Children were assigned to groups on the basis of parental reporting of wheezy breathing or asthma and additional questions identified atopic disorders. Ventilatory function was also assessed in the cohort. Only three quarters of the original cohort were re-sampled by randomly selecting a subgroup of previously identified asthmatics and controls for follow-up. Current respiratory symptoms and lung function were reassessed. They found that 75% of childhood asthmatics had become symptom free at follow-up. They also demonstrated recall bias by showing that nearly half the respondents who had had parentally reported asthma were unable to recall wheezing in the first seven years of life. About 11% of the cohort who had not wheezed as children had developed wheeze during the period of follow-up. Risk factors that were identified during childhood as having a material affect on prognosis were female sex and concomitant atopy, reduced lung function, a family history of asthma and a personal history of asthma as a child, especially if symptoms were severe and onset occurred after the age of 2. The strength of these conclusions are potentially weakened by the incomplete follow-up of the cohort, although randomised follow-up was attempted to counter this. (Jenkins, Hopper, Bowes, et al 1994).

In Sweden, a prospective study of a hospital-based sample of infants and children presenting with wheeze was able to look at the relationship between the natural history of wheeze, allergy (as evidenced clinically and by skin prick tests and IgE levels) and
family history of atopy. The cohort of 81 children was followed for 12 years by which time 72% were free from symptoms of wheeze. It was noted that there was a higher prevalence of family history of atopy/asthma in the family in children with persisting symptoms when compared to those who had outgrown their wheeze. In this group, onset of wheeze after 18 months of age was associated with a poorer prognosis, as was development of atopy. A high level of IgE was seen in children with persistent symptoms who also had proven allergies, but high levels were also seen in children who had ceased wheezing, and who had no history of allergies. The detailed prospective profiling of this small group of children was informative but difficult to generalise because of the severity bias engendered by following children recruited following in-patient admission for, on the whole, symptoms of wheeze (Foucard and Sjorberg 1984).

The prognosis of pre-school wheezing in a large population-based sample was assessed on a birth cohort of British children born in 1970. Over 11 thousand children were studied at 5 and 10 years of life and 2345 out of 11465 children (20.45%) were identified as having at least one wheezing attack before the age of 5. When these wheezy children were resampled at age 10, 80% were free of wheeze. Analysis revealed that the total number of attacks in the pre-school period was important prognostically but that the age of onset of wheeze had no effect. Half of those children whose wheeze was labelled as asthma were still symptomatic at follow-up compared to only one eight of children whose wheeze was not diagnosed as asthma. This was a more important prognostic indicator than if wheeze occurred together with, or apart from 'bronchitis'. An important limitation of this study was that the questions identifying wheezing in the two phases of the study differed and the criteria by which asthma was diagnosed was not analysed (Park, Golding, Carswell, et al 1986). A similar exercise
was carried out upon the 1958 British birth cohort. The population comprised all children born during 1 week in March 1958. This group was studied at ages 7, 11, 16 and 23 and drew on limited medical information collected as part of a large social, educational and demographic survey. Longitudinal information collected on wheeze, asthma, eczema and hayfever demonstrated that eczema and hayfever were independently related to persistence of symptoms, and that the wheeze and asthma was commoner in males up to age 16, after which the sex ratio reversed (Anderson, Pottier and Strachan 1992). The association between persistence of symptoms and atopy was also seen in a follow-up of asthmatics attending an asthma clinic in Finland. This was a selected population of 108 relatively severe asthmatics who were first identified as children (up to age 14 years). The cohort was re-examined when aged 20 to 24 years to assess symptomatic and functional outcome. Symptomatic outcome was similar to that seen in the Melbourne study with this severe group faring relatively poorly; one third were symptom-free and 22% had symptoms at least once a week. Skin prick testing showed that 86% were atopic and a high prevalence of atopic disease (rhinitis and eczema) was reported. About half demonstrated bronchial hyperreactivity and persisting abnormalities in ventilatory function was demonstrable in 18%. In contrast to the Melbourne study, these workers found that early onset and early severity of wheeze (including the need for admission to hospital) were not shown to be risk factors for asthma in early adulthood, but rather that symptoms, lung function and atopic illness at school age were predictive of subsequent prognosis. Once again the use of a clinic-based population (of whom one third had been admitted acutely at least once) produced results relevant to a more severely affected population (Kokkonen and Linna 1993). Similarly, a long term follow-up of Dutch children showed that childhood atopy was a risk factor for symptoms in the young adults investigated. Here children were enrolled as a population-based sample at 8-11 years and divided
into three groups; an asymptomatic group; a group of asymptomatic children who had a family history of atopy; and a group of children with recurrent respiratory symptoms (cough, phlegm, wheeze or dyspnoea). At follow-up, just over half (53%) of the symptomatic group still had symptoms and in an analysis of childhood predictors, symptoms were related to childhood atopy. Whilst this was a population-based study with a good follow-up rate (85%), numbers were small, limiting the robustness of the results (de Goojer, Brand, Gerritsen, et al 1993). The same group examined risk factors recorded in a group of childhood asthmatics that predicted the persistence of respiratory symptoms into adult life. This was a 15 year follow-up of a group of children attending a pulmonology clinic and was therefore biased in severity – children were labelled by the authors as having moderate to severe asthma. At follow-up only one quarter were symptom free, which is similar to the outcome of severe childhood asthma cohorts followed in Melbourne (McNichol and Williams 1969) and in Finland (Kokkonen and Linna 1993). Lung function and bronchial reactivity had been recorded on a substantial proportion of the subjects during childhood and it was found that women were more likely to have symptoms at follow-up and that symptom severity, poor lung function associated with bronchial hyperreactivity were all associated with persistence. Symptom profile had been assessed at enrolment when the children were between 8 and 12 years so the impact of early symptoms was not addressed in this study (Roorda, Gerritsen, van Aalderen, et al 1993).

A detailed physiological assessment of a small birth cohort of children from Southern England at risk of developing atopic disease was carried out to look at the natural history of childhood asthma and examine its relation to atopy. These 67 children were followed from birth to age 11. Half the group were found to be atopic on the basis of positive skin tests and the expression of atopy increased with age. Nearly two thirds of
this highly selected population had experienced wheeze by the time they were 11 years old. In this small sample it was demonstrated that wheeze occurring prior to the 2nd year of life was associated with a much better prognosis for continuing wheeze, the prevalence of atopy and bronchial hyperresponsiveness than equivalent children whose wheeze started after the 2nd year. The small size and highly selective nature of the population limited the generalisability of these observations to the wider asthmatic population (Sporik, Holgate and Cogswell 1991). These findings were echoed by workers from Australia who prospectively followed a similarly sized birth cohort (Van Asperen and Mukhi, 1994). The majority of studies looking at age of onset have indicated that early wheezing is not a poor prognostic indicator for later outcome (Roorda, 1996).

Another recently reported longer-term follow-up focused on the prognosis of subjects from Scotland in whom a diagnosis of either asthma or wheezy bronchitis had been made during childhood. These children were originally studied when aged between 9 and 15 years old and were a random population-based sample. They were assigned to three groups; children without wheeze formed the comparison group, children who only wheezed in the presence of infection formed the 'wheezy bronchitis' group and children who had wheezed in the absence of infection were assigned to the 'asthma' group. The outcomes of symptom-profile, lung function and bronchial reactivity were assessed at follow-up 25 years later. Subjects from the wheezy bronchitis group had a better outcome symptomatically than those from the asthma group. Although subjects from both groups were more likely to wheeze than those from the comparison group, wheeze reported in the bronchitis group was less likely to interfere with normal activities. The arbitrary and subjective nature of this outcome should be acknowledged (Ross, Godden, Friend, Legge and Douglas, 1996). Lung function and bronchial
responsiveness was no different to that seen in the comparison group. This contrasted with subjects from the asthma group who had the highest chance of still wheezing and had significantly worse ventilatory function and higher levels of bronchial responsiveness. It is of interest that in those subjects from the asthma group who had outgrown their wheeze, measured bronchial responsiveness was increased in comparison to the original control group (Godden, Ross, Abdalla, et al 1994).

A more focused attempt to examine the effects of early respiratory events was reported by workers from Boston, USA. In this study, a representative sample of 5-9 year old children were randomly enrolled into a prospective cohort and followed through time. After 13 years follow-up, the outcome of parentally, or self reported doctor diagnosed asthma (DDA) was assessed in relation to factors reported at the time of enrolment. Many of these factors concerned early respiratory tract illnesses and family history of parental asthma/atopy. The study identified that 91 out of 770 enrolled children (11.8%) were in receipt of a diagnosis of asthma during the period of follow-up (1975-1988). They identified early pneumonia, bronchitis, hayfever, sinusitis, parental asthma and parental hayfever as significant independent risk factors for subsequent DDA. No associations were found with prior bronchiolitis, eczema, croup, personal cigarette smoking, parental cigarette smoking or perinatal events. The results of the study suggested that both genetic and environmental influences were important in determining whether this condition was expressed. Many of the respiratory infections examined would of occurred in infancy and so they may well have been biased or incomplete recall. The conditions of pneumonia, bronchitis, hayfever and sinusitis were recognised by the authors as being hard to distinguish from one another in young children. This admission was itself based upon the fact that these factors were highly related to one another in the multivariate analysis. Furthermore, the designated
outcome of doctor diagnosed asthma was not itself defined (Sherman, Tosteson, Tager, et al 1990).

Another group of researchers in the US has attempted to chart the clinical course of wheeze in childhood by carrying out a population-based birth cohort study. The study was centred on the defined geographical area of Tuscon, Arizona where healthcare arrangements facilitated the selection, recruitment and follow-up of the cohort. Over 1200 new-borns were recruited into the study between 1980 and 1984. The population was studied with respect to pre-morbid markers of disease: blood was taken for immunological studies at birth and subsequently (9 to 15 months), sub-groups underwent lung function testing, and all children were carefully followed in order to document lower respiratory tract illnesses and detail the agents responsible for these infections. Whilst this was without doubt one of the most robust studies undertaken to date, the families enrolled differed from subjects who refused to take part or who dropped out early on: participating parents had a higher rate of marriage, higher average age, increased incidence of respiratory problems, higher educational achievement and were less likely to be of Mexican–American origin. These differences would have incurred some bias in data obtained (Taussig, Wright, Morgan, et al 1989). Initial reports looked at lung function, environmental exposures, and immune status of the population as predictors for subsequent wheezing illnesses. They found that poor lung function (low flow rates and airway conductance), measured before any lower respiratory illnesses had occurred predicted wheezing illnesses in the first 3 years of life (Martinez, Morgan, Wright, et al 1991). Data from this population at six years of life have now been published and showed that just over half had wheezed during the first six years of life. About 20% had wheezed prior to three years but had outgrown the symptom at follow-up. Fifteen percent of the cohort had started wheezing between
three and six years; approximately 15% wheezed both before three years and at follow-up. Analysis of lung function, atopic status and familial and environmental factors revealed that children who wheezed in the first three years of life had diminished airway function in infancy and at follow-up; were more likely to have mothers who smoked and less likely to have mothers with asthma. They did not have high levels of serum IgE or skin test reactivity. Conversely, children who wheezed throughout the course of the study were more likely to have asthmatic mothers and have high levels of serum IgE in both infancy and at 6 years. Lung function in infancy was initially normal, but was reduced at follow-up. Children with late onset wheeze demonstrated levels of IgE at age 6 which were between those of early and persistent wheezers. There was no relationship between late onset wheeze and cord IgE and lung function in this sub group was similar to the never-wheezed group (Martinez, Wright, Taussig, et al 1995).

1.2.2.3 THE RELATIONSHIP BETWEEN COUGH AND ASTHMA

Although it is well known that attacks of asthma are characterised by wheeze, cough and shortness of breath, it has only been recently recognised that chronic cough alone may represent a variant form of asthma. The following reviews the progress in this area.

In 1975 an article published in the New England Journal of Medicine reported the findings on a group of adults with asthma who also complained intercurrently of either shortness of breath or cough. In these 21 adult patients asthma had been diagnosed on the basis of a history of paroxysmal wheeze. When these individuals were investigated during attacks of cough (7 out of the 21), ventilatory function revealed an
obstructive picture. Furthermore, this obstruction was demonstrated to be reversible on the application of anti-asthma therapy (McFadden 1975). Later, findings were published on a group of patients in whom cough was proposed to have been the sole manifestation of their asthma. In this study, 6 adults with cough as a sole respiratory complaint were investigated. Lung mechanics were within normal limits, but bronchial hyperactivity was demonstrable upon methacholine challenge, when compared to an age/sex matched control group. The symptoms were abolished rapidly upon the institution of theophylline or terbutaline, but returned when therapy was withdrawn.

Following the study, 2 out of the 6 patients went on to develop wheeze (Carrao, Braman, and Irwin 1979). Shortly after this, data were presented on 15 children whose sole respiratory complaint was of cough. Baseline spirometry in these children was essentially normal but all displayed changes in ventilatory function upon exercise testing that were similar to those seen in exercise-induced bronchospasm. These exercise-induced changes were abolished once theophylline was started. Once the drug was stopped, 11 out of the 15 children started coughing once again and in those children who were restudied after their cough returned (9 subjects), all again demonstrated exercise-induced reductions in ventilatory function. Cough in these children was once again eliminated as soon as the theophylline was restarted. In this group of children, there was a negative personal history of atopy, and two out of the 15 had positive skin tests. The authors did not say that these children were asthmatic, but rather that they exhibited cough and airway hyperactivity which could be blocked with appropriate therapy. The population studied was small in number and recruited from a pulmonology clinic (Cloutier and Loughlin 1981). A similar series was reported by König, in which 11 children with cough but no wheeze were investigated with exercise challenge and trial of anti-asthma therapy. In all cases, the cough was dry and non-productive and other pulmonary causes had been excluded. In contrast to Cloutier's
series, many of the children were atopic on skin prick testing (7/11). Exercise testing revealed most to have labile airways and symptoms were alleviated once treatment with either theophylline or metaproterenol was started. A recrudescence of symptoms was noted within a few days of stopping such therapy and was subsequently controlled with antiasthma medication on a 'as needed' basis. On the basis of the demonstration that the condition was characterised by exercise induced bronchospasm, and that symptoms were reversible with anti-asthma medication, the authors conclusion was that these children had a 'hidden' form of asthma. Upon follow-up (time unspecified), 8 out of 10 in the series went on to develop attacks of wheeze. This was again a small clinic-based series (Konig 1981).

Similar findings were reported in 15 children from Israel. In this group, all had a personal or family history of atopy. As well as demonstrating exercise induced bronchospasm, hyperinflation was noted in about half the children when chest x-rays were performed. The symptoms in all children improved within 2 to 3 days once therapy was started (oral steroids, salbutamol and/or theophylline). These children were followed for 3 to 31 months after initial assessment, and in this time 5 developed wheeze and in four children in whom therapy was stopped by the parents, symptoms of cough returned. The authors concluded that this small, highly selective group of children had reversible airway obstruction, which was consistent with a diagnosis of asthma, with cough as the sole symptom (Yahav, Katznelson and Benzaray 1982). Hannaway's study of 32 children, who were mostly under 10 and referred for evaluation of chronic cough (average duration 20.6 months), revealed that all responded to theophylline. Analysis of the symptom itself revealed that it was usually worse at night and often exacerbated by exercise. About half of this group had positive skin prick tests, 12 out of 32 had a personal history of atopy, 14 had a positive family
history of atopy and none showed evidence of hyperexpansion on chest x ray. In one third of these children however, subtle wheezing could be elicited when the subjects performed forced expiratory manoeuvres. Follow-up of 24 children from this group over a period of 5 to 96 months revealed that 18 started wheezing, although how many of these were initially found to wheeze on forced expiratory manoeuvres was not detailed. Despite this confounding factor and the highly selective nature of the study population, it was concluded that cough variant asthma was a distinct entity and further, that it was often the prelude to mild to moderate childhood asthma (Hannaway and Hopper 1982).

A large population-based study of 7 and 11 year old children in Southampton, UK provided evidence that cough alone could not be used in an epidemiological setting as a diagnostic feature of asthma. The study recorded the respiratory symptom-status of about 2500 school children whom were then divided into 7 mutually exclusive groups, depending on symptom profile. One such group comprised children reporting cough alone; another comprised children with cough and shortness of breath; a third was made up of children with wheezing and cough whilst a fourth comprised children with wheezing, cough and shortness of breath. A subgroup of 330 children from the entire study population underwent bronchial challenge with methacholine and skin prick testing. The results showed that cough in the absence of wheeze was not significantly related to bronchial hyperresponsiveness. Questions regarding cough referred to symptoms within the year that the questionnaire was conducted and a population-based sample was analysed. Furthermore, not all questions concerning cough excluded cough in the presence of upper respiratory tract infections; indeed, the authors finding that the prevalence of cough decreased between the two age groups under investigation was cited as evidence for the fact that cough was merely a marker of viral respiratory tract infections. This would mean that the cough group would have
undoubtedly comprised less severe cohort of coughers than those hitherto reported. Whilst this was undoubtedly a population-based cohort, neither the severity or chronicity of cough was taken into account during analysis so the association between chronic or recurrent cough could not be reliably tested (Clifford, Howell, Radford, et al 1989). American workers have also shown that children with recurrent cough without wheeze had similar lung function and atopic status to asymptomatic children, casting doubt onto the relationship between recurrent cough and asthma in childhood. These data were based upon the large Tuscon population-based cohort, but defined recurrent cough as 2 or more attacks per year without a cold, which may have spuriously discounted associations between chronic cough (usually defined as cough lasting longer than 3 months) and asthma (Wright, Holberg, Morgan, et al, 1996). Another large population based cohort study into respiratory symptoms demonstrated that cough as a sole symptom (though not specifically chronic cough) was associated with different risk factors when compared to wheeze and shortness of breath, casting further doubt onto the relationship between cough and asthma. Despite having the strength of being a relatively large population-based study, no objective data were collected to permit the association to be refuted more strongly. Furthermore the question on cough was comparative with respect to other children making comparison with other definitions (of recurrent or chronic cough) problematic (Kelly, Brabin, Milligan, Reid, Heaf and Pearson, 1996).

The relationship between chronic cough and asthma was further illuminated by studies of adults and children attending a cough clinic. In a recent adult series, a variety of diagnostic tests were undertaken in otherwise well patients to determine the cause of their cough. Cough had lasted from 3 weeks to 50 years (mean 53 months) and the investigations performed (where appropriate) were oesophageal pH monitoring,
bronchial challenge with methacholine, spirometry, sinus x rays, chest x rays, fibreoptic bronchoscopy. Therapeutic trials were also used as diagnostic tools. In this population asthma was identified as the second commonest cause for the cough (24% of the time). In 28% of these patients, cough was the sole presenting symptom of their asthma, and the cough had been present for an average of 48 months. Bronchial hyperresponsiveness was demonstrable in 28 out the 32 subjects from this larger but severely affected (and therefore biased) clinic-based population (Irwin, Curley and French 1990). An equivalent series was reported on 72 infants and children attending a cough clinic and therefore suffered from the same biases. These subjects had complained of cough for at least 4 weeks and subjects were divided into three age groups; under 18 months, 18 months to 6 years, and 6 to 16 years. In the youngest, middle and oldest age band, asthma was the third, second and first most common cause identified respectively, and was the most common cause identified in the group as a whole (Holinger and Sanders 1991).

1.2.2.4 RELATIONSHIP BETWEEN BRONCHIAL RESPONSIVENESS AND ASTHMA

Bronchial responsiveness is the propensity of the airways to react to inhaled substances. The reaction may result in bronchodilation or bronchoconstriction. It is known that the airways of asthmatics have a heightened sensitivity to such inhalants (see asthma definitions). Methods using a standardised test of bronchial responsiveness have been developed in the hope that this phenomenon could be used as a consistent marker for asthma and a way of discriminating asthmatics from non-asthmatics. Once again problems in validating this as a true marker for asthma occur because of a lack of precise disease definition.
1.2.2.4.i Basis of bronchial challenge

The basis of bronchial challenge is the inhalation of increasing amounts of substances known to change airway calibre, together with serial measurements of ventilatory function until a pre-specified drop has occurred. In practice, the inhalants used on a large scale are non-specific bronchoconstricting agents (e.g. methacholine and histamine) and the usual ventilatory function test is the forced expiratory volume in 1 second (FEV$_1$). A fall of 20% in FEV$_1$ from baseline is usually taken as the endpoint. This fall in FEV$_1$ occurs at either a cumulative dose (PD$_{20}$) or at a concentration (PC$_{20}$) of the inhaled agent, depending on the delivery method used in the challenge (see below). The endpoints are calculated by interpolation of the dose response curve on a log-linear graph and hence a quantitative measure of responsiveness is derived (Cockcroft, Killian, Mellon, et al 1977).

1.2.2.4.ii Methods of bronchial challenge

Three principal methods have come into widespread use in adults and children old enough to reliably perform forced expiratory manoeuvres. In Cockcroft et al's method (1977) increasing concentrations of histamine or methacholine are inhaled via a Wright nebuliser run at an output of 0.13 to 0.16 ml/minute for a two minute period, followed by FEV$_1$ estimations at 30 and 90 seconds. The cycle is repeated at 5 minute intervals until either the 20% decrease in FEV$_1$ is achieved or the maximum dose step is reached. In the second method described by Chai et al (Chai, Farr, Froehlich, et al 1975), increasing doses of the provoking agent are delivered via a De Vilbiss no 42.
nebuliser attached to a French Rosenthal dosimeter which delivers discrete doses of the provoking agent over a 0.6 second period. The device is driven by compressed air and delivered during inspiration from slightly below functional residual capacity (FRC) to near total lung capacity (TLC). One minute later, FEV₁ is assessed. The challenge continues again until the 20% fall in FEV₁ has occurred or the maximum dose has been administered. More recently Yan et al described a rapid method based upon dosimetry, but using a hand held device whereby the dose of agonist is delivered by squeezing a bulb attached to the base of the nebuliser. FEV₁ is assessed 1 minute later and the procedure repeated until similar endpoints to those described above are achieved (Yan, Salome and Woolcock 1983). Comparison of the former two methods has shown that in adults each records a similar level of bronchial responsiveness in the subjects and that both have an similar level of reproducibility. Interestingly, this occurs despite the differential deposition of the agonist in the lung produced by each method (Ryan, Dolovich, Roberts, et al 1981). In a limited series comprising 30 children, the Cockroft method was found to be more reproducible and easier for children to perform than the Chai method (Asher, Betrand, Beaudry, et al 1983). The Yan method was also found to be highly reproducible in the short term when used to assess the level of BHR in a large population-based study of 7 and 11 year old school children from Southampton (Clifford, Radford, Howell, et al 1989).

Most methods were initially developed for use in adults and used initially to show that asthmatic patients would react to the agonist at particular dose leading to a decrease in FEV₁ of 20% and that non-asthmatics would not (Cade and Pain 1971, Parker, Bilbo and Reed 1965). This led to workers classifying subjects as either hyperresponsive or not, and different arbitrary cut-off points have been used (Townley and Hopp 1988). Further early work on normal adult populations defined the distribution of bronchial
responsiveness as unimodal, with all asthmatic subjects representing a subgroup within the hyperresponsive end of the distribution graph (Cockcroft, Berscheid and Murdoch 1983). A point on this continuous distribution curve was therefore chosen to separate the asthmatic from non asthmatic population. These cut-off points were used on adult subjects and then applied to children, without consideration of differences in the drug delivery between adults and children (Le Souef 1992, Stick, Turnbull, Chua, et al 1990). The importance of this phenomenon was underlined when the presence of bronchial hyperresponsiveness (BHR) was incorporated into the definition of asthma by the American Thoracic Society (1962). Hargreave's group reviewed the use and relation of BHR to clinical measures of asthma severity and showed that subjects with a $PC_{20}$ of less than 8mg/ml all had recent symptoms and required treatment whereas non asthmatic subjects (including ex asthmatics) had a $PC_{20}$ of > 8mg/ml. The relationship between BHR and peak flow variability was also highlighted (Ryan, Latimer, Dolovich, et al 1982) although the relationship was not as clear cut. The relationship to improvement in FEV$_1$ after administration of salbutamol was also discussed; the authors implication was that reversibility of FEV$_1$ of >20% was likely to indicate that the subjects $PC_{20}$ would be less than 0.4mg/ml. These workers also demonstrated a correlation between non-specific bronchial responsiveness to methacholine and the response to cold dry air, as well as a relationship between the level of BHR and treatment requirements (Hargreave, Ryan, Thomson, et al 1981). Other workers have shown that in large adult-based studies using clinic-based populations BHR is related to both asthma symptoms and peak expiratory flow rate (PEFR) variability, although once again considerable overlap in levels of BHR between symptom group and of PEFR variability for a given level of BHR was noted at an individual level (Brand, Postma, Kerstjens, et al 1991).
Reservations were registered about the apparently close relationship of BHR to methacholine or histamine and asthma in Pauwels review (Pauwels, Joos, Van de Straeten, 1988). They argued that methacholine and histamine were thought to work directly on the airway causing bronchoconstriction, whereas the constriction accompanying attacks of asthma was felt to result from indirect mechanisms. Supportive evidence was cited in the work of Sears et al, who found that the epidemiology of BHR was poorly related to that of asthma in children. In this large New Zealand study of 9 year olds, 8% of children with BHR had no respiratory symptoms and conversely, 33% of children with current asthma were unresponsive to the methacholine challenge. Furthermore, the presence of asymptomatic BHR only predicted future symptoms of asthma in less than 20% of the children from this group. The main weakness of the study was the poor follow-up rate of the birth cohort with less than half taking part in the study (Sears, Jones, Holdaway, et al 1986). Similarly inexact relationships between the prevalence of BHR and asthma in the community were found by Salome et al, in their study of a highly representative population-based sample of 8-11 year old Australian children. Here 6.7% of children with BHR were asymptomatic and lacked a prior history of asthma and 5.6% had a diagnosis of asthma but did not exhibit BHR. The authors acknowledged, however, that on the whole there was a good association between BHR and respiratory symptoms (Salome, Peat, Britton, et al 1987). Using a different method of eliciting BHR, namely eucapnic hyperpnoea to subfreezing air, workers from Boston USA showed that in a population study that 92% of children with currently active asthma had BHR. However they also showed that nearly one fifth of asymptomatic children demonstrated the same abnormality. The inexact relationship between BHR and asthma symptoms has been postulated as being due to the variability of BHR itself (Cockcroft and Hargreaves 1990). This variability was demonstrated in children by Clough et al who performed
monthly inhalational tests of BHR on 183 7 and 8 year old children for 1 year. These were symptomatic children drawn from a representative population-based sample. Whilst the study confirmed the relationship between wheeze and both the prevalence and severity of BHR it also demonstrated that responsiveness to methacholine changed by >4 doubling doses in 1/3 and by >6 doubling doses in 13.4% of the population studied (Clough, Williams and Holgate 1992).

It can be seen that a large volume of data have been generated over many years from all over the world regarding the relationship between bronchial hyperresponsiveness and asthma/asthma-symptoms. These data suggests that at a population level in both adults and school-aged children there is a definite relationship between non-specific bronchial hyperresponsiveness and asthma. Furthermore despite the undoubted variability of BHR at an individual level, most subjects with significant asthma demonstrate this abnormality. Thus despite its undoubted limitations, its objective nature and ease with which its measurement may be standardised make a useful tool for the epidemiological study of asthma.

1.2.2.5 LUNG FUNCTION AND ASTHMA

It can be seen from the various definitions of asthma (Milner 1993, Campbell and McIntosh 1992, Clark, Godfrey and Lee 1992, American Thoracic Society 1962) (see above) that measurement of airway calibre in the lower respiratory tract is an essential tool for providing evidence to support the diagnosis.
The diameter of the airways can be indirectly gauged by measuring airway resistance and this has been performed on adults and older children using plethysmography. In this technique airflow is measured at by a pneumotachograph at the lips. The subject sits in a sealed box to allow measurement of gas pressure within the box, which is then compared to that outside. In this fashion instantaneous values of pressure (P) and flow ($\dot{V}$) are computed. During the dynamic process of breathing the pressure and resultant airflow changes are related by airways resistance ($\text{Raw} = P/\dot{V}$). This technique is however difficult for young children as a high degree of co-operation is required. Airway resistance may also be estimated by superimposing forced oscillation of airflow onto the respiratory tree of a spontaneously breathing subject. The corresponding fluctuations in pressure (usually measured at the mouth using a pneumotachograph) are recorded. By using Fourier transformation and numerical analysis analogous to alternating current theory the amplitude and phase relationship of the pressure and airflow oscillations can be measured and a value of airway resistance may be derived (Landser, Nagels, Demedts, et al 1976).

Another way that lower airway calibre can be assessed is by measuring airflow limitation, as the two are related by Poiseille’s equation. Expiratory airflow limitation occurs during forced expiratory manoeuvres, as $\dot{V}$ is independent of the driving pressure once a certain value of driving pressure is exceeded. Maximum expiratory flow ($\dot{V}_{\text{max}}$) is itself related to wave speed, which is the maximum speed that a fluid can propagate down an compliant tube. This value is dependant upon the cross sectional area of the tube. The site at which $\dot{V}_{\text{max}}$ occurs varies during the expiratory phase, residing centrally at high lung volume and becoming increasingly peripheral (residing in the smaller airways) as lung volume diminishes. The flow limitation may be
accompanied by flutter. This is a dissipation of the driving force sideways through the elastic airway wall as the force exceeds that which is required to produce $\dot{V}$ max. This flutter is heard as wheeze.

1.2.2.5.i Measuring airflow limitation

It follows that measurement of airflow limitation is possible providing there is sufficient effort over most of expired vital capacity to provide a driving force which exceeds the threshold after which airflow becomes independent. When flow and volume are measured during this manoeuvre, a graph of flow against volume can be plotted. In health the expiratory limb of this curve is usually convex but in airway obstruction (because of flow limitation) the curve becomes concave. During forced expiratory testing it is possible to record forced vital capacity (FVC), forced expiratory volume over 1 second (FEV$_1$) and the flow over the middle 50% of the expiratory manoeuvre (FEF$_{25-75}$ or MEF$_{25-75}$). This technique is not routinely performed in children under 7 years but in laboratories with special expertise it has been attempted on younger children. In young children whose lung volumes are smaller the forced expiratory manoeuvre may empty the lungs too quickly to allow the reliable measurement of FEV$_1$. The technique has been shown to have acceptable reproducibility in a well selected random group of children aged 6½ to 7½ years, with little data on younger subjects (Strachan 1989).
1.2.2.5.ii Relationship between ventilatory function measurements and asthma

It is well recognised that decreases in ventilatory function accompany acute exacerbations of asthma. Changes in peak expiratory flow rate (PEFR) are currently used by many physicians to aid self management plans of patients with asthma. In such cases, changes in PEFR are used as a marker of disease activity and act as a prompt to either increase or decrease anti-asthma therapy (The British Thoracic Society guidelines on asthma management, 1997). The strong relationship of lung function to the clinical severity of asthma has also been demonstrated in clinic based (Linna 1996, De Benedictis, Tuteri, Pazzelli, et al 1996) population-based (Cuijpers, Wessling, Swaen, et al 1994) samples of children and is exploited in the assessment (in highly selected, severely affected clinic-based populations) of the efficacy of bronchodilators (De Benedictis, Tuteri, Pazzelli, et al 1996), inhaled steroids (Hoekstra, Grol, Bouman, et al 1996) and other therapeutic interventions (Perin, Weldon and McGeady 1994).

Studies have also shown persisting abnormalities in lung function present during periods of clinical remission from the symptoms of asthma (Ferguson 1988, Engstrom, Escardo, Kalberg et al 1959, Hill, Landau McNichol 1972). Reduced lung function during childhood has also been shown in many studies to be an important predictor of continuing morbidity later on in life (Jenkins, Hopper, Bowes, et al 1994,Kokkonen and Linna 1993, Roorda, Gerritsen, Van Aalderen, et al 1988). Interestingly, work from the Tuscon prospective birth cohort study has shown that infant lung function is an important pre-morbid determinant of wheeze in infancy (Martinez, Wayne, Wright, et al 1988).
1.2.2.5.iii Peak expiratory flow rate (PEFR)

This is defined as the maximum flow achieved during forced expiration starting from maximum lung inflation. Recent work has suggested that PEFR measures flow limitation at high lung volume (Kano, Burton, Lanteri, et al 1990) but the manoeuvre requires maximum effort, although only for a short time. The peak flow meter has become a widely used tool both clinically and epidemiologically due to its ease and relative simplicity of use. More recent data have questioned the validity of the device, highlighting inaccuracies in the flow rates measured between 200-400L/min (which is pertinent to studies of children) by comparing flow rates against pre-determined flow rates generated by a computer-controlled servo pump. (Miller, Dickinson and Hutchins 1992). The device however, remains widely used and may be used by young children after suitable instruction (Wille and Svensson 1989)

1.2.2.5.iv Peak expiratory flow variability (PEFV)

As peak flow is designed to give a measure of airflow limitation, studies have looked at the variability of this phenomenon. Normal subjects exhibit diurnal variability in peak flow. The maximum value (acrophase) is recorded during the period 2 -10pm whilst the minimum, or bathyphase is recorded in the early morning hours of 2.30-5.15am. (Hetzel and Clark 1980). In Hetzel and Clark's influential study peak flows were performed at 4 times of day for a week and diurnal variability was modelled mathematically with cosinor analysis, the fitting of a sine wave to the daily peak flow
record. The model fitted the collected data in about half of a large group of (145) normal and all of a smaller group (56) of moderate to severe asthmatic subjects. The amplitude of the sine wave was taken as a measure of the diurnal variability in airflow and hence airway calibre. This diurnal variation was shown to be increased in the severe adult asthmatics recovering from an acute exacerbation compared to healthy controls (50.9% Vs 8.3%). This increased diurnal variation was postulated as being responsible for the phenomenon of nocturnal and early morning asthma (1980). Normal diurnal variability is greater in children, reducing the power of the technique to discriminate asthmatic from non-asthmatic children (Quakenboss, Leibowitz and Krzyzanowski 1991). Subsequently various workers have looked at possible factors which contribute to the diurnal variability in symptoms and lung function in asthmatic subjects. These include changes in BHR in a small group of adults, (Wempe, Tammeling, Postma, et al 1992) catecholamine release in another small selected group of young adults (Bates, Clayton, Cahoun, et al 1994) and in yet another small group of nine patients, allergen sensitivity (Platts-Mills, Mitchell, Nock, et al 1982).

1.2.2.5. Calculation of Peak Expiratory Flow Variability (PEFV)

An important limitation to Hetzel and Clarks method of using cosinor analysis was the inability of the method to explain all the data collected. The model was able to fit the observed data in just over half the subjects (1980). This led to others attempting to assess the validity of using other numerical expressions of peak flow variability in order to demonstrate a relationship with asthma or bronchial hyperresponsiveness (Ryan, Latimer, Dolovich, et al 1982). The most comprehensive evaluation of the different indices which could be derived from PEF readings was performed on a community
adult population of asthmatics and controls in Nottingham, UK by Higgins et al. Subjects completed peak flow recordings every two hours during waking hours for one week. The data collected were analysed using seven different indices of peak flow variability. The best discriminator between the asthmatic and non-asthmatic populations was amplitude percent mean. This is the difference between the highest and lowest PEF divided by the mean PEF for the recording period. The result is multiplied by one hundred. The data were found in both groups to show a positive skew and there was also considerable overlap between asthmatic and normal subjects, in contrast to the earlier studies (Higgins, Britton, Chinn, et al 1989)

1.2.2.5.vi Relationship between PEFV and asthma

Once again the lack of an accepted definition of asthma means that studies looking at the relationship between PEFV and asthma are usually studies between PEFV and symptoms of asthma, physician-based diagnosis or physiological measures asserted by the researchers to represent asthma. Further study of the latter cohort used to derive the best indices of peak flow variability showed that excessive PEFV (as gauged by amplitude % mean) was significantly associated with wheeze. Excessive PEFV was defined as amplitude % mean lying outwith the 90th centile of the variability distribution from the random sample. Furthermore they demonstrated correlation of PEFV with frequency of wheeze (Higgins, Britton, Chinn, et al 1988). In a study of adult volunteers, PEFV was increased in asthmatics and in individuals who wheezed without a cold. The authors suggested that this index could be used as an indicator of BHR,
although this again was based on adult data (Neukrich, Liard and Segala 1992). A further study of (mainly) adults and children using physician diagnosed asthmatics and controls showed that excessive PEFV (calculated as amplitude percent minimum) was a valid test for asthma (Jamison and McKinley 1993). In a population-study, adolescents with asthma and asthma-like conditions were compared to healthy controls with respect to PEFV and response to inhaled methacholine. The presence of increased variability on its own was a poor predictor of asthma, but when taken with response to methacholine achieved a sensitivity of 77% in detecting the condition in a sample of over 400 adolescents (Siersted, Hansen, Hansen, et al 1994). In a three-year study of peak flow variability in highly selective group of children with well controlled asthma, the authors found a significant relationship between both symptoms of asthma and reactivity to inhaled methacholine (Gern, Eggleston, Schuberth, et al 1994).

Thus although there appears to be relationship between PEFV and asthma, the wide range of this index as documented in the literature limits its usefulness as a tool for diagnosing asthma at an epidemiological level.
1.2.2.6 ATOPY AND ASTHMA

Atopy may be immunologically defined as the propensity to produce exuberant amounts of immunoglobulin E (IgE) in response to commonly encountered environmental antigens.

The term has been closely linked with that of asthma since the concept of atopy was first coined in the early years of this century (Cooke RA and Vander Veer 1916; Coca and Cooke 1923; Spain and Cooke 1924) as it was used to describe the mechanism by which familial clustering of wheeze was observed. This close relationship remains and recent studies into the prevalence of atopic disease (regardless of the age range under consideration) have used wheeze as one indicator of atopic illness (Aberg 1993).

1.2.2.6.i Relationship between wheeze and atopy in childhood

Numerous studies have been conducted to examine the relationship between atopy and asthma in childhood which inevitably engendered the problems of how asthma was defined. Workers have therefore examined the relationship between both atopy and wheeze and atopy and bronchial hyperresponsiveness in childhood.

By using levels of IgE in cord blood as a marker for the development of future atopic disease, workers from Tuscon conducting a well designed prospective population-
based birth cohort on a large sample (767 newborns in the reported studies) and found an inverse relationship between IgE and wheezing in infancy. The levels were however positively predictive of wheeze starting in the third year of life (Halonen et al 1992, Halonen et al 1990). A similar relationship was demonstrated in a British cohort where wheeze occurring in children under two was not found to relate to the presence of atopy at 11 years, although wheeze at age 11 was related to atopy. The population was small and highly selected to look at children with high risk of developing atopic illness (Sporik, Holgate and Cogswell 1991). In Wilson's study of a small group of hospital-based wheezers, no relationship was found between atopy and either severity or frequency of wheeze in three year olds and an inverse relationship was found between bronchial responsiveness and atopy (Wilson, Phagoo and Silverman, 1992). This contrasts with the findings in a well conducted study upon a large birth cohort of 11 year old New Zealand children (Sears et al 1991) and a large population-based sample of American adults (Burrows et al 1989) where a close proportional relationship was found between serum IgE concentrations, bronchial hyperresponsiveness (BHR) to methacholine and wheeze. More recent work on the birth cohort from New Zealand has found that atopy not only related to the prevalence of wheeze but was an important determinant of the frequency of wheeze and the degree of impairment in lung function in older children (Burrows et al, 1995).

Another group from New Zealand examined the relationship between markers of asthma and atopy (in this study defined as positive skin prick test with wheal greater than four millimetres in diameter) in a migrant population and found that in atopic children the proportion with BHR remained constant with increasing age (7 years vs. 15 years). This was in contrast to the group without atopy in whom the proportion decreased dramatically (25% at 7 vs. 3% at 15). Interestingly the former prevalence was affected by a positive family history of asthma but not the latter. The study was
cross sectional across the age range and not longitudinal, limiting the robustness of the authors' assertions regarding changes in BHR with age (Crane et al, 1989). In Peat's large population-based study of BHR in several thousand Australian school-aged children and adults, atopy (defined as skin prick testing producing a wheal of three millimetres diameter) was found to be the most important risk factor for BHR at all ages (Peat, Salome and Woolcock, 1992). Further work by this group showed that the increase in asthma over a ten year period was limited to the atopic population which itself had not increased in relation to the general population over the same time span. They hypothesised that the increase in asthma might be partly due to an increased allergen load (Woolcock, Peat and Trevillion, 1995), although data from the different climatic regions of Australia showed an imprecise relationship between atopy (as manifested by skin test sensitivity) and asthma (Phelan, 1995). The area of allergen load as an aspect of the relationship between atopy and childhood asthma has been studied by others who mirror the findings from Australia (Platts-Mills et al, 1995).

A large population-based study in the UK showed that in 7 and 11 year old children atopy was strongly associated with both an increased prevalence and degree of BHR (Clough, Williams and Holgate, 1992). Investigators from this study have cited the increased prevalence of atopy in boys as one of the causes of the higher proportion of wheeze seen in male children (Clough, 1993). In a recent case-control study from the US of school aged children with recurrent wheeze, the proportion with positive skin tests compared to controls was 77% or 90% (depending on the frequency of current wheeze) Vs 35%. Interestingly, wheeze before the second year of life was associated with only a modest risk of recurrent wheeze later in childhood, a risk unaffected by atopy (Henderson et al, 1995). The relationship between persistence of wheeze to
adulthood and atopy, evidenced by positive skin tests, has been demonstrated by others (Gerritsen, Koeter, de Monchy and Knol, 1990; Roorda, Gerritsen, van Aalderen and Knol 1993).

It thus seems there is a large body of evidence which suggests there is a relationship between recurrent wheeze and atopy and BHR and atopy in older children (Roorda, 1996). Recent data question the relationship between atopy and wheeze in infants and young children.
1.2.2.7 RELATIONSHIP BETWEEN NOCTURNAL COUGH AND ASTHMA

Nocturnal symptoms are common in asthma and most asthmatics have nocturnal bouts of cough, wheeze, dyspnoea or chest tightness. In Turner Warwick's (1988) epidemiological study of symptoms in a large non-hospital-based sample of asthmatic adults 74% reported bouts of nocturnal cough. The sample was recruited via general practice and consisted of patients receiving an aerosol bronchodilator. Thus the rate of nocturnal cough was that found in mildly affected patients. In a group of older, more severely affected children attending an asthma clinic, 47% reported nocturnal symptoms, and the most commonly reported symptom was cough (Meijer, Postma, Wempe, Gerritsen, Knol and van Aalderen, 1995). Montplaisirs, Walsh and Malo's small study of 8 unstable asthmatic adults showed that those who were symptomatic had less REM sleep than compared with controls. Furthermore, sleep architecture returned to normal once nocturnal symptoms had been "treated" (1982). Nocturnal symptoms have in turn been demonstrated to interfere with daytime activities. In a study of 12 stable adult asthmatics and 12 controls, polysomnographic analysis and psychometric testing showed the disease group to have poorer sleep efficiency and lower scores on psychometric testing (Fitzpatrick, Engleman, Whyte, Deary, Chapiro and Douglas 1991). The same group has recently shown an improvement in day time cognitive function after treatment with long acting beta 2 agonists to abolish nocturnal symptoms in asthma in adults (Selby, Engelman, Fitzpatrick, Sime, Mackay and Douglas, 1997). Nocturnal cough can be a troublesome symptom in asthmatic children and can negatively affect daytime performance and activities (Meijer, Postma, Wempe, Gerritsen, Knol and van Aalderen, 1995). Using epidemiological data from a large population-based study, isolated nocturnal cough has not been demonstrated to be a manifestation of asthma (Ninan, Macdonald and Russell, 1995).
Despite the high prevalence of night-time symptoms in asthma, elucidation of the mechanisms underlying nocturnal worsening of asthma remains incomplete. Putative explanations relate to Circadian phenomena. Increased bronchial responsiveness was first demonstrated on 11 young asthmatic subjects over 30 years ago (de Vries, Goei, Booy-Noord and Orie, 1962) whilst more recently Wempe and co-workers have explored the potential to modulate this diurnal variation in bronchial responsiveness using drug therapies (Wempe, Tammeling, Postma, Auffarth, Teengs and Koeter, 1992). Increased airway lability has been demonstrated to be present in a small group of 11 adults with nocturnal asthma using the magnitude of the morning dip in peak flow (Bellia, Visconti, Insalaco, Cuttitta, Ferrara and Bonsignore, 1988). Increased sensitivity to inhaled allergens at night has been shown using commonly encountered aeroallergens in small groups of adult subjects (Gervais, Reinberg, Gervais, et al, 1977; Platts-Mills, Mitchell, Nock, Tuvey, Moszoro and Wilkins, 1982). Autonomic imbalance has been implicated as a possible contributory factor in a small group of young adults by studying the relationship between plasma concentrations of adrenaline and nocturnal asthma symptoms (Bates, Clayton, Calhoun, Jarjour, Schrader, Geiger, Schultz, Sedgwick, Swenson and Busse, 1994), urinary metabolites of adrenaline and peak flow measurements (Soutar, Carruthers and Pickering, 1977), and by partially abolishing the reduction in nocturnal peak flow by infusing adrenaline in five asthmatic adults with nocturnal symptoms (Barnes, Fitzgerald and Dollergy, 1986). Finally it has been reported that in healthy children decreased airway calibre occurs at night (Gaultier, Reinberg and Girard, 1977).

Circadian rhythms have been demonstrated for peak expiratory flow rate in a population sample of wheezy children (Johnson, Anderson and Patel, 1984), bronchial
responsiveness in young adults (de Vries, Goei, Booy-Noord and Orie, 1962) and catecholamine secretion (Bates, Clayton, Calhoun, Jarjour, Schrader, Geiger, Schultz, Sedgwick, Swenson and Busse, 1994). This work has shown that these cyclical phenomena reach a bathysphase (lowest point) during the night. The timing of nocturnal cough does not tally with the bathysphase of these same measures, possibly indicating an imprecise relationship between cough and other measures of asthma severity.

Clarification of the precise relationships between nocturnal cough and measures of respiratory function are hindered by the poor reporting of nocturnal cough, which has been demonstrated in small groups of asthmatic children (Archer and Simpson, 1985; Falconer, Oldman and Helms, 1993). In addition the reported studies in the main have concerned small highly selected groups of children with severe asthma and/or asthmatics undergoing therapeutic trials of treatments to reduce night cough (Hoskyns, Thomson, Decker, Hutchins and Simpson, 1991). Finally it has been recognised in epidemiological studies that the analysis of factors important in determining night cough may be confounded by environmental exposures such as tobacco smoke (Somerville, Rona and Chinn, 1988), pollutants (Ostro, Lipsett, Mann, Wiener and Selner, 1994) and dampness (Strachan and Sanders, 1989).

Few studies have looked at night cough and nocturnal asthma in childhood and no studies report upon the relationship between recent wheeze (within the last year) and recorded night cough. There is a paucity of data comparing the reported frequency of night cough with that actually recorded at night (Archer and Simpson, 1985; Falconer, Oldman and Helms, 1993) and no reports defining the nature and timing of nocturnal
cough in those with and without wheeze in the preceding year. Although there is
evidence in adults with moderate to severe asthma, in childhood it is currently
unknown whether factors such as lung function, bronchial reactivity and environmental
exposure predict, or are associated with, nocturnal cough.

From the review of literature the key points pertaining to this area of research and the
important questions which are outstanding can be summarised as follows:

**Key points:**

- Prevalence of asthma in school age populations appears to have increased in
  recent years, and prevalence of wheeze appears higher still in younger
  children.

- Asthma morbidity has also increased over the same period.

- No precise disease definition of "asthma" exists.

- Studies on the natural history of wheeze provide conflicting evidence on the
  importance of early onset of wheeze, pattern of wheeze, atopy, lung function,
  bronchial responsiveness and family history of atopy in determining long-term
  symptomatic and functional outcome in later childhood and adulthood.

- Many studies on the natural history of wheeze are flawed by using
  unrepresentative population samples and/or relying on parental recall of early
  symptoms.
• Very few studies are population-based and use data on symptoms collected early on in life.

• Chronic cough has been proposed as a manifestation of asthma in children from the study of highly selected patient series; population studies of chronic cough in children have not confirmed this.

• At a population level there appears to be a distinct but imprecise relationship between bronchial hyperresponsiveness and asthma in childhood. A similar phenomenon exists for peak flow variability, although the overlap between normal and asthmatic populations is considerable, reducing its discriminatory usefulness.

• Atopy and wheeze in older children appear related, but the relationship in younger children is less clear-cut.

• Whilst nocturnal cough is a common symptom in asthma, its causation and relationship to other measures of asthma severity remain very poorly defined.
Key questions:

- What is the impact of wheeze and recurrent cough that occurs early on in childhood upon later respiratory health?

- Does wheeze in the first five years of life in a representative population-based sample predict the symptoms and physiological abnormalities consistent with the diagnosis 'asthma' by the time children are in the early school years?

- Does recurrent cough in the absence of colds in the first five years of life in a representative population-based sample predict the symptoms and physiological abnormalities consistent with the diagnosis 'asthma' by the time children are in the early school years?

- Do children with recurrent cough in the pre-school years go on to develop asthma characterised by episodic wheeze later on in childhood?

- Are patterns of wheeze early in life predictive of persistent wheeze later?

- Are there other factors which are ascertainable early on in life which help predict the outcome of wheeze in pre-school children?

- Are there measurable factors in young children that help predict the presence of night cough?
CHAPTER TWO

HYPOTHESIS AND AIMS
2.1 HYPOTHESIS

Pre-school cough and wheeze predict a constellation of symptomatic and functional abnormalities in the early school years and that these abnormalities are characteristic of the condition labelled asthma.

2.2 AIMS

To test the hypothesis upon a population-based sample of children whose symptom status had been previously ascertained during the pre-school period (0-5 years) by recalling all symptomatic, and age/sex matched controls in the early school years (4-7 years) in order to assess respiratory symptoms at follow-up and measure suitable physiological parameters, abnormalities of which are usually considered indicative of an asthmatic diathesis, namely; lung function, atopic status, airway responsiveness, peak flow rate variability, recorded nocturnal cough and transcutaneous oxygen saturation.
CHAPTER THREE

METHODS
3.1 SUBJECT SELECTION

Subjects were selected from the cohort of respondents to a postal questionnaire issued in 1990. At that time 1650 subjects were selected from the child health register kept by Leicestershire Area Health Authority. The register contains information about name, address, date of birth, demography and ethnicity. Children of Caucasian extraction were selected at random with dates of birth between 1985 and 1989. Response rate to this postal questionnaire was 86.2% giving a total cohort of 1422 children (709 boys and 713 girls).

Subject selection was determined by response to key questions concerning cough and wheeze. A sample indicating how to respond to the questions and a definition of wheeze was given prior to the start of the questions. Children whose parents had affirmatively answered the question 'has your child ever suffered from attacks of wheezing?' were designated 'wheezers'. Some of these children also answered positively the question 'Does your child usually cough without a cold?' Other children whose parents answered in the affirmative to this question and negatively to the question on wheeze were designated as 'coughers'. Children with negative responses to both these questions were designated as 'controls' for the purpose of the follow-up study. It can be seen that a sub-group of the 'wheezers' also had reported recurrent cough. The total pool of 'wheezers', 'coughers' and 'controls' available from the 1990 cohort were 222, 226 and 974 children respectively.
3.1.1 SAMPLE SIZE/POWER CALCULATION AND PRIMARY STATISTICAL ANALYSIS

The sample size power estimates were based upon a single component of the outcomes measured. This was the response to inhaled methacholine, defined as a response to methacholine at a concentration of 8mg/ml or less [yes/no]. Numbers required were computed to analyse this as a binary endpoint based upon contingency tables. Formal tests of significance were to be based upon chi-squared test for the comparison of proportions with no continuity correction. Cockcroft, Bersheid and Murdoch (1983) found that 30% of normal individuals demonstrated bronchial responsiveness to histamine at concentrations at or below 8mg/ml (compared to 100% of a small sample of asthmatics in the study). Little comparable data were available at the time for children and the influence of age on bronchial responsiveness was unknown. It was therefore decided that, (empirically) given a putative response rate of 30% amongst normal individuals, the study should be designed to have a 90% power to detect a primary response of 50% or greater in either of the symptomatic groups. Standard sample-size/power calculation based upon the comparison of two proportions (Armitage, 1987) suggested that in order to have a 90% power to detect, at the 5% (2-tailed) level of statistical significance, a true difference of 50% v 30% in the proportion responding in two equally sized groups, it was necessary for both groups to consist of 120 subjects. It was therefore decided to base the study design on a sample including 120 wheezers, 120 coughers and 120 normals. The following table was used to illustrate a more detailed summary of the power profile offered by this particular study design.
TABLE 2.1 POWER PROFILE OF STUDY DESIGN

<table>
<thead>
<tr>
<th>True difference in proportions</th>
<th>Power</th>
<th>True difference in proportions</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>10% v 30%</td>
<td>97.9%</td>
<td>20% v 45%</td>
<td>99.0%</td>
</tr>
<tr>
<td>15% v 35%</td>
<td>95.7%</td>
<td>30% v 55%</td>
<td>98.2%</td>
</tr>
<tr>
<td>20% v 40%</td>
<td>93.4%</td>
<td>40% v 65%</td>
<td>98.0%</td>
</tr>
<tr>
<td>25% v 45%</td>
<td>91.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30% v 50%</td>
<td>89.8%</td>
<td>20% v 35%</td>
<td>75.2%</td>
</tr>
<tr>
<td>35% v 55%</td>
<td>88.9%</td>
<td>30% v 45%</td>
<td>68.1%</td>
</tr>
<tr>
<td>40% v 60%</td>
<td>88.5%</td>
<td>40% v 55%</td>
<td>65.3%</td>
</tr>
<tr>
<td>70% v 90%</td>
<td>97.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Thus if the true proportion of normal children with a level of bronchial responsiveness of 8mg/ml or less was not 30%, but 25%, the study, as designed, would have a 91.3% power to detect (as different) a true primary response rate of 45% or higher amongst the children with either wheeze or cough. Similarly, if the true proportion of coughers who responded at 8mg/lml or less were 40%, the study would have an 88.5% power to detect (as different) a true primary response of 60% or higher amongst the children with either wheeze or cough.

3.2 ENROLMENT PROCEDURE

All parents of symptomatic children within the specified age-bands and a random sample of age-matched controls were mailed. The letter was addressed to the parents and briefly explained the main findings of the previous postal questionnaire. The intention to see what had happened to the children from the original study was explained and the parents and children were invited to the hospital for follow-up questionnaire and tests of breathing. A photocopy of a newspaper feature in the local press highlighting and explaining the aims
of the study was enclosed for parental information (figure 1). Parents were instructed to sign a form indicating their agreement to take part in the study and to return this using a freepost envelope. The form also asked about intercurrent illness and family contact with respiratory illness. Once these had been returned, the families were contacted (by telephone where possible) and an appointment finalised, depending on the current health of the child.

Parents who failed to respond to the first mailing were re-mailed at 1 and 2 months and offered further opportunities to take part in the study. Parents who failed to reply to any of the mailings were presumed to have moved and so new addresses were sought by rechecking the current address on the appropriate child health record. Where a change of address was found, the parents were re-mailed as above.

Parents who declined to take part either wholly or in part were invited to fill out a further postal questionnaire identical to that asked of parents taking part in the complete study.
Asthmatics needed to help study

by Barry Nelson, Health Correspondent

Scientists in Leicester are appealing for help to crack the secret of childhood asthma.

Very little is known about the reasons why some youngsters who cough and wheeze on to develop asthma and others do not.

With childhood asthma on the increase — about one in five of Leicester's preschool age group shows signs of recurrent wheezing — the race is on to increase scientific knowledge about this potentially dangerous breathing disease.

Scientists at Leicester University have been given £160,000 by the National Asthma Campaign to put childhood coughs and wheezes under the microscope to see if there is a firm link with asthma in adults.

"We can't stress too much how important this research project may turn out to be. It could help to improve the diagnosis and treatment of asthma."

Researchers based at Leicester Royal Infirmary need to hear from 300 or so parents of children aged between four and seven who took part in a study two years ago, and who have now cleared up.

"We had a fantastic response from parents, virtually 90 per cent of the people we approached filled in the consent form," said research fellow Dr Adrian Brooks.

"Now we need those parents to contact us again and help us carry out some simple tests on their children."

RESEARCH HELP: Dr Adrian Brooks with centre Christine Clarke and Thomas Chalmers.

"We need people to contact us again and help us carry out some simple tests on their children for the child to be monitored as they grow."

Mrs Christine Clarke, who arranges for the child to be monitored as they grow, said: "Mr. six-year-old Thomas used to have a persistent cough, but that has cleared up. He has really
3.2.1 ENROLMENT OF THE PRE-SCHOOL COHORT

The population under study was originally chosen from a random sample of pre-school children in Leicestershire. The sampling frame used was Leicestershire Health Authority community child health register. This register is designed to contain the names of all children born or living within the Leicestershire health district. All children are entered onto the register at birth and the roll is thought to be an accurate register of all children in Leicestershire. The details recorded on the register are name, date of birth, child health number, registered address, sex and ethnicity. Utilising this information, the original respiratory symptom questionnaire was mailed to 1650 Caucasian pre-school children between March and September 1990. The selected children were born between January 1985 and January 1990 and 330 children from each year of birth were sampled. A response rate of 86.2% was obtained resulting in 1422 replies. In this way, the respiratory symptom status and related factors, together with an array of environmental, familial and social variables were available for a large cohort of children. The questionnaire used in the original survey to ascertain this baseline information was abstracted largely from the children's questionnaire recommended by the epidemiological standardisation project of the American Thoracic Society (ATS) (Ferris, 1978). In order to maintain consistency in symptom reporting between the two questionnaires and to enable the long term repeatability of the key questions to be addressed, a very similar style, format and wording of the questionnaire was used in both phases of the study. The questionnaire is discussed in detail below.
3.3 QUESTIONNAIRE

The questionnaire delivered to the population was designed to assess the prevalence of the respiratory symptoms of wheeze and cough; to enquire about associated factors (for example, precipitants of wheezing or the number of wheezing attacks), personal, familial and environmental factors. A number of questionnaires have been used in adults and these have been applied in the past to respiratory surveys in childhood. However, because of the particular age group under study, a new questionnaire was designed and developed using previously validated questions where possible. The questionnaire used is contained in appendix 1.

3.3.1 ASSESSMENT OF SYMPTOM STATUS

The question ascertaining a history of wheezing was question 1 of the survey (see appendix) "has your child ever wheezed?" This question was prefaced with a description of wheeze as "a high pitched whistling noise coming from the chest, not the throat". This definition of wheeze is well recognised and widely used in epidemiological settings (Clifford, Radford, Howell and Holgate, 1988; Park, Golding, Carswell and Stewart Brown, 1986). There were three questions pertaining to cough. These were question 13, "does he/she usually have a cough with a cold?" question 14, "Does he/she usually have a cough apart from colds?" and question 12, "Has your child been woken at night by an attack of coughing when he/she has not had a cold or a chest infection?" Both of the first two questions were abstracted from the ATS childhood questionnaire. It is known that
upper respiratory tract infections are relatively common in the pre-school age group and also that cough is a common accompaniment of these infections. It is also recognised that chronic cough in childhood in the absence of respiratory infections may represent variant asthma and for these reasons the presence of cough in the absence of colds was sought. The question concerning night cough was further qualified by an enquiry as to whether night cough was a regular occurrence (question 12a). The age of the child when this symptoms started and (where applicable) stopped was also elicited.

Questions concerning wheeze behaviour and severity were detailed as it was felt that recall of past events would be relatively good in view of the young age of the original cohort under study. Parents who answered affirmatively to the question concerning wheeze were next asked the age of onset in years and months (question 2). For children commencing with wheeze before six months of life, the age in weeks was asked to facilitate an accurate answer (question 2a). At follow-up, parents of children whose wheezing had ceased were asked the age (in years and months) at which this had occurred (question 2b). An estimation of the total number of attacks suffered by the child was then asked (question 3). Closed format ranges were used to answer this and were "None", "1-2", "3-5", "6-10", "11-20", "20-40", and "more than 40". At follow-up, to take into account the increased age ranges were added at the end of this question, namely "40-60" and "More than 60". Question 4 enquired about the total number of attacks within the past year. Again closed format answers were used and valid responses were "none", "1-2", "3-5", "6-10", "11-24" and "more than 24". Question 5 concerned the average length of wheezing attacks, given normal treatment. The responses available here were "about 1 day", "2-3 days", "4-7 days", or "more than 7 days". The length of time since the last attack
of wheeze was then ascertained using similarly formatted answers: "less than 1 month", "1-3 months", "4-6 months", "7-12 months", "13-24 months" or "more than 25 months" (question 6). Children who had been free of wheeze at follow-up for longer than 25 months were not then asked subsequent questions concerning wheeze behaviour and severity because of the concerns for poor recall of symptoms occurring over two years prior to follow-up. For those with more recent wheeze however, question 7 enquired as to whether the attacks of wheeze caused shortness of breath. Answers were in the form of "yes, always", "yes, occasionally" and "no, never". At follow-up an additional answer of "not now, but used to" was provided. This question is abstracted from the ATS questionnaire. Question 8 asked about the presence of shortness of breath in the absence of wheezing attacks and used the same answer format as the previous question. Question 9 asked about triggers to wheezing attacks by enquiring if wheezing attacks ever occurred when the child had a cold, (9a) ever occurred apart from colds (9b), with exercise (9c), with ingestants (9d), or finally if attacks were ever precipitated by the inhalants (9e). Question 10 enquired as to whether wheezing attacks were more frequent at any particular time of year. An affirmative answer was followed by a prompt to indicated which months during the year were "bad" months for wheezing. These were arranged in 4 trimesters, with winter comprising two trimesters (October to March) and summer the remaining two (April to September). Question 11 sought whether diurnal variation in the severity of wheezè was present and if so, if it worse during the day or the night.

The next section of the questionnaire screened for nocturnal cough, coughing with a cold and coughing in the absence of colds. These questions (12, 13 and 14) have been described above. At follow-up the presence of prior coughing in the absence of colds was
asked in order to assess the long term reproducibility of this question from the first pre-school survey. The age of the child when this symptom commenced and (where applicable) ceased was also obtained. Question 15 elicited whether the child had been in receipt of a diagnosis of "wheeziness", "asthma", or bronchitis" from a doctor or hospital. This question allowed more than one answer. The age(s) of the child at receipt of the diagnoses was also asked. Question 16 concerned clinic attendance for any of the diagnoses named previously and was couched in the present tense to screen for children receiving current medical follow up. Question 17 asked whether the child had ever received medication for any the diagnoses and this was followed by enquiry as to the age of the child when medication was first prescribed and (if applicable), when it was stopped. This question also asked about which symptom the medication was prescribed for. Answers available were "recurrent cough", "recurrent wheeze", or "asthma/bronchitis". Question 18 asked whether the child had ever been admitted to hospital with wheezing, asthma, and bronchitis or chest trouble other than wheezing. Question 19 elicited any previous illnesses of relevance; namely upper and lower respiratory tract infections and chronic cardiorespiratory disorders. Enquiry was also made as to the presence of any other serious illnesses and whether the child had ever had tonsillectomy or adenoidectomy. The next question asked about eczema (defined with the question) together with date(s) of start and cessation. A similar formatted question screened for the presence of recurrent or chronic nasal symptoms. This was followed by specific enquiry into the presence of any allergy with identifiable cause. Question 23 asked about perinatal problems, including prematurity. School absence was next assessed by dividing responses into three categories; "never", "sometimes" and "frequently". The penultimate question concerned breast-feeding and a positive response to this was followed by
enquiry to the length of time for which breast milk was the exclusive dietary component. The final question allowed parents to make any other comments about their child’s health.

3.4 BRONCHIAL CHALLENGE PROTOCOL

All children attending to take part in the study were seen in the afternoon. Subjects taking medication for asthma had abstained from treatment in accordance with standard protocols. All children were free of inter current respiratory illness for at least four weeks prior to their appointment. The nature and outline of the tests are explained to both the child and parents. Following this the weight and height of the child was ascertained using standard ward scales (Avery, Birmingham UK). On returning to the challenge laboratory the child was seated for a half hour rest period and at the start of which a transcutaneous oxygen electrode (Drager Transoxode) was applied to the medial aspect of the non-dominant upper arm (figure 2).
3.4.1 SPIROMETRIC ASSESSMENT

During the rest period, base-line ventilatory function was assessed using an Erich Jaeger pneumoscreen II spirometer. The subject was seated with their nose clipped. They were then instructed to inhale to inspiratory capacity and then to forcibly exhale for as long and as hard as possible (figure 3). The investigator demonstrated the method and then the child was observed to ensure that technique was acceptable. The blows were repeated until reproducible readings were obtained, that is flow volumes within 100mls of each other. This was the standard suggested by the American Thoracic Society. The spirometer produced a hard copy after each blow that allowed visual inspection of the flow volume curve; this in turn allowed an assessment to be made of how long forced expiration had
been sustained. The data from children whose flow volumes were outside this range or who were unable to exhale for long enough (at least 0.5 of a second) were excluded from analysis.

3.4.2 PEAK FLOW ASSESSMENT

All children used the same type of mini Wright peak flow meter (Clement Clarke). The child was separately shown the correct measurement techniques as follows. Children were instructed to hold the device horizontally whilst standing up. The pointer was returned to the bottom of the scale. Subjects then inhaled to as near total lung a full capacity as possible, put their lips tightly around the mouthpiece of the device and exhale as quickly as possible. Acceptable technique was deemed to have occurred when repeatable values were obtained. The best of the three technically satisfactory blows was taken as representing the peak flow for that time. The subjects were observed carefully to ensure that they had mastered the technique and were able to repeatedly exhale with sufficient force and speed.
Figure 3 - use of the pneumoscreen
Both MEF$_{25-75}$ and PEF were expressed as a percent of the value predicted (Zapletal, Paul and Samanek, 1997; Wille and Svensson, 1989). Each subject was examined during the rest period clinically with particular reference to the respiratory system. The presence or absence of cough and nasal discharge was noted; any skin rash (particularly eczema) was observed. The configuration of the thorax was observed for any deformity and percussed. Auscultation was carried out in all areas to pick up wheeze. Finally the ears, nose and oropharynx were examined (see appendix 2). Any child with audible wheeze was excluded from bronchial provocation with inhaled methacholine.
Once the signals from the transcutaneous oxygen electrode had stabilised a finger clip oxygen saturation probe (Ohmeda) was applied to the index finger of the subjects non-dominant hand. At one-minute intervals for six minutes the values of arterial oxygen saturation ($\text{SaO}_2$) and transcutaneous oxygen tension ($\text{tc-pO}_2$) were recorded. The six values of $\text{tc-pO}_2$ and $\text{SaO}_2$ were then averaged to establish a baseline for these readings prior to the inhalational challenge. The endpoint was then calculated for $\text{tc-pO}_2$, which was a 20% decrease from the initial mean value.

The protocol for inhalational challenge was explained to the child and then commenced. Phosphate-buffered saline containing increasing doses of methacholine chloride was aerosolised using a Wright's nebuliser. The device was driven by air at a rate of 10 litres per minute from a cylinder to produce an output of 0.12mls/min. The aerosol was inhaled during tidal breathing through a mask held loosely over the subject's mouth. The nose was clipped during the two-minute inhalation period (figure 5).
At the end of the period of inhalation the nose clip was removed and the subject rested for one minute before commencing the measurement period. During the two-minute measurement period the minimum value of transcutaneous oxygen tension and the corresponding arterial oxygen saturation was noted. Following this the whole process was repeated with doubling concentrations of methacholine. All subjects were given an initial dose of phosphate buffered saline to control for the effect of this carrier on airway calibre during the challenge. The whole protocol was repeated until the tc-pO₂ had decreased to equal or less than the calculated endpoint.

When then endpoints were attained then clinical status of the subject was noted (coughing, and/or wheeze). Following this the peak flow was recorded as the best of three technically good blows. The subject was then administered 2.5mg salbutamol via a normal
medical nebuliser (Micro-med) with $O_2$ as the driving gas at a flow rate of 6 litres per minute. This was given for a period of 5 minutes during which time the patient inhaled the salbutamol via a facemask (figure 6).

Figure 6 administration of salbutamol via nebuliser and mask
The provoking concentration of methacholine that produced a 20% decrease from baseline values of tc-pO₂ \( (PC_{20}tc-pO_2) \) was derived from the dose response curve obtained.

### 3.5 SKIN PRICK TESTING

After the salbutamol inhalation a 15 minute rest period followed and during this time skin prick testing according to Pepys method (Pepys, 1975) was carried out. The technique was explained to the subject and administered as follows. Ink dots were placed on the skin on the volar aspect of the forearm. Each test was performed in triplicate and six solutions were applied; negative control, cat dander, dog dander, Dermatophagoides pterynismus, mixed grass pollens and histamine. By each ink dot a drop of the test solution was applied to the skin and a 25-gauge needle was introduced at an angle of 45 degrees through the droplet until it was felt to contact the epidermis. It was then lifted directly upward, pulling the skin up slightly in the process. Three such scratches were applied for each allergen and the droplets of test solution were dried off within twenty seconds of each scratch. Subjects were designated atopic if they responded by producing a weal of size 2mm or greater in response to 1 or more of the allergens tested (Bencard Allergens, Bencard, Essex, UK) within the time frame of 5 to 15 minutes, and were of at least the same size as the weal produced in response to histamine control solution (concentration 1mg/ml). Hence a subject producing a weal of size of 2mm or greater in response to dog dander but not responding to anything else would be designated atopic, whereas another who produced 1mm weals in response to all allergens would be deemed
to be non-atopic. One-millimetre weals were felt to be too sensitive as they may be produced by the traumatic action of the needle puncturing the top layer of epidermis. This response may not be indicative of atopy, but of a non-specific response to trauma. As the population under study was relatively young it was felt that using a 3mm cut off may be too insensitive to detect atopic responses. Hence the size of weal 2mm or greater was selected to ensure a reasonable compromise between sensitivity and specificity of the technique. This size cut-off has been used by other investigators looking at populations of similarly aged children elsewhere (Martinez, Wright, Taussig, Holberg, Halonen and Morgan, 1995).

After the 15-minute rest period had expired a final measurement of tc-pO₂ and peak flow were made, together with a last assessment of any reaction to the skin prick tests. The former insured that all parameters of lung function had returned to normal following the challenge.

The Child and parent were then thanked for their help and the subject was presented with a certificate to commemorate their visit (appendix 3). The trancutaneous probe was then removed from the arm and checked to exclude excessive drift (>15mm Hg).
3.6 PEAK FLOW AND SYMPTOM DIARY

Parents attending the study with their children were asked to help complete peak flow and symptom diary cards. The aim of assessing peak flow variability and symptoms was explained to the parent and the technique for measuring peak flow demonstrated. All children used the same type of Mini Wright peak flow meter (Clement-Clarke). The child was separately shown the correct measurement technique as follows. Children were instructed to hold the device horizontally whilst standing up. The pointer was returned to the bottom of the scale. Subjects then inhaled to as near total lung capacity as possible, put their lips tightly around the mouthpiece of the device and exhaled as quickly as possible. The best of three technically satisfactory blows was taken as representing the peak flow for that time. Peak flow was assessed prior to the inhalational challenge, at the time of maximum broncho-constriction and finally 15 minutes after the inhalation of salbutamol.

Peak flow diaries were kept for 14 days after the initial appointment and peak flow was measured at three times during the day; 8am, 4pm and 8pm. The importance of adhering closely to these times was stressed to the parents at the outset of the study and parents were instructed to miss measurements of peak flow if they could not be made within half an hour of the times allocated. The symptoms for each day were noted as the presence or absence of the following five; cough, wheeze, shortness of breath, nocturnal symptoms and illness causing school absence.
3.7 OVERNIGHT HOME MONITORING STUDIES

Following the visit to hospital all subjects were visited at home by a research nurse. The visit was timed to occur during the two-week period of peak flow and symptom diary completion. At this visit the child’s technique of making repeatable peak flow measurements was assessed, together with inspection of the diary. Any child with poor technique during either the initial appointment or on assessment at home was noted and the peak flow data discarded. During the visit a domestic questionnaire was completed to provide details about the child’s physical home environment (form of heating, presence of damp/mould) indices of crowding, socio-economic information, exposure to environmental tobacco smoke and family history of respiratory, atopic and asthmatic disease (appendix 4).

3.7.1 DETECTING AND ANALYSING COUGH

A Uhertape recorder was installed in the child’s bedroom connected to the cough monitor and thence to two uni-directional microphones mounted at the head of the bed. These microphones detected noises made by the child during sleep (figures 7 and 8).

The cough monitor was a device used for compressing the events overnight on to a reel to reel tape machine. The device worked by triggering the reel to reel recorder when a noise of critical decibel threshold was exceeded. The cough monitor captured the noise recorded by the microphones and stored it temporarily by sending it around an electronic
loop whilst the tape recorder switched on and got up to speed. At the same time a clock in
the monitor electronically recorded the time and length of the event recorded on the reel to
reel tape. The cough monitor stopped the tape once the event had finished.

All equipment was returned to the laboratory where the tape was analysed using BBC
computer software (Hedgehog version 1.00). This programme searched the tape for
triggering episodes and displayed the timing. The episodes identified were then replayed
to the listener. If the episode consisted of a cough or series of coughs, this could be
registered in the programme. If the episode consisted of some other noise (for example
throat clearing or extraneous noises) then this episode could be skipped and not
registered as a cough event by the programme. At the end of the tape the software
generated a report of all entered and validated cough episodes together with the
appropriate timings and the length of each episode. As each episode had been listened
to, the number of coughs occurring during each episode was also noted. In this way, the
number of cough episodes per hour overnight and the total number of coughs heard in
that hour were recorded.
figure 7 - microphones to detect night cough
The cough monitor was a device for triggering the Uher to record loud noises and then switch off the recorder after cessation of the noise. In addition a clock mechanism electronically encoded the precise time of the event onto the tape.
The device was adjustable to allow sufficient sensitivity to detect cough without triggering indiscriminately to sounds of low volume. Sensitivity was set by allowing the child to practice coughing and allowing the child to sing whilst lying on the bed prior to the study. At the same time a saturation probe was placed under the bed together with a data logger to record saturation, pulse rate and relative air humidity at one-minute intervals over the course of the night (figure 10).
A second data logger recorded ambient room temperature at the same rate. Transcutaneous arterial oxygen saturation was recorded by taping a finger probe to the child's finger and running the lead up the arm of the child's nightgown (figure 10).
The lead emerged under the upper part of the subject's nightclothes (e.g. at bottom of pyjama jacket) and from there was connected to the saturation probe. The parents were shown how to disconnect the probe from the saturation monitor in order to allow the child to get out of bed during the night if this became necessary. The following morning the equipment was collected by the research nurse and the domestic part of the questionnaire was completed at this time. For the purposes of the study, night cough was defined as the
presence of at least one episode of multiple coughing. This excluded children with repeated episodes comprising a single cough. After this the data loggers were downloaded using appropriate software (Squirrel data, Grant instruments, Cambridge). In this case the software displayed graphs of the recorded pulse rate, arterial oxygen saturation, temperature and relative humidity. These were visually inspected to ensure that the study was of sufficient length and technically satisfactory. The saturation record was analysed using purpose-designed software which excluded saturation readings recorded when a low pulse rate was recorded in order to exclude erroneously low readings due to poor probe contact. However, little data were lost from the studies in this way. The data were then saved and subsequently uploaded to a data acquisition program (SAS).

At the end of the two week study period diary cards and peak flow meters were returned to the investigator by wrapping the diary sheet around the meter and then returning the meter in its cardboard cylinder through the post using a freepost address label.

3.8 DATA ENTRY

Once all information regarding a child had been collected the questionnaire data were first numerically encoded using a data manual (see appendix 5). Thus dichotomous answers were translated into 1's or 0's and inapplicable and missing fields, as well as those answered as "don't know" were assigned the appropriate numeric values and entered onto a data entry sheet. The numeric values arising from the physiological studies were entered directly onto the sheet as were the peak flow measurements from the returned
diary cards. The symptom diary was scored with each receiving a value of 1 for each day it was recorded. For instance, a child reporting 4 days of wheezing out of 14 would get a score of four. The completed data sheets were entered onto the mainframe Unix computer operated by the University of Leicester computer centre using a data capture program which produced the data files subsequently used for analysis.

3.9 THE ASSESSMENT OF REPEATABILITY

As the questionnaires used in both the 1990 study and the follow up study were very similar and the key questions were identical, it was possible to assess the long-term repeatability of questions concerning wheeze, recurrent cough and asthma diagnosis. To assess the short-term repeatability of the same questions and of the measures used in the follow-up study, 30 children were asked to re-attend to repeat the entire study protocol. Subjects were selected equally from each symptom group. The short-term repeatability was assessed in 30 children. These were divided into three groups: Ten children were seen within six months of their original follow up. Another group was seen between six months to one year after follow up. The last 10 were seen between one and two years after follow-up. The precise length between initial follow-up and the repeatability study is shown in a table 2.2. The mean interval between attending the study and participating in the reproducibility exercise was 9 months with a range of 1 to 20 months.
Table 2.2 LENGTH OF TIME BETWEEN FOLLOW-UP AND SHORT-TERM REPEATABILITY STUDY

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<td>2</td>
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<td>12</td>
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<td>1</td>
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<tr>
<td>13</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
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<tr>
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<td>16</td>
<td>2</td>
</tr>
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<td>16</td>
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<tr>
<td>28</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>29</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>20</td>
<td>3</td>
</tr>
</tbody>
</table>
3.10 TRANSCUTANEOUS OXYGEN MEASUREMENT

This technique for measuring arterial oxygen tension has been used for many years in the neonatal intensive care setting. It is a particularly attractive technique of assessing changes in oxygen tension because its measurement is closely correlated with, and rapidly responsive to, changes in arterial PaO₂; further it provides continuous information and is non-invasive. This apparatus has been applied to detect changes in arterial oxygen tension which result from response to inhalational challenge with methacholine. This is the only method for determining bronchial responsiveness that is totally independent of subject effort and requires no co-operation. These properties mean that the technique is extremely useful in children who are too young to co-operate in the lung function tests conventionally employed in the measurement of this index.

3.10.1 THEORY OF TRANSCUTANEOUS OXYGEN MEASUREMENT

Under normal conditions, the diffusion of oxygen from the skin capillaries through the epidermis is very small, and transcutaneous oxygen tension (tc-pO₂) is negligible. If however the skin is heated, then local vasodilatation causes hyperaemia of the skin and in addition heat causes increased permeability of the skin to oxygen. The transcutaneous oxygen tension soon equalises with partial pressure of oxygen (PaO₂) in the skin capillaries. After some minutes the hyperaemia ensures that the PaO₂ of the arterialised superficial vessels equalises with that of the central arteries, and hence tc-pO₂ closely correlates with the arterial PaO₂.
Measurement of transcutaneous oxygen tension is by polargraphic means using an electro-chemical electrode chain. The basic principle of polargraphic measurement is that when a constant electrode potential (voltage) is applied between suitable electrodes placed in the appropriate electrolyte solution, the magnitude of the current is proportional to the concentration of oxygen in solution. Hence this apparatus can be adapted to measure the diffusion of oxygen from the skin surface and therefore tc-pO₂. This consists of a platinum sensor electrode (the cathode) and a reference electrode (anode). The current generation occurs by reduction of oxygen at the cathode surface,

\[ \text{O}_2 + 2\text{H}_2\text{O} + 4e^- \rightarrow 4\text{OH}^- \]

with the following reaction occurring at the anode,

\[ 4\text{Ag} + 4\text{Cl}^- \rightarrow 4\text{AgCl} + 4e^- . \]

The current is dependent not just upon the concentration of the dissolved oxygen but also upon the diffusion characteristics of the solution. To stabilise diffusion conditions the cathode is covered with a thin membrane through which the oxygen diffuses and is then consumed by the electrode. The modified electrode therefore consists of a platinum cathode and silver anode, both covered by an oxygen permeable, hydrophobic membrane. A reservoir of electrolyte containing buffer, with an admixture of chloride ions that serve to stabilise the reference electrode, is contained between the electrodes and membrane. This is referred to as a Clark-type oxygen electrode. The silver anode is used
to conduct heat generated by an element through the apparatus to the skin via a contact gel, which arterializes the skin capillaries.

3.10.2 HISTORICAL REVIEW OF TRANSCUTANEOUS OXYGEN MEASUREMENT

Baumberger and Goodfriend (1951) observed that by immersing a finger into phosphate buffer solution heated to 45 degrees, the oxygen tension in the buffer equilibrated with the arterial oxygen tension within 15-60 minutes. The oxygen tension of the solution was determined poligraphically. In 1967 Evans and Naylor used a modified Clarke-type electrode to show that the permeability of human skin to oxygen was low; in adults the skin oxygen tension was 3.5mm Hg. These findings were confirmed by other workers (Huch and Lubbers, 1972). Huch et al (1973) reported on the use of a Clarke-electrode modified to heat the skin thereby producing local hyperaemia. In these circumstances they were able to show that transcutaneous oxygen could be continually monitored and that it correlated highly with simultaneous measures of arterial $P_{aO_2}$. Again this work was confirmed by others (Peabody, Gregory, et al, 1978) and showed that the two measures were linearly related over a wide range of $P_{aO_2}$ values. The technique has largely been confined clinically to the non-invasive assessment of oxygenation in neonatal intensive care units and is currently much used in this clinical area. The technique has been shown to produce reliable estimates of $P_{aO_2}$ in intensive care units when applied to children beyond the neonatal period (Vyas, 1988) providing that the patients undergoing monitoring were haemodynamically stable. Subsequent to this a Japanese group reported using the same technique to detect changes in oxygenation produced in response to
bronchoconstricting agents inhaled by pre-school children (Mochizuko et al, 1985). The group were able to show that changes in oxygenation were not due to local vasoconstriction. This work was confirmed by others (Wilson, Phagoo and Silverman, 1991; van Broekhoven et al 1991) who also compared the change in tc-pO2 with other indices of ventilatory function. Silverman’s group compared the change with total respiratory resistance, measured using a pseudo-random forced oscillation technique and found that a 20% decrease in tcPO2 correlated closely with a 40% rise in total respiratory resistance. Van Broekhoven’s (1991) group compared changes in FEV1 and tc-pO2. In their study of 51 children (mean age 8.7 years) they found that a 20% decrease in FEV1 correlated closely with an equivalent decrease in tc-pO2. Silverman’s group found it to be the most reliable method of recording responsiveness to inhaled methacholine in five year olds (Wilson, Bridge, Phagoo and Silverman, 1995)

3.11 STATISTICAL ANALYSIS

Statistical analysis was carried out in SAS (Statistical analysis software. Cary, North Carolina: SAS Institute Inc, 1985) and S plus (Becker, Chambers and Wilks, 1988). Comparison of quantitative outcomes between groups was based upon one-way analysis of variance or upon t-tests (Armitage and Berry, 1987). Where necessary, normality and homoscedasticity were assessed prior to analysis. Wherever appropriate, data were summarised using means and 95% confidence intervals, and for the purposes of clarity, the quoted confidence intervals are always enclosed in square parentheses. Categorical data were presented using contingency tables and formal statistical inference was based upon the chi-squared test for homogeneity (without continuity correction) (Armitage and
Berry, 1987). The 95% confidence interval for a proportion was obtained using the standard normal approximation for the standard error of a proportion (Armitage and Berry, 1987). For proportions based upon small numbers, exact 95% confidence intervals were obtained and Fisher's exact test (Armitage and Berry, 1987) was used to formally test for non-homogeneity. The repeatability of binary outcomes was assessed using percentage agreement and more formally by Cohen's Kappa statistic. (Armitage and Berry, 1987). The repeatability of continuous variables is presented graphically and was quantified using the intra-class correlation coefficient (ICC) (Clayton and Hills, 1993). Where necessary, modelling using standard multiple linear regression (Armitage and Berry, 1987) was used to investigate the joint influence of a number of correlated explanatory covariates upon a quantitative response (dependent) variable and multiple logistic regression (Clayton and Hills, 1993) was used when the response variable was binary. Modelling was performed in S-plus (Becker, Chambers and Wilks, 1988). Model construction was based upon the systematic addition of covariates to an initial null model. Formal tests of significance of the improvement of fit following the addition of the regression terms relating to specific variables were based upon the likelihood ratio test (McCullagh and Nelder, 1989). Before drawing definitive conclusions the model was subjected to standard model checking procedures, including tests for non-linearity and interaction, the analysis of Pearson residuals and the investigation of leverage (McCullagh and Nelder, 1989). In order to alleviate the problem of rounding errors, all multivariate analyses centralised the age at original study and follow-up time around three years. This means that three was subtracted from these two variables.

The rational for the statistical methods used in the study are outlined below:
3.11.1 CHI SQUARED ($\chi^2$)

This is a method for comparing the distribution of a discrete variable in a group to the distribution of a discrete variable in another group in order to determine whether it is likely that the differences in the distributions between the two samples occur systematically or by chance. For example in our study we may want to see if the prevalence of wheeze at follow-up is higher in previously wheezy children compared to children who were previously asymptomatic. The null hypothesis in this instance would be that there was no difference in the proportions with current wheeze between the two groups. The test calculates the expected frequencies which would occur if this were the case and by comparing this with the observed frequencies calculates a value for $\chi^2$ which has a corresponding probability (P value) depending on the size of the contingency table (and therefore the degrees of freedom). In this study P values of less than or equal 0.05 were taken as being statistically significant. The arbitrary nature of this cut-off point should, however, not be forgotten. Certain assumptions are made for this test, namely that data must be frequency data, there must be an adequate sample size, measures must be independent of each another and there must be some theoretical basis for the categorisation of the variables.

Yates continuity correction was not applied to the chi squared test. This is an adaptation of chi squared where the test is to determine whether the observed frequency or a more extreme frequency than that predicted by the null hypothesis is likely to occur or not. It is in some ways similar to the exact test outlined below and in practice yields a lower value for
chi squared for the same degrees of freedom. This practice follows the recommendation of Armitage and Berry (1987).

3.11.2 ODDS RATIOS

A way of quantifying the association between categorical variables arranged in two by two type tables is to compare the two groups with respect to a particular outcome dependant upon the presence or absence of a particular risk factor. The odds of the pertinent outcome in the exposed and non-exposed groups are calculated and the ratio between the two expressed. A confidence interval can be obtained using the standard error of the logarithm of the odds ratio. An increased risk is signified by an odds ratio (and its corresponding confidence interval) of greater than one whilst reduced risk is indicated by a ratio less than one. As the outcomes in this study (i.e. wheeze or cough) are common in relation to the general population, the odds ratio obtained does not approximate to the relative risk.

3.11.3 EXACT PROBABILITY TEST

This test is a way of analysing contingency tables when the observed frequencies are small and therefore the use of $\chi^2$ is invalidated. The use however is exactly the same, namely an attempt to see if the observed frequencies seen in samples differ systematically or merely result from sampling error. In this instance the exact probability of getting the observed frequency, or a more extreme frequency is calculated. This method
assumes that the column and row totals in the table are fixed and that the data are independent. As the name of the test suggests, an exact value of $P$ is calculated.

### 3.11.4 COHEN'S KAPPAN ($\kappa$)

This method formally tests the agreement of either different methods of assessing the same categorical variable or the agreement in assessment of a categorical variable at different times. This tests whether the observed percentage agreement exceeds the percentage agreement that would be expected to occur by chance. The statistic is a ratio with complete agreement represented by 1.0 and no agreement beyond chance corresponding to 0. Good agreement beyond chance is arbitrarily classified as a $\kappa$ of greater than 0.4.

### 3.11.5 INTRACLASS CORRELATION COEFFICIENT (ICC)

This test measures the repeatability of continuous measures by assessing the correlation between observations on the same person. Whilst it is recognised that there are differences in measurement between individuals (the between person variability) a highly repeatable test will (providing the subject's response remains constant) yield little within person variability. This test derives the within person variability and the between person variability. The intraclass coefficient (ICC) is expressed as the ratio of the between person variability to that of the between-person variability plus the within person variability. Perfect
repeatability is therefore represented by a ratio of 1.0 and merely chance repeatability by 0.0. Acceptable values for ICC are arbitrarily taken to be above 0.5.

3.11.6 STUDENT'S T TEST

This test compares whether the mean value of a normally distributed continuous variable in one group is systematically different from that found in another, or whether such differences merely reflect sampling error. For example in this study we may want to see if peak flow variability is higher in previously wheezy children compared to those who were previously asymptomatic. With a knowledge of the means, number of observations and the standard deviations of the variable measured in the two samples a value of t may be computed and this value has a corresponding probability, depending on the degrees of freedom (equivalent to the number of observations - 1 in each sample). This test can only be used to compare quantitative outcomes between two groups.

3.11.7 ONE-WAY ANALYSIS OF VARIANCE (ANOVA)

This test compares quantitative outcomes between three or more groups to compare whether the mean value of a normally distributed continuous variable in one group is systematically different from that found in another, or whether such differences merely reflect sampling error. In this case, the number of observations, means and variances, of each group under consideration are computed. In this way, the within group variance is calculated and compared to the between group variance (calculated by analysing the
differences between the group means and the pooled mean of all the groups). If the null hypothesis is true, then the between group variance will be of similar magnitude to the within group variance. A ratio between these two variances is expressed as the \( F \) statistic. Its associated probability is dependent on the degrees of freedom associated with the two contributing variances.

### 3.11.8 MULTIPLE LINEAR REGRESSION

This technique of statistical modelling examines the relationship between a single quantitative dependant variable and many quantitative explanatory (sometimes called independent) variables. The advantage of this method is that the independent effect of many factors upon the variable of interest (for example, level of bronchial responsiveness) may be analysed whilst taking into account the other important factors. The relationship is quantified by computing partial correlation coefficients for each term and hence gives an idea of the magnitude of the effect of the explanatory variable on the dependant variable when the other factors are held constant. The completed model should be parsimonious and hence contain the minimum number of important terms (explanatory variables) sufficient to account for the maximum amount of the observed variation in the dependant variable. Removal of the explanatory terms will result in a deterioration of fit of the data to the remaining model and the size of this deterioration is used to test the statistical significance of the effect of the explanatory variables (likelihood ratio test). Such modelling has the additional advantage of allowing the synergistic effects of explanatory factors to be investigated by testing for interactions between factors. It can also detect whether the effect of one explanatory factor masks or obscures that of another (confounding). All
models are checked to ensure that they are in fact representative of the observed data (model checking).

3.11.9 MULTIPLE OR UNCONDITIONAL LOGISTIC REGRESSION

This is a similar modelling technique to that of multiple linear regression but in this case the technique is used to assess the relationship between explanatory variables and a binary (qualitative) dependant variable. Such a variable can be either 0 (not present) or 1 (present). This technique works by logistic transformation of the dependant variable so that regardless of the effect(s) of the explanatory variables, it is constrained to lie between 0 and 1. In this way the partial correlation coefficients are computed as log-odds ratios and can be transformed back to a probability for ease of interpretation. The same advantages and rules of parsimony as for multiple linear regression apply, together with the same requirements for model testing.

3.11.10 WILCOXON RANK SUM TEST

This is a test for comparing the medians of quantitative, non-parametrically distributed data from two groups. This method makes no assumptions concerning the distribution of the data and is based upon first pooling and then ranking the data from the two groups in increasing magnitude. The distribution of the rankings is then compared between the two samples. If there is no difference between the two groups (the null hypothesis) then the sum of the ranks will be very similar and any differences present will merely be due to
sampling error. If a large difference is obtained then it is likely that the samples are truly different. The rank sum value conforms to a probability distribution, rather like that of 't' or 'chi squared'. The value of rank sum appropriate to the sample size may be looked up in a table and has a level of probability associated with it.
CHAPTER FOUR

RESULTS
4.1.1 RESPONSE RATE AND BASELINE DEMOGRAPHY

Of the 347 asymptomatic children, 222 wheezers and 226 coughers invited to participate in the follow-up study, 145 (42%), 114 (51%) and 93 (41%) attended respectively. As non-attenders were mailed the follow-up questionnaire, we were able to investigate follow-up symptoms alone in a further 68 (20%) asymptomatic children, 31 (14%) wheezers and 37 (16%) coughers. The age distribution of these subjects in 1990 is shown in table 4.1.

Table 4.1: Age at original survey of those followed up

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>48</td>
<td>9.8</td>
</tr>
<tr>
<td>1-2</td>
<td>83</td>
<td>17.0</td>
</tr>
<tr>
<td>2-3</td>
<td>95</td>
<td>19.5</td>
</tr>
<tr>
<td>3-4</td>
<td>122</td>
<td>25.0</td>
</tr>
<tr>
<td>&gt;4</td>
<td>140</td>
<td>28.7</td>
</tr>
<tr>
<td>all</td>
<td>488</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Therefore, the overall response for the questionnaire was 61% for asymptomatic children, 65% for wheezers and 58% for coughers. Demographic and anthropometric data are shown in table 4.2.
Table 4.2. Demographic and anthropometric details of cohort.

<table>
<thead>
<tr>
<th>Description</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at original survey [range] in years</td>
<td>3.0 [0.3 to 5.4]</td>
</tr>
<tr>
<td>Mean age at follow-up [range] in years</td>
<td>6.1 [3.9 to 8.8]</td>
</tr>
<tr>
<td>Mean follow-up time [range] in years</td>
<td>3.0 [1.8 to 4.1]</td>
</tr>
<tr>
<td>Number (percentage) of boys</td>
<td>248 (50.8%)</td>
</tr>
<tr>
<td>Number (percentage) of girls</td>
<td>240 (49.2%)</td>
</tr>
<tr>
<td>Mean height [range] in metres*</td>
<td>1.17 [0.98 to 1.35]</td>
</tr>
<tr>
<td>Mean weight [range] in kilogrammes*</td>
<td>22.1 [15.0 to 40.0]</td>
</tr>
</tbody>
</table>

*There were no significant differences between the pre-school symptom groups.
**Table 4.3** FOLLOW-UP SYMPTOM PROFILE OF CHILDREN ATTENDING FOR STUDY COMPARED TO THOSE WHO ONLY RETURNED UPDATE SYMPTOM QUESTIONNAIRE

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Attended full study</th>
<th>Completed questionnaire only</th>
<th>χ²</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No symptoms</td>
<td>216 (62%)</td>
<td>97 (75%)</td>
<td>13.659, p=0.001</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>70 (20%)</td>
<td>8 (6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>65 (18%)</td>
<td>24 (19%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>351</td>
<td>129</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without eczema</td>
<td>223 (64%)</td>
<td>103 (76%)</td>
<td>6.224, p=0.013</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With eczema</td>
<td>126 (36%)</td>
<td>33 (24%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>351</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without doctor-diagnosed asthma</td>
<td>270 (77%)</td>
<td>117 (86%)</td>
<td>4.981, p=0.026</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With doctor-diagnosed asthma</td>
<td>81 (23%)</td>
<td>19 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>351</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother smokes</td>
<td>255 (74%)</td>
<td>91 (70%)</td>
<td>0.855, p=0.355</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother does not smoke</td>
<td>91 (26%)</td>
<td>40 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>351</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father manual worker</td>
<td>162 (52%)</td>
<td>70 (58%)</td>
<td>1.358, p=0.244</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father non-manual worker</td>
<td>149 (48%)</td>
<td>50 (42%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>351</td>
<td>120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father smokes</td>
<td>225 (70%)</td>
<td>74 (60%)</td>
<td>4.172, p=0.041</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Father does not smoke</td>
<td>95 (30%)</td>
<td>49 (40%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>351</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>351</td>
<td>131</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural domicile</td>
<td>214 (61%)</td>
<td>67 (49%)</td>
<td>5.340, p=0.021</td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>352</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban domicile</td>
<td>138 (39%)</td>
<td>69 (51%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N (%)</td>
<td>352</td>
<td>136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>352</td>
<td>136</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.3 indicates that the non-attending group had systematically more favourable outcomes with respect to wheeze than the attending group. The diagnosis by a doctor of asthma was also more common in the attending group as was a history of eczema. Due to small numbers of non-attenders who wheezed at follow-up, differences in the wheeze severity indices of the two groups could not be meaningfully examined. Scrutiny of demographic and environmental factors showed that there was little difference in the exposure to environmental tobacco smoke from maternal smoking between the two groups, paternal occupation in a manual or non-manual job.

Differences between the groups were more apparent when considering exposure to paternal smoking or urban/rural domicile.

4.1.2 REPEATABILITY

4.1.2.i Questionnaire

Tables 4.4 and 4.5 show the long and short-term repeatability of key questions concerning respiratory symptoms and assessment of atopy. It can be seen that the questions concerning wheeze and asthma show good repeatability in both the short and long-term. The questions concerning cough were not as repeatable, showing only a moderate value for the Cohen's Kappa statistic.
Table 4.4. **Long Term Repetability of Follow-up Study; Comparing Responses Between 1990 Questionnaire and Follow-up Questionnaire (1992-1994)**

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>Percentage Agreement</th>
<th>Cohen's Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has your child ever had attacks of wheezing?</td>
<td>88.2%</td>
<td>0.87</td>
</tr>
<tr>
<td>Has your child coughed without a cold in the past?</td>
<td>71.6%</td>
<td>0.38</td>
</tr>
<tr>
<td>Has any doctor or hospital told you that he/she has asthma?</td>
<td>85.4%</td>
<td>0.64</td>
</tr>
</tbody>
</table>

Table 4.5. **Short Term Repetability of Follow-up Study; Comparing Responses Between Subjects in Repeatability Study (N=30) Conducted During Follow-up Study**

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>Percentage Agreement</th>
<th>Cohen's Kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Has your child ever had attacks of wheezing?</td>
<td>86.7%</td>
<td>0.70</td>
</tr>
<tr>
<td>Does he/she usually have a cough without a cold?</td>
<td>76.7%</td>
<td>0.46</td>
</tr>
<tr>
<td>Has any doctor or hospital told you that he/she has asthma?</td>
<td>96.7%</td>
<td>0.93</td>
</tr>
</tbody>
</table>

**Physiological Measures**

| Atopic Assessment | 100.0% | 1.00 |

4.1.2.ii Physiological Measures

Assessment of atopic status was completely repeatable (Cohen's Kappa =1.0).

Assessment of the repeatability of the quantitative outcomes is shown in figure 1. Measurement of bronchial responsiveness proved highly repeatable, with the difference between the two occasions being less than one doubling dose in 19 out of 24 children (figure 1a; ICC=0.738). The reproducibility of MEF$_{25-75}$ proved to be acceptable (figure 1b; ICC=0.564) and PEF also exhibited good repeatability (figure 1c;
ICC = 0.615). Conversely, peak flow variability showed relatively poor repeatability (figure 1d; ICC = 0.230).

Figure 1a: Repeatability of assessment of responsiveness

$\log_2(\text{PC}_{\text{tcpO}_2})$

--- = line of perfect agreement
Figure 1b: Repeatability of assessment of initial peak flow

peak flow as percent of predicted

--- = line of perfect agreement
Figure 1c: Repeatability of assessment of MEF25-75

MEF25-75 as percent predicted
Figure 1d: Repeatability of assessment of peak flow variability

\[ \ln(\text{amplitude percent mean}) \]

--- = line of perfect agreement
4.1.2.iii REPEATABILITY OF SKIN PRICK TESTING

Repeatability of response to atopy was assessed using the same criteria to assign children as atopic as at their first visit. All children who were designated atopic originally at follow-up were atopic when re-tested. Children who did not respond to skin prick testing at follow-up again remained unresponsive when retested during the repeatability study. The repeatability of response to any one particular allergen was not analysed.

SEASONAL VARIATION

The time course of the follow-up study over two years throughout the year was designed to control for seasonal changes in atopic expression. In order to ensure that seasonal variation did not unduly influence the results, atopic expression (regardless of symptom group) was analysed in relation to the season during which the child was followed up.

Table 4.6 Expression of atopy in individuals by season of testing

<table>
<thead>
<tr>
<th>Season</th>
<th>Non-atopic (%)</th>
<th>N</th>
<th>Atopic N (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Winter (Dec-Feb)</td>
<td>48 (65%)</td>
<td>26</td>
<td>(35%)</td>
<td>74</td>
</tr>
<tr>
<td>Spring (Mar-May)</td>
<td>47 (71%)</td>
<td>19</td>
<td>(29%)</td>
<td>66</td>
</tr>
<tr>
<td>Summer (Jun – Aug)</td>
<td>49 (67%)</td>
<td>24</td>
<td>(33%)</td>
<td>73</td>
</tr>
<tr>
<td>Autumn (Sep-Nov)</td>
<td>44 (72%)</td>
<td>17</td>
<td>(28%)</td>
<td>61</td>
</tr>
</tbody>
</table>

This table demonstrates that the expression of atopy did not vary significantly between the seasons ($\chi^2 = 1.116; p=0.773$).
The following graphs (figure 4.2 and 4.3) show the prevalence of positive skin prick tests to the particular allergens tested by 1990 symptom status and symptoms at follow-up. Of the four allergens tested, the most prevalent reactions were to house dust mite, mixed grass pollens and cat dander.
Figure 4.2
Proportion of Subjects with Positive Skin Prick Tests by 1990 Symptom Group

Figure 4.3
Proportion of Subjects with Positive Skin Prick Tests by Symptoms at Follow-up
4.2.1 SYMPTOMS AT FOLLOW-UP

Table 4.7 shows the relationship between those symptoms reported in the pre-school age range and those found at follow-up. At follow-up 83.3% [95% CI 78.3% to 88.3%] of the 1990 asymptomatic group remained symptom free, however, 6.7% [3.3% to 10.1%] had started to wheeze and 10.0% [5.9% to 14.1%] reported recurrent cough. Just under half (46.9%[38.8% to 55.0%]) of the 1990 wheeze group had become entirely symptom free at follow-up while 37.9%[30.0% to 45.8%] reported continuing wheeze and 15.2% [9.4% to 21.0%] had stopped wheezing but reported recurrent cough. Over half (56.0% [47.3% to 64.7%]) of the 1990 cough group were symptom-free at follow-up, 7.2% [2.7% to 11.7%] reported current wheeze and 36.8% [28.3% to 45.3%] reported continuing cough.

Table 4.7 Symptom profile at follow-up.

<table>
<thead>
<tr>
<th>1990 SYMPTOMS</th>
<th>FOLLOW-UP SYMPTOMS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Asymptomatic</td>
<td>Wheeze</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>175 (83.3%)</td>
<td>14 (6.7%)</td>
</tr>
<tr>
<td>Wheeze</td>
<td>68 (46.9%)</td>
<td>55 (37.9%)</td>
</tr>
<tr>
<td>Cough</td>
<td>70 (56.0%)</td>
<td>9 (7.2%)</td>
</tr>
</tbody>
</table>

*Follow-up symptom-status was not available from 3/213 children from the asymptomatic group and 5/130 from the 1990 cough group.
4.2.2 The Relationship Between Symptom Status And Physiological Profile

As would be anticipated there were strong relationships between current symptoms and most of the physiological test results at follow-up (table 4.8).

Table 4.8 Relationship between symptoms at follow-up and physiological outcomes

<table>
<thead>
<tr>
<th>Physiological outcome</th>
<th>Current symptoms</th>
<th>asymptomatic</th>
<th>Wheezers</th>
<th>Coughers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PC_{20tc-PO},</strong></td>
<td>(log_2) mean (SD)</td>
<td>n=159</td>
<td>n=47</td>
<td>n=47</td>
</tr>
<tr>
<td>1.66 (1.08)</td>
<td>0.61 (1.51)</td>
<td>1.25 (1.19)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>F</em>_{2,250} = 14.46, <em>p</em>=0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEF_{26-75}</strong></td>
<td>mean (SD)</td>
<td>n=163</td>
<td>n=52</td>
<td>n=48</td>
</tr>
<tr>
<td>89.6% (23.2%)</td>
<td>77.4% (23.0%)</td>
<td>83.3% (24.2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>F</em>_{2,260} = 5.81, <em>p</em>=0.0034</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peak flow</strong></td>
<td>mean (SD)</td>
<td>n=176</td>
<td>n=50</td>
<td>n=55</td>
</tr>
<tr>
<td>106.8% (17.8%)</td>
<td>99.3% (18.4%)</td>
<td>103.6% (18.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>F</em>_{2,278} = 3.46, <em>p</em>=0.033</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>log_{10} amplitude percent</strong></td>
<td>mean (SD)</td>
<td>n=155</td>
<td>n=43</td>
<td>n=50</td>
</tr>
<tr>
<td>2.29 (0.52)</td>
<td>2.42 (0.51)</td>
<td>2.45 (0.48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>F</em>_{2,246} = 2.42, <em>p</em>=0.091</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>proportion with atopy</strong></td>
<td>no/tota l (%)</td>
<td>39/168 (23.2%)</td>
<td>29/54 (53.7%)</td>
<td>18/52 (34.6%)</td>
</tr>
<tr>
<td><em>χ^2</em> = 17.95, <em>p</em>&lt;0.0001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
However, the relationships of greatest interest were those between 1990 symptoms and physiological measures at follow-up and these were generally less well-defined (table 4.9). Nevertheless, there was a strong association between 1990 symptoms and bronchial responsiveness to inhaled methacholine at follow-up ($F_{2,251}=10.73$, $P=0.0001$). Children who were asymptomatic in 1990 had the least responsive airways with a geometric mean of $3.39\text{mg/ml} \ [2.94\text{mg/ml} \text{ to } 3.91\text{mg/ml}]$; $3.39=2^{1.76}$ (see table 4.9). Children with reported wheeze in 1990 recorded the lowest geometric mean of $1.91\text{mg/ml} \ [1.54\text{mg/ml} \text{ to } 2.35\text{mg/ml}]$, while children who were reported to cough in 1990 had an intermediate level of responsiveness with a geometric mean of $2.62\text{mg/ml} \ [2.18\text{mg/ml} \text{ to } 3.16\text{mg/ml}]$. Although the associations between 1990 symptoms and $\text{MEF}_{25-75}$ were not formally significant ($F_{2,261}=1.61$, $P=0.202$), the biological gradient was again in the same direction. An equivalent non-significant relationship was also found for $\text{PEF}$ as a percent of predicted ($F_{2,279}=1.70$, $P=0.186$). On the other hand, peak flow variability as measured by the $\log_e$ amplitude percent mean was very similar in all three 1990 symptom groups ($F_{2,246}=0.11$, $P=0.895$).
Table 4.9. Physiological profile of subjects attending follow-up

<table>
<thead>
<tr>
<th>1990 SYMPTOM GROUP</th>
<th>Asymptomatic</th>
<th>Wheeze</th>
<th>Cough</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Log2 of PC20 tC-P02</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>n=87</td>
<td>1.63 (0.99)</td>
<td>1.09 (1.64)</td>
<td>1.36 (1.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.100=1.97, p=0.145</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>n=37</td>
<td>1.23 (1.23)</td>
<td>0.43 (1.50)</td>
<td>1.45 (1.35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.79=3.98, p=0.023</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>n=35</td>
<td>1.67 (1.04)</td>
<td>1.05 (1.50)</td>
<td>1.11 (1.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.65=2.21, p=0.118</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>MEF25-75 as percentage of predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>n=92</td>
<td>89.8 (23.8)</td>
<td>86.0 (36.7)</td>
<td>84.1 (26.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.100=0.30, p=0.743</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>n=42</td>
<td>91.6 (20.8)</td>
<td>73.6 (18.9)</td>
<td>83.1 (31.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.87=7.01, p=0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>n=29</td>
<td>86.3 (25.3)</td>
<td>90.1 (20.6)</td>
<td>83.1 (21.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.68=0.28, p=0.759</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Peak Flow as percentage of predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>n=97</td>
<td>106.1 (16.3)</td>
<td>105.4 (30.5)</td>
<td>112.3 (26.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.112=0.53, p=0.590</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>n=40</td>
<td>108.5 (18.0)</td>
<td>97.4 (15.8)</td>
<td>96.0 (20.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.86=4.76, p=0.011</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>n=39</td>
<td>106.6 (21.1)</td>
<td>102.9 (12.9)</td>
<td>104.0 (13.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.74=0.25, p=0.783</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Loge of amplitude percent mean</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>n=85</td>
<td>2.34 (0.51)</td>
<td>2.33 (0.92)</td>
<td>2.44 (0.18)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.97=0.18, p=0.836</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wheeze</td>
<td>n=34</td>
<td>2.13 (0.55)</td>
<td>2.46 (0.44)</td>
<td>2.52 (0.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.75=4.53, p=0.014</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>n=36</td>
<td>2.33 (0.52)</td>
<td>2.27 (0.56)</td>
<td>2.42 (0.51)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>F2.67=0.38, p=0.683</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
There was a clear relationship between the prevalence of atopy and pre-school symptom-status ($\chi^2 = 10.1, P = 0.006$) (table 4.10). The lowest prevalence (23.8% [15.7% to 31.9%]) was seen in children who were asymptomatic in 1990 and the highest prevalence (43.6% [33.6% to 53.6%]) was seen in those who reported wheeze in the original survey. Amongst coughers in the original survey the prevalence of atopy was 26.7% [16.7% to 36.7%]) which was marginally higher than in the asymptomatic group.

Using multiple regression techniques, a more formal assessment of the joint effect of 1990 and current symptoms upon physiological outcomes confirmed that both current wheeze ($P = 0.0002$) and a past history of wheeze ($P = 0.008$) exerted independent and significant effects upon bronchial responsiveness. The effect of current wheeze (to reduce the mean level of bronchial responsiveness by 0.81 of a doubling dose [0.39 to 1.23 doubling doses]) was rather larger than that for a past history of wheeze (a reduction of 0.51 doubling doses [0.13 to 0.89]). The effect of current cough (0.34 [-0.06 to 0.74]) was smaller still and was of borderline significance ($P = 0.10$) while the effect of a past history of cough was both small and clearly non-significant (0.21 [-0.17 to 0.59], $P = 0.27$). For atopy the only independent yet significant effect was of current wheeze ($P = 0.001$), while current cough ($P = 0.07$) and past history wheeze ($P = 0.12$) were of borderline significance. For MEF$_{25-75}$ and PEF as a percent of predicted, the only independent associations of note were those with current wheeze ($P = 0.005$ and $P = 0.043$ respectively). Finally, for peak flow variability, the predominant relationship was with current wheeze ($P = 0.08$) and current cough ($P = 0.04$). The magnitude of these individual effects is not reported in greater detail because it would not add substantially to the information already provided by the data presented in tables 4.8 and 4.9.
It may be seen from figure 4.4 that when separate analyses were carried out in each 1990 symptom group independently, the presence of atopy was still strongly associated with the probability of wheeze at follow-up. The association was particularly strong for children who were originally in the asymptomatic group ($\chi^2 = 15.84$, $P=0.0001$; Fishers exact test (2-tailed), $P=0.001$) but an association of borderline significance was also found in those who were originally said to wheeze ($\chi^2 = 3.52$, $P=0.06$). In both of these symptom groups, atopy was associated with a marked increased probability of wheeze at follow-up. On the other hand, amongst those who coughed in the original survey, atopic status appeared to be unrelated to the probability of later wheeze ($\chi^2 = 0.10$, $P=0.75$).

Figure 4.4: The relationship between past symptoms, atopic status and wheeze at follow up
4.2.3 QUESTIONS OF SPECIFIC CLINICAL INTEREST

On clinical grounds, there are several questions of interest that may be addressed using the data obtained. However, caution should be taken when interpreting these subgroup analyses because of problems such as multiple significance testing and low statistical power. Three questions of obvious interest were: (i) was the physiological profile of persistently wheezy children qualitatively different to that of other children?; (ii) were the physiological measures in children with prior wheeze who subsequently become asymptomatic different from other children; and finally, (iii) what was the outcome of children whose wheeze started in the first year of life, and how did this differ from those whose wheeze started beyond infancy?

(i) It is clear from tables 4.9 and 4.10 that in every instance the physiological outcomes for the persistent wheezers (in bold) were the worst or second worst of all nine subgroups.

<table>
<thead>
<tr>
<th>1990 SYMPTOM GROUP</th>
<th>1990 Atopic</th>
<th>SYMPTOMS AT FOLLOW-UP</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>asymptomatic wheeze cough</td>
<td></td>
</tr>
<tr>
<td>asymptomatic</td>
<td>yes</td>
<td>16/89 (18.0%) 6/7 (85.7%) 3/9 (33.3%)</td>
<td>25/105 (23.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2=16.91, p&lt;0.0001$</td>
<td></td>
</tr>
<tr>
<td>wheezers</td>
<td>yes</td>
<td>15/45 (33.3%) 21/38 (55.3%) 5/11 (45.4%)</td>
<td>41/94 (43.6%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2=4.05, p=0.132$</td>
<td></td>
</tr>
<tr>
<td>coughers</td>
<td>yes</td>
<td>8/34 (23.5%) 2/9 (22.2%) 10/32 (31.2%)</td>
<td>20/75 (26.7%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2=0.606, p=0.739$</td>
<td></td>
</tr>
</tbody>
</table>

(ii) Although children with initial wheeze who were asymptomatic at follow-up had a significantly higher ($\chi^2=3.96, P=0.046$) prevalence of atopy (33.3%[19.5% to 47.1%]) than children who were consistently asymptomatic (18.0% [10.0% to 26.0%]) they had a lower prevalence of atopy than those with persistent wheeze (55.3% [39.5% to
71.1\%); \ \chi^2 = 4.034, P = 0.045). A similar pattern was observed when looking at bronchial responsiveness to inhaled methacholine: children with prior wheeze who became asymptomatic at follow-up (geometric mean 2.35mg/ml [1.79mg/ml to 3.10mg/ml]) had more sensitive airways than persistently asymptomatic children (geometric mean 3.56mg/ml [3.08mg/ml to 4.11mg/ml]) \text{ } t_{122} = 2.86, P = 0.005, but were less sensitive than children with persistent wheeze (geometric mean 1.35mg/ml [0.95mg/ml to 1.91mg/ml]) \text{ } t_{69} = 2.47, P = 0.016. On the other hand, with respect to all of the other physiological outcome measures (table 7), wheezers who subsequently became asymptomatic were consistently the least severe, or second least severe, of all nine sub-groups.

(iii) To avoid recall bias in the assessment of the age at commencement of initial symptoms, only children whose wheeze had started within a year of the original survey were used in this analysis. These children were subdivided into those whose wheeze had started in the first year of life and those whose wheeze had started beyond the first year of life. Of the 14 first year wheezers identified, 3 (21.4\%) wheezed at follow-up compared to 4 out of 12 (33.3\%) of children who had started to wheeze beyond infancy. Although the difference between these two proportions is not statistically significant (\chi^2 = 0.465, P = 0.495, Fishers exact test \{2-tailed, P = 0.665\}) given the small sample size it would not be appropriate to conclude that this proved that there was equivalence of outcome between those who started wheezing in the first year and those who started later.
4.3.1 PATTERNS OF WHEEZE AND OTHER RISK FACTORS RECORDED IN EARLY LIFE AND THE RELATIONSHIP WITH WHEEZE AT FOLLOW UP

An important question to try and determine is whether there is a relationship between early patterns of wheeze or factors which may be demonstrated early on in childhood and wheeze later on. These factors are difficult to demonstrate with this cross sectional cohort because of its age structure. Information on these factors was first accrued on children with a range of ages from 0 to 5 years. Follow up commenced with the oldest children and over two years progressed to the youngest. This means that follow-up time was different for different age groups and differing ages were achieved at follow up by different year bands. For example, a five year old recruited first in 1990 and followed up two years later would be seven. A one year old recruited at the same time would not have been seen until towards the end of the study by which time four years between contact would have elapsed. This child would therefore be five years old, equivalent to the oldest age band at the time of the original study. By grouping the whole cohort together when considering possible factors responsible for persistence of wheeze, the assumption must be made that the same factors operate in exactly the same fashion, regardless of the age of the child. This assumption may not be valid. The heterogeneous age structure of the cohort therefore precludes the use of the whole group when looking at risk factors for persistence of wheeze. A more robust approach was used by limiting the consideration of wheeze persistence factors to the youngest 3 years of the original cohort. These children were aged between 4 years 2 months and 6 years 5 months (mean age 5 years 3 months) at follow up. Due to young age of this part of the cohort only 29/60 (48%) of this group were able to complete the lung function tests satisfactorily, 27 (45%) completed bronchial challenge and 20 (33%) were able to partake of the peak flow diary. Only the symptomatic outcomes are therefore presented.
There were 60 children under age 3 in 1990 who wheezed in the year prior to the original survey of whom 21 (35%) reported current wheeze at follow up.

Table 4.11 shows the age and sex structure of this subgroup. It can be seen that neither attained age at the time of the original study nor sex had an impact upon the proportions continuing to wheeze at follow up.

Table 4.11: Persistence of wheeze by demography

<table>
<thead>
<tr>
<th>Factor</th>
<th>wheezing in last year No/Total (%)</th>
<th>degrees of freedom</th>
<th>Chi squared</th>
<th>p</th>
<th>odds ratio (OR)</th>
<th>95% CI of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1990 age band</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2/12(17)</td>
<td></td>
<td></td>
<td>1.00</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>11/23(48)</td>
<td></td>
<td>3.535</td>
<td>0.171</td>
<td>2.35</td>
<td>0.35, 26.50</td>
</tr>
<tr>
<td>2</td>
<td>8/25(32)</td>
<td>2</td>
<td>3.695</td>
<td>0.158</td>
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</tr>
<tr>
<td>test for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>13/40(33)</td>
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<td>0.330</td>
<td>0.566</td>
<td>0.72</td>
<td>0.21, 2.53</td>
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<tr>
<td>female</td>
<td>8/20(40)</td>
<td>1</td>
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</table>

Table 4.12 details the proportions continuing to wheeze at follow up dependant upon the personal, family and drug histories recorded at original survey. The bivariate analyses show that short gestation, low birth weight and exposure to maternal cigarette smoking all increase the risk of wheezing at follow up, whilst a personal history of eczema, recurrent cough without a cold, lower respiratory tract infection (bronchiolitis, pneumonia and pertussis) appeared not to affect the proportions continuing to have symptoms. Atopic status at follow up was determined by skin prick testing in 52 children from this sub group. No differences were seen with respect to continuing wheeze between the atopic and non-atopic children (33% vs. 35%, $\chi^2 = 0.02$; p=0.888). No effect was seen either for a parental history of asthma/bronchitis, hay fever or eczema. The location of the child's home, socio-economic status, sharing of

122
bedrooms and exposure to paternal cigarette smoke or cats appeared to have little effect. Treatment with anti asthma medications at the time of the initial study also made little impact upon symptomatic outcome.
Table 4.12: Persistence of wheeze by personal, family and drug history

<table>
<thead>
<tr>
<th>Factor</th>
<th>wheezing in last year No/Total (%)</th>
<th>degrees of freedom</th>
<th>Chi squared</th>
<th>p *Fishers exact test (2 tailed)</th>
<th>odds ratio (OR)</th>
<th>95% CI of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>gestation</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>&gt;38 weeks</td>
<td>16/53 (30)</td>
<td>5/7 (71)</td>
<td>1</td>
<td>0.045*</td>
<td>5.78</td>
<td>0.81, 64.61</td>
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<tr>
<td>&lt;38 weeks</td>
<td>5/7 (71)</td>
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<td></td>
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<tr>
<td>birth weight</td>
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<tr>
<td>&gt;2500g</td>
<td>17/55 (31)</td>
<td>4/4 (100)</td>
<td>1</td>
<td>0.013*</td>
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<td>no</td>
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<td>12/26 (46)</td>
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<td>history of recurrent cough</td>
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<tr>
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<td>rural domicile</td>
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<td>14/32 (44)</td>
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<td>2.308</td>
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<td>0.43</td>
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<td>urban domicile</td>
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<td>14/42 (33)</td>
<td>7/18 (39)</td>
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<td>0.171</td>
<td>0.679</td>
<td>1.27</td>
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<td>cat at home</td>
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<td>no sharing bedroom</td>
<td>11/38 (29)</td>
<td>10/22 (45)</td>
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</tr>
<tr>
<td>no treatment in 1990</td>
<td>5/19 (26)</td>
<td>16/40 (40)</td>
<td>1</td>
<td>1.052</td>
<td>0.305</td>
<td>0.54</td>
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<tr>
<td>treatment in 1990</td>
<td></td>
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</table>

†Odds ratio undefined
Table 4.13 shows the effect of pattern of wheezing upon outcome. It can be seen that a greater proportion continue to have symptoms when earlier wheeze occurred in the absence of colds and was deemed worse at night. A similar effect was seen when wheezing was worse at certain times of the year (in virtually all cases during the winter), although this was only of borderline significance.

Table 4.13: persistence of wheeze according to pattern of wheezing recorded in 1990

<table>
<thead>
<tr>
<th>Factor</th>
<th>wheezing in last year No/Total (%)</th>
<th>degrees of freedom</th>
<th>Chi square</th>
<th>p *Fishers exact test (2 tailed)</th>
<th>odds ratio (OR)</th>
<th>95% CI of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>wheeze precipitated only by colds</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>No</td>
<td>2/7(29)</td>
<td>1</td>
<td>0.101</td>
<td>0.751</td>
<td>1.32</td>
<td>0.19, 15.14</td>
</tr>
<tr>
<td>Yes</td>
<td>18/52(35)</td>
<td></td>
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<tr>
<td>wheeze precipitated without colds</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>8/37(22)</td>
<td>1</td>
<td>10.618</td>
<td>0.001</td>
<td>7.25</td>
<td>1.77, 31.48</td>
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<tr>
<td>Yes</td>
<td>12/18(67)</td>
<td></td>
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<tr>
<td>exercise induced wheeze</td>
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<tr>
<td>no</td>
<td>15/46(33)</td>
<td>1</td>
<td>*0.491</td>
<td>1.72</td>
<td>0.35, 7.98</td>
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<td>yes</td>
<td>5/11(45)</td>
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<tr>
<td>wheeze precipitated by eating/drinking</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>17/50(34)</td>
<td>1</td>
<td>*0.183</td>
<td>3.88</td>
<td>0.49, 45.81</td>
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</tr>
<tr>
<td>yes</td>
<td>4/6(67)</td>
<td></td>
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<td></td>
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<tr>
<td>wheeze precipitated by inhalants</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>no</td>
<td>17/52(33)</td>
<td>1</td>
<td>*0.433</td>
<td>2.06</td>
<td>0.34, 12.37</td>
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</tr>
<tr>
<td>yes</td>
<td>4/8(50)</td>
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<td></td>
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<tr>
<td>wheeze worse at different times of the year</td>
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<td></td>
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</tr>
<tr>
<td>no</td>
<td>13/46(28)</td>
<td>1</td>
<td>*0.061</td>
<td>3.38</td>
<td>0.84, 14.02</td>
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<tr>
<td>yes</td>
<td>8/14(57)</td>
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<tr>
<td>wheeze worse at night</td>
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<td>5.862</td>
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<td>16/33(48)</td>
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</table>

In table 4.14 the wheeze severity factors are scrutinised in relation to outcome. The total number of attacks in the year preceding the original survey seems important in determining outcome whereas the age of onset, length of times since last attack, length of attack and shortness of breath with attacks do not appear important in determining the proportions still wheezing.
Table 4.14: persistence of wheeze by severity of wheeze recorded in 1990

<table>
<thead>
<tr>
<th>Factor</th>
<th>wheezing in last year No/Total (%)</th>
<th>degrees of freedom</th>
<th>Chi squared</th>
<th>p</th>
<th>odds ratio (OR)</th>
<th>95% CI of OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no of attacks in year prior to 1990</td>
<td></td>
<td></td>
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</tr>
<tr>
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<td>1/11(9)</td>
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<td>1.00</td>
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<tr>
<td>1-2</td>
<td>2/16(13)</td>
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<td>1.43</td>
<td>0.06</td>
<td>92.59</td>
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<tr>
<td>3-5</td>
<td>7/18(39)</td>
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<td>6.36</td>
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<td>0.59, 314.98</td>
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<tr>
<td>6-10</td>
<td>8/10(80)</td>
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<td>40.00</td>
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<td>2.32, 1943.78</td>
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<td>&gt;11</td>
<td>3/4(75)</td>
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<td>18.489</td>
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<td>0.87, 1723.48</td>
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<tr>
<td>length of time since last attack in 1990</td>
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<td>&gt;13 months</td>
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<td>7-12 months</td>
<td>1/3(30)</td>
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<tr>
<td>4-6 months</td>
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<td>1-3 months</td>
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<td>0.169</td>
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<td>0.06, 117.80</td>
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<td>4/12(33)</td>
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</tr>
<tr>
<td>Age of onset (yrs)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>17/46(37)</td>
<td></td>
<td>1.00</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>3/11(27)</td>
<td></td>
<td>0.64</td>
<td>0.1</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>2-3</td>
<td>1/3(33)</td>
<td>2</td>
<td>0.370</td>
<td>0.831</td>
<td>0.95</td>
<td>0.01, 17.6</td>
</tr>
<tr>
<td>test for trend</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness off breath with attacks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>5/23(22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>16/37(43)</td>
<td>1</td>
<td>2.883</td>
<td>0.090</td>
<td>2.74</td>
<td>0.75, 11.35</td>
</tr>
</tbody>
</table>

† Odds ratio undefined against this stratum
4.4 OUTCOME OF PRE SCHOOL COUGHING GROUP

Two hundred and twenty six children were identified in the 1990 questionnaire as having recurrent cough without wheeze (115 males and 111 females). Of these children follow-up questionnaires were completed by 130 parents and full physiological studies were performed on 93. Of the 130 children (64 girls and 66 boys), follow-up information on current symptoms was available for 125 children. Of these, 70 (56.0%) were symptom-free at follow-up and 46 (36.8%) continued to report recurrent cough in the absence of colds but did not report wheeze. Nine children (7.2%) reported one or more attacks of wheeze in the year prior to follow-up. Of these 9 children, 5 reported cough and wheeze, whereas 4 reported wheeze alone. Children were grouped according to these symptomatic outcomes (group I - symptom-free at follow up; group II - continuing recurrent cough without a cold and group III - current wheeze at follow-up). These three groups were in turn compared to the control group asymptomatic children from 1990 who remained symptom free (group O). The four groups were compared against factors deemed important in the literature for diagnosis of cough variant asthma (CVA).

4.4.1 COMPARISON BETWEEN COUGH GROUPS

Tables 4.15 and 4.16 detail the different groups in respect to factors deemed to represent CVA. There were no apparent differences between the groups with regard to either atopy, a personal history of eczema or a parental history of atopy. There was a greater prevalence of night cough in children with current symptoms of either cough or wheeze. Only 10.9% of children who continued to cough received treatment whilst about one quarter were diagnosed as asthmatic. Of those 9 children who had started
wheezing, 5 were being treated and 5 were diagnosed as having asthma. Very few children who were free of symptoms at follow-up were either in receipt of anti-asthma medication or an asthma diagnosis. No systematic differences were observed between the groups when considering peak flow variability, MEF_{25-75}, or peak flow as percent of predicted. The responsiveness to inhaled methacholine was similar in children without current symptoms but was lower in for those with persistent cough or those few with recent wheeze.
Table 4.15: Comparison of qualitative outcomes between groups

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atopy At Follow-Up</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 0</td>
<td>16/89 (18.0%)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>Group I</td>
<td>8/34 (23.5%)</td>
<td>1.40 (0.54, 3.67)</td>
</tr>
<tr>
<td>Group II</td>
<td>10/32 (31.3%)</td>
<td>2.07 (0.82, 5.22)</td>
</tr>
<tr>
<td>Group III</td>
<td>2/9 (22.2%)</td>
<td>1.30 (0.25, 6.87)</td>
</tr>
<tr>
<td>$\chi^2_3=2.485$, p=0.478</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Recorded night cough</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 0</td>
<td>17/101 (16.8%)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>Group I</td>
<td>10/40 (25.0%)</td>
<td>1.65 (0.68, 3.99)</td>
</tr>
<tr>
<td>Group II</td>
<td>15/30 (50.0%)</td>
<td>4.94 (2.03, 11.98)</td>
</tr>
<tr>
<td>Group III</td>
<td>4/9 (44.4%)</td>
<td>3.95 (1.04, 16.26)</td>
</tr>
<tr>
<td>$\chi^2_3=15.157$, p=0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Family History Of Atopy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 0</td>
<td>89/175 (50.9%)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>Group I</td>
<td>40/70 (57.1%)</td>
<td>1.29 (0.74, 2.25)</td>
</tr>
<tr>
<td>Group II</td>
<td>22/46 (47.8%)</td>
<td>0.86 (0.46, 1.70)</td>
</tr>
<tr>
<td>Group III</td>
<td>4/9 (44.4%)</td>
<td>0.77 (0.33, 5.06)</td>
</tr>
<tr>
<td>$\chi^2_3=1.346$, p=0.718</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Personal History Of Eczema</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 0</td>
<td>57/175 (32.6%)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>Group I</td>
<td>34/70 (48.6%)</td>
<td>1.96 (1.11, 3.44)</td>
</tr>
<tr>
<td>Group II</td>
<td>17/46 (37.0%)</td>
<td>1.21 (0.62, 2.38)</td>
</tr>
<tr>
<td>Group III</td>
<td>2/9 (22.2%)</td>
<td>0.59 (0.12, 2.94)</td>
</tr>
<tr>
<td>$\chi^2_3=6.346$, p=0.096</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Receiving Current Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 0</td>
<td>3/175 (1.7%)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>Group I</td>
<td>3/70 (4.3%)</td>
<td>2.57 (0.51, 13.04)</td>
</tr>
<tr>
<td>Group II</td>
<td>5/46 (10.9%)</td>
<td>6.99 (1.61, 30.45)</td>
</tr>
<tr>
<td>Group III</td>
<td>5/9 (55.6%)</td>
<td>71.66 (12.57, 408.74)</td>
</tr>
<tr>
<td>$\chi^2_3=5.2446$, p&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Diagnosed Asthmatic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 0</td>
<td>10/175 (5.7%)</td>
<td>1.00 (-)</td>
</tr>
<tr>
<td>Group I</td>
<td>4/69 (5.8%)</td>
<td>0.02 (0.31, 3.35)</td>
</tr>
<tr>
<td>Group II</td>
<td>12/46 (26.1%)</td>
<td>5.82 (2.32, 14.57)</td>
</tr>
<tr>
<td>Group III</td>
<td>5/9 (55.6%)</td>
<td>20.62 (4.78, 88.95)</td>
</tr>
<tr>
<td>$\chi^2_3=37.636$, p&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4.16: Comparison of quantitative outcomes between groups

<table>
<thead>
<tr>
<th></th>
<th>PEAK FLOW VARIABILITY</th>
<th>N</th>
<th>MEF_{25-75} AS PERCENT PREDICTED</th>
<th>N</th>
<th>PEAK FLOW AS PERCENT PREDICTED</th>
<th>N</th>
<th>LOG\textsubscript{2} OF PC-tcpO\textsubscript{2} (MG/ML)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 0</td>
<td>2.34 (0.507)</td>
<td>85</td>
<td>89.82 (23.76)</td>
<td>92</td>
<td>106.1 (16.31)</td>
<td>97</td>
<td>1.83 (0.99)</td>
<td>87</td>
</tr>
<tr>
<td>Group I</td>
<td>2.33 (0.517)</td>
<td>36</td>
<td>86.29 (25.27)</td>
<td>29</td>
<td>106.6 (21.13)</td>
<td>39</td>
<td>1.67 (1.04)</td>
<td>35</td>
</tr>
<tr>
<td>Group II</td>
<td>2.42 (0.513)</td>
<td>28</td>
<td>83.13 (21.30)</td>
<td>28</td>
<td>104.0 (13.06)</td>
<td>32</td>
<td>1.11 (1.09)</td>
<td>25</td>
</tr>
<tr>
<td>Group III</td>
<td>2.27 (0.559)</td>
<td>6</td>
<td>90.11 (20.65)</td>
<td>6</td>
<td>102.9 (12.91)</td>
<td>6</td>
<td>1.05 (1.50)</td>
<td>8</td>
</tr>
</tbody>
</table>

\[ F_{3,151} = 0.29 \quad p = 0.8318 \]
\[ F_{3,151} = 0.65 \quad p = 0.5838 \]
\[ F_{3,170} = 0.22 \quad p = 0.8839 \]
\[ F_{3,151} = 3.96 \quad p = 0.0094 \]
4.5 NIGHT COUGH

Of the 222 children identified in the pre-school period as having wheeze, 145 were reassessed by questionnaire to determine current symptoms and 114 (61 boys and 53 girls) attended for physiological assessment. Night studies were carried out on 100 of these children. The data were analysed and presented as follows.

Table 4.17 shows that the relationship between reported and recorded night cough was relatively poor with low values of Cohen's kappa for agreement between the different methods of reporting the presence of night cough.

Table 4.17 Relationship between recorded night cough and reported night cough

<table>
<thead>
<tr>
<th>reported symptom</th>
<th>recorded night cough</th>
<th>percentage agreement</th>
<th>Cohen's kappa</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td></td>
</tr>
<tr>
<td>current night Cough yes</td>
<td>9 (37.5%)</td>
<td>15 (62.5%)</td>
<td>68.5%</td>
</tr>
<tr>
<td>no</td>
<td>19 (25.0%)</td>
<td>57 (75.0%)</td>
<td></td>
</tr>
<tr>
<td>night cough  reported in symptom diary yes</td>
<td>6 (40.0%)</td>
<td>9 (60.0%)</td>
<td>69.3%</td>
</tr>
<tr>
<td>no</td>
<td>18 (24.7%)</td>
<td>55 (75.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.18 shows the rate of night cough detected by questionnaire or recorded overnight in previously wheezy children depending on current wheeze status. It can be seen that a higher proportion of children with current wheeze report night cough within the previous year and that night cough is actually recorded in a higher proportion of children with current wheeze. There was no statistically significant difference in the proportions reporting night cough in the symptom diary between persistent wheezers and in those whose wheeze had ceased.
Table 4.18 Relationship between measures of night cough in previously wheezy children and current wheeze

<table>
<thead>
<tr>
<th>current wheeze</th>
<th>reported current night cough</th>
<th>recorded night cough</th>
<th>night cough reported in diary</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>&gt;4 days</td>
</tr>
<tr>
<td></td>
<td>17 (36.2%)</td>
<td>16 (39.0%)</td>
<td>2 (4.9%)</td>
</tr>
<tr>
<td>no</td>
<td>30 (63.8%)</td>
<td>25 (61.0%)</td>
<td>1 (1.8%)</td>
</tr>
</tbody>
</table>

chi squared | 5.389 | P | 0.020

Table 4.19 examines the relationship between the asthma-related outcomes measured and the presence of recorded night cough, depending on whether wheeze was still present at follow-up. It can be seen that although children with persistent wheeze have poorer ventilatory function, decreased mean overnight saturation, increased bronchial responsiveness, increased peak flow variability and increased degree of morning dip, the presence of recorded night cough was not associated with large changes in any of the measured indices. The presence or night cough had little impact on any of the asthma-related outcomes, regardless of whether wheeze had persisted or not.
Table 4.19 Relationship between recorded night cough and other asthma-related outcomes

<table>
<thead>
<tr>
<th></th>
<th>current wheeze</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>log₂(PC2O tc-pO₂) (mg/ml) night cough</td>
<td>mean (SD)</td>
<td>n</td>
<td>mean (SD)</td>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>yes</td>
<td>0.60(1.77)</td>
<td>12</td>
<td>1.51(1.43)</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>0.30(1.46)</td>
<td>18</td>
<td>1.28(1.22)</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.494</td>
<td></td>
<td>0.4314</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.6266</td>
<td></td>
<td>0.6761</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>logₑ(AMplitude percent mean) night cough</td>
<td>yes</td>
<td>2.67(0.48)</td>
<td>12</td>
<td>2.26(0.72)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>2.46(0.33)</td>
<td>18</td>
<td>2.18(0.53)</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>1.3897</td>
<td></td>
<td>0.3740</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.1756</td>
<td></td>
<td>0.7103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>morning dip (as % predicted) night cough</td>
<td>yes</td>
<td>14.8(11.79)</td>
<td>5</td>
<td>-0.2(12.48)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>4.78(14.70)</td>
<td>11</td>
<td>2.67(11.03)</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>1.3338</td>
<td></td>
<td>0.5599</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.2036</td>
<td></td>
<td>0.5798</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean overnight SaO₂(%) night cough</td>
<td>yes</td>
<td>96.45(1.45)</td>
<td>13</td>
<td>96.81(1.14)</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>96.21(1.47)</td>
<td>18</td>
<td>96.55(1.78)</td>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.4516</td>
<td></td>
<td>0.3444</td>
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<tr>
<td>P</td>
<td></td>
<td>0.6550</td>
<td></td>
<td>0.7324</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEF₂₆₋₇₅ as percent predicted night cough</td>
<td>yes</td>
<td>79.13(20.48)</td>
<td>12</td>
<td>100.79(29.71)</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>73.18(19.43)</td>
<td>19</td>
<td>87.49(20.33)</td>
<td>38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.8127</td>
<td></td>
<td>1.6652</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.4230</td>
<td></td>
<td>0.1027</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>peak expiratory flow as percent predicted night cough</td>
<td>yes</td>
<td>95.01(14.05)</td>
<td>12</td>
<td>101.83(22.90)</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>no</td>
<td>99.04(18.03)</td>
<td>20</td>
<td>106.48(18.36)</td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.6612</td>
<td></td>
<td>0.6540</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.5135</td>
<td></td>
<td>0.5164</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.20 details the temperature and humidity measures recorded during the night studies and examines the relation with night cough and environment, depending on the presence or absence of current wheeze. Due to problems with data retrieval following
the night studies, only 32 overnight temperature records were available for analysis. It can be seen that in children with persistent wheeze, the presence of night cough was associated with decreased temperature, whilst there was a borderline association with increased humidity.

Table 4.20 Relationship between recorded night cough and the overnight bedroom environment

<table>
<thead>
<tr>
<th></th>
<th>current wheeze</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes mean (SD)</td>
</tr>
<tr>
<td>mean overnight room air humidity (%) night cough</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>63.51(10.78)</td>
</tr>
<tr>
<td>no</td>
<td>56.94(11.75)</td>
</tr>
<tr>
<td>T</td>
<td>1.7252</td>
</tr>
<tr>
<td>P</td>
<td></td>
</tr>
<tr>
<td>mean overnight room air temperature (%) night cough</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>17.70(2.41)</td>
</tr>
<tr>
<td>no</td>
<td>21.58(2.76)</td>
</tr>
<tr>
<td>t</td>
<td>2.8057</td>
</tr>
<tr>
<td>P</td>
<td></td>
</tr>
</tbody>
</table>
Tables 4.21 and 4.22 examine the relationship between recorded night cough, maternal smoking, and receipt of antiasthma medication, depending on current symptom status. It can be seen that no important relationships were demonstrated.

**Table 4.21 Relationship between recorded night cough and maternal smoking**

<table>
<thead>
<tr>
<th>Night Cough</th>
<th>Current Wheeze</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Maternal Smoking</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>6/15 (40.0%)</td>
</tr>
<tr>
<td>No</td>
<td>9/15 (60.0%)</td>
</tr>
</tbody>
</table>

Chi squared: Yes 0.009, No 0.593
Degrees of freedom: Yes 1, No 1

P: Yes 0.923, No 0.441

**Table 4.22 Relationship between recorded night cough and receipt of antiasthma medication**

<table>
<thead>
<tr>
<th>Night Cough</th>
<th>Current Wheeze</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Receiving Treatment</td>
<td>Yes</td>
</tr>
<tr>
<td>Yes</td>
<td>10/28 (35.7%)</td>
</tr>
<tr>
<td>No</td>
<td>18/28 (64.3%)</td>
</tr>
</tbody>
</table>

Chi squared: Yes 0.407, No 1.511
Degrees of freedom: Yes 1, No 1

P: Yes 0.524, No 0.219

Figure 4.5 illustrates the chronology of nocturnal cough by comparing timing of multiple cough episodes between children who were wheezy or wheeze-free at follow-up. It can be seen that children who were symptom free coughed little over night, but that most coughing occurred in the morning between 5am and 7am. A similar proportion of children with wheeze at follow-up coughed at night but these episodes occurred throughout the night, with most coughing occurring early in the night between 8pm and 10pm.
Figure 4.5 Timing of cough episodes overnight in previously identified wheezy children by symptom status at follow-up

- Purple bars: percentage coughing per hour in children wheeze free at follow-up
- Green bars: percentage coughing per hour in children wheezing at follow-up
Key Results:

- 46.9% of the pre-school wheezing group were asymptomatic at follow-up, with 37.9% continuing to wheeze and 15.2% complaining of recurrent cough.

- 56.0% of the pre-school cough group were asymptomatic at follow-up, with only 7.2% starting to wheeze by follow-up and 36.8% continuing to complain of recurrent cough.

- 83.3% of the pre-school asymptomatic group remain so at follow-up, with 6.7% starting to wheeze and 10% complaining of recurrent cough.

- Whilst there were strong relationships between current symptom status and the indices of lung function, bronchial responsiveness and proportion of children with atopy, systematic differences in the level of bronchial responsiveness ($F_{2.25}=10.73$, $P=0.0001$) and proportion with atopy ($\chi^2=10.1$, $P=0.006$) were apparent with respect to the children's pre-school symptoms.

- Children who wheezed both in the pre-school period and at follow-up demonstrated the highest level of bronchial responsiveness, the lowest levels of lung function and a high prevalence of atopy.

- Children who were initially wheezing but had outgrown it by follow-up showed an level of bronchial responsiveness which was intermediate between those who were persistently wheezy and those who were persistently asymptomatic. A similar intermediate pattern was demonstrable in the proportions of children who were atopic.
Lung function on the other hand appeared to be indistinguishable from that of consistently asymptomatic subjects.

- Wheezy children from the age group of three and under appeared more likely to continue wheezing if they were of low birth weight, premature, wheezed without having colds, had mothers who smoked, had a high number of wheezing episodes per year, or had wheeze which was worse at night.

- The proportion of children from the pre-school cough group who went on to develop wheeze at follow-up was no greater than that seen from the asymptomatic group (7.2% Vs 6.7%). Compared to consistently asymptomatic children or those who had outgrown their cough, those pre-school coughers with continuing symptoms at follow-up coughed more at night ($\chi^2 = 15.157$, $p=0.002$), were more likely to be receiving treatment for ($\chi^2 = 52.446$, $p<0.001$), or be in receipt of a diagnosis of ($\chi^2 = 37.636$, $p<0.001$) asthma and had an increased level of bronchial responsiveness $F_{3.151} = 3.96$, $p=0.0094$.

- In children from the preschool wheeze group who had night studies completed it was apparent that night cough was very poorly reported compared to night cough actually recorded in the child's home (Cohen's kappa = 0.18). No indices of lung function, bronchial responsiveness of peak flow lability recorded on this group predicted the presence of night cough, although colder bedroom temperature overnight was associated with the presence of night cough in children with continuing wheeze. The timing of cough episodes overnight appeared to differ between the children who continued to wheeze and those who had outgrown this symptom.
The study has investigated the natural history of wheeze and recurrent cough in pre-school children. By reassessing a population-based sample of 488 children whose initial symptom status had already been defined in the pre-school years (Luyt, Burton and Simpson, 1993), the prognosis of pre-school symptoms was examined by focusing upon current symptoms, lung function, bronchial responsiveness, atopic status and peak flow variability. Of particular interest was the relationship of pre-school symptom status with symptomatic and physiological correlates at follow-up which may reasonably be deemed to represent asthma.

5.1.1 THE VALIDITY OF THE STUDY

It has already been demonstrated that the original sample provided a valid representation of pre-school Caucasian children in Leicestershire (Luyt, Burton and Simpson, 1993). However, the response rate of the examination component of the follow-up study - that is, the clinical examination and physiological testing - was relatively low (44.3%), particularly when compared to the original survey (86%). However, this was not unexpected given the arduous nature of the follow-up protocol and, fortunately, it was possible to achieve a markedly better response rate for the questionnaire component (61.4%) by mailing non-attenders.

The relatively poor response rate to this follow-up study introduces the limitation of possible bias in those subjects who attended. Analysis of the demographic details of those children who attended compared to those non-attenders shows some differences in exposure to paternal environmental tobacco smoke and place of domicile. However the other demographic indices were similar between the two groups as was exposure to
maternal environmental tobacco smoke. The symptomatic outcomes differed significantly between the two groups in that the attending children had more wheeze and cough than those children who did not. Attending children also were more likely to be labeled by a doctor as having asthma and more of them had a personal history of eczema. The implications of this are that the results presented are from a population of children with less favourable symptomatic outcomes. Thus the results are likely to convey some bias. However the similar demographic features of both attending and non-attending children make it unlikely that the inclusion of data from a full study in those children who did not attend would have systematically altered the substantive conclusions drawn. The data on symptomatic outcome would suggest that inclusion of these children in the full study would have at most lessened associations and relationships between early symptomatic status and physiological profile at follow up. Substantively different results would only occur if the non-attending group had physiological parameters, which differed fundamentally (and in a diametrically opposite direction) from the children who attended.

5.1.2 REPEATABILITY

Following on from previous work (Luyt, Burton and Simpson, 1993), the study allowed assessment of the long term repeatability of the key questions used to identify the preschool children with respect to their original symptom groups. The precision of measures employed in the follow-up study was also assessed using a small group of children to determine short-term repeatability.

In assessing the long-term repeatability of the questions it is important to bear in mind the exact wording of the prompts. Furthermore recall bias may also be operating in the
respondents causing yet more difficulty in interpreting the data. It is also vital to accept that the natural history of respiratory illness during the period of follow-up may affect these measures. This is because some children with wheeze or cough may cease the symptom between surveys whilst other children who were initially asymptomatic may start to suffer from them. This latter factor could be taken partly into account by ensuring that children who reported onset of wheeze and cough after the date of the initial 1990 questionnaire were excluded from repeatability analyses.

With these factors in mind, the question regarding whether a child had ever wheezed ("has your child ever had attacks of wheezing") proved to be highly repeatable. Similarly the question regarding diagnosis of asthma which was couched in the past tense ("Has any doctor or hospital told you that he/she has asthma?") demonstrated acceptable repeatability, confirming the findings of other studies (Luyt, Burton and Simpson, 1993; Clifford, Radford, Howell and Holgate, 1989; Salome, Peat, Britton and Woolcock, 1987). Repeatability of the cough question was harder to assess. In of the follow-up the study a question was asked about recurrent cough in the past. This was "has your child coughed without a cold in the past?" This was compared to the question in the original 1990 survey that asked the question "does he/she usually cough without a cold?" The long-term repeatability of this question was less robust, which is again consistent with previous work (Luyt, Burton and Simpson, 1993). Once again to try and avoid the affect of subjects starting to cough after the original survey, all children recording starting to cough after 1990 were excluded from this analysis.

The age of the cohort precluded the use of more formal assessments of lung function to derive an index of bronchial responsiveness and hence the effort independent method of
recording changes in transcutaneous oxygen tension was used. This index proved to be repeatable, even over the relatively long period of time between the repeated measurements and compares favourably with the literature (James and Ryan, 1997). The effort-dependent outcomes were not as repeatable. For example, MEF25.75 (expressed as a percent of predicted) generally decreased between initial assessment and repeatability testing. This was probably due to improved technique at the time of repeatability assessment, although no large changes in rankings of individual children were observed. The poor reproducibility of peak expiratory flow variability may be due to the young age of the population under study and is similar to the findings of other investigators (Frischer, Meinert, Urbanek and Kuehr, 1995).

As lung function measurements were recorded immediately prior to the inhalational challenge with methacholine, it was not possible to remove short-term airway lability as a factor that may have influenced the results by giving a bronchodilator. To do this prior to commencing the challenge may have had serious implications for the validity of the measurement of bronchial responsiveness. However, any airway lability that was present may of course have influenced the results obtained from the children with ongoing wheeze and should be borne in mind when interpreting the data.

5.2.1 SYMPTOMS AT FOLLOW-UP

From the data it would appear that the three symptom groups identified in 1990 have very different symptom profiles at follow-up. Amongst children who were symptom-free in the initial survey over 80% remained asymptomatic at follow-up. Interestingly, the proportion reporting having started to wheeze (6.7%) was consistent with data obtained from some other studies (Gergen, Turkeltaub, and Kramer, 1992; Anderson, Bland, Patel and
Peckham, 1986), but smaller than the proportion of late onset wheezers identified in the Tuscon birth cohort (Martinez, Wright, Taussig, et al, 1995).

Although the 1990 coughing cohort may be an ill-defined group, it is of interest to note that some 37% continue to report recurrent cough. It is also of interest that the proportion of coughers who started to wheeze (7.2%) was very similar to the proportion of new wheezers (6.7%) in the 1990 asymptomatic group. This observation (upper 95% confidence limit = 11.7%) would not appear to support the contention that a large proportion of young children with recurrent cough become wheezy asthmatics, and may reflect that fact that this hypothesis (O'Connell, Rojas and Sachs, 1991) was originally generated from observations of clinic-based populations. On the basis of these symptomatic outcome data, recurrent cough and wheeze in pre-school children do not appear to represent the differing symptoms of the same underlying disorder.

Of the 1990 wheeze group almost half reported no symptoms in the year prior to follow-up, however, nearly 40% reported persistent wheeze and 15% reported recurrent coughing. It should be noted that the interpretation of these latter data is potentially complicated by two issues. Firstly, the wheeze group consisted of children reporting ever having wheezed in the initial survey and a proportion would not therefore have wheezed in the year prior to the first survey and should not therefore be viewed as having been current wheezers in 1990. Secondly, the study included a small number of children who may have wheezed only in the first year of life. The results might therefore be criticized for having been based upon a data set including some children with mild or nascent symptoms. In order to ensure that these issues did not distort the primary conclusions, a sub-group analysis was undertaken in which the children in the initial wheeze group were separated into three sub-
populations: (i) Children aged under two at the time of first survey; if children in this group had reported wheeze in the 12 months prior to the initial survey, it could potentially have been restricted to the first year of life. (ii) Children over two years of age reporting that they had been free of wheeze in the 12 months prior to the initial survey. (iii) Children over two years of age who were reported to have wheezed in the 12 month period preceding the initial survey; this subgroup represents children with on-going wheeze beyond the first year of life. There were 35 children in the first sub-group, 30 in the second and 80 in the third. The proportions reporting current wheeze at follow-up were 37.1%, 3.3% and 351.3% respectively. These results indicate that the inclusion of the mild sub-groups means that, if anything, the prognostic severity of the wheeze group has been understated, and that exclusion of these children would therefore have strengthened the principal conclusions. Crucially these data represent the outcome of pre-school wheeze including mild and nascent groups, providing a more realistic population-based indication of the natural history of this symptom.
5.2.2 PHYSIOLOGICAL OUTCOMES

As might have been expected, physiological parameters were generally found to provide a faithful reflection of current symptoms. On the other hand, their relationship with 1990 symptoms was less clearly defined. Nevertheless, the levels of bronchial responsiveness and the prevalence of atopy did appear to vary between the different 1990 symptom groups. To be specific, bronchial responsiveness was greater in the 1990 wheeze group than in the asymptomatic group and the cough group was intermediate. The prevalence of atopy was also greatest in the wheeze group and lowest in the asymptomatic group; however, the prevalence amongst coughers was only marginally higher than that in the controls. These data confirm the inter-relationship between wheeze, atopy and bronchial responsiveness found in older children (Clifford, Radford, Howell and Holgate, 1989; Salome, Peat, Britton and Woolcock, 1987). The other physiological outcomes measured did not show unequivocal relationships with the 1990 symptom groups. However these same measures are associated with significant differences in the lung function of children with respect to current symptom-status. This suggests that current symptoms probably are more closely associated with effort-dependent physiological outcomes than are historical symptoms.

One of the consequences of the study design adopted was that children were reassessed after a range of different follow-up periods (1.8 years to 4.1 years) starting from a variety of different ages (0.3 years to 5.4 years) in 1990. In order to ensure that this issue had not distorted the principal inferences, linear and quadratic terms for age at first survey and follow-up time were added to the multiple regression models described above. However, the inclusion of these additional terms made no material difference to any of the inferences discussed.
Children in the 1990 asymptomatic group who developed wheeze at follow-up had a high prevalence of atopy and a marked, though formally non-significant (P=0.12), increase in bronchial responsiveness to inhaled methacholine compared to children who remained asymptomatic. Tentatively, these data suggest that children with wheeze of relatively late onset may often present with the features typical of classical atopic asthma (Gergen, Turkeltaub, and Kramer, 1992) and the increased level of atopy seen is in agreement with other population-based studies (Martinez, Wright Taussig, et al, 1995). It is also interesting to note that the prevalence of atopy amongst 1990 coughers who started wheezing was much lower than that in previously asymptomatic children with late onset wheeze, despite the fact that the mean level of bronchial responsiveness was very similar in the two groups. This might suggest that these sub-populations are clinically distinct (Clifford, Howell, Radford and Holgate, 1989) and that the aetiological mechanism for the wheeze may be different in the two groups. However these findings must be interpreted with extreme caution in view of the small sample size.

Amongst 1990 wheezers a number of interesting associations were apparent. Firstly, those wheezers who still wheezed at follow-up seemed to have an overall physiological profile that was poorer than any other population sub-group. Secondly, previously wheezy children who were asymptomatic at follow-up had a prevalence of atopy and a mean level of bronchial responsiveness that were mid-way between persistent wheezers and children who remained asymptomatic. However, the lung function in this subgroup seemed to be indistinguishable from those that remained persistently asymptomatic. Thus, there would appear to be a group of pre-school wheezers who out-grow their symptoms and yet, although they subsequently exhibit normal ventilatory function, they nevertheless
demonstrate abnormal airway reactivity and evidence of an atopic diathesis. Further study of this sub-group may reveal important insights into the pathogenesis of childhood asthma. Ultimately identification of the factors responsible for this process may point the way to therapeutic modalities that modify the expression of, rather than the underlying tendency to, asthma. Interestingly, these observations would not be consistent with the suggestion arising from the data in the Tuscon birth cohort study (Martinez, Morgan Wright et al, 1991). In this population transient early wheezers were found to have similar patterns of atopic expression as seen in the Leicester population but in contrast, ventilatory function was diminished. A possible explanation was that early wheeze may simply be a function of narrow small-airways (Martinez, Wright, Taussig, et al, 1995). Our results suggest that wheeze restricted to early life cannot be completely explained by this phenomenon. Further follow-up may reveal a divergent outcome of this group into similar subgroups to those identified in the most recent data from Tuscon, namely the transient early wheezers and the non atopic wheezers of the toddler and early school years (Stein, Holberg, Morgan, Wright, Lombardi, Taussig and Martinez, 1997)

Because the study included some children who were aged less than one at the time of the original survey, and because it has been suggested that first year wheezers may be a clinically distinct sub-population (Martinez, Morgan Wright et al, 1991), it is of relevance to consider the outcome in these children specifically and to determine what impact they may have had upon overall results. The results show that a smaller proportion of children who wheeze in the first year of life continue to do so at follow-up when compared to older children within the cohort. Although these data are far from statistically significant, they would be consistent with the hypothesis that wheeze in the first year of life is less strongly related to outcome in the early school years than wheeze occurring later in childhood. It is
important to realize that the only way of separating these two subgroups whilst avoiding reliance on the recall of the age at which wheeze first occurred was to limit the analysis to the few children whose wheeze had commenced within the year prior to the original study. It would therefore be unwise to draw strong conclusions from these limited data.

A small number of children 13/488 (2.7%) were aged less than 1 year in the initial survey had not started school at the time of the second survey and were therefore not truly followed-up "in the early school years". A further 34 (7.0%) children were aged between 5 years and 5.36 years at the time of the first survey and their initial data should not really be viewed as being "pre-school". However, the exclusion of these two groups made no qualitative difference to any of the principal conclusions.

It is clear that a significant proportion (in our study, 37.9%) of pre-school wheezers continue to wheeze in the early school years. Furthermore, there is objective evidence that those children with pre-school wheeze who continue to wheeze at school age have, as a population, the poorest outcome in terms of a range of relevant physiological end-points. Although there is no universally accepted definition of asthma, this population of children would fulfil most clinical criteria for the condition. This is similar to the findings from the Tuscon cohort which demonstrated that ongoing wheeze which persists through the latter part of the pre-school era (3 to 4 years) is associated with future asthma (Dodge, Martinez, Cline, et al, 1996). Long term population studies of school aged children with decreased pulmonary function and bronchial hyperresponsiveness predict persistence of wheeze into adult life (Strachan and Gerritsen, 1996).
Nevertheless, nearly half (46.9%) of children who had a history of wheeze in the initial survey were entirely symptom free at follow-up. Furthermore, even if attention is restricted solely to those children who wheezed beyond the first year of life and who had wheezed at least once in the 12 months prior to the first survey, more than one third (36.3%) were symptom free at follow-up. However, although clinically well, both in terms of symptoms and objective ventilatory function, these population of children exhibited levels of bronchial responsiveness and a prevalence of atopy intermediate between those children who were consistently symptom free and those who were persistently wheezy.

The data presented are therefore echoed in part by the study of wheeze in six-year-olds from the Tuscon birth cohort. This showed that children with wheeze in the first three years of life that persisted through to six years had diminished lung function and high levels of atopy, a similar finding to those persistent wheezers from this study. Children from Tuscon who had outgrown wheeze between three and six years had reduced lung function and a level of atopy intermediate between the never wheezed children and the persistent wheezers. In our study, preschool wheezers who had outgrown the symptom did not have reduced levels of lung function, but had a similar intermediate level of atopy. Interesting in both this study and the results from Tuscon, the highest proportions of children with positive skin prick tests were seen in children whose wheeze was of late onset (Martinez, Wright, Taussig, et al, 1995).
5.3. PATTERNS OF WHEEZE AND OTHER RISK FACTORS RECORDED IN EARLY LIFE AND THE RELATIONSHIP WITH WHEEZE AT FOLLOW UP (Tables 4.11-4.14)

It has been shown that the reporting of wheeze was highly reproducible. Thus the children followed come from a well-defined group. These children from the youngest three age bands were reassessed in the early school years, a time when most cases of long term asthma have declared themselves (Williams and McNichol, 1969). Some information from the non-attending children was obtained via a postal questionnaire. Investigation of the symptom profiles of this subgroup indicated that their symptoms were less severe, although the factors that are reported to be associated with the persistence of wheeze operated in a similar fashion in the two sub-groups. Although the attenders may represent a slightly more severe group than exists in the general population, the factors identified are likely to be important in the population as a whole. The persistence of wheezing as measured by recording its presence in the year prior to follow up was chosen as it is a well recognized epidemiological measure of asthma. Only the bivariate relationships are presented because multivariate analysis could be potentially misleading given the small numbers followed from the younger part of the cohort.

5.3.1 GENDER AND AGE AT ORIGINAL STUDY

No gender differences were identified on bivariate analysis, nor was an effect of attained age in 1990 seen. These data agree with the findings of Blair (1977) but do not support previous assertions that early wheeze is a predictor of either a poor (McNichol and Williams 1969) or favourable outcome (Jenkins, Hopper, Bowes, et al 1994) in the short term.
5.3.2 BIRTH WEIGHT AND GESTATION

The data show that low birth weight, and to a lesser extent decreased gestation, both increase the risk of wheeze at follow up. These two factors are likely to be highly interrelated. However, there were only 9 children from the low birth weight group and seven from the short gestation group. None of the premature infants required ventilation or prolonged oxygen therapy after birth. Other workers have shown from larger population based studies that low birth weight is independently associated with frequent wheeze in childhood (Schwartz, Gold, Dockery, Weiss and Speizer, 1990). The results of therapeutic work on symptomatic children with a positive airway response to inhaled histamine from a low birthweight group questions whether wheeze in this subgroup of children has a different aetiology to that found in children of normal birthweight (Chan and Silverman, 1993). As both low birth weight and reduced gestation are known to adversely effect lung growth, the ongoing wheeze seen in this very small group may result from these early insults (Chan, Noble-Jamieson, Elliman, Bryan and Silverman, 1989).

5.3.3 ATOPY

Children with a personal history of eczema were no more likely to wheeze at follow-up than those without this condition and no relationship between atopy at follow up in this young age group and continuing wheeze could be demonstrated. This observation does not support the findings of Aberg and Engstrom (1990) who found in their questionnaire-based study of Swedish children that early eczema carried a high risk of allergic airways disease or support the hypothesis tested by Kaplan and Mascie-Taylor (1987) that children with long standing asthma were more likely to suffer from allergy-related
conditions such as eczema. This may reflect the young age group under study in our dataset compared to the populations studied by the above workers. Interestingly the findings are echoed by Wilson, Phagoo and Silverman who initially found little relationship between wheezing and atopy in 3 year old children from a hospital-based cohort (1992), although it was related to ongoing symptoms and severity at age 5 (Wilson, Dore and Silverman, 1997). These data may suggest that there is not a closely defined relationship between early eczema and ongoing wheeze. However as this part of the dataset was too small to carry out meaningful multivariate analysis to take account of other factors (for example, patterns of wheeze) it would be unwise to speculate too much on its significance.

No effect was seen with respect to recurrent cough in the absence of colds. This interesting finding is consistent with the findings in the whole cohort and is more closely analysed below. A past history of lower respiratory tract infections had little effect upon symptoms at follow up. At first glance this finding is at odds with much published data on wheezing following bronchiolitis. However it should be remembered that few from this community based cohort would have had severe illness and most studies of wheeze following bronchiolitis are derived from hospital-based populations. (Foucard and Sjorberg 1984; Noble, Murray, Webb, Alexander, Swarbrick and Milner, 1997)

5.3.4 FAMILIAL INFLUENCES

A parental history of asthma did not increase the likelihood of wheezing at follow-up. These results are inconsistent with those of Clifford et al (1989) who showed that wheeze
was independently associated with a parental history of asthma in their sample of 7 and 11 year old children. The analysis did not show a relationship between continuing symptoms and parental hayfever or eczema, which partially mirrors the results of Dold et al (1992) who found that in families of 9-11 year old children the risk of asthma in the child was not increased by the presence of a parental history of eczema or hayfever. He did however find that asthma in a single parent increased risk of wheezing in his population, which is at variance with the results from the Leicester population. Once again small numbers and the inability to control for possible confounding variables may explain why no relationship was demonstrated.

5.3.6 SMOKING

Maternal smoking increased the likelihood of wheezing at follow-up. This is consistent with other studies (Weitzman, Gortmaker, Klein and Sobol, 1990; Cunningham, O’Connor Dockery and Speizer, 1996; Ehrlich, Du Toit, Jordaan, Zwarenstein, Potter, Volmink and Weinberg, 1996) and systematic quantitative reviews (Cook and Strachan, 1997) that have shown smoking to be related to wheeze and persistence of wheeze (Weiss, Tager, Speizer and Rosner, 1980; Wennnergren, Amark, Amark, Oskarsdottir, Sten and Redfors, 1997). However, nearly all of the mothers who smoked at the time of the original study also smoked during pregnancy (92%) and at follow-up (96%). Thus, it is impossible to determine the timing of this insult. The data suggest that the magnitude of the effect is large even on the small group under scrutiny. The mechanism by which exposure to environmental tobacco smoke increases the chances of continued wheeze are still
unknown, although both increases in bronchial reactivity (O’Connor, Weiss, Tager and Speizer, 1987) and skin test reactivity (Weiss, Tager, Muñoz and Speizer, 1985) have been suggested. Paternal smoking was not related and may reflect the reduced contact fathers have with their children compared to mothers. Social class, location of domicile, exposure to cat epithelia, sharing of bedrooms and treatment in the pre-school period showed no effect on wheeze at follow up. It is important to realise that parental smoking, social class and sharing of bedrooms are all likely to be interrelated. However the multivariate techniques required to account for these co-varyates would render the results unreliable given the small size of the subgroup under scrutiny in this part of the study. The observation that “early treatment” has little effect on outcome is open to various interpretations. It may be that early treatment is only considered when symptoms are ‘severe’ and therefore associated with a poorer prognosis or it is possible that early treatment is ineffective in altering outcome. The original questionnaire prompted respondents to indicate whether any anti asthma medication had been given to the child and hence no analysis the effect of different sorts of treatment (e.g., bronchodilator, bronchodilator and steroid) was possible.

5.3.7 EFFECT OF EARLY PATTERNS OF WHEEZE

Children whose wheeze was precipitated without having a cold had an increased likelihood of wheezing at follow up. This is in contrast to the children who wheezed only in response to colds. This divergence in prognosis reflects findings of much longer term work by Godden et al (1994) which showed children recruited in mid childhood with histories of ‘wheezy bronchitis’ (defined in their study as wheezing only in response to colds) falled significantly better in adult life with respect to continuing symptoms and lung function.
compared to counterparts who experienced wheezing without having a cold. It is interesting that this difference is detected in the data set after a relatively short period of follow-up. It may suggest that pattern of wheeze early in life indicates a fundamental difference in the disease processes, but that these putatively distinct entities are clinically expressed by the common symptom of wheeze. The small sample size however places severe limitations on the degree of interpretation that can be made.

In children whose wheeze was reported to worsen at night there was an increased risk of wheezing at follow-up. This factor describes diurnal variability of wheeze severity. This factor has not been described as a predictor of wheeze persistence in other studies and may merit further study.

The total number of attacks in the year prior to the original survey showed a positive relationship with the risk of wheezing at follow up which is consistent with the data of others (Park, Golding, Carswell, et al 1986; Blair, 1977; McNicol and Williams 1969). Similar but non-significant relationships were seen with length of time since last attack and shortness of breath with attack. Whilst the former is likely to be highly related to total number of attacks, the latter is a subjective measure by parents of severity during an attack and is hence difficult to standardise as a measure of severity. These data appear to indicate that the severity of the disease has an important impact upon the likelihood of persistence of symptoms, but the relationship is weakened by the lack of definition of exactly what constitutes an 'attack' of wheezing.

The data allows a tentative exploration of which factors are important in determining the persistence of wheeze. It shows that low birth weight, maternal cigarette smoking,
wheezing in the absence of colds, nocturnal worsening of wheeze and number of attacks of wheeze in the year prior to original survey were all related to a poor outcome on bivariate analysis. Further work on larger cohorts are required to investigate these factors and then it may be hoped that the accuracy of the diagnostic labeling of wheeze in pre school children as representing long term asthma and hence prognostic accuracy may be improved.

5.4 OUTCOME OF THE PRE SCHOOL COUGHING GROUPS (tables 4.15 and 4.16)

The study enabled the follow up of the sample of pre-school children complaining of recurrent cough in the absence of colds and characterized them in terms of symptom status, lung function, bronchial responsiveness, atopy, peak flow variability and nocturnal cough to investigate whether children with this symptom have cough variant asthma (CVA).

The poor response rate to the follow-up study and the long and short term repeatability of questions concerning cough (which proved not to be as repeatable as those found for wheeze (Cohen’s $\kappa$ was 0.38 and 0.46 respectively)) restrict the validity of any inferences drawn. Both these findings may be due to the fact that cough in children was not perceived by many parents to represent a serious symptom and hence as a result the sample may be biased to some extent. Evidence for this can be seen in the analysis of
symptom profile at follow-up in the attending and non-attending group. In those who attended 46/93 (49.5%) were asymptomatic compared to 25/33 (75.8%) of the non-attending group, $\chi^2=6.85, P=0.009$. This indicates that when considering the physiological profiles obtained, the group studied was more symptomatic and therefore potentially more severe than that which exists in the true population. However there are few previous studies at a population level which look at this question and so even with these reservations in mind the group is still of interest.

The results indicate that over half of pre school children with recurrent cough outgrow the symptom in the early school years. Just over a third have continuing recurrent cough and less than ten percent start wheezing. The proportion starting to wheeze, 9/125 (7.2%) was no greater than that observed in the asymptomatic group 14/210 (6.7%) (table 4.7). This suggests that young children with recurrent cough have a favourable prognosis with respect to classical wheezy asthma, certainly within the time frame of follow-up.

The data also suggest that children still coughing at follow-up differ in some respects to children who have outgrown their cough. This group of chronic coughers shows an increased prevalence of nocturnal cough and an increased responsiveness to inhaled methacholine. Both these characteristics have been described as features of cough variant asthma (Holinger and Sanders, 1991; Yahav, Katznelson and Benzaray, 1982) and increased bronchial responsiveness has been described almost invariably in such cases (Holinger and Sanders, 1991; Yahav, Katznelson and Benzaray, 1982; Cloutier and Loughlin, 1981). It is interesting to note that nearly 17% of the control population exhibited the phenomenon of night cough. No normative data is available on night cough in this age group and therefore it is not possible to comment on the importance of this figure as an
absolute prevalence, other than to note that it is substantially less than that observed for
the chronic cough and wheeze group. A recent study, into the prevalence of cough in
healthy 8-12 year olds who were selected only if there was no family or personal history of
asthma/atopy showed that approximately 5% were heard to cough at night (Munyard and
Bush, 1996). However, the normal population in the Leicester cohort was younger with
approximately one third having a personal history of atopy and half with a family history of
atopic disease. When intergroup comparisons were carried out with respect to the various
risk factors for cough, namely recurrent otitis media, and lower respiratory tract infection,
no systematic differences between subgroups could be discerned. The same analysis was
conducted for exposure to environmental tobacco smoke. The proportion of children
exposed in each group was similar; group 0 - 25.7%; group I - 27.5%; group II - 39.5% and
group III - 40.0%; $\chi^2=3.88$, p=0.28. However, to ensure that none of these factors affected
the proportions with night cough, multivariate analysis was conducted and in the event
virtually identical results were obtained to those in the bivariate table (table 4.15) already
presented.

All four groups had a high incidence of family and personal histories of atopy. However the
numbers were too small to allow a meaningful analysis of the relationship between atopy
and the diagnosis or treatment of asthma. The chronic cough group did not exhibit
increased atopy compared to the other groups and did not have a higher prevalence of
eczema or a greater proportion with a parental history of atopy. Atopic personal and family
histories are described in some reports of CVA (Yahav, Katznelson and Benzaray, 1982;
Hannaway and Hopper, 1982; Konig 1981). No differences in lung function were
discernable between groups which is consistent with the many other studies of CVA where
ventilatory function was often within normal limits (Yahav, Katznelson and Benzaray,
Hannaway and Hopper, 1982; Cloutier and Loughlin, 1982; Konig 1981). In the Tuscon Study of recurrent cough, children with this symptom had ventilatory function indistinguishable from children who were symptom free; children with recurrent cough and wheeze had reduced ventilatory function (Wright, Holberg, Morgan, Taussig, Halonen and Martinez, 1996). Peak flow variability was not significantly increased in the chronic cough or wheeze group. This has not been widely investigated in other studies. This fact is consistent with the hypothesis that cough and bronchoconstriction operate through distinct and separate airway reflexes (Fujimura, Sakamoto, Kamio and Matsuda, 1992;) and therefore peak flow variability (a presumed marker of airway lability) may not necessarily be increased. It is at odds however with the results of small study of Japanese children with Cough Variant Asthma who had increased peak flow variability when compared to controls (Tokuyama, Shigeta, Maeda, Takei, Hoshino and Morikawa, 1998).

Thus on a population level, chronic coughers appear to exhibit some features consistent with cough variant asthma. About one quarter of these children are diagnosed by their doctors as having asthma in the absence of reported wheeze, although only one tenth of these chronic coughers are prescribed treatment for their condition. If this group do indeed suffer from CVA then these two facts may indicate that both under diagnosis and under treatment are occurring. Reproducibility of questions on cough was relatively poor and some questionnaires from this group were incompletely answered. This reinforces the view that cough is not treated as a serious complaint by many parents and so it is perhaps not surprising that a low rate of diagnosis and treatment is seen.

If it is accepted that chronic coughers form a distinct group it would be of interest to investigate if any factors were important in increasing the likelihood of this outcome, as
large population-based studies have implicated various environmental exposures to be related to chronic cough (cough lasting at least three months) (Neas, Dockery, Ware, Spengler, Speizer and Ferris, 1991). This was investigated in the dataset using both bivariate comparisons and multiple logistic regression investigating the possible effects of age, follow-up time, gender, personal history of eczema, recurrent cough without a cold, lower respiratory tract infections, parental history of atopy, parental smoking, socioeconomic group, urban/rural domicile, pet keeping, child sharing bedroom and presence of mould in the bedroom. However, no important relationships were observed to operate in this relatively small number of children who we defined as having chronic cough. In our group chronic cough was defined as recurrent cough in the absence of colds continuing from original recruitment through to follow up. This will inevitably define a group distinct from that characterised by other workers as having cough lasting at least three months (Neas et al, 1991). It is possible that the cross sectional nature of the original study and the differential follow-up time used in the study may affect the results. To investigate this issue, the analysis was repeated using multivariate techniques (proc glm and proc logistic in SAS (Statistical analysis software, 1985)) to take these factors into account but the results were unchanged.

Epidemiological studies focusing on the putative relationship between cough in children and asthma have not demonstrated the relationship between this symptom and bronchial hyperresponsiveness, but these looked only at current cough (within the last year) rather than chronic cough (Clifford, Howell, Radford and Holgate, 1989), or recurrent cough defined as two or more episodes of cough without a cold (Wright, Holberg, Morgan, et al, 1996). Data from our study indicates that children with persistent recurrent cough have increased bronchial responsiveness but do not have the lung function abnormalities or
atopic disposition of the children who have persistent wheeze. This may suggest that these two groups of children have fundamentally different disease processes operating or that chronic recurrent cough may be a manifestation of bronchial hyperreactivity; for chronic wheeze to persist additional factors such as an atopic diathesis and lung function abnormality may also be required to be present. Demonstrating which of these are causative and which are markers of these different respiratory symptoms is not possible from the data collected.

Other published series following up clinic-based populations of children with cough variant asthma have reported that a significant proportion go on to develop asthma characterised by episodes of wheeze and dyspnoea (Yahav, Katznelson and Benzaray, 1982; Hannaway and Hopper, 1982). These results are not comparable to our population-based study and relatively few of the recurrent cough group have developed wheeze within the time frame of follow-up. A longer-term follow-up of such children is required to determine their outcome later on in childhood.

5.5 NIGHT COUGH

This part of the study looked at the relationship between current wheeze and recorded night cough. It has described the nature and timing of overnight cough recorded in children with prior wheeze depending on their current symptom-status. It assessed the agreement between reported and recorded night cough and examined the relationship of recorded night cough with other measures of lung function, overnight arterial oxygen saturation as well as environmental influences.
It is clear that there is a relationship between current wheeze (within the last year) and both reported and recorded night cough. This is despite the poor agreement between reported and recorded night cough. This poor agreement occurred even when parents were asked to specifically report night cough during the two weeks of the study. The question in the symptom diary asked about cough which woke the child at night and this may be why the observed agreement is so poor. Overnight readings were only made on one visit and a repeatability study on our cohort revealed that there was poor repeatability in the recording of night cough, with a Cohen's kappa of 0.36. It should therefore be remembered that the overnight recording made on a random night during the two weeks which followed the study merely registered a "snap-shot" of overnight cough which should not be regarded as being representative of the clinical picture occurring every night. In this study at least one episode of multiple coughing was required to be heard before children were defined as having night cough. Other studies have classified children as having night cough even if only one single cough is recorded during the entire course of the study. Whilst the definition of night cough must be arbitrary, it is possible that a definition on the basis of one single cough overnight may be too sensitive and thereby obscure important differences between children with and without significant nocturnal cough. In the event, the proportion of children recording single episodes of cough was very similar to the proportion recording episodes of multiple cough. Twelve out of 59 (20.3%) currently asymptomatic recorded at least one single cough overnight compared to 11 out of 59 (18.6%) recording at least one episode of multiple coughing. The equivalent figures for the currently wheezy group were 18 out of 41 (43.9%) and 16 out of 41 (39.0%) respectively. Thus about 40% of currently wheezy children from our sample were heard to cough overnight whilst 36.2% were reported to cough at night regularly. A smaller proportion still
reported night cough in the diary, which is consistent with the under-reporting seen in other studies (Archer and Simpson, 1985).

Analysis of the other measures of bronchial reactivity, peak flow variability, overnight saturation and ventilatory function showed that there was little association between these measures of asthma-severity and the presence of recorded night cough. In no case did the presence of recorded night cough make a significant difference in the magnitude of the observed parameter. In the case of bronchial reactivity, the lowest value for this index was seen in the children in whom no cough was heard, which was the opposite of what may have been expected. This runs counter to the argument that excessive airway reactivity is an important sole determinant of night cough. Similarly, differences in mid expiratory flow and peak expiratory flow were not associated with the presence of night cough which indicates that night cough is not directly related to these aspects of ventilatory function. Although an increased variability and increased morning dip was found to be present in currently wheezy children with recorded cough, the change was not statistically significant. This contrasts with the literature where excessive morning dip and peak flow variability have been used to predict nocturnal worsening of asthma (Bellia, Visconti, et al, 1988). Children heard coughing at night had very similar mean levels of arterial oxygen saturation to those in whom no coughing occurred and no relationships were demonstrated. This may indicate that in our community-based sample, children were well or had well controlled asthma which contrasts with other studies looking at this aspect of overnight monitoring (Hoskyns, Heaton, Beardsmore and Simpson, 1991).
5.5.1 ENVIRONMENTAL INFLUENCES

The data on overnight temperature showed that lower average temperatures were associated with overnight cough and significantly so for those children with current wheeze despite the fact that due to problems with data handling, only 32 observations were available for analysis. This contrasts with previous data. (Melia, de Ve Florey, Morris, Goldstein, Clark and John, 1982; Strachan and Sanders, 1989). A borderline association of increased humidity was also found for current wheezy children with nocturnal cough. Although the presence of patches of mould or damp are associated with nocturnal worsening of asthma, workers in the UK studying data on the effect of humidity have previously shown no specific association (Strachan and Sanders, 1989). However an increased prevalence of damp housing conditions was found in young Norwegian asthmatics when compared to controls (Nafstad, Oie, Mehl, Gaarder, et al 1998). The temperature and humidity of the child’s bedroom may have direct effects on the subject's airway or may act indirectly by changing the environment to enhance the population of house dust mites or fungal spores.

No effect of maternal smoking was shown which is contrary to many other large scale epidemiological studies, although these looked at reported night cough rather than recorded night cough (Somerville, Rona and Chinn, 1988). The data also suggests that the receipt of antiasthma medication makes little impact on the proportion of children with recorded night cough, although it should be borne in mind that the sample size is relatively small.
5.5.2 TIMING OF COUGH EPISODES

It is of interest to note that children with a past history of wheeze who were asymptomatic at follow-up tended to cough in the morning, whereas children with current wheeze coughed throughout the night, but particularly so in the early part of the night. This data is similar to the observations of Thompson et al (1987), and is out of phase with the nadir in peak flow (Johnson, Anderson and Patel, 1984). As it was not possible to demonstrate any indices of either lung function, airway lability or bronchial responsiveness that would predict night cough, it is difficult to suggest which factors are responsible for the differences in the timing of overnight cough or indeed what significance the observation represents.
This study aimed to follow a population-based sample of pre-school children whose respiratory symptoms were identified in the first five years of life and obtain updated symptomatic and sociodemographic information from the cohort, measure lung function, airway reactivity, airway lability, atopic status and record night cough and overnight oxygen saturation. In this way it was hoped to test the hypothesis that pre-school wheeze and cough would predict a constellation of symptomatic and functional abnormalities in the early school years and that the abnormalities identified would be characteristic of the condition labelled asthma.

6.1 HOW WELL WERE THE AIMS REALISED?

The aims were only partially realised because of several factors.

The relatively poor follow-up rate meant only limited data were obtained on the cohorts who complained of respiratory symptoms in the original survey. These small symptomatic populations reduced the power of the study to identify early risk factors or tease out confounding variables. Symptomatic severity which did not reflect the true picture of these respiratory symptoms may have occurred via an attendance bias in those children more severely affected when contacted again at the time of follow up.

The cross sectional nature of the original cohort which ranged from 0 to 5 years at the time of the original study meant that even the original symptoms recorded may have been open to recall bias. The differential follow-up time which was unavoidable given the age structure of the original cohort and the manpower constraints imposed by the follow-up methodology led to a complex age structure at follow-up, seriously compromising the ability of the study to give insights into the natural history of early
respiratory symptoms. The design of the study meant that data were accrued in children whose original symptoms had been disclosed at a variety of ages from 0 to 5 years and were then followed up for a variable length of time depending on the age at the time of the original survey and their age when seen again in this study. Children who were still complaining of wheeze and recurrent cough would have reported symptomatic and functional outcomes at a span of differing ages. In this situation the analysis of the whole cohort (required by the power considerations of the study) became largely unworkable due to the complex multivariate techniques required to adjust for the variation in age at onset, follow-up time and age at follow-up.

The use of the unidimensional endpoint of bronchial hyperresponsiveness from which to calculate numbers required to test the hypothesis was another reason that the study failed to fully achieve its aims. The use of this single endpoint to test a hypothesis which is measured by assessing several different outcomes (i.e. symptoms, lung function, and airway lability) as well as bronchial hyperresponsiveness meant that the study lacked the power to provide sufficient data to robustly test the hypothesis. Although the data showed that a substantial proportion of pre-school children with wheeze continued to have symptoms, lung function and bronchial hyperreactivity consistent with the diagnosis of asthma, the data was unable to clearly delineate why some children with wheeze in the pre-school period outgrow their symptoms.

Analysis of a single symptom such as cough and wheeze across the whole pre-school age-range for the purposes of assigning risk of persistence or outcome requires the assumption that the symptom is indicative of an identical pathological process occurring in the population, regardless of age. That this assumption may not be valid has been alluded to already in the introduction and discussion of the thesis.
Despite these important reservations, the cohort remains of interest because of its relatively large size and its population-based origin. Some reasonably robust inferences may be drawn from looking at broad symptomatic and functional outcomes and by restricting subgroup analysis to narrow age bands.

**6.2 WHAT HAS BEEN LEARNED?**

Of obvious interest is the symptomatic outcome of the groups who in the pre-school era reported wheeze and recurrent cough. The ability to record data on some objective measures which have been used widely to characterise populations in terms of asthma severity provided some fascinating information. It is interest to see the divergent functional outcome of the pre-school wheeze group depending on whether or not ongoing wheeze was identified at follow up, even though the period of time between symptom ascertainment and recall was relatively short.

It has been shown that power calculations based on a single dimension of a condition characterised by a constellation of abnormalities yields inconclusive results. It may be possible in the future to plan more robust studies in the future by computing more complex power calculations based on detecting differences across a range of outcomes.

Whilst the relatively poor proportion attending for follow-up may have indicated that some of original group had more nascent symptomatology, another possible explanation was the arduous nature of the follow-up protocol. This has implications for future study design. Detailed physiological profiling could be undertaken more locally to
try to encourage a better follow-up rate; recent improvements in the portability of
testing equipment may make this a viable option for future studies.

The reassuring symptomatic outcome of the pre-school coughing group is of interest.
Very few of these children went on to develop asthma characterised by recurrent
wheezeing attacks. Much recent literature, including recent national guidelines (British
asthma guidelines co-ordinating committee, 1997) encourage clinicians to consider the
diagnosis of asthma in all children with recurrent cough and this has obvious cost and
safety implications if these children then receive anti-asthma therapy. Further study of
this group is required to see what the long-term outcome of this common, troublesome
early symptom is later on in childhood.

The analysis of early patterns of wheeze was necessarily limited but still provided some
intriguing insights. Children who wheezed only in response to colds in the pre-school
era had a lower risk of ongoing symptoms when compared to those who wheezed at
other times. This divergent outcome has not be apparent so early on in any other study
population and questions the blanket labelling of all wheeze as representing the same
underlying condition (Williams and McNichol, 1969).

The information gained from studying children overnight was limited and demonstrated
that measures of lung function, bronchial reactivity, atopic status and peak flow
variability were poor predictors of recorded overnight cough. The validity of these
observations are limited by the fact that recording over only a single night was
possible. However the data demonstrated a relationship between recorded night cough
and room temperature.
6.3 FUTURE RESEARCH QUESTIONS

An obvious area of future work would be to study a sufficiently large birth cohort prospectively to track wheezy children as they age in order to look at divergent symptomatic and functional outcomes to see if factors could be identified that operate to switch off the symptom of wheeze. The identification of such a factor or group of factors has obvious and potentially far reaching therapeutic implications. The influence of early viral infections has been cited by some as a potential modifier of the evolving immune response (Holt, 1994) and circumstantial evidence has been identified from epidemiological work (Strachan, 1989). This has stimulated much interest and would be amenable to future study when considering future prospective birth cohorts.

In a well-planned study the impact of pattern of wheeze (e.g. only with colds or with multiple triggers) could be tracked to determine whether early patterns truly reflect different underlying pathological processes.

A similar birth cohort study focussing on recurrent cough in the absence of colds may permit the identification of the small group of children with recurrent cough who go on to develop wheeze. This may in turn to more accurate diagnosis and treatment of children with cough and may prevent the indiscriminate treatment of this large group of children with anti-asthma drugs.

The demonstration of a relationship between recorded night cough and room temperature is worthy of further study and could perhaps yield data that could be used therapeutically to minimise the impact of night cough in sufferers.


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APPENDIX 1 - FOLLOW-UP QUESTIONNAIRE
INTERVIEW QUESTIONNAIRE

NAME OF CHILD:__________________________________________________________

M/F

DATE OF BIRTH:___________________________________________________________

ADDRESS:______________________________________________________________

_________________________________ POSTAL CODE ____________________________

TELEPHONE:_____________________________________________________________

DATE (AND TIME) QUESTIONNAIRE COMPLETED: ______________________________

Date

_________________________ Time

INFORMANT(S):____________________________________________________________

RELATION TO CHILD:_____________________________________________________

NAME OF GENERAL PRACTITIONER:________________________________________

ADDRESS OF GENERAL PRACTITIONER:_____________________________________

_________________________________________________________________________

_________________________________________________________________________

TELEPHONE:_____________________________________________________________

(Comments in brackets refer to prompts the interviewer may use)
1. Has your child ever had ATTACKS OF WHEEZING?  
   Yes[ ]  No[ ]

   If the answer is YES, please answer from question number 2. If the answer is NO, please leave out questions 2-12 and answer from question 12.

2. How old was he/she when the first attack of wheezing occurred?  
   Years [ ]  Months [ ]

2a. If the first attack occurred before the age of 6 months, please specify the age of onset (as near as you can say) in WEEKS
   Weeks [ ]

2b. If the wheezing has now stopped, at what age did it stop?  
   Years [ ]  Months [ ]

3. Since the first attack, approximately HOW MANY has he/she had?  
   Tick one only
   None [ ]  1-2 [ ]  3-5 [ ]  6-10 [ ]  11-20 [ ]  20-40 [ ]  40-60 [ ]  More than 60 [ ]

4. During the past 12 MONTHS, HOW MANY attacks of wheezing has he/she had?  
   Tick one only
   None [ ]  1-2 [ ]  3-5 [ ]  6-10 [ ]  11-24 [ ]  More than 24 [ ]

   If NONE, please go to question 6.

5. During the past 12 MONTHS, on average (as near as you can say) HOW LONG do these attacks last?  
   About 1 day [ ]  2-3 days [ ]  4-7 days [ ]  More than 7 days [ ]

6. How long is it since his/her LAST attack of wheezing?  
   Tick one only
   Less than 1 month [ ]  1-3 months [ ]  4-6 months [ ]  7-12 months [ ]  13-24 months [ ]  More than 25 months [ ]
7. Do these attacks cause him/her to be SHORT OF BREATH?
   Yes, always [ ]
   Yes, occasionally [ ]
   Not now, but used to [ ]
   No, never [ ]

8. Is his/her breathing ever ABNORMAL between attacks?
   Yes, always [ ]
   Yes, occasionally [ ]
   Not now, but used to [ ]
   No, never [ ]

9. Do these attacks occur: (Answer ALL please)
   a. When he/she has a cold? Yes [ ] No [ ]
   b. Occasionally apart from colds? Yes [ ] No [ ]
   c. When he/she is running or playing? Yes [ ] No [ ]
   d. With drinking or eating? Yes [ ] No [ ]
      If yes, please say which food or drink:________________________

10. When he/she is near, for example animals, dust, grass and so on?
    Yes [ ] No [ ]
    If YES, please say which:
        Animals [ ]
        Dust [ ]
        Grass [ ]

11. Do these attacks occur more frequently at any particular time of year?
    Yes [ ] No [ ]
    If the answer is YES, please indicate the 'BAD' months by ticking the appropriate box or boxes. If the answer is NO, please leave a blank.
    January [ ] April [ ] July [ ] October [ ]
    February [ ] May [ ] August [ ] November [ ]
    March [ ] June [ ] September [ ] December [ ]

12. Is the wheezing worse at any particular TIME OF DAY?
    Yes [ ] No [ ]
    If the answer is YES, is it WORSE: during the DAY [ ]
        during the NIGHT [ ]
12 Has your child at any time in the last 12 MONTHS been wakened at night by an attack of coughing when he/she DOES NOT have a cold or chest infection?  Yes [ ]  No [ ]

12a Has he/she been woken like this on a regular basis?  Yes [ ]  No [ ]
At what age did this start?  Years [ ]  Months [ ]
Still being woken regularly  Yes [ ]  No [ ]
At what age did it stop?  Years [ ]  Months [ ]

13 Does he/she usually have a cough WITH COLDS?  Yes [ ]  No [ ]

14 Does he/she usually have a cough APART FROM COLDS?  Yes [ ]  No [ ]

14a Has he/she coughed without a cold in the past?  Yes [ ]  No [ ]
What age did this start?  Years [ ]  Months [ ]
What age did this stop?  Years [ ]  Months [ ]

15 Has any doctor or Hospital told you that he/she has WHEEZINESS [ ]
ASTHMA [ ]
BRONCHITIS? [ ]
If the answer is YES, at what age was the diagnosis made?  WHEEZINESS  Years [ ]  Months [ ]
ASTHMA  Years [ ]  Months [ ]
BRONCHITIS  Years [ ]  Months [ ]

16 Does your child attend a clinic or see a doctor for wheezing? (or asthma or bronchitis)  Yes [ ]  No [ ]

17 Has your child ever taken any medicine for wheezing? (or asthma or bronchitis)  Yes [ ]  No [ ]
If YES, what date was it started?  Years [ ]  Months [ ]
If it has been stopped, when was it stopped?  Years [ ]  Months [ ]
What was the main symptom for which the medicine was prescribed?  Recurrent cough [ ]
Recurrent wheeze [ ]
Asthma/"bronchitis" [ ]
18 Has your child ever been admitted to Hospital with any of the following?

- Wheezing? [ ] Yes [ ] No
- Asthma? [ ] Yes [ ] No
- Bronchitis? [ ] Yes [ ] No
- Chest trouble other than wheezing [ ] Yes [ ] No

Please give details: ________________________________

19 Has your child ever suffered from any of the following conditions? If the answer is YES, please state the age at which it was diagnosed.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes - at age</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>a pneumonia</td>
<td>[ ]___________</td>
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<td>[ ] [ ]</td>
</tr>
<tr>
<td>b whooping cough</td>
<td>[ ]___________</td>
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<td>c croup</td>
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<td>d cystic fibrosis</td>
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<td>e bronchiolitis</td>
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<td>f other chest infection</td>
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<td>g recurrent ear infections</td>
<td>[ ]___________</td>
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<tr>
<td>h chest problems in the newborn period</td>
<td>[ ]___________</td>
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<tr>
<td>i a heart condition</td>
<td>[ ]___________</td>
<td>[ ]</td>
<td>[ ] [ ]</td>
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<tr>
<td>j any other serious condition</td>
<td>[ ]___________</td>
<td>[ ]</td>
<td>[ ] [ ]</td>
</tr>
<tr>
<td>k Had an operation to remove TONSILS</td>
<td>[ ]___________</td>
<td>[ ]</td>
<td>[ ] [ ]</td>
</tr>
<tr>
<td>l Had an operation to remove ADENOIDS</td>
<td>[ ]___________</td>
<td>[ ]</td>
<td>[ ] [ ]</td>
</tr>
</tbody>
</table>

Please give details: ________________________________

20 Has he/she ever had ECZEMA? (an itchy, dry rash on arms, face and legs) [ ] Yes [ ] No

At what age did this start? Years [ ] Months [ ]
If this has now stopped, at what age did it stop? Years [ ] Months [ ]

21 Does your child have recurrent/chronic nasal symptoms? [ ] Yes [ ] No

At what age did this start? Years [ ] Months [ ]
If this has now stopped, at what age did it stop? Years [ ] Months [ ]
22 Has your child had any allergies? Yes [ ] No [ ]
   If YES, please specify:__________________________

23 When your child was born, did he/she need to be admitted to the special care baby unit/neonatal unit? Yes[ ] No[ ]
   If the answer is YES, please give details:____________

24 Does he/she ever MISS SCHOOL because of chest problems? Never [ ] Sometimes [ ] Frequently [ ]

25 Was your child BREAST FED as a baby? Yes [ ] No [ ]
   If YES, for how long was he/she breast fed for Months [ ]

26 Have you any other comments about your child's health that you would like to make?__________________________

__________________________________________________________
__________________________________________________________
__________________________________________________________
__________________________________________________________
__________________________________________________________
__________________________________________________________
__________________________________________________________
__________________________________________________________
__________________________________________________________
__________________________________________________________
APPENDIX 2 - EXAMINATION FORM
CLINICAL EXAMINATION

GROWTH:  Height____ cm  centile  Weight____ cm  centile

NUTRITION: (Comment)  Normal [ ]  Overweight [ ]  Underweight [ ]

NOISY BREATHING:  Yes [ ]  No [ ]
If YES, then  Inspiratory [ ]  Expiratory [ ]  Upper Airway [ ]  Lower Airway [ ]

COUGH:  Yes [ ]  No [ ]  Dry [ ]  Wet [ ]

NASAL DISCHARGE:  Yes [ ]  No [ ]  Clear [ ]  Mucoid [ ]  Purulent [ ]

SKIN RASH:  Yes [ ]  No [ ]

ECZEMA:  Yes [ ]  No [ ]

CHEST DEFORMITY:  Yes [ ]  No [ ]  Excavatum [ ]  Carinatum [ ]  Other [ ] (Specify)_____
Retractions [ ]  Wheeze on auscultation: During tidal breathing [ ]  On forced expiration [ ]

ENT:  Retracted ear drums [ ]  Light reflex [ ]  Blocked nose: unilateral [ ]  Bilateral [ ]

HEART:  Normal heart sounds Yes [ ]  No [ ]

OTHER SYSTEMS:  Abnormality present Yes [ ]  No [ ]
If YES, specify_________________________
APPENDIX 3 - CERTIFICATE
JOE BLOGGS is a STAR!
APPENDIX 4 - DOMESTIC QUESTIONNAIRE
DOMESTIC QUESTIONNAIRE

NAME OF CHILD:______________________________

M/F

DATE OF BIRTH:______________________________

ADDRESS:____________________________________

____________________________________________

POSTAL CODE________________________________

TELEPHONE:__________________________________

DATE (AND TIME) QUESTIONNAIRE COMPLETED:__________

Date

Time

INFORMANT(S):________________________________

RELATION TO CHILD:______________________________

(Comments in brackets refer to prompts the interviewer may use)
YOUR HOUSE

In these questions, 'YOUR HOUSE' refers to the home where your child usually lives.

1  How long has he/she lived in the house? Years [  ]
   Months [  ]
1a Have you moved since answering the last questionnaire? Yes [ ] No [ ]
1b If YES, what date did you move here Yr [ ] Mo [ ]

2  How many rooms are there in your house?
   (NOT counting kitchens, bathrooms and toilets) Number of Rooms [  ]

3  Which fuel(s) do you use for cooking? none [ ] gas [ ]
   electricity [ ] other [ ]

4  Which fuels do you use for heating?
   (Tick more than one box if necessary)
   none [ ] coal [ ]
   electricity [ ] wood [ ]
   paraffin [ ] oil [ ]
   mains gas [ ] other [ ]
   bottled gas [ ]

5  Does your house have central heating? Yes [ ] No [ ]
5a If this has been installed since answering the previous questionnaire, when was this? Year [ ] Month [ ]

6  Do you keep a pet or bird Yes [ ] No [ ]
   If the answer is YES, Dog [ ] Years[ ] Months[ ]
   which pet(s)? Please Bird [ ] Years[ ] Months[ ]
   indicate how long you have had them Cat [ ] Years[ ] Months[ ]
   Horse [ ] Years[ ] Months[ ]
   (Tick more than one box if necessary)
   Other (please state which) Years[ ] Months[ ]

7  Does your child regularly (at least once a week) come into contact with friends' or relatives' pets or animals (eg pony)? Yes [ ] No [ ]

If the answer is YES, say which one.
In these questions, YOUR CHILD'S BEDROOM is the room in which he/she usually sleeps.

8 Does your child share his/her bedroom with others? Yes [  ] No [  ]

If YES, please state how many. ______________________

9 In your child's bedroom, during the winter months:

a is the room heated during the day? Yes[  ] No[  ]
b is the room heated during the night? Yes[  ] No[  ]
c is the window usually left open at night? Yes[  ] No[  ]
d does condensation ever form on the windows? Yes[  ] No[  ]
e does condensation ever form on the walls? Yes[  ] No[  ]
f are there patches of mould or fungus? Yes[  ] No[  ]

10 Please list any other rooms in your house affected by:

a Condensation or damp______________________________

b mould or fungus_________________________________

11 Do you think that your house is cold in winter? Yes [  ] No [  ]
YOUR FAMILY

We would like some information about the family living with your child, and in particular about the parents or guardians living with your child. (In single parent families, complete only A or B as appropriate). Section C should be completed by all families.

A FATHER or MALE guardian

Tick one only

Is he the: natural father? [ ] 
step father? [ ]
male guardian? [ ]
other? (eg grandfather) [ ]
please specify _____________________

2 How old is he? Years [ ]

3 Has he ever suffered from any of the following conditions?
   [ ] [ ] [ ] Don't know
   a asthma? [ ] [ ] [ ]
   b bronchitis? [ ] [ ] [ ]
   c hayfever? (sneezing, runny or blocked nose, sometimes itchy eyes, NOT associated with a cold [ ] [ ] [ ]
   d eczema? [ ] [ ] [ ]
   e other chest problems? [ ] [ ] [ ]

Please specify _____________________

4 Does he smoke cigarettes? Yes [ ] No [ ]
   If the answer is YES, how many does he smoke each day in the house? number [ ]

5 Has he smoked AT ALL since the year before your child was born?
   Yes, consistently [ ]
   Yes, intermittently[ ]
   Yes, but only before the birth [ ]
   Yes, but only after the birth [ ]
   No [ ]

If he has now stopped smoking since the last questionnaire, when did he stop? Year [ ] Month [ ]

6 What is his present job? Please give:
   a job title__________________________________________
   b grade or seniority_________________________________
B. MOTHER or FEMALE guardian

1. Is she the: Natural mother? [ ]
   step mother? [ ]
   female guardian? [ ]
   other (eg grandmother) [ ]

   Please specify__________________________

2. How old is she? Years [ ]
3. Has she ever suffered from any of the following conditions?
   a. asthma [ ] [ ] [ ]
   b. bronchitis [ ] [ ] [ ]
   c. hayfever [ ] [ ] [ ]
   d. eczema [ ] [ ] [ ]
   e. other chest conditions [ ] [ ] [ ]

   Please specify________________________________________

4. Does she smoke cigarettes? Yes [ ] No [ ]

   If the answer is YES, how many does she smoke each day in the house? number [ ]

5. Has she smoked AT ALL since the year before your child was born?
   Yes, consistently [ ]
   Yes, intermittently[ ]
   Yes, but only before the birth [ ]
   Yes, but only after the birth [ ]
   No [ ]

   If she has now stopped smoking since the last questionnaire, when did she stop?
   Year [ ] Month [ ]
6 Is she working at present? Yes [ ] No [ ]
If the answer is YES, please give:

a job title
b grade or seniority
c description of work

SECTION C

1 How many adults (aged 16 and over) usually live in your house? number [ ]

2 Not counting your child, how many CHILDREN under 16 usually live in your house? number [ ]

3 Please state the AGES (in years and months) and SEXES of these children

a: Years[ ] Months[ ] Male [ ] Female [ ]
b: Years[ ] Months[ ] Male [ ] Female [ ]
c: Years[ ] Months[ ] Male [ ] Female [ ]
d: Years[ ] Months[ ] Male [ ] Female [ ]
e: Years[ ] Months[ ] Male [ ] Female [ ]
f: Years[ ] Months[ ] Male [ ] Female [ ]
g: Years[ ] Months[ ] Male [ ] Female [ ]
h: Years[ ] Months[ ] Male [ ] Female [ ]
i: Years[ ] Months[ ] Male [ ] Female [ ]

4 How many of your child's BROTHERS suffer/suffered from the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>a asthma</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>b bronchitis</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>c hayfever</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>d eczema</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>e other chest conditions</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Please specify ____________________________
5 How many of your child's SISTERS suffer/suffered from the following conditions?  

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>a asthma</td>
<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
<td></td>
<td></td>
</tr>
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<td></td>
</tr>
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<td>d eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e other chest conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please specify ________________________________________

6 Does your child have a twin? Yes [ ] No [ ]
6a Are they identical? Yes [ ] No [ ]
6b If NOT, what sex are they? Male [ ] Female [ ]
6c Does the twin suffer from any of the following conditions?  

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b bronchitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c hayfever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d eczema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e other chest conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please specify ________________________________________

7 Are there any other household members who smoke? (not counting those mentioned) Yes [ ] No [ ]

If YES, please state HOW MANY Number of smokers [ ]

If any of the other household members have STOPPED SMOKING since the last questionnaire, please state WHEN they gave it up Year [ ] Month [ ]
This is the question for your child. Please answer accurately as possible.

The questions can be answered by filling in a number.

Example: Do you work full or part-time?

**UNIVERSITY OF LEICESTER MEMORANDUM**

**NAME**

**DATE FROM** .......................................................... **DATE** ..........................................................

**ADDR:**

To: ..........................................................

**OCCUPATIONAL CODING**

- Missing or not codeable

**DATI**

- code m#3 979

**PER**

- code m#2 97

**SEG**

- code m#1 99

**SC**

- 6 - housewife
- 7 - student/armed forces
- 8 - not applicable
- 9 - missing/uncodable
- 0 - unemployed

**ALL 4 3 FOR RETIRED**

Manual/nonmanual only important for group 3
YOUR CHILD

The questions in this section refer to the health of your child. Several questions are about WHEEZING. By this we mean breathing that makes a high-pitched whistling sound from the chest, not the throat.

1 Has your child ever had ATTACKS OF WHEEZING? Yes[ ] No[ ]

If the answer is YES, please answer from question number 2. If the answer is NO, please leave out questions 2-12 and answer from question 13.

2 How old was he/she when the first attack of wheezing occurred? 

   years months

2a If the first attack occurred before the age of 6 months, please specify the age of onset (as near as you can say) in WEEKS.

   weeks

3 Since the first attack, approximately HOW MANY has he/she had? Tick one only

   None [ ] 1 - 2 [ ] 3 - 5 [ ] 6 - 10 [ ] 10 - 20 [ ] More than 20 [ ] Missing [ ]

4 During the past 12 MONTHS, HOW MANY attacks of wheezing has he/she had? Tick one only

   None [ ] 1 - 2 [ ] 3 - 5 [ ] 6 - 10 [ ] More than 10 [ ] Missing [ ]

If NONE, please go to question 6.

5 During the past 12 MONTHS, on average (as near as you can say) HOW LONG do these attacks last? (with the normal treatment) Tick one only

   About 1 day [ ] 2 - 3 days [ ] 4 - 7 days [ ] More than 7 days [ ] Missing [ ]

   N/A [ ]
6 How long is it since his/her LAST attack of wheezing?  
Tick one only  
Less than 1 month
1 - 3 months
4 - 6 months
7 - 12 months
13 months or more

7 Do these attacks cause him/her to be SHORT OF BREATH?  
Yes, always
Yes, occasionally
No, never

8 Is his/her breathing completely normal between attacks?  
Yes  No

9 Do these attacks occur: (Answer ALL please)  
a. when he/she has a cold?  
Yes  No
b. occasionally apart from colds?  
Yes  No
c. when he/she is running or playing?  
Yes  No
d. with drinking or eating?  
Yes  No
If yes, please say which food or drink:

c. when he/she is near, for example animals, dust, grass and so on?  
Yes  No
If yes, please say which:

10 Do these attacks occur more frequently at any particular time of year?  
Yes  No

If the answer is YES, please indicate the 'BAD' months by ticking the appropriate box or boxes. If the answer is NO, please leave blank.

January [ ] April [ ] July [ ] October [ ]
February [ ] May [ ] August [ ] November [ ]
March [ ] June [ ] September [ ] December [ ]

Tick 1 2 3 4
Yes [ ] No [ ]
11 Is the wheezing worse at any particular TIME OF DAY?  
   Yes[1]  No[0]

   If the answer is YES, is it WORSE: during the DAY?  
   during the NIGHT?  

12 Has your child at any time in the last 12 MONTHS been wakened at night by an attack of coughing when he/she does NOT have a cold or chest infection?  
   Yes[1]  No[0]

13 Does he/she usually have a cough WITH Colds?  
   Yes[1]  No[0]

14 Does he/she usually have a cough APART FROM Colds?  
   Yes[1]  No[0]

15 Has any doctor or hospital told you that he/she has ASTHMA or BRONCHITIS?  
   Yes[1]  No[0]

   If the answer is YES, at what age was asthma or bronchitis diagnosed?
   [ ] years  [ ] months

16 Has your child ever suffered from any of the following conditions? If the answer for any is YES, please state the age at which it was diagnosed.

   a. pneumonia  [ ] Yes -at age  [ ]  No [ ]
   b. whooping cough  [ ] Yes -at age  [ ]  No [ ]
   c. croup  [ ] Yes -at age  [ ]  No [ ]
   d. cystic fibrosis  [ ] Yes [ ]
   e. bronchiolitis  [ ] Yes [ ]
   f. other chest infection  [ ] Yes [ ]
   g. recurrent ear infections  [ ] Yes [ ]

   Please give details:
   [ ] 4 yrs.
   [ ] 1-2 yrs.
   [ ] 2-3 yrs.
   [ ] 3-4 yrs.
   [ ] 4-5 yrs.
   Missing [ ]
17 Has he/she ever had ECZEMA? (An itchy, rash on arms, face and legs)  
Yes[ ]  No[ ]

18 Does your child attend a clinic or see a doctor for wheezing? (or asthma or bronchitis)  
Yes[ ]  No[ ]

19 Has your child ever taken any medicine for wheezing? (or asthma or bronchitis)  
Yes[ ]  No[ ]

20 Has your child ever been admitted to hospital: with wheezing? (or asthma or bronchitis) Yes[ ]  No[ ]
:with chest trouble other than wheezing? Yes[ ]  No[ ]
Please give details: __________________________________________

21 When your child was born, did he/she need to stay in hospital after his/her mother went home?  
Yes[ ]  No[ ]
If the answer is YES, please give details: __________________________

22 Does he/she attend day care, nursery school or play school?  
Yes[ ]  No[ ]
If you wish to make any other comments about your child’s health, please do so in the space below.
________________________________________
________________________________________
________________________________________
________________________________________
________________________________________
________________________________________
YOUR HOUSE

In these questions, 'YOUR HOUSE' refers to the home where your child usually lives.

1. How long has he/she lived in the house?
   - years
   - months

2. How many rooms are there in your house? (NOT counting kitchens, bathrooms and toilets)
   - number of rooms

3. Which fuel(s) do you use for cooking?
   - electricity
   - gas
   - main gas
   - bottled gas
   - other

4. Which fuel(s) do you use for heating?
   - electricity
   - paraffin
   - mains gas
   - oil
   - other

5. Does your house have central heating? Yes [ ] No [ ]

6. Do you keep a pet animal or bird? Yes [ ] No [ ]
   - Pet type
   - Dog
   - Cat
   - Horse
   - other
   - None
   - More than one

7. Does your child regularly (at least once a week) come into contact with friends' or relatives' pets or or animals (eg pony)? Yes [ ] No [ ]
   - IF the answer is YES, say which.
In these questions, YOUR CHILD’S BEDROOM is the room in which he/she sleeps.

8 Does your child share his/her bedroom with others? 
   [ ] Yes [ ] No

If YES, please state how many. _______ number of people

9 In your child’s bedroom, during the winter months:
   a. is the room heated during the day? [ ] Yes [ ] No
   b. is the room heated during the night? [ ] Yes [ ] No
   c. is the window usually left open at night? [ ] Yes [ ] No
   d. does condensation ever form on the windows? [ ] Yes [ ] No
   e. does condensation ever form on the walls? [ ] Yes [ ] No
   f. are there patches of mould or fungus? [ ] Yes [ ] No

10 Please list any other rooms in your house affected by:
   a. condensation or damp. [ ] Yes [ ] No
   b. mould or fungus. [ ] Yes [ ] No

11 Do you think that your house is cold during winter? [ ] Yes [ ] No

If you would like to add any comments about your housing, please do so in the space provided below.

____________________
____________________
____________________
____________________
____________________
____________________
____________________
____________________
____________________
____________________
YOUR FAMILY

We would like some information about the family living with your child, and in particular about the parents or guardians living with your child. (In single parent families, complete only A or B as appropriate). Section C should be completed by all families.

A FATHER or Male guardian

Tick one only

1 Is he the: natural father? [ ]
step father? [ ]
male guardian? [ ]
other? (eg. grandfather) [ ]

Please specify

2 How old is he? [ ]

3 Has he ever suffered from any of the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
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<td>c. hayfever? (sneezing, runny or blocked nose, sometimes itchy eyes or nose, NOT associated with a cold)</td>
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<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>e. other chest problems?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Please specify

4 Does he smoke cigarettes? [ ]

If the answer is YES, how many does he smoke each day in the house? [ ]
5 Did he smoke cigarettes during the year in which your child was born? Yes[ ] No[ ]

6 At what age did he finish full-time education? [11] years

7 What is his present job? Please give:
   a. job title ________________________
   b. grade or seniority __________________
   c. description of work __________________

   Is he self-employed? Yes[ ] No[ ]

   If he is at present unemployed, please tick box [ ] and give nature of last job. ______________________________

B MOTHER or female guardian

   Please specify ________

2 How old is she? [11] years
3 Has she ever suffered from any of the following conditions? 

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
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<tr>
<td>e. other chest conditions?</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
</tbody>
</table>

Please specify ________________________

4 Does she smoke cigarettes? Yes [ ] No [ ]

If the answer is YES, how many does she smoke each day in the house?

5 Did she smoke in the year that your child was born? Yes [ ] No [ ]

6 At what age did she finish full-time education? ______ years

7 Is she working at present? Yes [ ] No [ ]

If the answer is YES, please give:

a. job title: ________________________

b. grade or seniority: ________________

c. description of work: ________________

If the answer is YES, please state:

[ ] amount of time
[ ] hours per week
[ ] days per week
[ ] months per year
[ ] weeks per year
SECTION C

1 How many ADULTS (16 years and older) usually live in your house? [ ] number of adults

2 Not counting your child, how many CHILDREN under 16 usually live in your house? [ ] number of children

Please state the AGES of these children (in years and months)

a. b. c.
d. e. f.
g. h. i.

if no age code 88

3 Have any of your child's BROTHERS or SISTERS suffered from any of the following conditions?

a. attacks of wheezing?
   Yes [ ] No [ ] Don't know [ ]
   [ ] [ ] [ ]

b. asthma?
   Yes [ ] No [ ] Don't know [ ]
   [ ] [ ] [ ]
c. bronchitis?
   Yes [ ] No [ ] Don't know [ ]
   [ ] [ ] [ ]
d. eczema?
   Yes [ ] No [ ] Don't know [ ]
   [ ] [ ] [ ]
e. hay fever?
   Yes [ ] No [ ] Don't know [ ]
   [ ] [ ] [ ]
f. other chest conditions?
   Yes [ ] No [ ] Don't know [ ]
   [ ] [ ] [ ]

Please specify___________________________________________

___________________________________________

___________________________________________

4 Are there any other household members who smoke? (not counting those mentioned)
   Yes [ ] No [ ]

If the answer is YES, please state HOW MANY.

[ ] number of people

Yes - give number

Missing [99]
INTERVIEW QUESTIONNAIRE

NAME OF CHILD:______________________________

M/F

DATE OF BIRTH: day 6 11 mons 11 years 1:

ADDRESS:________________________________________

POSTAL CODE pc 1 1111 pc 2

TELEPHONE:

DATE (AND TIME) QUESTIONNAIRE COMPLETED: Day 11 mons 11

Date yq 11

Time

INFORMANT(S): inform [ ] mother [1]

RELATION TO CHILD: [ ] father [12]

NAME OF GENERAL PRACTITIONER: [ ] male guardian [3]

ADDRESS OF GENERAL PRACTITIONER: [ ] male guardian [4]

[ ] other

[ ]宪 parent

TELEPHONE:

(Comments in brackets refer to prompts the interviewer may use)

unless otherwise stated: no 101; yes 11

Don't know 12, 1919

Not applicable 18, 1818

Missing, uninterpretable 17, 1717
1. Has your child ever had attacks of wheezing?  
   Yes [ ]  No [ ]

   If the answer is YES, please answer from question number 2. If the answer is NO, please leave out questions 2-12 and answer from question 12.

2. How old was he/she when the first attack of wheezing occurred?  
   Year [ ]  Month [ ]

2a. If the first attack occurred before the age of 6 months, please specify the age of onset (as near as you can say) in WEEKS.
   Weeks [ ]

2b. If the wheezing has now stopped, at what age did it stop?  
   Year [ ]  Month [ ]

3. Since the first attack, approximately how many has he/she had?  
   Tick one only
   None [ ]  1-2 [ ]  3-5 [ ]  6-10 [ ]  11-20 [ ]  20-40 [ ]  40-60 [ ]  More than 60 [ ]

   During the past 12 months, how many attacks of wheezing has he/she had?  
   Last year [ ]

   If NONE, please go to question 6.

5. During the past 12 months, on average (as near as you can say) how long do these attacks last?  
   About 1 day [ ]  2-3 days [ ]  4-7 days [ ]  More than 7 days [ ]

   With the normal treatment.

6. How long is it since his/her last attack of wheezing?  
   Less than 1 month [ ]  1-3 months [ ]  4-6 months [ ]  7-12 months [ ]  13-24 months [ ]  More than 25 months [ ]
7. Do these attacks cause him/her to be SHORT OF BREATH? 
   - Yes, always [ ]
   - Yes, occasionally [ ]
   - Not now, but used to [ ]
   - No, never [ ]
   - N/A [ ]

8. Is his/her breathing ever ABNORMAL between attacks? 
   - Yes, always [ ]
   - Yes, occasionally [ ]
   - Not now, but used to [ ]
   - No, never [ ]
   - N/A [ ]

9. Do these attacks occur: (Answer ALL please)
   a. When he/she has a cold? 
      - Yes [ ]  No [ ]
   b. Occasionally apart from colds? 
      - Yes [ ]  No [ ]
   c. When he/she is running or playing? 
      - Yes [ ]  No [ ]
   d. With drinking or eating? 
      - Yes [ ]  No [ ]
   e. When he/she is near, for example animals, dust, grass and so on? 
      - Yes [ ]  No [ ]
   - Animals [ ]
   - Dust [ ]
   - Grass [ ]

10. Do these attacks occur more frequently at any particular time of year? 
    - Yes [ ]  No [ ]

   If the answer is YES, please indicate the 'BAD' months by ticking the appropriate box or boxes. If the answer is NO, please leave a blank.
   - January [ ]
   - February [ ]
   - March [ ]
   - April [ ]
   - May [ ]
   - June [ ]
   - July [ ]
   - August [ ]
   - September [ ]
   - October [ ]
   - November [ ]
   - December [ ]

11. Is the wheezing worse at any particular TIME OF DAY? 
    - Yes [ ]  No [ ]

   If the answer is YES, is it WORSE: during the DAY [ ]
   - during the NIGHT [ ]
12 Has your child at any time in the last 12 MONTHS been wakened at night by an attack of coughing when he/she DOES NOT have a cold or chest infection? Yes [ ] No [ ]

12a Has he/she been waken like this on a regular basis? Yes [ ] No [ ]
At what age did this start? Years [ ] Months [ ]
Still being waken regularly? Yes [ ] No [ ]
At what age did it stop? Years [ ] Months [ ]

13 Does he/she usually have a cough WITH Colds? Yes [ ] No [ ]

14 Does he/she usually have a cough APART FROM Colds? Yes [ ] No [ ]

14a Has he/she coughed without a cold in the past? Yes [ ] No [ ]
What age did this start? Years [ ] Months [ ]
What age did this stop? Years [ ] Months [ ]

15 Has any doctor or hospital told you that he/she has WHEEZINESS? Yes [ ] No [ ]
ASTHMA? Yes [ ] No [ ]
BRONCHITIS? Yes [ ] No [ ]

If the answer is YES, at what age was the diagnosis made? WHEEZINESS Years [ ] Months [ ]
ASTHMA Years [ ] Months [ ]
BRONCHITIS Years [ ] Months [ ]

16 Does your child attend a clinic or see a doctor for wheezing? (or asthma or bronchitis) Yes [ ] No [ ]

17 Has your child ever taken any medicine for wheezing? (or asthma or bronchitis) Yes [ ] No [ ]

If YES, what date was it started? Years [ ] Months [ ]
If it has been stopped, when was it stopped? Years [ ] Months [ ]

What was the main symptom for which the medicine was prescribed? Recurrent cough [ ]
Recurrent wheeze [ ]
Asthma/"bronchitis" [ ]
18 Has your child ever been admitted to Hospital with any of the following?

- Wheezing? Yes [ ] No [ ]
- Asthma? Yes [ ] No [ ]
- Bronchitis? Yes [ ] No [ ]
- Chest trouble other than wheezing Yes [ ] No [ ]

Please give details: ____________________________

19 Has your child ever suffered from any of the following conditions? If the answer is YES, please state the age at which it was diagnosed.

- pneumonia Yes [ ] No [ ] Don't know
- whooping cough Yes [ ] No [ ]
- croup Yes [ ] No [ ]
- cystic fibrosis Yes [ ] No [ ]
- bronchiolitis Yes [ ] No [ ]
- other chest infection Yes [ ] No [ ]
- recurrent ear infections Yes [ ] No [ ]
- chest problems in the newborn period Yes [ ] No [ ]
- a heart condition Yes [ ] No [ ]
- any other serious condition Yes [ ] No [ ]
- Had an operation to remove TONSILS Yes [ ] No [ ]
- or ADENOIDs Yes [ ] No [ ]

Please give details: ____________________________

20 Has he/she ever had ECZEMA? (an itchy, dry rash on arms, face and legs) Yes [ ] No [ ]

At what age did this start? Years [ ] Months [ ]
If this has now stopped, Years [ ] Months [ ]
At what age did it stop? Years [ ] Months [ ]

21 Does your child have recurrent/chronic nasal symptoms? Yes [ ] No [ ]

At what age did this start? Years [ ] Months [ ]
If this has now stopped, Years [ ] Months [ ]
At what age did it stop? Years [ ] Months [ ]
Has your child had any allergies? Yes [1] No [0] 
If YES, please specify: ______________________________________________________

When your child was born, did he/she need to be admitted to the special care baby unit/neonatal unit? Yes [1] No [0] 
If the answer is YES, please give details: ______________________________________________________


Was your child BREAST FED as a baby? Yes [1] No [0] 
If YES, for how long was he/she breast fed for Months [ ]

Have you any other comments about your child’s health that you would like to make? ______________________________________________________

Breathing _____ Blackouts [ ] Bouts [ ]

Hesitation [ ]
CLINICAL EXAMINATION

GROWTH:
Height 111

Weight 111

NUTRITION: (Comment)
Normal [ ]
Overweight [ ]
Underweight [ ]

NOISY BREATHING:
Yes [ ] No [ ]

If YES, then

Inspiratory [ ]
Expiratory [ ]
Upper Airway [ ]
Lower Airway [ ]

COUGH:
Yes [ ] No [ ]

Dry [ ]
Wet [ ]

NASAL DISCHARGE:
Yes [ ] No [ ]

Clear [ ]
Mucoid [ ]
Purulent [ ]

SKIN RASH:
Yes [ ] No [ ]

ECZEMA:
Yes [ ] No [ ]

CHEST DEFORMITY:

Recess [ ]
Excavatum [ ]
Carinatum [ ]
Other [ ]

ENT:
Retracted ear drums [ ]
Light reflex [ ]
Blocked nose: unilateral [ ]
Bilateral [ ]

HEART:
Normal heart sounds Yes [ ] No [ ]

OTHER SYSTEMS:
Abnormality present Yes [ ] No [ ]

If YES, specify_________
DOMESTIC QUESTIONNAIRE

NAME OF CHILD: ____________________________

M/F  MALE [ ]  FEMALE [ ]

DATE OF BIRTH: ___________ ___________ ___________

ADDRESS: ____________________________________________

POSTAL CODE: ___________ ___________ ___________

TELEPHONE: __________________________________________

DATE (AND TIME) QUESTIONNAIRE COMPLETED: ___________ ___________ ___________

INFORMANT(S): MOTHER [ ]  INFORMANT [ ]

RELATION TO CHILD: FATHER [ ]

female guardian [ ]

male guardian [ ]

other [ ]

road [ ]

UNLESS OTHERWISE STATED: no [ ]  yes [ ]

Don't know [ ]  [ ]

not applicable [ ]  [ ]

missing, uninterpretable [ ]  [ ]

(Comments in brackets refer to prompts the interviewer may use)
YOUR HOUSE

In these questions, 'YOUR HOUSE' refers to the home where your child usually lives.

1. How long has he/she lived in the house? Years [ ] Months [ ]

1a. Have you moved since answering the last questionnaire? Yes [ ] No [ ]

1b. If YES, what date did you move here? Yr [ ] Mo [ ]

2. How many rooms are there in your house? (NOT counting kitchens, bathrooms and toilets) Number of Rooms [ ]

3. Which fuel(s) do you use for cooking? none [ ] gas [ ] electricity [ ] other [ ]

4. Which fuels do you use for heating? none [ ] coal [ ] electricity [ ] wood [ ] paraffin [ ] oil [ ] mains gas [ ] other [ ]

5. Does your house have central heating? Yes [ ] No [ ]

5a. If this has been installed since answering the previous questionnaire, when was this? Year [ ] Month [ ]

6. Do you keep a pet or bird? Yes [ ] No [ ]

6a. If the answer is YES, indicate how long you have had the pet(s) (please state which) Years[ ] Months[ ]

7. Does your child regularly (at least once a week) come into contact with friends' or relatives' pets or animals (eg pony)? Yes [ ] No [ ]

7a. If the answer is YES, say which one.
In these questions, YOUR CHILD’S BEDROOM is the room in which he/she usually sleeps.

8 Does your child share his/her bedroom with others? Yes [ | ] No [ ]

If YES, please state how many.

9 In your child’s bedroom, during the winter months:

a is the room heated during the day? Yes [ | ] No [ ]

b is the room heated during the night? Yes [ | ] No [ ]

c is the window usually left open at night? Yes [ | ] No [ ]

d does condensation ever form on the windows? Yes [ | ] No [ ]

e does condensation ever form on the walls? Yes [ | ] No [ ]

f are there patches of mould or fungus? Yes [ | ] No [ ]

10 Please list any other rooms in your house affected by:

a Condensation or damp [ ]

b mould or fungus [ ]

11 Do you think that your house is cold in winter? Yes [ | ] No [ ]
YOUR FAMILY

We would like some information about the family living with your child, and in particular about the parents or guardians living with your child. (In single parent families, complete only A or B as appropriate). Section C should be completed by all families.

A FATHER or MALE guardian

Is he the: natural father? [ ]
step father? [ ]
other? (eg grandfather) [ ]
please specify _____________________

How old is he? [ ] Years [ ]

Has he ever suffered from any of the following conditions?

a. asthma? [ ] Yes [ ] No [ ] Don't know [ ]
b. bronchitis? [ ] Yes [ ] No [ ]
c. hayfever? (sneezing, runny or blocked nose, sometimes itchy eyes, NOT associated with a cold) [ ]
d. eczema? [ ] Yes [ ] No [ ]
e. other chest problems? [ ]
please specify________________________________________

Does he smoke cigarettes? [ ] Yes [ ] No [ ]

If the answer is YES, how many does he smoke each day in the house? number [ ]

Has he smoked AT ALL since the year before your child was born?

[ ] Yes, consistently [ ] Yes, intermittently [ ]
[ ] Yes, but only before the birth [ ]
[ ] Yes, but only after the birth [ ]
[ ] No [ ]

If he has now stopped smoking since the last questionnaire, year [ ] month [ ]

What is his present job? Please give:

a. job title _______________

b. grade or seniority _______________
c description of work

Is he self employed

If he is at present unemployed, please tick box and give nature of last job.

B MOTHER or FEMALE guardian

1 Is she the: Natural mother? [ ] step mother? [ ]
   female guardian? [ ]
   other (eg grandmother) [ ]

Please specify__________________________

2 How old is she? 2646 Years [ ]

3 Has she ever suffered from any of the following conditions? Don’t know

   a asthma [ ] [ ] [ ]
   b bronchitis [ ] [ ] [ ]
   c hayfever [ ] [ ] [ ]
   d eczema [ ] [ ] [ ]
   e other chest conditions [ ] [ ] [ ]

Please specify__________________________

4 Does she smoke cigarettes? Yes [ ] No [ ]

If the answer is YES, how many does she smoke each day in the house? number [ ]

5 Has she smoked AT ALL since the year before your child was born?

Yes, consistently [ ]
Yes, intermittently [ ]
Yes, but only before the birth [ ]
Yes, but only after the birth [ ]
No [ ]

If she has now stopped smoking since the last questionnaire, when did she stop?

Yes [ ] Month [ ]

Year [ ]
6 Is she working at present? Yes [ ] No [ ]

If the answer is YES, please give:

a job title

b grade or seniority

c description of work

1 How many adults (aged 16 and over) usually live in your house? number [ ]

2 Not counting your child, how many CHILDREN under 16 usually live in your house? number [ ]

3 Please state the AGES (in years and months) and SEXES of these children:

   sex

   a: Years[ ] Months[ ] Male [ ] Female [ ]
   b: Years[ ] Months[ ] Male [ ] Female [ ]
   c: Years[ ] Months[ ] Male [ ] Female [ ]
   d: Years[ ] Months[ ] Male [ ] Female [ ]
   e: Years[ ] Months[ ] Male [ ] Female [ ]
   f: Years[ ] Months[ ] Male [ ] Female [ ]
   g: Years[ ] Months[ ] Male [ ] Female [ ]
   h: Years[ ] Months[ ] Male [ ] Female [ ]
   i: Years[ ] Months[ ] Male [ ] Female [ ]

4 How many of your child's BROTHERS suffer/suffered from the following conditions? sex

   a: asthma
   b: bronchitis
   c: hayfever
   d: eczema
   e: other chest conditions

   sex

   Yes No Don't

   a: [ ] [ ] [ ]
   b: [ ] [ ] [ ]
   c: [ ] [ ] [ ]
   d: [ ] [ ] [ ]
   e: [ ] [ ] [ ]

Please specify

Note: If no. = 1 or 2 (ie. large family)

Keep 2 nd hard copy and code 17

male child

female child

male sibling

female sibling

male cousin

female cousin

uncle

aunt

unrelated male

unrelated female

Keep an questionnaire how many

subs affected are half subs or unrelated subs
5 How many of your child's SISTERS suffer/suffered from the following conditions?  

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>bronchitis</td>
<td></td>
<td></td>
<td></td>
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<td>eczema</td>
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<td></td>
<td></td>
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<tr>
<td>other chest conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please specify \[ \] how many suffer

If 2 or more suffer, then make +1.

6 Does your child have a twin? Twin [ ] No [ ]
6a Are they identical? Identical [ ]
6b If NOT, what sex are they? Male [ ] Female [ ]
6c Does the twin suffer from any of the following conditions?

<table>
<thead>
<tr>
<th>Condition</th>
<th>Yes</th>
<th>No</th>
<th>Don't know</th>
</tr>
</thead>
<tbody>
<tr>
<td>asthma</td>
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<tr>
<td>other chest conditions</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Please specify \[ \] how many suffer

If any suffer, make +1.

7 Are there any other household members who smoke? (not counting those mentioned) Yes [ ] No [ ]

If YES, please state HOW MANY Number of smokers [ ]

If any of the other household members have STOPPED SMOKING since the last questionnaire please state WHEN they gave it up Year [ ] Month [ ]

How many of the other smokers have stopped smoking since the last questionnaire? \[ \]
FLOW VOLUME LOOP

NAME: [Handwritten name]

STUDY NUMBER: SERIAL 6211

STUDY GROUP: [Handwritten numbers]

TECHNIQUE: Technique = GOOD/SATISFACTORY/UNSATISFACTORY (please circle)

BEST LOOP: (greatest sum of FVC and FEV1)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>FVC</td>
<td>L</td>
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<tr>
<td>FEV 0.5</td>
<td>L</td>
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<tr>
<td>FEV 1</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>MEF 25-75</td>
<td>L/min</td>
<td></td>
</tr>
</tbody>
</table>
CLINICAL INVESTIGATION SHEET

NAME CODED PREVIOUSLY NUMBER CODED PREVIOUSLY
DOB CODED PAST AGE DATE CHALLENGE
HEIGHT WEIGHT TIME MONDAY
ASTHMA YES [ ] NO [ ]
BASELINE 1 2 3 4 5 6 MEAN
Rrs6 mean vs baseline: Rrs6 = Rrs0
Tco2 mean vs baseline: Tco2 = Tco0
Fr mean vs baseline: Fr = Fr0

PRE-CHALLENGE PEAK FLOW L/MIN: P2 1

Asthma (mg/ml) 0 25 0.5 1.0 2.0 4.0 8.0 16.0 32.0
Nasthma (mg/ml) 2.0 4.0 8.0 16.0 32.0
Rrs6
Tco2
Fr

POST CHALLENGE PEAK FLOW L/MIN:
P2

CLINICAL ENDPOINT:
SALBUTAMOL
COUGH YES [ ] NO [ ]
WHEEZE YES [ ] NO [ ]
UNCO-OPERATIVE YES [ ] NO [ ]

B' DILATOR TEST YES [ ] NO [ ]
15 MINS POST SALBUTAMOL
Rrs6Hz (Rps) Tco2 (TcoPs) Fr (Rps) Sats (Satsps) 1

SKIN PRICK TEST (Positive if wheal > 1mm at 5-15 mins)
CD EL 3 CONTROL POS [ ] NEG [ ] HISTAMINE POS [ ] NEG [ ]
H D MITE POS [ ] NEG [ ] DOG POS [ ] NEG [ ]
CAT POS [ ] NEG [ ] GRASS POS [ ] NEG [ ]

BLOOD TEST YES [ ] NO [ ]
IgE RESULT (U/ml)

PTO +/

comment

0 = 4/3
1 = 3/3

VOLATILE THRESHOLD:

D40 RRs = confers [III]
D20 TCO2 = calms to [III]

0 - 99

Comment 1 is general comment about

1  = uneventful
2  = TCO2 endpoint not reached.
3  = RRs endpoint not reached due to rejection of
   first volume appeal by osmotic
   - RRs endpoint not reached.
4  = patient uncooperative
5  = patient RRs > 25D above predicted e
   bronchodilator tol.
6  = pt/patient rempt.
7  = pr wheezy o/e.
8  = kawmian factor (eg concurrent envir osc il)
9  = Excessive drift on transuteroin
   electrode (>1%).
10 = Excessive drift on transuteroin electrode (>1%).

Expected peak flow for height = except [III]
(see table of peaks for s' + v' vi height)

Kempt - please look at peak flow curve before

loading

   working

12 = no endpoint reached, although both
   oscilartce and TCO2 warranted res魅力

13 = no endpoint. TCO2 working. Oscilantce
   not working. No cough. No fluid from
c

14 = could not find/endosc"
COMMENT FOR METHACHOLINE CHALLENGE

0  uneventful
1  TcpO2 endpoint not reached
2  Rrs endpoint not reached because of rejection of flow-volume signals by oscillaire
3  Rrs endpoint not reached
4  patient uncooperative
5  patient Rrs0 >2SD's above predicted, ie broncholdilator test
6  subject/parent refused
7  subject wheezy on examination
8  Technical factor: computer not working
9  Excessive drift on tcpO2 probe (>10%)
10  Excessive drift on tcpO2 probe (>10%) and Rrs endpoint not reached, ie no endpoint.
11  Technical factor: tcpO2 probe not working
12  No endpoint reached for oscillaire and tcpO2, although both seemed to work well, and child responded clinically (cough or decr. PEFR).
13  No endpoint reached. TcpO2 probe worked normally, oscillaire did not; no cough from child.
14  Child unable/unwilling to use oscillaire, but successful challenge performed with tcpO2 probe
15  No endpoint reached although both oscillaire and tcpO2 probe worked normally; no response to methacholine from child (no cough or decr. PEFR)
SYMPTOMS: (Please tick box)

a. Did you cough today?  
b. Did you wheeze today?  
c. Were you short of breath today?  
d. Did your asthma wake you at night?  
e. Were you off school/work today?

NOTE: Peak flow measurements that are frequently one-third or more below your best may mean that your asthma is not properly controlled. Please check with your Doctor/Asthma Clinic about your treatment.

TREATMENT: Ask your doctor to write down the treatments prescribed for you below.

<table>
<thead>
<tr>
<th>WEEK 2</th>
<th>MON</th>
<th>TUE</th>
<th>WED</th>
<th>THUR</th>
<th>FRI</th>
<th>SAT</th>
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<th>MON</th>
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</tr>
</tbody>
</table>
10 cough episodes

DA study not completed on same day due to

No study parental refusal

cep = cough episodes

vol = number of coughs

cep 23 = number of cough episodes from 11pm -

12 midnightr

vol 23 = number of coughs heard (in total) from

how 11pm to 12 midnight.
AS OTHERWISE STATED, 0 = no, 1 = yes, 
= don't know, 8,88 = not applicable, 
= missing/uninterpretable, 

FINAL IDENTIFICATION,

NO:_, INITIALS:- 1st and last), serial: [ ] init: [ ]

DATE OF BIRTH),

p1: [ ] p2: [ ]

DATE OF QUESTIONNAIRE),

dayq: [ ] monq: [ ] yrq: [ ]

FIRMANT COMPLETER),

inform: [ ]

DATE ASTHMA SURVEY

CHILD,

FOR [0,1], wheeze: [ ]

AT 1st ATTACK, IF NON-WHEEZER TYPE <RETURN>),

year1 [ ] mon1: [ ] week1: [ ]

YEARIZING STOPPED),

totalno: [ ] lastyear: [ ] length: [ ]

SOBA: [ ] SOBN: [ ]
cold: [ ] nocol: [ ] run: [ ] eat: [ ] dust: [ ]

ING),

month: [ ] trim1: [ ] trim2: [ ] trim3: [ ] trim4: [ ]

time: [ ] day: [ ] night: [ ]

DATE ASTHMA SURVEY

UGH AWAKE?),

cawake: [ ] cawaker: [ ] yrcaws: [ ] moncaws: [ ]
cawstill: [ ] yrcawe: [ ] moncawe: [ ]
UGHING),

ccold: [ ] cnocold: [ ]
cncpast: [ ] yrcncs: [ ] monncns: [ ] yrcnce: [ ] monncne: [ ]
AGNOSIS?), diag: [ ] yrwhee: [ ] monwhee: [ ]

yrast: [ ] monast: [ ]
J A L  NUMBER), serial:

(HEMOPHILIA ONSET), yrbron: monbron:

CLINIC?), asclin:

ATION?), asmed: yrmeds: monmeds:

ITALIZATION), medsym:

hospwhee: hospast: hospbron: hospches:

TE ASTHMA SURVEY" ILLNESS [1]?

...
<table>
<thead>
<tr>
<th>Code</th>
<th>Male Guardian</th>
<th>Female Guardian</th>
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<tbody>
<tr>
<td>3</td>
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**Household Information**

- mould:
- damp:
- cold in winter:
- affected rooms:
- guardian:
- relation:

**National Coding**

- code3
- code2
- code1

**Additional Information**

- serial:
- page: 11
### Asthma Survey

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### Challenge Peak Flows

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### Challenge Function

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### Volume Loop

- Volume: V
- Flow: F

### Technical Details

- TechPF: P
- TechFV: F

### Additional Information

- Serial Numbers: 0, 1, 2, 3, 4, 5, 6, 7
- Challenge Peak Flows: P1, P2
Asthma Survey

People in House:
- Adults:
- Children:

Ails of Children; If None Type <Return>, 1

- c1yr: [ ] c1mon: [ ] c1sex: [ ]
- c2yr: [ ] c2mon: [ ] c2sex: [ ]
- c3yr: [ ] c3mon: [ ] c3sex: [ ]
- c4yr: [ ] c4mon: [ ] c4sex: [ ]
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- c7yr: [ ] c7mon: [ ] c7sex: [ ]
- c8yr: [ ] c8mon: [ ] c8sex: [ ]
- c9yr: [ ] c9mon: [ ] c9sex: [ ]

Ails of Boys; If None Type <Return>, 1

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- brms: [ ]
- hayms: [ ]
- eczms: [ ]
- othms: [ ]

Ails of Girls; If None Type <Return>, 1

- asfs: [ ]
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- hayfs: [ ]
- eczfs: [ ]
- othfs: [ ]

Ails of Twins; If None Type <Return>, 1

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