UNIVERSITY OF SOUTHAMPTON

THE NATURAL HISTORY OF ASTHMA AND ATOPIC DISEASE IN CHILDHOOD AND THE RISK FACTORS CONTRIBUTING TO THEIR DEVELOPMENT

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Doctor of Medicine

MEDICINE

FACULTY OF MEDICINE, HEALTH AND BIOLOGICAL SCIENCES

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ABSTRACT

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Childhood asthma and allergic diseases are now commonplace. Work on a global basis has identified a dramatic rise in frequency of such conditions. This has been especially so in affluent developed nations. The search to identify the reasons for this phenomenon is ongoing but as yet clear answers have not been forthcoming. From existing knowledge it appears likely that a combination of genetic and environmental factors is responsible for these diseases.

This study represents the 10-year follow-up of the Isle of Wight 1989 Whole Population Birth Cohort. An important objective of this study was to clearly document the prevalence of asthma and atopic disease amongst a population of 10-year old children. However the primary aim of this study was to define the natural history of asthma and atopic diseases during the first decade of life. In the case of childhood asthma a phenotypic classification based upon patterns of wheezing over the first decade of life was employed. Using data obtained throughout the study a secondary aim was to identify risk factors conferring significant risk of developing childhood asthma and atopic disease.

The study population consisted of 1456 children from the Isle of Wight who had been recruited at birth in 1989. Previously information had been updated on subjects at 1,2 and 4-years of age. At 10-years, 1373 children completed ISAAC (International Study of Asthma and Allergies in Childhood) as well as supplementary questionnaires. In 1043 children further testing was completed including skin prick testing (SPT), baseline spirometry and methacholine bronchial challenge. Blood was taken for total and inhalant IgE screen testing.

Results identified considerable prevalence for asthma ever, current asthma and current allergies (eczema, rhinitis, urticaria) at 10-years. Phenotypic analysis revealed that a substantial proportion of early life wheezers (40%) were still wheezing at 10-years of age (Persistent Wheezers – PW). Such children typified the diagnosed asthmatic showing high degrees of atopy throughout childhood plus raised total IgE, impaired lung function and increased bronchial hyper-responsiveness (BHR) at 10-years. Furthermore they showed high disease morbidity and treatment needs. Considerable homology was observed between PW and Late Onset Wheezers (LW), who appeared to form a later manifestation of the same 'atopic asthmatic' state. A genetic predisposition for being asthmatic and atopic appeared to be the paramount risk factor for these states. Environmental factors appeared to be of secondary importance with early life smoking exposure, low Social Class and recurrent chest infections being of importance for PW but not LW. By contrast Early Transient Wheezers (ETW) who outgrew their symptoms displayed little evidence of atopy or BHR at 10-years. However they did show evidence of impaired lung function at 10-years which may be an inherent feature of their constitution. Analysis identified that recurrent chest infections, an asthmatic family history and atopic 4-year SPT were predictive of PW rather than ETW in a child wheezing during the first 4-years of life. Using such results it may be possible to target high-asthma risk children for specific early intervention. Risk factor analysis for current asthma, rhinitis and eczema at 10-years confirmed the importance of an inherited predisposition towards atopy for these conditions. The search to further clarify the aetiology of childhood asthma and atopy may therefore benefit from scrutinising the genetic characteristics of these states.

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Consent Form
ISAAC Written Questionnaire
Childhood Immunisation History
Physical Examination Record
Family History Questionnaire
Modified Postal Questionnaire
ISAAC Video Questionnaire
Supplementary Atopic Disease Questionnaire
Skin Prick Test Results Form
Baseline Spirometry Printout
Methacholine Bronchial Challenge Printout

PREFACE

This thesis reflects the work produced as a result of my involvement in the 10-year update of the Isle of Wight 1989 Whole Population Birth Cohort Study. I conducted this phase of the study, with the assistance of my *Research Team*, whilst registered as a postgraduate research fellow at the University of Southampton (1999-2001). Whilst the majority of work presented in this thesis is borne out of the 10-year study follow-up it should be noted that some data collected from earlier phases of this prospective study has been incorporated into phenotypic and risk factor analysis. Certainly without the hard work of my predecessors this phase of the cohort study would not have been possible in the form displayed within these pages. Finally I would like to take this opportunity to acknowledge the foresight and vision of my predecessors, Dr David Hide and Dr Hasan Arshad who originally established this unique birth cohort in 1989.

Ramesh J Kurukulaaratchy
February 2002

ACKNOWLEDGEMENTS

Firstly I would like to pay a very large tribute to the children and parents who returned in such large number for the 10-year update of the Isle of Wight 1989 Whole Population Birth Cohort Study. Without them this work would simply not have been possible. In addition, their great enthusiasm, generous support and genuine interest helped to make this study a fascinating experience to participate in.

I must thank my Supervisor Dr Hasan Arshad for initially giving me the opportunity to be involved with this remarkable study and also for his very considerable support and guidance since then. Sincere thanks are also extended to Professor Stephen Holgate for his immense interest in and ceaseless enthusiasm for this study.

The 10-year follow-up of this study was funded with the assistance of the National Asthma Campaign (UK). I must also acknowledge Pharmacia, UK, for providing kits for the measurement of total IgE and inhalant screen.

In a study of this magnitude, the presence of an excellent research team is an invaluable boon. The results obtained in this update of the study reflect the remarkable dedication and enthusiasm shown by the 1989 Study Team for their task. It was a pleasure to work with the 'team' and I thank them for enabling us to achieve what appeared impossible at the outset of this phase of the study. In this regard I must thank the Research Nurses Monica Fenn, Linda Waterhouse, Cathy Wilby and Sharon Matthews for their considerable roles in assisting me in the duty of seeing all these children. I also thank Heidi Savory and Tessa Booth for their tireless assistance in this context. I am grateful too to Roger Twiselton for his major assistance in providing analysis of IgE samples during this study. A well-coordinated and highly efficient administrative base for this phase of the study was another essential component for success. My secretarial colleagues Linda Terry and Gail Poulton nobly and faultlessly rose to this challenge and it is a testament to their efficiency (not to mention their 'never say die' attitude) that this follow-up of the cohort showed such a high follow-up rate. Furthermore their (and the rest of the 'teams') tolerance, enthusiasm, good humour and endless supplies of coffee were vital in keeping me going during the long journey that was this study.

Such was the scale of this study that most people working at the David Hide Asthma and Allergy Research Centre came to play some part in its conduct; whether it be photocopying mountains of paperwork or helping to keep the many children and families occupied as they passed through the Research Centre. To all these members of staff I extend my deepest gratitude.

Lastly, I would also like to thank one person, Padmini Kurukulaaratchy, who did not directly work on the study but whose support and guidance in unravelling the mysteries of computing and statistics was truly invaluable to me throughout the two years of this project. Thanks mother!

CHAPTER 1

ASTHMA AND ALLERGIC DISEASE IN CHILDHOOD
A LITERATURE REVIEW

1.1 BACKGROUND

1.1.1 Definitions of Asthma, Allergy and Atopy

Asthma is a condition that is not readily encompassed within a single defining phrase. However it may be considered a disorder of airway inflammation that displays very characteristic features. Central amongst these is obstruction of the lower airways that typically leads to one or more of the symptoms of wheeze, breathlessness or cough. By definition such obstruction shows some degree of reversibility, either spontaneously or after therapeutic intervention [1]. Associated with this airways obstruction is an increase in lower airway responsiveness to a variety of non-specific triggers including exercise, cold or dry air plus several pharmacological agents such as histamine and methacholine. Allergic causes too can act as potent triggers of such airways hyper-responsiveness.

Allergy refers to an abnormal immunological reaction to a foreign substance that leads to symptoms of disease. By definition the relationship of exposure and subsequent reaction is a specific and a repeatable one. A substance that may elicit this response is in turn called an allergen. In order to show such behaviour an individual must bear some predisposition to do so.

Atopy describes the tendency to produce specific antibodies of the Immunoglobulin E (IgE) class upon allergen exposure. The resulting reactions can play a role in a variety of clinical disorders including asthma as well as allergic rhinitis and atopic eczema.

1.1.2 The Ancient Origins of a Current Problem [2,3] – A Historical Understanding of Asthma and Atopic Diseases

Symptoms have been recorded since the very dawn of civilisation that might be attributable to asthma and the other atopic diseases. Indeed the terms *asthma* ('wind' or 'to blow'),

atopy ('strange disease') and *eczema* ('to bubble, boil, burst forth') were derived from the language of the Ancient Greeks to enable the description of a variety of symptoms. The word *allergy*, too, was created from a union of the Greek words *allos* ('different' or 'changed') and *ergos* ('work' or 'action') by the Austrian paediatrician Clemens Von Pirquet in 1906 [2].

Perhaps the earliest recorded descriptions of what we now term asthma appear in the Ancient Chinese scriptures [3]. During the time of 'The Red Emperor' Shen Nong *(c2700 BC)* mention is made of a disorder characterised by wheezing in the great reference work *Nei Ching Su Wen* (Canon of Internal Medicine). Shen Nong, known as the 'Father of Chinese Herbal Medicine' is credited as being the first to taste the substance ephedra used in the treatment of wheezing illnesses. The active ingredient of ephedra is now known to be ephedrine. That other ancient civilisations were aware of these diseases is illustrated by the Egyptians description of a condition akin to asthma in the *Ebers Papyrus (c1550BC)* [3]. Treatment of this condition included use of frankincense, yellow ochre, grapes and occasionally sweet beer.

There is much evidence from records of the Greco-Roman period to support a rudimentary awareness of allergic conditions during that era [3]. The Roman poet Lucretius *(c96-55BC)* observed that 'what is food for some, may be fierce poison for others' in what is widely regarded as a reference to food allergy. Meanwhile, Hippocrates *(c460-377BC)* is known to have hypothesised greatly about the aetiology of asthma. He proposed that asthma arose from an imbalance of the humors causing excess phlegm production in the brain, which then passed through the pituitary gland before condensing in the nasal cavities and finally accumulating in the lungs. Subsequently, Pliny the Elder *(AD 23-79)* described a possible role for pollens in causing respiratory distress. Others during this era such as Galen *(AD 129-199)* and Aretaeus the Cappadocian also added considerably to an evolving knowledge about asthma and its associations.

During the Middle Ages [3] understanding of asthma and related conditions developed steadily in Europe and the Arab world. The Persian Rhazes *(865-932)* is widely credited with the first characterisation of hay fever – which he described as 'rose fever'. A century later, the Jewish physician Maimonides *(1135-1204)* discussed the possible associations of

diet with asthma in his *Treatise on Asthma*. He is thought to have used such dietary intervention to treat the asthmatic son of the sultan Saladin. The Italian physician Cardan *(1501-1576)* meanwhile used an environmental intervention to treat the asthma of a Scottish Archbishop. It was only when the long-suffering priest's bed was changed from a feather to a silk one that his asthma began to improve. In the next century, the famous English physician Thomas Willis *(1621-1675)* proposed a neural mechanism for bronchoconstriction in asthma [3]. At this time several Europeans including Leonardo Botallo *(1519-1587)*, Johannes Rhodius *(1587-1659)*, Johann Binninger *(1628-1692)* and Jan Baptista van Helmont *(1577-1644)* described various aspects of pollen allergy induced symptoms. By the Eighteenth Century the phrase 'hay fever' had become commonplace in the English language [3].

In 1819, John Bostock *(1773-1846)* presented the classical description of hay fever or 'summer catarrh', largely based upon his own symptoms of recurrent seasonal nasal, ocular and chest complaints. Meanwhile John Elliotson *(1791-1868)* identified pollen as a major cause of hay fever. Both Elliotson and George Miller Beard *(1839-1883)* hypothesised that hay fever was commoner amongst the more affluent classes of the day. Later Charles Blackley [2,3] *(1820-1900)* was to conclusively demonstrate the role of pollen in hay fever through a series of meticulous experiments. Blackley conducted many of these studies upon himself and he was able to self induce symptoms of rhinitis, conjunctivitis and asthma following exposure to various pollens. He also correlated pollen counts to allergic symptom severity and demonstrated that using a filter to prevent inhalation of pollen could alleviate symptoms.

Understanding of asthma was revolutionised in the nineteenth-century by the invention of the stethoscope by Laennec *(1781-1826)*. Henry Hyde Salter *(1823-1871)* further enhanced this understanding by recognising various triggers for asthma – both environmental and psychological [3]. Trousseau *(1801-1867)* later made the important observations that asthmatics would often suffer with eczema or hives at some point in their lives whilst also recognising that there was a familial tendency for these conditions [3]. It was at this time that Quincke *(1842-1922)* [2] described angioneurotic oedema for the first time.

The twentieth-century has witnessed tremendous advancements in the field of asthma and atopic disease. Charles Richet *(1850-1935)* demonstrated anaphylaxis following a second injection of jellyfish antigen into a dog, *Neptunus*, which subsequently died [3]. At this time Von Pirquet *(1874-1929)* coined the term allergy to encompass a state of altered reactivity whilst also advancing an antigen-antibody theory as the basis for this state[2]. Following on from this Samuel Meltzer *(1851-1920)* proposed that asthma, rhinitis and eczema may be caused by allergic mechanisms [3]. It also became recognised that histamine played a significant role in allergic reactions following the work of Sir Henry Dale *(1875-1968)* [3]. However, mast cells and basophils were not identified as the source for histamine until the work of James Riley *(1912-1985)* and Geoffrey West *(1916-1990)* on a dog, *Julie*, which had a mast cell tumour [3]. Prausnitz *(1876-1963)* and Kustner *(1897-1963)* showed that transfer of allergen sensitisation could be done passively with serum transfer from an allergic to a non-allergic individual [2]. This led to the notion that a serum factor could be responsible for this allergic tendency and thus would be present in much greater quantity in an allergic individual. In the 1920s, Coca and Cooke [2] identified this serum factor as *reagin*. They characterised this factor as not being precipitated in serum by conventional methods, being heat labile and being capable of adhering to cells in the skin and inducing a wheal and flare response. These workers heralded the currently accepted classification of atopy with the inclusion of asthma, rhinitis, eczema and food induced urticaria as atopic diseases. Despite these developments it was not until 1967 that the husband and wife Ishizaka team identified *reagin* as being Immunoglobulin E (IgE) [2]. Taking serum from a patient highly allergic to ragweed pollen they raised antiserum in rabbits adopting the Prausnitz-Kustner technique. Then human immunoglobulins G, M, D and A were added to the serum to precipitate anti IgG, M, A and D antibodies. It was noted that following precipitation of known antibodies the Prausnitz-Kustner phenomenon persisted, suggesting the presence of another antibody for the identity of *reagin*. Indeed when the initial serum, rich in *reagin* was added, a precipitate was obtained. This was taken to be evidence for a new class of immunoglobulin crucial in atopy, and thus *reagin* became known as IgE.

1.1.3 An Inflammatory Condition – Cellular Mechanisms

Over a century ago Sir William Osler *(1849-1919)* is known to have speculated that asthma was an inflammatory disorder [3].

During the last few decades an enhanced understanding has arisen of the inflammatory mechanisms that contribute to the development of asthma and atopy [4,5]. There is now a large body of evidence that the major atopic states (asthma, rhinitis and atopic dermatitis) share very similar IgE mediated inflammatory mechanisms [5,6]. IgE, a symmetrical molecule produced by Type B lymphocytes and plasma cells, is normally the least abundant of the immunoglobulins in the circulation. In common with the other immunoglobulins, IgE has two antigen binding sites known as *Fab* regions that permit binding to allergen. These regions show a variability that allows a particular antibody to show characteristic specificity for different allergen types. The IgE molecule also possesses a single region, known as the *Fc* fragment, for attaching to cells that are effectors of inflammation such as mast cells, basophils, eosinophils, macrophages and platelets. This interaction has been shown to arise via the presence of specific IgE cell surface receptors borne by these cells. In the case of mast cells and basophils these receptors are of high affinity whilst eosinophils possess low affinity receptors. Consequently allergen binding by IgE will result in degranulation of IgE cross bound effector cells with release of mediators that orchestrate the allergic response.

Atopic inflammation is known to arise by stimulation of Type 2 Helper (TH_2) T lymphocytes upon allergen exposure rather than the alternate response pattern of Type 1 Helper (TH_1) T lymphocyte stimulation [5]. Stimulation of TH_1 cells results in cell mediated immunity against bacterial pathogens and also inhibits TH_2 responses through production of the soluble protein molecule, or cytokine, interferon gamma. In atopy [6], allergen binding to IgE antibody results in release of products from IgE bound effector cells. These cause activation of TH_2 lymphocytes leading to a distinct pattern of soluble protein molecule or cytokine production. Cytokines are now recognised to have a key role in the atopic process by acting as messenger proteins and modifying the behaviour of inflammatory cells [6]. In atopy, TH_2 derived production of Interleukin-4 (IL-4) and Interleukin-5 (IL-5) cytokines causes the recruitment of inflammatory cells like mast cells, basophils and eosinophils that produce a variety of inflammatory mediators [5].

First identified by Ehrlich in the 1870s, mast cells and basophils show brilliantly staining cytoplasmic granules when viewed at microscopy containing histamine, proteolytic enzymes, proteoglycans and chemotactic factors [2]. Additionally, mast cells and basophils

produce a variety of mediators including prostaglandins, leukotrienes and platelet activating factor (PAF) [6]. The most abundant of these mediators, histamine exerts a variety of effects including smooth muscle constriction with resulting bronchoconstriction [6]. Other actions include vasodilatation and increased vascular permeability as well as stimulation of nerve endings. Lipid mediators like cysteinyl leukotrienes, prostaglandins, thromboxane and PAF are also capable of potent inflammatory effects. Formerly known by the term *slow reacting substance of anaphylaxis* (SRSA) cysteinyl leukotrienes [7] comprise LTC4, LTD4 and LTE4. They exert their actions via specific receptors on target cells. In bronchial smooth muscle this leads to bronchoconstriction. Leukotrienes also cause increased vascular permeability contributing to the mucosal oedema seen in the asthmatic airway as well as increasing mucus secretion. Another important property of the leukotrienes is the ability to act as potent chemoattractants for inflammatory cells. PAF may be implicated in the formation of lipid mediators like the leukotrienes. PAF may also be partly responsible for stimulation of eosinophils and development of bronchoconstriction [8]. Prostaglandin D2 (PGD2) is another mast cell product with a potent role in bronchoconstriction [6].

In asthma, eosinophils under cytokine stimulation have long been identified as central players in the inflammatory process – so much so that the term *chronic eosinophilic bronchitis* has been used to describe asthma [9]. Their origin from precursor cells located within the bone marrow, predominantly in response to stimulation by IL-5, has been clearly documented [8]. IL-5 mediated stimulation also leads to production of a variety of granular proteins within the maturing eosinophil. These basic proteins like major basic protein (MBP), eosinophil peroxidase (EPO), eosinophil-derived neurotoxin (EDN) and eosinophil cationic protein (ECP) have been identified as possessing cytotoxic properties. Furthermore eosinophils themselves produce a range of cytokines and chemoattractants as well as lipid mediators and reactive oxygen intermediates that all contribute to the inflammatory response [8]. In addition to a vital role in eosinophil development, IL-5 along with the chemoattractant eotaxin is also influential in controlling eosinophil migration from the bone marrow [8]. Once in the peripheral blood eosinophils migrate to the target organ, which they then penetrate by passing through the vascular wall. Under the stimulation of IL-4 this process is facilitated by adherence to adhesion molecules within the vessel wall such as VCAM-1 and ICAM-1 [8]. Continual up-regulation of these cellular adhesion molecules may well facilitate the ongoing passage of inflammatory cells from circulating blood into

'allergic' tissues. In order to pass successfully through the basement membrane zone of the vessel wall eosinophils deploy metalloproteinases (MMP), the best characterised of which is currently MMP-9 [8]. Once in the target tissue the eosinophils become partially activated under the influence of IL-5, eotaxin and platelet activating factor (PAF) in conjunction with the action of β_2 Integrins. Further interaction with cytokines, immunoglobulins, lipid mediators and complement components ultimately results in eosinophil degranulation with release of toxic mediators and resulting inflammation [8]. Within the airway this leads to bronchial epithelial shedding and damage. Eosinophils have been shown to contribute to bronchial hyper-responsiveness (BHR) with evidence of a correlation between MBP levels and BHR [8]. It has been proposed that this may be in part due to an effect of MBP on bronchial epithelium as well as possible effects of MBP on M2 muscarinic receptors within the airways. In asthma, neural regulation by the autonomic nervous system is an important cofactor in the development of bronchoconstriction. Disordered neural regulation in the airways with loss of the M2 muscarinic receptor function that normally inhibits parasympathetic mediated bronchoconstriction could make an important contribution towards airways hyper-responsiveness [10]. MBP might mediate this loss of M2 muscarinic function [8].

Such inflammation has now been identified even in the well or asymptomatic atopic individual giving rise to the idea of a state of 'minimal persistent inflammation' in atopic disease. Thus atopic childhood asthmatics have been shown to possess evidence of significant eosinophil and mast cell infiltration in bronchial lavage aspirates even when clinically asymptomatic [11]. By contrast, non-atopic children with viral associated wheeze have not shown evidence of such inflammation when studied similarly.

This enhanced understanding of the mechanisms underlying atopic disorders has led to important developments in therapies acting through anti-inflammatory pathways [9]. The treatment of asthma has been revolutionised in this context by the use of inhaled corticosteroids [12,13] and most recently by leukotriene receptor antagonists [7].

1.1.4 The Natural History of Atopy in Childhood – The 'Allergic March'

The idea that a spectrum of common disorders share a similar aetiology but with varying end-organ expression has obvious attractions as a basis upon which to plan an effective

disease intervention strategy. Observation of the development of atopic diseases has made this notion even more inviting, for it is now well established that the evolution of atopy follows a characteristic pattern in many individuals [14-16]. It is highly likely that an interaction of genetic and environmental factors leads to the presence of an atopic state and that early childhood is the crucial time when such interactions occur. It has also long been known that allergen sensitisation in infancy initially happens to foods such as milk or egg but later becomes overshadowed by sensitivity to inhalant allergens like house dust mite, pollens and cat allergen [3]. This is clearly reflected in the prevalence of the different atopic conditions with atopic dermatitis and food allergy predominating in early life only to be replaced by asthma and rhinitis in later childhood [15,16]. The recognition that a similar inflammatory process underlies these seemingly distinct disorders has given birth to the concept of an 'Allergic March' describing the manner in which an atopic individual can develop different atopic states as time progresses [17]. This is not an entirely new idea. Since the beginning of the twentieth- century it has been felt that a child with atopic dermatitis may be at increased risk of developing asthma [3]. However, strong epidemiological correlates have now been established between asthma and atopic dermatitis. Work showing evidence of bronchial hyper-responsiveness (BHR) in both adults and children who had atopic dermatitis but no active respiratory symptoms [14,18,19] has further strengthened this link. As many as 40% of infants with atopic dermatitis may go on to develop asthmatic symptoms by the age of four [14]. Similar relationships have been established with regard to food allergy in infancy and the subsequent development of respiratory allergy [16,20-22]. For instance infants with a long-lasting sensitisation to food allergens have been shown to have a ten fold increased risk of developing asthma when compared with those who have never been food sensitised [16]. Additionally egg sensitisation in infancy has been shown to be associated with eczema, asthma, house dust mite sensitivity and high serum IgE at 7-years of age [22]. In a prospective Swedish study [21], 57% of children with IgE antibodies to egg white allergen in infancy developed IgE antibodies to inhalant allergens within the next 2 years. Further to this notion of an 'Allergic March', the presence of allergic rhinitis in later childhood has also been shown [23,24] to be strongly associated with coexistence of asthma.

Already intervention strategies have been aimed at interrupting this progressive metamorphosis of atopic conditions during childhood. Work concentrating on food allergen

avoidance in infancy has not been tremendously successful in this respect. In one such study [20] these measures led to reduced food allergy in infancy but failed to prevent the development of dermatitis, rhinitis and asthma at 7-years of age. Several projects have used anti-inflammatory strategies in those with the earliest manifestations of atopy in an attempt to curtail the later development of asthma. The agents used have included a variety of oral antihistamine preparations [25-28]. Bustos et al [26] used ketotifen in infants with a family history of major allergy plus elevated serum IgE levels but no history of bronchial obstruction. Treatment was for a 3-year period in this double blind placebo controlled study. Significantly fewer children treated with ketotifen became asthmatic. In previous work by Iikura [27], ketotifen had also been used for this purpose with encouraging results. Only 9% of a ketotifen treated group of atopic children developed asthma as opposed to 35% of those given a placebo. The population in this study had a history of atopic dermatitis without evidence of bronchial obstruction. Neither atopic family history nor IgE levels were regarded as inclusion criteria. It might therefore be claimed that children in this study had a narrower atopic potential than those studied in the later study by Bustos et al. The recently conducted ETAC study [25,29] has demonstrated a particularly effective role for another antihistamine, certirizine. This had already been shown to be effective at inhibiting bronchial eosinophil recruitment following bronchial challenge in allergic subjects [28]. Although a protective effect of certirizine was not seen in the overall ETAC Study [25], a different picture was noted when particularly high-risk subgroups were examined. In children sensitised to house dust mite and grass pollen a significant protective effect was conferred by using certirizine. The risk of developing asthma in those with atopic dermatitis plus a family history of atopy and either grass pollen or house dust mite sensitisation was reduced 50% by the use of certirizine when compared with placebo.

1.2 THE EPIDEMIOLOGY OF ASTHMA AND ATOPY IN CHILDHOOD

1.2.1 A Global Twenty-first-century Epidemic? Evidence from Prevalence Studies

At the advent of the twenty-first-century the high prevalence of asthma and atopic disease is a cause of major concern. The apparently high incidence of these conditions has not only been seen amongst the adult population but more worryingly in children too.

Over the past five decades studies have consistently shown a high incidence of asthma and atopy in children. Large geographical variations in these prevalence figures have also been noted. Whether the major influences upon these differences are environmental or genetic remains a matter of much debate.

One of the first to examine childhood asthma prevalence was Morrison-Smith [30,31] with work on schoolchildren in Birmingham, England commencing in the 1950s. In the first of a series of studies in Birmingham, the prevalence of diagnosed asthma in 20,958 children aged 5 to18-years was 4%, whilst wheezing was present in 6%. Boys were more commonly affected than girls at all ages studied. Furthermore, Asian or Black children born outside the UK were found to have lower asthma prevalence than those born in England. Since this pioneering survey many British studies have shown childhood prevalence rates for symptoms of asthma and atopic disease that are consistently among the highest in the world.

In a follow up of 2,702 British children born during a week in April 1970, a lifetime prevalence of wheezing of 21% was found at the age of 5-years [32]. Similar findings were shown in the 1970 British National Cohort with a lifetime prevalence of wheezing illness of 21% at 5-years and 27% at 10-years [32]. In a study of 2,700 7-year old schoolchildren in North Tyneside [33] in 1979, a lifetime prevalence of 11% for asthma symptoms was found amongst the whole population. Of these children the majority showed symptoms of asthma in the year immediately before the survey with twice as many boys experiencing wheeze as girls. The lower cumulative prevalence rate of wheeze in this study may reflect an underestimation of wheeze in early life owing to the manner in which data was obtained retrospectively. Nevertheless it is worth noting that in this, as with many other studies the prevalence of wheezing symptoms remained considerably greater than that of diagnosed

asthma. In a survey of 2,503 7 and 11-year old children in Southampton [34-36] in 1986, lifetime prevalence of wheezing in 7-year olds was 16% in girls and 23% in boys. Amongst 11-year olds the corresponding figures were 17% in girls and 20% in boys. Interestingly in this study, although at both ages asthma was commoner in boys, the male: female ratio for asthma was shown to decline throughout the first decade of life with peak incidence occurring earlier in males (5-years) than females (8-years). Additionally, this study also demonstrated substantial prevalence of atopy at both 7-years (26%) and at 11-years (32%). The National Survey of Asthma Prevalence in Great Britain [37] in 1992 further confirmed the high prevalence of such states in UK children revealing lifetime prevalence for wheeze of 24% amongst 1573 5 to 7-year olds with self-reported asthma among 13%, current nocturnal cough in 16% and exercise induced symptoms in 10%. A survey of 3,000 6 to 7-year old children in the North East of England [38] in 1999 has recently shown an even higher frequency of asthma symptoms. Lifetime prevalence of wheeze in this population was 30%. Figures for self-reported asthma were 23%; current nocturnal cough 28% and exercise induced wheezing 13%. Boys were more likely to show these symptoms or report an asthma diagnosis. Other atopic conditions were also common within this population. In addition to asthma, a lifetime prevalence of 28% for eczema and 10% for hay fever were seen. Whilst hay fever was commoner again amongst boys no significant gender difference existed with regard to eczema. Another nationwide survey [39] of 27,507 older British schoolchildren aged 12 to 14-years was conducted in 1995 as part of ISAAC - The International Study of Asthma and Allergies in Childhood. In this older age group 49% of the whole population had ever experienced wheezing, whilst only 21% had ever been diagnosed asthmatic. Exercise induced symptoms occurred in 29% of all children. Girls were more likely to have wheezed recently at this age although the opposite pattern was observed when diagnosed asthma was considered. Interestingly the geographical variation in asthma symptoms across the UK was small. Scotland was found to harbour higher prevalence of wheezing symptoms but not asthma diagnosis than England. This difference was small but significant. A similar higher prevalence for both wheeze and asthma diagnosis was found in non-metropolitan areas than metropolitan ones.

Several studies of asthma prevalence in the Antipodes have shown very high prevalence figures for asthma and atopy. The Australian arm of ISAAC [40] in 1993-94 revealed lifetime prevalence for wheeze of 39% among 6 to 7-year olds, with *diagnosed asthma ever* in 27%

and *current wheeze* in 25% of this group. Amongst 13 to14-year olds surveyed rates were even greater with lifetime prevalence for wheeze of 43%, *diagnosed asthma ever* in 28% and *current wheeze* in 29%. Whilst *current wheeze* was commoner in boys at 6 to 7-years an opposite pattern of female predominance was found in the group of 13 to14-year olds. *Eczema ever* was found in 23% 6 to 7-year olds with *current eczema* in 11% at that age. Corresponding figures for the older age group were 16% for having had eczema and 10% for *current eczema*. For both age groups eczema was commoner in girls. Rhinitis too was common with 18% 6 to 7-year olds having had *hay fever ever* whilst the corresponding figure amongst 13 to14-year olds was 43%. As with wheezing, rhinitis was commoner in boys for the younger age group but more frequent in girls for the older group. A study of regional differences in childhood asthma prevalence and atopy in New South Wales [41] has confirmed the high Australian incidence of asthma and atopic disorder. In a group of 6,394 8 to11-year olds, *recent wheeze* was found in 27% whilst diagnosed asthma rates were as high as 38% in some communities. High incidence of hay fever (as much as 43%) was also recorded. Atopic sensitisation rates ranging from 35% of the population to 42% were seen in this study. Similar findings have emerged from New Zealand. Data from the Dunedin birth cohort [42], 1981-82, showed lifetime prevalence for wheezing of 27% amongst 9-year old children. Almost 67% of such wheezing children were classed as having clinically significant asthma. In this population, high prevalence of atopy at skin test (46%) was recorded at 13-years of age. A comparative study of asthma prevalence in 12-year olds [43] showed higher prevalence figures in New Zealand children than their counterparts from South Wales, UK. Lifetime prevalence for asthma was 17%, with lifetime wheezing in 27% and exercise induced symptoms in 16% of the New Zealand group. These figures were all significantly higher than those of the Welsh group. Furthermore, 21% of the New Zealand children gave a history of hay fever – again significantly higher than the Welsh.

Studies in the USA have also demonstrated high prevalence for asthma and atopy in that region. The landmark Tucson Children's Respiratory Study [44] of 1,246 children found lifetime prevalence for wheezing illness at 6-years of age of 49%, with *current wheezing* in 29%. In Los Alamos, New Mexico [45] prevalence was examined in a high altitude environment amongst 567 12 to 14-year old children in 1992. It was perceived that such an environment would be associated with lower rates of atopy and asthma. Lifetime diagnosis

for asthma was still reported for 18% of children with *current wheeze* also reported for 18%. Boys were more commonly symptomatic than girls.

Prevalence studies in mainland Europe have tended to show intermediate prevalence rates for asthma and atopy with a tendency for lower prevalence in Eastern Europe. This was clearly illustrated by Von Mutius et al [46] in the early 1990s who compared asthma prevalence between 9 to 11-year old children in the former East and West Germany following reunification. This study showed significantly greater lifetime asthma prevalence in the West German (9%) than East German (7%) communities. Similar trends in prevalence of hay fever were noted with prevalence of 9% in the West and 3% in the East. Rates of atopic sensitisation also showed major differences with 37% being sensitised in the former West Germany but only 18% in the former East Germany.

A significant problem with interpretation of prevalence studies in this field has been the range of measurements and definitions used by different workers to describe respiratory symptoms. For instance although most studies have used lifetime and period prevalence measures some have used point prevalence as an indicator. Similarly some studies use a physician diagnosis as evidence of asthma whilst other studies take self-reported asthma as being indicative. Other studies look at wheezing symptoms rather than use the label of asthma. Thus comparison of figures from surveys using different methodologies is not always straightforward or valid. It is difficult to draw definitive conclusions that asthma prevalence is greater in one area than another if different means of classifying or recording asthma were used. The utilisation of standardised study techniques to collect and interpret data would negate this problem.

It was with this in mind that The International Study Of Asthma and Allergies in Childhood (ISAAC) was established in the 1990s. ISAAC has now reported global results on 463,801 13 to14-year old children in 56 countries [47]. Wide geographic variation in prevalence of asthma and other atopic states were identified despite standardised methodology. Asthma symptom prevalence was highest in largely English speaking 'westernised' countries like the UK, New Zealand, Australia, Eire, Canada, USA plus Central and South American countries. Rates in these countries were almost 20 times higher than those countries with lowest prevalence rates such as Indonesia, Greece, China, India and Ethiopia [47]. Atopic

eczema too showed high prevalence in regions showing high frequency of asthma [47]. However allergic rhinitis [47] did not necessarily follow the same prevalence patterns as asthma and eczema, with high levels of rhinitis occurring in some areas with low asthma prevalence. Whether this reflects differing aetiological mechanisms for these closely related conditions has yet to be determined.

ISAAC has consistently shown far lower incidence of asthma and atopic disease in many developing countries compared with more affluent Westernised countries. This has led to considerable debate as to whether features of a Western lifestyle might predispose to asthma and atopy. Previously [48-51]assessment of asthma prevalence in developing countries had not been as extensive as that achieved in more affluent countries. This may reflect poor funding and resources to conduct such work or alternatively a low incentive to investigate a condition that is perceived to be relatively uncommon in such countries. In the early 1970s, Anderson [49] examined asthma prevalence among a community of 2,000 in the Eastern Highlands of Papua New Guinea – an area where European contact was only established in 1933. No children or adolescents complained of past or present wheeze but prevalence of atopy amongst 122 6 to13-year olds skin prick tested in this survey was 14%. It was proposed that local environmental factors such as heavy parasitisation leading to high production of IgE were protective for asthma development and reactions to common allergens. Investigating this point, prevalence of asthma and atopy was assessed in Gambia, West Africa in 1974 [50]. Interestingly whilst asthma was not found at all in a rural population of 1,200 subjects, cases of childhood asthma were identified in the urban setting of Banjul, the capital city. Recently asthma prevalence was assessed in Ethiopia [48]. Almost 3,000 children under 10-years of age were assessed as part of a general population survey in 1996. Prevalence of wheeze in this age group was low – 2% in urban and 1% in rural communities. Atopic sensitisation rates to house dust mite were also low, being found in only 1% urban children. What factors are responsible for the lower prevalence of asthma and atopy found in developing countries remains a matter of speculation.

There is now a large body of work that shows a high prevalence for asthma and atopy in many different countries. However a large geographical variation in prevalence clearly exists between countries. The reasons for the high prevalence of these conditions in certain

countries will be a matter of great interest to researchers at the beginning of the twenty-first-century.

1.2.2 Are Asthma and Atopy in Childhood Really Becoming Commoner?

Prevalence studies of asthma and atopy appear to have shown a progressively increasing incidence for these conditions during the last decades of the twentieth-century. However methodological differences between studies carried out over time mean that it is difficult to claim a real increase in recorded prevalence unless similar methodology, definitions of asthma and interpretation of results were used in such work. Methodological variation may partly explain the findings of Anderson [52] who performed a meta-analysis of studies of asthma prevalence in the UK that were conducted between 1948 and 1964 using a variety of definitions. When *current wheeze* was compared between studies there appeared to be little change in prevalence over time. Alternatively *Asthma diagnosis* did show a trend towards increased prevalence with time. An additional problem with comparisons of prevalence studies is that as outlined above there are very real geographical variations in the prevalence of these disorders. Therefore studies claiming to portray a rising incidence of asthma and atopy ideally need to be conducted within the same population at two points in time and using identical methodology. Only a few planned serial studies have managed to meet this aim.

As described previously Morrison Smith [30,31] began looking at asthma prevalence in Birmingham, England in the 1950s. Three surveys of children were performed over 20 years - in 1956, 1968 and 1974. During this time the prevalence of asthma and wheezing rose from 2% to 6% [31].

The National Study of Health and Growth (1973-86) looked at primary schoolchildren in England for development of asthma symptoms [53]. Over the 13-year period a highly significant increase in prevalence of both reported asthma and persistent wheeze was seen. This was particularly so amongst girls who showed a 378% increase in prevalence for reported asthma and a 117% rise in persistent wheeze during this time. It is crucial to recognise that both actual respiratory symptoms as well as asthma diagnosis increased in prevalence during the span of this survey. Therefore this may well signal a 'real' increase in asthma prevalence rather than the effect of increased parental and physician awareness

leading to higher diagnostic labelling of wheezing as asthma, which might have provided an alternative explanation for such findings.

Review of the results from two national surveys in the USA [54], NHANES I (1971-74) and NHANES II (1976-80) has provided evidence of this trend in North America too. Between surveys, asthma prevalence for 6 to11-year olds increased from 5% to 8% in the USA.

Serial observation of a pair of 8 to10-year old Australian populations [55] in 1982 and 1992 also showed a clear increase in asthma symptoms with time. In the coastal town of Belmont prevalence of current wheeze rose from 10% to 28% whilst rates of physician diagnosed asthma quadrupled during the study. A noteworthy feature of this study was the use of objective measures of asthma prevalence such as bronchial challenge testing. Airway hyper-responsiveness to histamine doubled in Belmont over the decade observed. Curiously, however, atopic sensitisation did not change significantly during this period. Another study to use objective markers for asthma similarly showed a significant increase in the prevalence of exercise-induced bronchoconstriction amongst Welsh schoolchildren who were tested 15 years apart [56].

Although studies have looked at objective markers for an increase in asthma prevalence few have done likewise for atopic sensitisation. Nagakomi et al [57] reported findings from a series of general population samples of 13 to14-year old girls in Northern Japan who were assessed in 1978, 1981, 1985 and 1991 respectively. Presence of specific serum IgE to a panel of 16 common allergens was recorded. Figures revealed a steady escalation in proportions of children showing evidence of specific IgE production to at least one allergen during the 13-year period. This rose from 21% in 1978 to 39% by 1991.

1.2.3 Changes in Asthma Morbidity and Mortality

Morbidity and mortality figures can also provide an important insight into the changing prevalence of asthma. Fleming [58] showed a large increase in British general practitioner consultations for childhood asthma between the early 1970s and early 1980s. Increased prevalence may not have been the sole influence on these findings. Diagnostic transfer, that is changes in diagnostic practices or 'fashions' resulting in increased asthma diagnosis, may also partly explain these results. Increased awareness of asthma by parents and physicians

could also have led to an increase in reported asthma cases without a true rise in asthma prevalence. More recent findings [59] from the UK have suggested that this pattern of increasing general practitioner consultation for asthma may finally have begun to decline since 1993.

Hospital treatment rates for asthma may serve as another indicator for changes in prevalence over time. Hospital admissions for asthmatic children in Britain have risen dramatically in recent years [52,53]. Respective increases of 186% and 56% in admissions of asthmatic children aged 0 to 4-years and 5 to14-years were observed in the South-West Thames Region between 1978-85 [60]. This may in part reflect a true rise in incidence for asthma. Increased readmission of asthmatic children because of a shift in favour of hospital management may also have contributed to this spectacular finding. Recent findings from Oslo, Norway have confirmed a steady rise in childhood asthma admissions between 1980 and 1995 [61]. This was predominantly observed in those children less than 3-years old. However, in this survey whilst first admission rates increased throughout the study, readmission rates for asthma declined at the same time. This latter finding may reflect changing long-term treatment patterns for childhood asthma with an increasing usage of prophylactic therapies like inhaled corticosteroids reducing readmission rates.

Including both adults and children figures for England and Wales showed a steady increase in asthma mortality during the 1970s and 1980s although by the 1990s this had begun to decline [62]. Asthma deaths in children and young adults in New Zealand increased even more dramatically through the 1970s until the late 1980s when rates finally began to fall [62]. Although asthma mortality in the USA[62] during this period has been relatively low it too has shown a small but steady increase amongst children and young adults. These alarming figures may have been a direct consequence of increased asthma prevalence, particularly of increases in cases with severe disease. A further explanation proposed [62] is that in these affluent countries it is particularly amongst urban poor that mortality has shown considerable escalation. Thus poor socio-economic situation and disproportionately reduced access to adequate medical care in these subjects may also be contributing to escalating mortality figures independently of increasing disease prevalence itself.

In summary, there is now clear evidence from serial studies of prevalence as well as from morbidity and mortality data for a genuine increase in the prevalence of asthma and atopy. Identification of causal factors for this phenomenon will be of prime importance in future research.

1.3 RISK FACTORS FOR CHILDHOOD ASTHMA AND ALLERGY DEVELOPMENT

It is now apparent that the development of asthma and atopy in childhood depends upon a complex interaction of factors – partly genetic and partly environmental [63,64]. The exact nature of these interactions remains to be elucidated. In this section current knowledge about factors relevant to the development of asthma and allergy is reviewed.

1.3.1 Genetic Factors

That heredity plays a role in the development of asthma and atopy has long been recognised. In fact, Hippocrates ranks among the first to have noted a familial tendency for these conditions during the Greco-Roman period [3]. More recently Cooke and Vander Veer highlighted a heritable component to asthma, hay fever and urticaria [65]. However, it has only been in the last few decades that the nature of this inheritance has become better understood.

Evidence for an inherited tendency for asthma has partly arisen from twin studies. These studies are based on the premise that twins sharing the same environmental background will show differences in asthma concordance because of genetic factors. Thus Monozygotic twins sharing a greater proportion of their genetic background would be expected to display higher concordance than Dizygotic twins. Indeed, a twin study in Sweden [66] showed concordance for asthma in 5% of Dizygotic twins with a corresponding figure of 19% for Monozygotic twins. Similar results were found in a twin study in Australia [67] with regard to both asthma and hay fever. Whether such studies are completely free of bias is not clear. Martinez [68] raised some interesting points in this context. Are Monozygotic twins more likely to share the same environmental exposures than Dizygotic ones? If one of a Monozygotic twin pair is diagnosed asthmatic is there a lower threshold for labelling the sibling asthmatic in the event of minor wheezing? Another important insight into asthma aetiology provided by twin studies is the relatively low concordance figures for asthma amongst the Monozygotic twins studied. This would indicate that genetic factors alone are insufficient for disease expression and that environmental factors too must play a significant role in triggering asthma development.

Familial aggregation studies have also revealed inheritance patterns for asthma and atopy. This is clearly demonstrated by a recent study of 325 American families [69] that showed high parent-child concordance for asthma, eczema, hay fever and food allergy. Thus parents with asthma were found to be more likely to have children with asthma than parents without asthma. The incidence of atopic illness amongst children also rose with the number of parents who had atopic illnesses. In addition, the number of atopic illnesses amongst children was related to the number in the parents. Maternal atopy appeared to be a stronger association for both asthma and hay fever development than paternal atopy. Strong maternal influences upon lung function too have been identified in an aggregation study of 309 American families [70]. This study found strong mother and offspring correlation for lung function among families with asthmatic members. Further objective evidence for the role of genetic factors has been provided by Young et al who examined bronchial hyper-responsiveness (BHR) amongst 63 4-week old Australian infants [71]. Family history of asthma was identified as one of the significant risk factors for BHR in these children. Such findings on a consistent basis would indicate a plausible genetic contribution to BHR in asthma. Another study incorporating objective measures of BHR and atopy at skin test was recently conducted in New South Wales, Australia [72]. The use of such measurements in this study did not strengthen the association between parent and child asthma or atopy. Unlike many other studies in this field, maternal atopy or asthma was no more significant a risk factor for the childhood condition than was paternal disease. However, risk of atopy in the child was again significantly greater if both parents were atopic. Similarly, controlling for the effect of atopy by looking at non-atopic children, BHR was greater in offspring of parents showing BHR. These findings might therefore suggest that atopy and BHR are inherited independently.

Prospective cohort studies have shown further evidence for an inherited component to asthma and atopy development. Additionally such studies have consistently demonstrated a stronger influence for maternal or sibling disease than for paternal disease. In the Tucson study [44], maternal asthma was shown to be a significant risk factor for persistent childhood wheezing. Comparable relationships for atopic sensitisation were demonstrated in this study with the finding that maternal skin test positivity to alternaria was significantly linked to alternaria sensitivity in the child at 6-years [73]. Similar associations between parental and childhood atopy were found amongst the 4-year old children from the Isle of Wight whole

population birth cohort study, UK [74]. In this study, family history of atopy was found to be the most important risk factor for atopy at 4-years of age. Childhood asthma was also strongly associated with maternal asthma as well as maternal or sibling atopy. General family history of atopy was another significant association for both asthma and atopy in early childhood. Furthermore, children born to asthmatic mothers carried a threefold increased risk of being asthmatic or having rhinitis in early childhood.

Why maternal disease appears to have a greater influence upon atopy and asthma in the child remains unclear. Purely inherited factors may be the reason. However, transplacental intrauterine priming of the developing immune system against common allergens may be one significant explanation as to why atopic mothers may bear atopic offspring [75]. Whether cord blood specific IgG to inhalant allergens particularly may influence childhood immune responses towards less atopy in this way has also been suggested – possibly through down regulation of specific IgE production [75].

Candidate gene identification for asthma and atopy has evolved rapidly in the last decade. From such work it is clear that these disorders are polygenic in nature with several loci contributing to disease development [76].

Chromosome 5q has been shown to contain several genes associated with asthma and allergy development. Linkage to this region has been demonstrated for total serum IgE levels as well as BHR in allergy and asthma [77]. Factors vital for asthma and allergy development like cytokine function (IL-3, IL-4, IL-5, IL-9, IL-13, GM-CSF) and β_2 adrenergic receptor function have also shown linkage to chromosome 5q [65]. Evidence for linkage of circulating eosinophils to chromosome 5q31-33 has also been found [78]. Polymorphisms of the genes coding for these factors have been shown to influence various dimensions of the asthma phenotype [79]. The asthma phenotype therefore appears to have strong associations with chromosome 5q. Chromosome 6 has shown linkage to some asthma phenotypes such as mite sensitive and aspirin sensitive disease [65]. Chromosome 11q linkage to allergy and asthma has also been proposed, associated with genetic variation in IgE receptor genes. However evidence for this has only arisen amongst certain populations [79]. Chromosome 12q and chromosome 13 linkages for asthma and atopy phenotypes have

been reported [80] amongst several populations. A similar role for genes located on chromosome 14q has also been shown in patients with asthma and atopy.

In summary, genetic factors clearly have a very significant role in the development of asthma and atopy. From current evidence this appears to be particularly so for maternal factors. However it remains to be seen whether genetic factors alone can explain the aetiology of these states. It is evident that other contributing factors may also have important roles to play.

1.3.2 Gender

Male predominance for asthma and atopic diseases has consistently been demonstrated during the first decade of life [34,42,44,81,82]. Objective assessments of childhood atopy and asthma such as skin test reactivity in infancy [82] and BHR at 11-years [83] have confirmed this association with male gender. It is also apparent that these gender differences become less apparent with time, with equalisation of the male: female asthma ratio by puberty [34,54]. For example in the NHANES studies [54], prevalence of asthma in boys declined with age from 3 to 17-years whilst prevalence in girls rose steadily. Similarly peak prevalence for asthma was found to be earlier in boys (5-years) than girls (8-years) in an English survey [34]. Lung size and structure have been implicated in these patterns. It is known that the ratio of airway size to lung parenchyma size is lower in boys during early life resulting in a lower effective airway calibre [84]. Resting airway tone may also be higher in boys at this age [84]. Boys may show more pronounced changes in thoracic dimensions during growth with resulting lower prevalence of respiratory symptoms. Alternatively, is this male asthmatic tendency in early life merely a reflection of the fact that boys show higher atopic sensitisation than girls during this time? Why do girls show increasing asthma prevalence with puberty? Hormonal influences may participate in this process although this has not been convincingly demonstrated to date.

Evidently clear childhood gender differences in asthma and atopy exist. The mechanisms responsible for these findings remain to be elucidated, but may help to considerably enhance understanding of these conditions.

1.3.3 Atopy and Allergen Exposures

Strong associations between asthma and the atopic state have been noted since the beginning of the last century [2]. Studies of childhood asthma have overwhelmingly demonstrated higher frequency of atopic status in children with asthmatic symptoms than those without [34,44,85-87]. Furthermore it appears that atopy, whether reflecting skin test sensitisation or reported presence of atopic conditions, is closely associated with persistence of asthmatic symptoms in childhood [81,85,88].

A variety of individual allergens have now been identified that appear to be associated with asthma. Of these, the house dust mite (HDM) allergens have been found to be most prevalent on a global basis and so have been studied most extensively. Several species have been characterised in temperate zones including *Dermatophagoides Pteronyssinus, Dermatophagoides Farinae* and *Dermatophagoides Microceras*. Among these the former is the most prevalent in the UK inhabiting carpets, bedding and soft furnishings where it feeds on human and animal skin scales [62]. Digestive enzymes with proteolytic activity found in mite faecal pellets can act as potent allergens (Der p-1, Der f-1) with regard to development of asthma, rhinitis and eczema. It has been shown that degree of exposure to these allergens in early life may correlate with asthma in later childhood [89]. A birth cohort study to the age of 11-years [89] demonstrated high association between Der p-1 levels greater than *10mc*g /g dust in early life and asthma at 11-years. Additionally, HDM sensitivity at 11-years was strongly related to asthma at this age. With global adoption of westernised lifestyles with carpeting, soft bedding and furnishings it is certainly possible that HDM allergy may be a significant contributing factor to asthma development. Findings [90] from Papua New Guinea appear to confirm this viewpoint in that a much higher than expected asthma prevalence was noted amongst a population who had previously been noted to have scant prevalence of asthma. The increasing domestic use of cotton blankets had been documented within this study community in a major departure from their traditional lifestyle. It was also observed that such bedding was rarely washed and could provide an ideal environment for HDM species. Indeed when questioned retrospectively 89% of the asthmatic subjects in this study linked onset of disease to acquisition of this type of bedding [90]. Evidence of high HDM exposure was readily demonstrated. Measured HDM counts were particularly high in blankets and bedding (47 times greater than counts made from door surroundings in the

same houses). Furthermore asthma prevalence amongst adults correlated strongly with skin test sensitivity to HDM in this population.

Sears et al [87] have illustrated the relative importance of HDM compared to other aeroallergen sensitivities for childhood asthma development in New Zealand. Along with cat dander, HDM was shown to be a significant independent risk factor for asthma and BHR development compared to other aeroallergens.

Trials of dust mite avoidance in infancy have tried to modify this process. One of the original studies to do this was the Isle of Wight Intervention Study [91-93]. In this pioneering research, children at high risk of atopy were randomised at birth to an intervention program reducing exposure to HDM allergen plus food allergens in the first year of life. Reduction in HDM exposure was achieved by using an acaricidal preparation on the bedroom and living room carpets as well as to upholstered furniture. At the end of the first year of life, both asthma and eczema were significantly lower in intervention children. Skin test positivity also showed a significantly lower level in intervention children at 2 and 4-years of age [92]. However by these ages, whilst prevalence of allergy and that of eczema continued to be lower amongst children in the intervention group, asthma was no longer significantly less common amongst these children. Whether such intervention therefore has only a limited duration of benefit and needs to be conducted for longer periods of time might explain the apparent loss of protection in this study. These results might also reflect escalating allergen exposure outside the home environment as the child matures. Another point to consider with regard to this study was that a combination of both food and HDM allergen avoidance was used. Therefore clarifying which branch of intervention has provided any observed benefit that has accrued is open to speculation with this particular study. Further insights from this study are currently awaited as these children have recently been reviewed again at 8-years of age.

A recent meta-analysis of 23 HDM intervention studies [94] amongst dust mite sensitive asthmatics did not demonstrate a significant beneficial effect for commonly employed intervention measures upon asthma symptoms or peak flow measurements. This finding may prompt a search for more effective strategies in the future.

That other allergens may also be of significance to this process has been suggested by studies of childhood asthma in different environments. Sporik et al [45] showed that even in a high altitude environment where HDM exposure and sensitisation was low, the prevalence of asthma remained relatively high. Domestic pet ownership was high in this community with high degrees of sensitisation to the cat allergen, Fel d-1, being observed in these children. Thus it appears that in asthma a genetic predisposition to atopy may be reflected by sensitisation to the most prevalent local allergens rather than predefined sensitisation to a specific allergen like HDM. Consequently a range of allergens might be implicated in childhood asthma depending on the local allergen spectrum. In the desert environment of Tucson, Arizona the mould spore alternaria seems to have a significant link to asthma [73] with greater persistence of childhood asthma found in those who were alternaria positive. A study [41] of asthma in different climatic regions of New South Wales, Australia, has also suggested that despite markedly different allergen sensitisations between regions childhood asthma symptoms occurred to similar degrees. Thus whilst in humid coastal areas, HDM sensitivity was predominant, in temperate inland areas sensitivity to rye grass was also encountered to a high degree. Meanwhile, in drier inland regions a tendency to higher alternaria sensitivity occurred. Prevalence of asthma symptoms did not vary significantly between these regions despite such differences.

An association between atopy and BHR [95] has been consistently identified although the nature of this relationship is still poorly understood. It is unlikely to be a simple case of atopy-induced inflammation leading to BHR since non-atopic individuals too are known to show BHR [95]. Nevertheless, the importance of individual allergen sensitisation to BHR was shown in the CAMP study [96], USA, with strong independent associations shown between BHR in asthmatic children and sensitivity to alternaria, cat or dog dander. HDM sensitivity did not show the same effect. Results from adults participating in the ECRHS [97] have however demonstrated associations between BHR and sensitisation to HDM, cat and timothy grass.

Do atopy and allergen exposure play a primary causal role in asthma development? Accepted knowledge has long favoured a positive answer to this question. However, it is clear that not all atopic children experience asthma or show BHR. Recent reviews have measured 'population attributable risk' for atopy and allergen exposure (the proportion of

cases of asthma attributable to atopy and allergen exposure respectively). These have failed to show a major primary causal relationship for these factors with asthma [98,99].

Therefore, although childhood asthma may show strong associations with atopic status and allergen exposure these are not necessarily on their own causal in nature. Consequently complex interactions of atopy with other risk factors are likely to be of importance in determining the final expression of asthma in any individual.

1.3.4 Serum Total IgE

Since its identification as a principal participant in atopic responses [2] in the 1960s, IgE has consistently been linked with childhood asthma. Strong associations [21,45,100] have been found between IgE antibody production and current or subsequent atopic disease in children. In a prospective survey [21] of Swedish children, 69% of those with positive screening for IgE antibody in infancy subsequently developed atopic disease. Studies of asthma prevalence have consistently shown that children with asthma or persistent wheezing possess higher total IgE levels than those without [44,45,100,101]. Data from the Tucson Children's Respiratory Cohort Study has revealed that total IgE may 'track' with age such that children destined to wheeze persistently already possess high IgE levels at 9-months of age [101]. Meanwhile, in the Los Alamos study serum total IgE was almost ten-fold greater in asthmatic than non-asthmatic children [45]. Prevalence of allergic rhinitis too has shown close correlation with total IgE in both adults and children [23,102].

The importance of total IgE levels to asthma in 11-year old children was clearly shown in the Dunedin study, New Zealand. Presence of both diagnosed asthma and BHR were rare amongst those children in this study with total IgE values less than 32 IU [100]. In addition an interaction was observed in this population between IgE levels and FEV_1 / FVC ratio that was predictive for BHR at 11-years [103]. A role for total IgE in BHR has also been speculated on following observations in the Dunedin cohort that BHR increased in both prevalence and severity as IgE levels rose. This link between BHR and total IgE was seen to persist [100] even in asymptomatic children, without previous history of atopic disease indicating that BHR may have a significant association with total IgE independent of atopic symptoms. Several other studies have also suggested that IgE might have a role that is independent of atopic status in asthma development. A general population survey of

Spanish adults [104] showed a link between asthma and increased total IgE independent of specific IgE levels. A study of children and adults in Tucson, Arizona found a linear association between total IgE and asthma regardless of age [105].This was also found to be the case regardless of atopic status. Thus there is a body of evidence to suggest that total IgE may be an independent risk factor for asthmatic disease.

Cord IgE has been studied as a marker for subsequent allergic disease in childhood with some evidence of associations to atopic disorder such as eczema in infancy [106,107]. It is now evident that cord IgE holds little predictive value above family history of allergy in this respect [107]. Familial aggregation work has shown that asthmatic parents with high IgE levels had children showing high asthma rates with a strong correlation existing for both maternal and paternal IgE to IgE levels in such children [108]. However asthmatic children possessed much higher levels of IgE than could be predicted from parental IgE values alone. Hence the inherited tendency to produce high IgE levels probably reflects only one factor in asthma aetiology. Current evidence therefore indicates that whilst serum total IgE has many significant links with asthma, it alone is unlikely to explain the development of asthma in childhood.

1.3.5 Birth Factors

Interest in perinatal factors that might influence development of asthma and atopy in childhood has grown in recent years.

Conflicting results have been obtained with regard to birth weight and subsequent asthma. Some studies have documented that low birth weight is a significant risk factor for asthma and wheezing in infancy [82]. Data from the 1970 British Cohort Study found association between wheeze at 5-years and low birth weight [81]. Similarly relationships have also been found between birth weight and both atopic disorder as well as atopy at skin test during early life [82], but follow up of very low birth weight children into later childhood has frequently not confirmed persistence of this relationship [109]. Though analysis of the 1970 British Cohort Study [110] did show significant correlation between lowest birth weights and asthma prevalence at 26-years of age, other studies have failed to confirm any relationship between low birth weight and subsequent asthma. Data from New Zealand [111] suggested

that low birth weight is associated with a lower prevalence of reported asthma at 13-years of age.

Associations between other anthropometric measurements at birth and development of asthma and atopy have also been suggested. Assessments of head circumference and body length were made in children from the Dunedin birth cohort [111]. Analysis in this study found a link between head circumference at birth (>37cm) and raised serum IgE at 11-years. No such associations for IgE and birth weight or body length at birth were established. However birth length and asthma symptoms were significantly correlated. No associations of skin test positivity, hay fever or eczema with birth measurements were found. Thus it would seem that increased fetal growth might actually be a risk factor for childhood asthma and atopy. The mechanism by which this association acts remains unclear but suggests some form of intrauterine programming as a possibility.

Premature infants show greater prevalence of respiratory morbidity in childhood. Some studies [109] have shown associations between recurrent childhood wheeze and prematurity although it is debatable whether such wheeze reflects mechanical factors related to pulmonary growth and dimensions rather than true asthma. Any predisposition towards asthma and atopy arising from prematurity has still to be convincingly demonstrated [112]. One study of 9 to11-year olds in Munich [113] has revealed that significantly more premature girls had current asthma, recurrent wheezing and recurrent shortness of breath than girls born at term. This was not observed in the boys studied. Lung function in late childhood amongst prematurely born girls who were mechanically ventilated was also significantly lower in this study. Whether mechanical factors, as described above, accounted for this association of prematurity and lung function as well as the gender differences observed in respiratory outcome of premature infants remains to be seen. No differences were found for atopy and BHR between premature and term children at 9 to 11-years [113].

Association of birth season with asthma and atopy have been highlighted in some populations [114]. One study of 18-year old males born in 1963, identified higher asthma prevalence amongst subjects born between August and January [114], whilst a Swedish study of schoolchildren born from 1964-1972 in Gothenburg, showed higher allergic rhinitis prevalence amongst those born between November and May [114]. Other studies have failed

to show the same seasonal correlations [114]. These differing patterns may reflect differences in relevant allergen exposure experienced by the various populations during the first months of life. Such differences could also conceivably vary year by year within the same geographical regions leading to further variation in effect of birth season upon atopy and asthma. Thus it may be that birth season does not represent a consistent risk factor for childhood asthma and atopy.

In summary, several birth factors may contribute significantly to the development of asthma and atopic diseases, although much of the evidence for these remains inconclusive. Evidence from ongoing studies will help clarify the importance of such factors.

1.3.6 Breastfeeding

The effect of breastfeeding upon subsequent asthma and atopic disease has been the focus of several studies over the last 60-years [115-118].

Wright et al [115] demonstrated that children who were breastfed were less likely to suffer wheezing illnesses within the first 4-months of life. Although breastfeeding has been linked to protection from asthma and atopic disease in a prospective study [118] up to the age of 17-years, it has also been noted that there are several confounding factors that may be associated with infant feeding method and might also influence asthma development. For example in the Isle of Wight 1989 birth cohort study [117], mothers who formula fed were more likely to belong to lower socio-economic groups and to smoke than mothers who breastfed. Whilst breastfeeding appeared to protect against wheezing in the first year of life in this study, when confounding factors were taken into account breastfeeding was not associated with any significant protective effect for asthma or atopy in infancy [82,117]. That any effects of breastfeeding on atopy may be complex was also shown in this study by the fact that formula feeding before 3-months of age predisposed to asthma at 4-years [74]. Early introduction of formula feed increased the risk of any atopic disease. Thus it may be the age of introduction of other feeds rather than duration of breastfeeding that is the more salient risk factor in this context. This was borne out by a recent Australian study [116] that showed significant risk reduction for asthma at 6-years of age when exclusive breastfeeding had been continued for at least 4-months. Introduction of milk other than breast milk before

4-months of age was a significant risk factor for development of a wide range of indices related to asthma and atopy at 6-years of age. Whether such studies support a primary protective role for breastfeeding or alternatively a protective effect for delayed introduction of other forms of milk needs to be clarified.

More intricate insights into the relationship of asthma with infant feeding have emerged from the Tucson study [119]. In an analysis of 664 children, breastfeeding was examined along with maternal total IgE and total IgE in childhood. Maternal IgE was shown to be a vital determinant of the effect of breastfeeding upon IgE in the child. In mothers with lowest IgE levels, breastfeeding was associated with lower total IgE in the offspring at 6 and 11-years of age. When mothers with the highest IgE levels were considered it was found that breastfeeding of longer than 4-months duration was associated with higher IgE values in the child than children who were either never breast fed or fed in that manner for less than 4-months.

Several mechanisms might account for the complex associations of breastfeeding, maternal atopy and development of atopy in the child. Whether cytokines in breast milk of atopic mothers may 'prime' offspring to be atopic or if breastfeeding protects against infection and therefore accentuates a TH_2 pattern of lymphocyte stimulation in infants of atopic mothers have been postulated as explanations [119].

It is clear that breastfeeding has complex and sometimes perhaps paradoxical relationships with asthma and atopy development. Whilst this mode of feeding may protect against such diseases in certain situations, it may well increase the risk of asthma in those already at highest risk. Further clarification of these relationships in future work could have important implications for health education and practice.

1.3.7 Environmental Tobacco Smoke Exposure

Parental smoking has attracted perhaps more attention than any other environmental risk factor for the development of asthma and atopy. Tobacco smoke is known to contain a wide variety of noxious substances including polycyclic hydrocarbons, carbon monoxide, carbon dioxide, nitric oxide and nicotine [62]. Numerous studies have correlated parental smoking

with presence of significant respiratory morbidity in children [71,120-125]. Both wheezing and non-wheezing lower respiratory tract illnesses in infancy have shown strong association with maternal smoking habits [125]. Smoking by caregivers in a day-care environment has also been independently linked to respiratory morbidity in infancy [126]. A three fold increased risk was found between wheezing illnesses in the third year of life and smoking by care givers indicating the significance of increased tobacco exposure independently of home environment [126]. Levels of salivary cotinine (a nicotine metabolite) were significantly greater in wheezing children under 2-years of age than amongst non-wheezing 'controls' in another study [127]. Asthma prevalence has also been shown to be greater in children of smoking parents [120].

Maternal smoking, especially in pregnancy, has been shown to be a strong independent risk factor for wheezing in the first 3-years of life [81,122]. Increased cigarette consumption by the mother appears to parallel respiratory morbidity in the infant [120,125]. Children of mothers smoking more than 12 cigarettes per day possessed a 2.5 fold increased risk of developing asthma than children of mothers smoking less than 10 cigarettes per day [120]. This relationship appeared to be reliant on maternal levels of education, raising the possibility that increased smoking amongst women of lower socio-economic status may be contributing to the rise in childhood asthma seen in many communities. Conversely paternal smoking has not demonstrated the same potency as a risk factor [82,117,120,123]. This may reflect the fact that mothers are more likely to have prolonged close contact with children in infancy and therefore convey greater tobacco exposure to their child than smoking fathers. Other explanations have focussed on the importance of tobacco exposure through materno-fetal contacts *in utero* as well as via practices such as breastfeeding in infancy [124].

Several studies have shown that *in utero* and early life tobacco exposure may exert a strong influence upon wheezing and asthma in infancy but that this action becomes steadily less significant with time [74,82,117,122]. Data from Tucson has suggested that this may be due to the fact that early tobacco smoke exposure may be related to reduced lung function in infancy. This in turn has been linked to a specific form of 'early life transient wheezing' which remits during later childhood [122]. A recent review of longitudinal and case-control studies [123] confirmed that a large proportion of children with wheezing related to parental tobacco

smoke exposure did show a more benign form of wheezing illness. However this review also highlighted that in established asthmatics, disease severity was worse in the presence of parental smoking.

Objective measurements of lung function in children have demonstrated significantly lower lung function in the presence of significant tobacco smoke exposure. Thus a 16% difference was described in maximal mid-expiratory flow between children of heavy smokers and those of parents smoking less than 10 cigarettes per day [120]. Data from the Dunedin cohort study [121] has revealed similar findings on children aged 9 to15-years. Even amongst the whole cohort a mild degree of impairment in FEV_1 /VC ratio was persistently noted in boys regularly exposed to cigarette smoke. Amongst asthmatic or 'wheezy' children of both sexes, significant progressive decrements in FEV_1 / VC ratios were observed in those with smoke exposure. This is suggestive of a significant contribution for passive tobacco smoke exposure in the airflow limitation of wheezing and asthma. Confirmation of this notion has emerged from studies examining childhood bronchial responsiveness in relation to parental smoking habits [71,124,128,129]. Young et al [71] measured airway responsiveness in 4-week old infants and found a correlation between increased airway responsiveness and parental smoking. A study of 9-year olds in Italy [129] found significant correlation between smoking amongst parents and BHR to carbachol for boys in general as well as for children with known asthma. In contrast to other studies, baseline FEV_1 values were not significantly different for children with or without regular tobacco smoke exposure in this study. In addition the Italian study showed that boys with smoking parents had increased aeroallergen skin test sensitisation. This finding suggests that cigarette smoke exposure could have a role in development of the atopic state itself.

Other studies [124,130] have confirmed associations of atopy to parental smoking. Ronchetti et al [130] looked at changes in parental smoking habits and their influence upon skin test reactivity in their offspring over a 4-year period. Skin test sensitivity significantly increased in boys of parents who smoked or gave up smoking compared to sons of persistent non-smokers. Again boys showed greater associations with atopic sensitisation and smoking exposure than girls.

Whether total IgE independently interacts with smoking in asthma risk has also been suggested by findings of high total IgE with smoking in a general population survey in Tucson [102]. Even amongst non-atopic smokers high IgE remained strongly associated with increased asthma diagnosis and wheeze.

It would seem apparent that interventions to influence parental smoking habits and reduce childhood wheezing morbidity are necessary. Relatively few such studies have been implemented. A recent randomised controlled trial in Scotland [131] assessed the impact of advising parents of asthmatic children to stop smoking by measuring salivary cotinine levels in the children 1-year later. No significant differences were found to indicate that the intervention had successfully reduced smoking prevalence.

In summary, environmental tobacco smoke exposure has strong associations with the development of wheezing associated respiratory illness in childhood. However there is also a body of evidence to suggest a plausible link between such exposure and development of true asthma and atopy too. The extent to which smoke inhalation contributes to these disorders remains to be answered. Nevertheless, there is clearly a need for provision of effective intervention measures to modify future parental smoking behaviour in this context.

1.3.8 Early Life Respiratory Infections

The association of wheezing symptoms with respiratory infections in childhood is well recognised by parent and physician alike. Respiratory infections are particularly commonplace in early life and known to cause considerable morbidity [127,132-134]. Investigation has implicated various viral pathogens as causes for these illnesses; prime amongst these have been *Respiratory Synctial* (RSV) and *Parainfluenza* viruses. RSV infection is known to be associated with epithelial damage and denudation within the airways [134]. This may contribute to bronchoconstriction following such infections. Increased production of TH_2 cytokines after RSV infection has also been noted which could plausibly skew immune reactions towards an allergic bias [134]. A significant correlation between RSV in the first 3-years of life and risk of wheezing during the first decade of life has been demonstrated [133]. Prospective follow-up in Tucson, Arizona, showed increased development of both infrequent and frequent childhood wheezing illnesses in children who

had evidence of RSV infection in infancy [133]. This link was shown to be greatest in early life and then diminish steadily in later childhood such that by the age of 13-years, wheezing was no longer related to early infection with RSV. Observation of 'ER' admissions in the USA [1274] has confirmed strong links between RSV infection and wheezing in the first 2-years of life. Less marked but similar trends have been seen regarding other viruses like *Parainfluenza* virus [133]. Conversely, childhood atopy has not shown significant linkage to early viral respiratory infections [133]. RSV infection in the first 3-years of life has also been associated with lower measures of lung function subsequently [133]. Whether such results indicate that these infections affect lung development and function in childhood is debatable. The alternative hypothesis that diminished airway size and lung function may predate and predispose to wheezing associated viral respiratory infections appears more attractive currently.

Measurement of lung function in very early infancy was conducted as part of the Tucson study [44,135,136]. Subsequent observations showed that low initial lung function measured from tidal breathing curves remained persistently lower in children (particularly boys) who experienced wheezing with infection in the first year of life [135]. Follow-up [44] to 6-years of age has shown the persistence of low lung function in those with viral associated wheeze in infancy. It has also revealed that many such infant wheezers become symptom free in later childhood [44]. Other analysis on these subjects has identified that children who wheeze transiently with viral infections in infancy possess different immunological responses during these episodes than those who go on to wheeze persistently. Thus 'transient wheezers' were found to have lower IgE responses to acute viral infections with lower associated eosinophil counts than children who wheezed persistently [137]. Furthermore children with low serum IgE at birth have been found to be at increased risk of respiratory illness in infancy [106]. This reduction in IgE levels has been observed to 'track' through childhood in children with non-wheezing lower respiratory infections [138]. Such children have also been found [138] to be less atopic than children without early life respiratory infections. Long-term follow-up studies have failed to show correlation between childhood infections and prevalence of adult asthma. Results from the WHEASE study group in Scotland [139] found no relation between parental reported infection in childhood and asthma or atopy prevalence by the fifth decade of life.

A range of factors may be associated with viral associated lower respiratory tract illnesses in childhood. Studies have identified increased risk of such illness in children who share bedrooms and are exposed to other children in day-care facilities [140]. Similarly young maternal age has been implicated as a risk factor [140]. This in turn may have been confounded by the fact that young mothers were less likely to breastfeed and more likely to be smokers or less educated than older mothers [140].

Therefore there is significant evidence linking viral infections in infancy with childhood wheezing. However there is growing awareness that much infant viral associated wheezing is not necessarily associated with typical childhood asthma or atopy and may represent a distinctly separate wheezing phenotype. In this regard the emerging 'hygiene hypothesis' of asthma and atopy development implicates some childhood infections in a protective rather than causal role with regard to these conditions.

1.3.9 The 'Hygiene Hypothesis' - The Explanation For Rising Asthma Prevalence?

It is evident that the prevalence of asthma and atopic disease has shown significant increase in recent years. Much of this increase has occurred in affluent countries with good nutrition, medical care and sanitation. Meanwhile developing, less affluent countries continue to show lower overall prevalence rates. Furthermore, an intriguing observation in such developing countries has been the consistent finding of higher asthma and atopy prevalence in urban 'westernised' environments than rural ones. Does urban western lifestyle play an important role in asthma development? Asthma was undetectable in a rural community in Gambia [50] but readily seen in that nation's more affluent capital city. Asthma was also found less often in rural subsistence areas than an urban region of Ethiopia where people led a more affluent, westernised existence [88]. Similar patterns have been identified between rural and urban regions of China [141]. Children leading a less westernised lifestyle in Sweden show less asthma and atopy than their more westernised contemporaries [142]. This was revealed by a study of asthma prevalence among 295 5 to13-year old children drawn from 'anthroposophic' communities near Stockholm. These children led a more traditional lifestyle with regard to diet and housing plus reduced exposure to modern influences including vaccinations and medications. They were found to have lower rates of asthma, rhinitis and atopic eczema than control subjects. Atopic sensitisation (24% v 33%) was also lower in these children. In the former East German city of Leipzig prevalence of hay fever

and atopic sensitisation amongst 9 to11-year olds increased significantly over the 4-years following reunification and adoption of a more affluent western lifestyle [143]. Recently 12 to19-year old children raised in a farming environment in Quebec, Canada [144] have been shown to have lower prevalence of asthma than children with an urban upbringing. Rates of diagnosed asthma, current wheeze, measured bronchial hyper-responsiveness and atopic sensitisation at skin prick test were all significantly reduced in those children who grew up in a farming habitat. This was especially so for girls. Broadly similar findings have emerged from assessment of asthma and atopy among children from farming communities in Bavaria [145], Austria [146] and Finland [147]. It is not clear precisely what factors within the farming environment have influenced these findings. Certainly exposure to microbial pathogens may have been greater for a variety of reasons. Farming communities tend to have larger families leading to more sibling contact and potentially higher frequency of infections. The diet experienced by these farming children also may not have been as hygienically prepared as that of their urban counterparts thus increasing the risk of microbial exposure. Children raised on a farm may be more likely to lead an outdoor existence with greater exposure to sources of infection from animals as well as the environment in general. In two of these studies regular contact with farm livestock was inversely related to prevalence of both atopic disease as well as objective markers of atopic sensitisation [145,146]. Contrary to previous suggestions [148], animal contact may confer a protective effect against allergy development in certain situations.

The 'hygiene hypothesis' as a cause for asthma and atopic disease development has evolved as a direct consequence of the observations such as those described above [149]. It has been proposed that children who are atopic in childhood demonstrate impaired TH_1 responses with reduced interferon gamma production (IFN-γ) [150-153]. TH_1 responses are typically seen in cell-mediated immune responses against a variety of pathogens. Through negative feedback mechanisms they also impair the TH_2 responses seen in atopic individuals after allergen exposure. By increasing interferon gamma production childhood infections may have a protective role against atopy. Consequently aspects of modern 'hygienic' western lifestyles such as the use of antibiotics in early childhood, cleaner home environments and more refined diets may lead to a predisposition towards atopy generating TH_2 reactions. There is also now clear evidence that immune responses *in utero* show a predominance of TH_2 reactions that then normally converts to TH_1 predominance during

the postnatal period [149]. Fetal cytokine profiles have been shown to be of the TH_2 variety with high IL-4, IL-5, 1L-6, 1L-10 and IL-13 and reduced IFN-γ levels [154]. The reasons for this phenomenon are unclear, but it is likely to be exacerbated by maternal allergen exposures leading to transplacental priming of the fetal immune system [154]. Consequently it has been suggested, perhaps for genetic reasons, that atopic children show a delayed immune maturation pattern with delayed TH_1 function during the postnatal period [149]. This might reflect deficiency of TH_1 responses, like IFN-γ production in these children [154]. Clearly this deficiency could be potentiated by the effects of a hygienic environment with low microbial stimulation of IFN-γ, ensuring an alternative increased atopic tendency in childhood.

This 'hygiene' theory has recently been elaborated upon in a study of Italian males aged 17 to 24-years [155]. Atopic sensitisation was inversely related to markers of infection transmitted via the orofecal route or borne by contaminated hands or foods. Prevalence of atopic asthma and rhinitis showed a similar inverse relationship to markers of infections through the oral route. Other routes of infection were not found to have the same influence. This could reflect the importance of stimulation of gut associated lymphoid tissue in the development of a predisposition for TH_1 responses and consequent protection against atopic disease. Such work would seem to suggest that sufficient TH_1 stimulation via the oral route during immune maturation in childhood might have some protective effect against asthma and atopy. However, work with children in East Germany has also shown a higher prevalence of respiratory infections, but coexistent lower incidence of asthma than children in West Germany [46]. Alternatively a follow-up study in the Grampian region of Scotland [139] failed to show a significant association between the majority of common childhood infections and any reduction in subsequent wheeze, asthma or atopy. Nevertheless asthma diagnosis was less frequent where the child had measles in the first three years of life indicating that specific infections may indeed show a protective effect. Indeed, it would not be inconceivable that certain infections might tend the immune system towards TH_1 responses whilst others might tend it towards TH_2 responses. Thus the current understanding of the 'hygiene hypothesis' is likely to be a simplification of a rather more complex state of affairs.

Exposure to infections is perceived to be greater in environments of overcrowding. This may partly explain why the incidence of atopy and asthma is lower in less affluent developing communities that often possess larger family sizes and hence display an associated high incidence of infections [88]. Conversely western communities have seen a steady decline in family size resulting in less sibling contact as well as a trend for larger less crowded homes [156]. Several workers have looked at the association of sibship and risk of asthma development in this context. At a time when family size has declined steadily in the typical affluent western society the number of siblings in a family has been found to be inversely associated with symptoms of asthma in an individual [157]. Having two or more younger siblings was identified as a strong protective factor against asthma development in a Scottish study [139]. An inverse relationship has also been highlighted amongst German children with regard to atopic sensitisation at skin test and number of siblings in the household [158]. Day-care centres in western society could provide a potent arena for exposure to infection that mimics the risk of infection seen in large families in the developing world. Indeed it has been shown in Germany that children without siblings who attended day-care centres in the first 6-months of life had lower prevalence of asthma, hay fever and general atopy than those who only attended day-care in later childhood [159]. Similar findings concerning day-care in infancy and subsequent asthma and wheezing in childhood have recently been shown by the Tucson Respiratory Group in the USA [160].

Current evidence therefore suggests that the 'hygiene hypothesis' may explain some aspects of the recent spectacular rise in prevalence of asthma and atopic diseases. It may also afford a mechanism for new therapeutic measures to be created. Recent findings from Guinea-Bissau in West Africa have revealed that BCG vaccination within the first 3-years of life is linked to lower levels of atopic sensitisation among children aged 3 to14-years [161]. Presumably this situation arose through mycobacterial stimulation of TH_1 immunological pathways following vaccination in early childhood with resultant protection from atopy. Similar therapeutic measures to stimulate TH_1 responses in order to reduce the 'atopic drive' in allergic individuals are currently being developed. The soil saprophyte *Mycobacterium vaccae* has already been tested in asthmatics for this purpose with some degree of success [153]. Meanwhile it is worth noting that other vaccinations like *pertussis* [162], perhaps acting via different immunological mechanisms have failed to show any associations with asthma or atopy prevalence.

1.4 THE NATURAL HISTORY OF CHILDHOOD WHEEZING

1.4.1 Childhood Wheezing Is Not Always Asthma

Results from several studies have enhanced understanding of the nature of childhood wheezing which is now recognised to be a heterogeneous condition not necessarily always associated with asthma [44,85,163]. Studies have consistently demonstrated a higher prevalence for wheezing symptoms in childhood than for diagnosed asthma [34,45,85]. This may reflect under recognition by both parents and physicians of the significance of early life wheezing with under diagnosis of childhood asthma. However it may also highlight that not all wheezing experienced in childhood is related to asthma. Observation of children with wheeze but without reported asthma in Oslo found significantly lower prevalence of BHR to methacholine, exercise induced bronchoconstriction and atopy at skin prick test than a group of wheezing children with known asthma [163]. In fact, in that study, children with wheeze, but not asthma, did not significantly differ in these parameters from children who had never wheezed. Other causes for wheezing in childhood have been recognised; other entities known to enter the differential diagnosis include chlamydia pneumonia [164], bronchiolitis[163], pertussis [163]and gastroesophageal reflux disease [163]. Recurrent ear, nose and throat (ENT) problems in infancy have also been postulated as another significant cause of wheezing [165]. Certainly recurrent ENT infections are common in infancy and could plausibly be associated with transient wheezing just as viral respiratory infections are known to be. Confirmation of this relationship is needed from formal studies.

An enhanced understanding of the natural history of childhood asthma and atopy has begun to emerge from prospective cohort studies. Prospective studies of general population samples have proved sparse in this field; high running costs and organisational demands as well as the long-term nature of such studies and the difficulties of maintaining subject participation have severely limited their use. Such studies have tended to show lower incidence of wheezing and diagnosed asthma plus less persistence of wheezing symptoms than studies drawn from either hospital or clinic derived populations [86,166]. However, studies of whole population samples probably provide a truer picture of the natural history of childhood asthma and atopy than more selected samples.

1.4.2 Wheezing Phenotypes in Childhood

A body of evidence has emerged to support the presence of distinctive wheezing phenotypes showing characteristic patterns of disease during childhood [11,44,74,85,167]. In 1995, Martinez and co-workers [44] proposed a landmark phenotypic classification based on disease natural history in the first 6-years of life. This comprised four distinct phenotypes:

1. *Non-wheezers* – Children who had never wheezed.
2. *Early life transient wheezers* – Children who wheezed in the first 3-years of life but were no longer wheezing at 6-years.
3. *Persistent wheezers* – Children who wheezed during the first 3-years of life and were still wheezing at 6-years.
4. *Late onset wheezers* – Children who commenced wheezing after 3-years of age and were wheezing at 6-years.

Observations from this and other whole population studies have revealed that the majority of early life wheezing is transient in nature: probably in association with viral respiratory infection. Transient wheezing was found in 47% of early life wheezers in a study in Leicestershire, UK [85], 54% infant wheezers in the Isle of Wight cohort, UK [74] and 59% of such wheezers in the Tucson cohort, USA [44]. Long-term follow-up of the 1970 British Cohort [81] found that 85% of infant wheezers had outgrown their symptoms by age 16-years. Data from Tucson has shown that symptoms such as cough or wheeze only with colds in the first year of life are not linked to subsequent asthma diagnosis [168]. Several factors have been identified that characterise 'early transient wheezing' as a distinct entity. Firstly, such children are known to possess lower lung function in infancy and at 6-years of age [44,135,136]. This suggests that airway dimensions may be a significant factor for transient wheezing in infancy. Secondly, markers of atopy are significantly lower in transiently wheezing children than those who wheeze persistently [44,83,85]. Furthermore, total IgE levels in transient wheezers are not significantly different to those of non-wheezing children [44,138].

By contrast persistently wheezing children have normal lung function in infancy with subsequent decline through childhood [44]. This may reflect the structural effects of an extended period of disease upon lung function in persistent wheezers. The CAMP Study, USA, provides further support for this theory by showing correlation between longer

duration of illness and decreased lung function, greater bronchial hyper-reactivity, higher symptom scores and greater eosinophils counts [169]. Measurement of BHR in these studies has found strongest associations for BHR with persistent wheezers compared to other wheezing types both at 6-years [85] and 11- years [83] of age. Assessment of peak flow variability has shown similar associations for persistent childhood wheezing [83,85]. In contrast children with early childhood transient wheezing have been found to have lesser BHR at 6 and 11-years of age [83,85]. Intermediate associations for children with 'late onset wheezing' commencing in later childhood have been identified with regard to BHR and atopy [83,85].

Atopy and inflammation appear to be strong features in persistent wheezers who show persistently raised total IgE throughout childhood [44,85]. These children also have higher eosinophil counts and IgE values in response to viral infections during infancy than children with transient wheezing [137]. Atopy at skin test throughout childhood [44,74,81,83,85,170] has been identified as a strong predictor of persistent wheeze. Unsurprisingly therefore persistent wheezing has also been linked to eczema in the first year of life [44,88] and co-existent rhinitis [44]. Positive family history (particularly maternal history) of asthma and atopy [44,74] has also been shown as a strong association of persistent rather than transient wheezing. Thus it appears that elevated serum IgE levels, atopy and eosinophilic inflammation are vital components of persistent childhood wheezing [137,170]. This appears consistent with the findings of Stevenson et al [11] who demonstrated ongoing eosinophilic inflammation at bronchoalveolar lavage in children with atopic asthma but not in children with largely transient viral associated wheeze. Observations from numerous studies have demonstrated that persistent wheezers show many of the hallmarks normally associated with a physician diagnosis of asthma. This in turn suggests that most childhood asthma may begin in infancy/early childhood since by definition this is when persistent wheezing commences. A significant association between wheezing with breathlessness occurring at ages 3 to 4-years and risk of being diagnosed asthmatic was demonstrated in the Tucson study [168]. Ultimately, better understanding of factors leading to development of the persistent wheezing state could facilitate significant reduction of asthma morbidity in childhood.

Results from the Tucson study [44,166] suggest that persistent wheezing is associated with male gender although other studies have linked female gender to persistent asthma [88]. Differences in the association of gender and persistent wheeze between studies may reflect the precise points of analysis used during childhood since male predominance of wheeze in early childhood transforms into a female pattern of predominance by puberty [34].

Whilst a natural history based classification of childhood wheezing has enhanced understanding of this condition in childhood, investigators in Tucson have attempted to modify such a system to incorporate pathological mechanisms. Thus in the Tucson cohort study, investigators have defined four patterns of childhood wheezing [83] during the first 11-years of life. These comprised *transient early wheezers* (wheezing confined to first 3-years of life and not related to airway lability), *non-atopic wheezers of early childhood* (wheezing associated with positive peak flow variability but not with BHR), *IgE associated wheeze* (associated with persistent wheezing and BHR, peak flow variability and atopy) and *never wheezers* [83]. What effect use of regular inhaled therapy, especially prophylactic steroids, has upon these patterns of wheezing in childhood and their associations is still unknown since current knowledge is based upon studies that predate the common usage of such therapies. Results from studies conducted in the era of steroid treatment of childhood asthma are now needed to clarify this understanding.

In summary, an enhanced comprehension of the natural history of childhood wheezing has arisen to date from a small number of prospective cohort studies. Further results from such studies have the potential to provide a framework that facilitates an increased knowledge of wheezing and asthma and guides future management of these common diseases.

CHAPTER 2

TEN YEAR FOLLOW-UP OF THE ISLE OF WIGHT 1989 WHOLE POPULATION BIRTH COHORT

INTRODUCTION

Wheezing in childhood, particularly wheezing in early childhood is a very common phenomenon [32,34,44,47,85,171,172]. Substantial geographical variations in the prevalence of this condition have been noted with a consistent tendency for highest prevalence rates within more affluent westernised communities [40,46,47]. Amongst some populations lifetime prevalence for childhood wheezing as high as 49% (at 6-years of age) has been reported [44]. Similar findings with regard to atopic sensitisation and other allergic conditions in childhood have also been observed [41]. There is now a general consensus that such conditions have shown a genuine increase in prevalence during the last forty years [54,55,57].

Considerable evidence now exists to suggest that a large proportion of early life wheezing is transient in nature and not necessarily associated with significant morbidity [32,85,167]. This has in turn led to the familiar perception amongst both physician and parent of the 'happy infant wheezer' [173] who wheezes only briefly and without serious consequence for their long-term health. The idea that most infant wheezers outgrow their symptoms has led to considerable debate as to the appropriateness of various treatments for wheezing in early life [174]. Complicating this issue is a growing realisation that persistent childhood wheezing too may originate in early life [168]. It appears entirely feasible that wheezing in childhood is a heterogeneous condition comprising several distinct phenotypes [167]. Therefore being able to identify those children in early life who will wheeze only briefly and differentiate them from those likely to develop persistent symptoms may provide an attractive model to assist with diagnosis and management of childhood asthma.

The association of childhood wheezing with allergic disease and atopic sensitisation has long been recognised [170]. Atopy seems to be a characteristic feature in children with persistent wheezing [44,85,88,170]. Different allergen sensitisations appear to adopt greater significance in this context depending upon the local environment [41,45,73]. However the

precise contribution of atopy to the natural history of childhood wheezing is not yet fully understood. Whether atopic sensitisation is merely an associated feature of persistent wheezing or actually plays a significant causal role in the development of this problem remains unknown [99].

Objective measures of asthma severity in childhood are essential to achieving an understanding of the evolution of this disease. However, only a few studies looking at asthma development in children have adopted such techniques [35,44,85,100]. Baseline lung function at spirometry offers a simple measure of lung function although it requires sufficient coordination by the subject. It has been demonstrated that children with viral associated early life transient wheezing show evidence of lower lung function in infancy compared both to those who do not wheeze as well as those who wheeze persistently [44,83,136]. Whether this anomaly is still detectable when these children reach later childhood remains to be seen. Conversely it has also been demonstrated that lung function may decline in relation to duration of wheezing illness [169]. Therefore it might be expected that by 10-years of age children with persistent wheezing might show significantly poorer lung function than their contemporaries who had either never wheezed or began wheezing only in later childhood. The influence of regular therapy with inhaled steroids upon lung function in such wheezing children has also yet to be assessed. No major prospective cohort study in this field has to date reported findings solely from an era when such treatment has been commonplace.

Bronchial hyper-responsiveness (BHR) is a characteristic feature of 'asthmatic airways' which may be readily and safely measured in children at bronchial challenge using a variety of agents including methacholine and histamine. Incorporation of BHR detected at bronchial challenge has been included in the gold standard definition of *current asthma* in recent epidemiological studies [41,104]. If BHR is present in those children who ultimately outgrow their wheezing symptoms during childhood is not known. Furthermore whether age of onset and duration of wheezing influence BHR also remains unclear. Whether at 10-years 'early life persistent wheezers' show differences in BHR compared to 'later onset wheezers' whose symptoms commenced in later childhood is yet to be clarified. In addition, the impact of regular long-term steroid usage upon BHR at 10-years also remains unclear.

Pioneering studies such as the Tucson cohort study[44] have provided an enhanced knowledge of the natural history of childhood wheezing. However, much still remains to be elucidated such as the patterns of disease morbidity that accompany common childhood wheezing phenotypes.

It is now well documented that asthma and allergic conditions like eczema and rhinitis share very similar underlying inflammatory mechanisms[6]. Also there appears to be a characteristic evolution of disease encountered in atopic individuals who may progress from eczema and food allergy in infancy to asthma and rhinitis later [15,16]. Factors relevant to this process have yet to be clearly defined although both genetic and environmental influences are suspected of being important for this 'Allergic March'. Thus atopic family history (particularly maternal or sibling atopy) has been linked to this process [44,69,74]. Some studies have found associations between asthma and low birth weight [81,82] or high birth length [111]. Whilst both genetic and perinatal risk factors for asthma and atopy may be beyond currently available therapeutic interventions, environmental risk factors (if confirmed) offer the possibility of readily accessible targets for new interventions. Potential factors such as early life respiratory infections [168], method of infant feeding [118], environmental tobacco smoke exposure [120] and the 'hygiene hypothesis' [155] should be examined further. The precise interplay of such factors remains unclear although it is readily apparent that early childhood is a critical time when such interactions could occur.

Prospective studies looking at the long-term outcome and natural history of childhood wheezing are essential to create a better understanding of asthma in early life. However population selection should be borne in mind when interpreting such studies. 'At risk' cohorts drawn from clinic or hospital populations have consistently magnified the degree of persistent symptoms and their severity [88,166].

The Isle of Wight 1989 Birth Cohort Study represents an unselected whole population birth cohort. This study was established in 1989 by Dr SH Arshad (then a Research Fellow) and the late Dr DW Hide (a local Consultant Allergist).

The Isle of Wight is located off the South coast of England and has a resident population of 100,000 people. The local community comprises a largely rural population. In contrast to urban areas of the UK, the population remains predominantly Caucasian and Anglo-Saxon, in nature. Agriculture, light industry and tourism form the backbone of the local economy. Migration from the Island remains low, thus providing an ideal stable environment in which to conduct prospective follow-up studies.

A whole population birth cohort was established on the Isle of Wight in 1989. The original intention was to prospectively study this whole population cohort for the development of asthma and allergic diseases during childhood and identify possible risk factors relevant to these conditions. Enrolment took place at birth. Out of a total of 1536 children born on the Isle of Wight between 1 January 1989 and 28 February 1990, informed consent was obtained from the parents of 1456 children. These children have since been seen at the ages of 1(n=1167), 2 (n=1174) and 4-years (n=1218). In the latest phase of the study, the children were seen again at the age of 10-years. All 1456 children originally recruited at birth were invited to participate again as they approached 10-years of age. The intention at 10-years was to create an enhanced understanding of the natural history of wheezing, asthma and allergic disease during the first decade of life whilst also identifying risk factors relevant to the development of these states. For this purpose information obtained during the 10-year follow-up was analysed in conjunction with that collected earlier for this cohort. The aims of this thesis are outlined overleaf.

AIMS

1. To define the natural history of wheezing illnesses and asthma during the first decade of life using a phenotypic classification.

2. To determine patterns of atopy, allergy, lung function and bronchial hyper-responsiveness associated with different forms of wheezing in the first decade of life.

3. To determine patterns of disease morbidity associated with different wheezing phenotypes.

4. To identify risk factors in early childhood which have predictive value for various wheezing phenotypes during the first decade of life.

5. To estimate the prevalence of wheezing, asthma and allergic disease in a geographically defined group of children at 10-years of age using standardised research materials that bear comparison to those used in other studies.

6. To identify risk factors in early childhood which have predictive value for wheezing and asthma in later childhood

7. To identify risk factors in early childhood which have predictive value for rhinitis and eczema in later childhood.

CHAPTER 3

MATERIALS, METHODS AND ANALYSIS

3.1 COHORT BACKGROUND

A whole population birth cohort was established on the Isle of Wight, in 1989 to prospectively assess the development of asthma and allergic disease. Enrolment took place at birth. Out of a total of 1536 children born on the Isle of Wight between 1 January 1989 and 28 February 1990, informed consent was obtained from the parents of 1456 children. These children have since been seen at the ages of 1(n=1167), 2 (n=1174) and 4-years (n=1218).

Information on personal and family history of allergic disorder, presence of household pets and smoking habit was recorded at enrolment. At birth, both cord blood IgE and maternal IgE were measured in the majority of cases. Birth weight was also obtained for each child. A Social Class classification using the Registrar General's Classification [117] was also made where possible at birth.

Information at each stage was collected regarding prevalence of asthma and atopic disease. Additionally, environmental risk factors for these conditions like tobacco smoke exposure and pet contact were recorded. Details of infant feeding method and weaning were also noted. Identical questionnaires were used each time. Definitions used relating to asthma were of *current wheeze* (occurring since the last visit) and *investigators diagnosis of asthma* (physician diagnosed asthma). Similarly history of current symptoms for other allergic conditions (eczema, rhinitis and food allergy) was noted along with a history of recurrent chest infections at 1 or 2-years. *Investigators diagnosis* of eczema, rhinitis and food allergy were also made each time. Skin prick testing to a battery of common food and inhalant allergens was performed in all symptomatic children at age 1 and 2-years. This was also performed to a wider panel of allergens in all children seen at 4-years of age. The individual allergens tested at 4-years [74] were house dust mite (*Dermatophagoides Pteronyssinus*), grass pollen mix, cat and dog epithelia, *Alternaria Alternata, Cladosporium Herbarum*, milk, hens' egg, soya, cod, wheat and peanut. Positive (histamine

dihydrochloride) and negative (physiological saline) controls were included in the panel. Positive skin test for any given allergen was regarded as mean wheal diameter of at least 3mm greater than the negative control, with results read after 10 minutes. At each follow-up, children who were seen underwent a brief physical examination documenting signs of allergic disease. Results from these follow-ups have been reported previously [74,82,117,175-177].

3.2 TEN-YEAR STUDY FOLLOW-UP

All 1456 children originally recruited were approached again when aged 10-years. This was done as close to their tenth birthday as possible. The Isle of Wight Local Research Ethics Committee gave ethical approval for follow-up at this age and informed written consent by both parent and child was obtained prior to participation.

3.2.1 Study Personnel and Recruitment

A multidisciplinary team, based at the *David Hide Asthma and Allergy Research Centre, St. Mary's Hospital, Newport, Isle of Wight* conducted the 10-year follow-up of this study over an 18-month period between October 1998 and April 2000. A Research Fellow (RJK) led this team under the supervision of the Principal Investigator (SHA). Full details of those participating in the *1989 Study Team* are given in **Appendix I**.

The Research Fellow was responsible for co-ordination of the study including planning of recruitment and administration as well as writing to General Practitioners with details of study results for each child. The Research Fellow was also responsible for seeing all study children, administering all interviews and subsequently performing data analysis. Several Research Nurses from the *David Hide Asthma and Allergy Research Centre* were also involved in the 10-year follow-up, participating in both recruitment, administration and seeing the children (MF, LW, HS, TB, SM and CW). A secretary (LT) performed secretarial tasks, such as production of recruitment letters, and also assisted in the co-ordination of recruitment for the study. Another part-time secretary (GP) was responsible for tracing 'missing children'.

Parents were approached to permit their children to reattend for the 10-year study follow-up according to birth order of the children in the original sample. Initial contact by letter was made to inform parents of the study follow-up, inviting them along with their children to participate again. This was backed up by telephone recruitment in cases that were slow to respond. Where families had moved since prior follow-up, tracing was done using the FHSA (Family Health Services Association) or by General Practitioner Surgeries wherever possible. Publicity measures to increase awareness of the study follow-up were also used including several articles in the local press and school newsletters as well as reports in local television and radio programmes.

The 10-year follow-up included an administered questionnaire completed with parents at interview, physical examination, skin prick testing to common allergens, blood sampling for IgE measurement, baseline lung function at spirometry and bronchial challenge to methacholine. Children were seen during a one and a half hour visit to the Research Centre. Testing was performed in one of two similar and well-ventilated rooms at the Research Centre using equipment dedicated for the purpose. On two afternoons a month children were also seen in the Outpatient Department at Ryde Hospital, Ryde on the Isle of Wight. This was done to facilitate follow-up among subjects living in the Ryde area, which is the largest urban population centre on the Island. To ensure standardisation in testing materials used at each location, all equipment was transported from the Research Centre to Ryde Hospital when these sessions were undertaken. In addition, to allow follow-up of some children who had moved to the mainland and were unable to visit the Isle of Wight for follow-up, three sessions were held at the Department of University Medicine, Southampton General Hospital. Again equipment was transported from the Research Centre for this purpose.

3.2.2 Questionnaires

Detailed interviewer administered questionnaires were completed with the parents of each child regarding asthma and allergy development. To maintain consistency the same individual conducted all interviews (RJK). Wherever possible this was performed face to face with the parents. Where a visit to the Research Centre was not possible (n=330) a questionnaire was completed by telephone with one of the parents. If this was not possible as a last resort a modified questionnaire (see Accompanying Materials, **p.228**) was sent by

post for the parent to complete and return. If a modified postal questionnaire was returned this was then transcribed onto the standard written forms by the Research Fellow.

ISAAC [47] was established to provide a standardised research tool for examination of the epidemiology of childhood asthma and allergic disease. In the 10-year follow-up of this study, ISAAC written questionnaires (see Accompanying Materials, **p.228**) were used assessing respiratory, nasal and dermatological symptoms. Additional information regarding natural history of symptoms and treatments was obtained using a *supplementary atopic disease questionnaire* (see Accompanying Materials, **p.228**) largely consistent with those completed at prior follow-ups. Data from prior follow-ups regarding age of symptom onset was incorporated with 10-year information to minimise the problem of 'recall bias'.

Asthma related definitions used at 10-years were of 'wheezing ever', 'wheezing in the last 12 months' (*current wheezing*) and 'physician diagnosis of asthma ever' (*diagnosed asthma*). Consultations with a hospital asthma specialist (*specialist referral*) were recorded along with details of hospital admissions or casualty attendances for wheezing episodes. Details of asthma treatment 'ever used' such as short acting bronchodilators, inhaled corticosteroids, other prophylactic medications (long acting β agonists, sodium cromoglycate, theophyllines, leukotrienes antagonists or antihistamines) and oral corticosteroid therapy were also obtained. Several measures of *current wheezing morbidity* (within the preceding 12 months) were recorded at 10-years. These included 'number of wheezing episodes' (*wheeze frequency*), 'sleep disturbance from wheezing more or less than once per week' (*sleep disturbance from wheezing)*, 'wheezing on exertion' (*exercise induced wheezing)*, 'wheezing severe enough to limit speech to one or two words between breaths' (*limitation of speech by wheezing*) and 'dry cough at night not associated with cold or flu' (*nocturnal cough*). Recognised triggers for wheezing episodes were also noted including chest infections, exercise, pollen, animals, house dust and stress.

In addition to wheezing details, a history of other allergic disorders like eczema, rhinitis and food allergy was also updated at 10-years. Definitions of diagnosed eczema and hay fever/rhinitis were *ever had eczema* and *ever had hay fever/rhinitis* respectively. Associated symptoms for these conditions were respectively of *itchy rash coming and going for at least 6 months within the last year* and *sneezing, runny or blocked nose when the child did*

not have a cold or the flu within the last year. Data from prior follow-ups, such as age of onset of symptoms, was again incorporated with that gathered at 10-years to minimise 'recall bias'.

Information was also recorded at 10-years about current exposure to relevant environmental factors like environmental tobacco smoke, household pets plus type of housing and household cooking appliance. Childhood immunisation history and family (mother, father, sibling) histories of atopic disease (diagnosed asthma, rhinitis, eczema, urticaria, food allergy ever) were also updated. Several measures of socio-economic status were made at 10-years including household income, parental occupation and level of maternal education. A social class classification based on paternal occupation was made using the 'Standard Occupational Classification'[178]. Where the mother provided the sole or more significant source of income in a family maternal occupation was used instead for classification purposes. Broad categories for social class were assigned as detailed below:

I. Professional Occupations.
II. Managerial and Technical Occupations.
III. Skilled Occupations:
(N) Non-manual.
(M) Manual.
IV. Partly Skilled Occupations.
V. Unskilled Occupations.

The ISAAC video questionnaire (see Accompanying Materials, **p.228**) was also used to obtain additional information about wheezing symptoms and morbidity from all children who attended the Research Centre. The children completed these questionnaires themselves.

Signs of allergic disease were documented at a brief physical examination of the respiratory system, skin plus ear, nose and throat. Height and weight for all children attending the Research Centre were also recorded.

3.2.3 Skin Prick Testing

Skin prick testing (SPT) permits a rapid, safe and sensitive method of assessing the presence of allergen specific IgE antibodies in an individual. At 10-years, skin prick testing was performed wherever possible to a battery of standardised common food and inhalant allergen extracts (ALK, Denmark). This panel was consistent with that used at the 4-year follow-up. A positive (histamine dihydrochloride, 10mg/ml) and negative control (physiological saline) was included in the panel. Inhalant allergens tested were house dust mite (*Dermatophagoides Pteronyssinus*), cat, dog, *Alternaria Alternata*, *Cladosporium Herbarium*, grass pollen mix (timothy grass, rye, meadow, colts foot, june, false oat), and tree pollen mix (alder, silver birch, hazel). Food allergens tested were cows milk, soya, hens' egg, peanut and cod.

In order to undergo this test the child had to have avoided antihistamine medication for at least 72 hours. All allergens tested were applied to the volar aspect of the forearm. The skin was then pricked through each allergen separately using a sterile lancet following a validated technique. Skin test results were read at 10 minutes. A mean wheal diameter of 3mm greater than that of the negative control was regarded as a positive test for any given allergen. One tester (RJK) performed 48% of skin tests whilst 85% of all skin tests were performed by one of three testers (RJK, MF, LW). To maintain consistency for the interpretation of skin test results all measurements were made by the same individual (RJK) throughout the study.

3.2.4. Pulmonary Function Testing and Bronchial Challenge to Methacholine

Baseline pulmonary function testing consisting of Forced Expiratory Volume in 1 Second (FEV_1), Forced Vital Capacity (FVC) and Peak Expiratory Flow (PEFR), was measured in all children attending the Research Centre using Koko spirometry software (PDS Instrumentation, Louisville, USA). To obtain consistency, the highest of three FEV_1 measurements that were within 5% of each other was recorded as a baseline value. To ensure standardisation spirometry was always performed with the child standing or sitting erect. One of six research nurses (MF, LW, HS, TB, SM, CW) conducted the test using a standardised technique.

Measurement of bronchial hyper-responsiveness (BHR) through induction of bronchoconstriction at bronchial challenge testing has been increasingly used to assist in the definition of asthma in epidemiological surveys [179,180]. Although not diagnostic of asthma such techniques can certainly enhance understanding of this condition [181,182]. Methacholine, a synthetic analogue of acetylcholine, has found increasing usage in such testing. Comparable results have been shown for this agent at bronchial challenge as found with histamine [182-187]. It appears [188] that these two agents induce bronchoconstriction through different mechanisms of action on the airways. Furthermore side effects may be higher with histamine testing [183]. Previous work [189] has established that methacholine bronchial challenge is a safe and informative test in children.

In our 10-year old population, all children with a history of past or current wheezing were invited to perform a bronchial challenge test with methacholine to assess BHR. A computerised dosimeter system (Koko Digidoser, PDS Instrumentation, Louisville, USA) with a fixed straw and baffle position Devilbiss 646 nebuliser was used to ensure reproducibility. This dosing system was characterised to deliver 5 breaths of methacholine with firing times of 0.6 seconds. It utilised 3ml of solution in the nebuliser bowl with a compressed air source set at 8 litres/minute, nebuliser output of approximately 0.8 litres/minute and a constant inspiratory flow rate of 0.5 litre/second. The nebuliser chambers used for this purpose were characterised in terms of output and numbered accordingly. One of six research nurses (MF, LW, HS, TB, SM, CW) conducted the bronchial challenge in either of two well-ventilated rooms using dedicated equipment.

Methacholine was stored in frozen form at -20°C and prepared in solution form on a weekly basis. A set protocol was followed for the preparation of methacholine. The same individual (RJK) always prepared the methacholine. Each test batch contained nine strengths of methacholine doubling in concentration each time from 0.0625 mg/ml to 16 mg/ml. The prepared methacholine was then refrigerated at 5°C for a maximum of seven days. Methacholine test batches were not used for more than one bronchial challenge and any unused prepared methacholine was discarded after seven days.

In order to perform a bronchial challenge, resting FEV_1 measurement was required to be at least 70% of predicted for height and age. Initial inhalation of five actuated doses of 0.9%

Saline was followed 1 minute later by spirometry recording to obtain a baseline set of values. For recording purposes two out of three FEV_1 values needed to be within 5% of each other, in which case the highest value was used as baseline. Subsequently, incrementally doubling concentrations from 0.0625 mg/ml to 16mg/ml of methacholine were serially administered using the methods of Chai and co-workers [190] on a continuous cycle. Children were required to wear a nose clip throughout periods of administration. The methacholine concentration causing a 20% fall in FEV_1 from the post-saline value was interpolated and expressed as the PC_{20} FEV_1 (provoking concentration of methacholine causing a 20% fall in FEV_1). Such a fall in FEV_1 was regarded as evidence of BHR with the test then being regarded as positive. A sample printout of baseline lung function and methacholine bronchial challenge testing results is provided in the Accompanying Materials section (**p.228**).

To perform this test children were required to be free from respiratory infection for fourteen days, not taking oral steroids, have not taken any β_2 agonist medication for six hours and abstained from caffeine intake for at least four hours prior to testing. If the child had evidence of recent respiratory infection they were asked to reattend for bronchial challenge once free of infection symptoms for two weeks. At the end of the bronchial challenge 200μcg salbutamol was routinely administered via a volumatic device and spirometry assessed 15 minutes later to ensure full recovery. Children were always observed until FEV_1 returned to within 10% of the original baseline value. For children who had an initial FEV_1 below 70% predicted a methacholine challenge was not performed for safety reasons. In such children a bronchial reversibility test measuring FEV_1 before and 15 minutes after inhalation of 200μcg salbutamol was performed instead. More than 15% improvement in FEV_1 during this test was taken to provide significant evidence of bronchial reversibility. Three hundred children categorised as 'non-wheezers' were randomly chosen and also underwent a bronchial challenge test using the same methodology.

3.2.5 Serum IgE Measurement

Blood samples were taken 1 hour after application of local anaesthetic cream (EMLA – Astra Pharmaceuticals, Hertfordshire, England) to the ante-cubital fossa. Venepuncture was always performed by RJK. Ten millilitres was taken for measurement of total serum IgE and an inhalant screen (qualitative) for IgE antibody to common inhalant allergens

(Phadiatop – Pharmacia Diagnostics; Uppsala, Sweden). The inhalant screen tested for house dust mite *(D. Pteronyssinus and D. Farinae)*, cat dander, dog dander, horse dander, timothy grass, cladosporium, silver birch, olive, mugwort and nettle. Blood samples were allowed to stand and coagulate in Gel and Clot Activator tubes (Vacutainer Systems, Europe) for at least 10 minutes. They were then centrifuged at 3000 revolutions per minute for a further 15 minutes. Serum was then stored at – 40°C until analysis. One individual, RT (see **Appendix I**), performed all IgE analysis in a laboratory at the Biochemistry Department of St. Mary's Hospital, Newport, Isle of Wight.

3.3 DATA ANALYSIS

Data was double entered onto SPSS for Windows Version 10.0 (SPSS Inc, Chicago, USA). First entry of data was done by RJK. MF and LT performed the second round of data entry. Data files for the two entries were compared using SPSS Data Entry Builder Version 1.0 (SPSS Inc, Chicago, USA). Details of analysis and statistical techniques used are outlined below.

3.3.1 Data Transformations and definitions

i. Total IgE – Total IgE measurements at 10-years were censored with a lower limit of detection of 2ku/l and upper limit set at 5000ku/l. Consequently Total IgE was found to follow a *lognormal* distribution **(see figure 10.1, p.141)** and transformation as Log_{10} Total IgE was used for analysis of this variable.

ii. Dose–Response Slope - In our population, including non-wheezing children, many subjects might not be expected to possess a measurable PC_{20} at bronchial challenge. Therefore, a continuous measure of BHR (least-square dose-response slope) was also estimated by least-square regression of percentage change in FEV_1 upon methacholine dose for each child [97]. Inverse transformation, 1/(10 - slope), was used to satisfy normality and homoscedasticity. Thus low values for 1/(10 - slope) or *inverse slope* would infer high BHR.

iii. ATS Categorisation of Bronchial hyper-responsiveness - BHR was categorised by PC_{20} FEV_1as 'Normal' (>16mg/ml), 'Borderline' (4-16mg/ml), 'Mild/Positive' (1-

4mg/ml) and 'Moderate-Severe' (<1mg/ml) following American Thoracic Society Guidelines [191]. The term *definite BHR* was used for those children who showed either 'Mild/Positive' or 'Moderate-Severe' BHR in this categorisation. *Definite BHR* therefore included children with a PC_{20} FEV_1 less than 4mg/ml.

iv. *Current asthma* at 10-years – The failure to adopt standardised definitions for *current asthma* has been a major criticism of epidemiological studies of childhood asthma. Thus comparisons between surveys may be difficult to interpret. In recent years the gold standard definition [104] for *current asthma* has involved a combination of both *current wheeze* and *current bronchial hyper-responsiveness* at bronchial challenge. Thus an element of objective measurement is brought into the definition rather than simply relying upon questionnaire data that might be open to misinterpretation. This of course has considerable resource implications since it necessitates the universal use of bronchial challenges as part of an epidemiological study. In our study at 10-years, bronchial challenges were performed in 784 out of 1043 children seen in person. For these children we have defined *current asthma* as being a combination of *current wheeze* and *bronchial hyper-responsiveness* (PC_{20} FEV_1 <8.0mg/ml) at methacholine challenge to provide a measure of symptomatic BHR. Given that questionnaire information at 10-years was actually available for 1373 children we have also provided a purely questionnaire derived definition of *currently diagnosed asthmatic (CDA)*. This uses a combination of *asthma ever* and *current wheeze* since this information was present in the ISAAC questionnaire.

v. *Current eczema* – This was defined at 10-years as a combination of *eczema ever* and *current symptoms of chronic itchy rash* (taken from the ISAAC questionnaire).

vi. *Current hay fever* – This was defined at 10-years as a combination of *hay fever ever* and *current nasal symptoms not associated with a cold* (taken from the ISAAC questionnaire).

vii. *Current urticaria* – This was defined at 10-years as occurrence of at least one urticarial episode in the previous 12 months.

viii. *Currently allergic* – This was taken as presence at 10-years of one of *currently diagnosed asthmatic, current hay fever, current eczema* or *current urticaria.*

3.3.2 Wheezing Phenotype Classification

A phenotypic classification was created to study the natural history of childhood wheezing similar to that of Martinez et al[44]. This was done using prospectively collected data from each study visit to minimise 'recall bias'. Because of this, analysis concerning wheezing phenotypes was restricted to 1034 (71% of the original 1456 enrolled at birth) children seen prospectively with information at all study visits; 1 or 2-years (data from these visits was combined providing information in 'infancy'), 4 and 10-years.

Of these1034, SPT results were available for 875 (85%) 4-year olds and 861 (83%) 10-year olds. In this group, serum IgE measurements, baseline lung function and bronchial challenge results were available for 798 (77%), 859 (82%) and 647 (63%) children respectively at 10-years. These children did not differ demographically or in major disease parameters from those observed at 10-years, but excluded from the present analysis because of prior missing follow-up (Table 3.1).

Table 3.1: Demographic/disease characteristics of children included and excluded from prospective wheezing phenotype classification.

	INCLUDED (Seen at all visits)	EXCLUDED (Seen at 10-years but not at all other visits)
No.	1034	339
% Male	50.8%	50.4%
Birth weight (Kg)	3.44	3.38
% Social class I-III at birth	47.2%	43.5%
% Parental atopy at birth	51.0%	50.1%
%'Wheeze ever' (retrospective; 10-yrs)	46.7%	41.9%
%'Current wheeze' at 10-yrs	19.9%	15.6%

Children were assigned a wheezing phenotype at 10-years by the presence of *current wheeze* at each follow-up:

i. **Non-wheezers (NW)-** Children who never wheezed during the first decade of life.

ii. **Early onset transient wheezers (ETW)-** Children with wheezing onset during the first 4-years of life which ceased and was not present within 12 months of being seen at 10-years.

iii. **Early onset persistent wheezers (PW)-** Children with wheezing onset during the first 4-years of life who still wheezed at 10-years.

iv. **Late onset wheezers (LW)-** Children with wheezing onset from 5-years onwards who still wheezed at 10-years.

3.3.3. Tests of Statistical Significance

For all statistical analysis used in this study, statistical significance was set at the 5% level ($p = 0.05$).

i. Independent Samples T-test - This parametric test was used to compare means for continuous variables in a pairwise fashion where normality and homogeneity of variance were satisfied.

ii. Mann-Whitney U Test – This non-parametric test makes no distributional assumptions. It was used to compare means for continuous variables in a pairwise fashion where normality and homogeneity of variance were not satisfied. For example mean duration of wheezing illness was assessed in this way.

iii. Chi-Square (χ^2) Test - This test was adopted to compare differences in proportions for categorical variables between two groups. In this test, data obtained as frequencies was entered into a *2x2 contingency table* with the assumption that each individual can belong in only one cell within this table (*mutual exclusivity*). From this table the proportion of individuals *expected* to have the characteristic under question if the two groups have equal proportions of that characteristic can be calculated. The χ^2 test statistic is based on the discrepancy between the *observed* and their corresponding *expected* frequencies within this table. A large discrepancy indicates a significant difference in proportions between the groups. Pairwise comparisons between wheezing phenotypes for prevalence of atopic skin prick test, prevalence of asthma and other allergic conditions plus proportions within ATS BHR categories were tested in this manner. Proportions of each wheezing type requiring various forms of medical consultation and pharmacological therapy for

their illness were also tested in this manner. Where cells with expected counts of less than 5 were encountered the Fishers Exact Test (which is not reliant on approximation to the χ^2 distribution) was adopted to generate a p-value.

iv. Odds Ratios – This test statistic represents the ratio of two odds and provides an estimate of relative risk. For example it may provide an indication of risk by looking at odds of a disease in individuals exposed and unexposed to a specific risk factor. This approach was used in univariate and multivariate risk factor analysis with regard to wheezing phenotypes, *current asthma, CDA, current wheeze, current rhinitis* and *current eczema* at 10-years.

v. Confidence Intervals – This test statistic provides an indication of precision for a sample estimate. The 95% Confidence Interval gives the range of values within which one is 95% confident that the population parameter lies. For example 95% Confidence Intervals are given for Odds Ratios determined in risk factor analysis.

vi. Multiple Comparisons Testing -

a. ANOVA - Comparisons between wheezing phenotypes for continuous variables were performed (with transformation where necessary) using one-way Analysis of Variance (ANOVA). This test provides an overall indication of whether there are significant differences in a variable between any groups. It looks at the total variability in the data according to that between individuals in different groups (*between group variation*) and the variability in data between individuals within each group (*within group variation*). The test is based on the ratio of these two variances.

b. Bonferroni Multiple Comparisons Test – In any statistical test involving multiple comparisons it is possible to generate apparently significant results by chance if sufficient comparisons are done. This is because the chance of rejecting the null hypothesis when it is true (Type I error) increases substantially as the number of comparisons increases. The *Bonferroni multiple comparisons test* was used as a post-hoc test to provide a measure of statistical significance during comparisons between wheezing phenotypes following ANOVA. Variables compared for wheezing phenotypes by this method included $\log_{10}$Total IgE, FEV_1, FVC, FEV_1 / FVC ratio, PEF and *inverse slope*. It is a rather conservative statistical approach. By multiplying each p-value by the number of comparisons performed it takes account

of the problems of multiple statistical comparisons to avoid the chance of obtaining spuriously significant results.

c. Bonferroni Correction Approach – The manner of correcting for multiple comparisons by multiplying the observed p-value by the number of comparisons was also adopted with regard to χ^2 testing and the Mann-Whitney U Test when those tests were used in that context (for example in comparing characteristics of wheezing phenotypes).

vii. Least-square Regression Analysis - This technique (also known as simple linear regression) was used to investigate the linear relationship of two continuous variables, x and y. The equation used to summarise this linear relationship is:

$$Y = a + bx$$

In this equation, x is termed the explanatory variable, Y is the value of y (the dependent variable) for any given value of x, a is the intercept of the line (Y value when $x = 0$) and b is the slope of the estimated line (the amount of change in Y for a unit change in x). Thus it can be seen that this technique can be used to determine the influence of change in one variable upon the value of another.

This method was used to provide a continuous measure of bronchial hyper-responsiveness at 10-years in all children who underwent bronchial challenge to methacholine. For this purpose, x represented methacholine dose administered (mg) at each stage of the challenge whilst y represented the corresponding percentage change in FEV_1 at each stage of the challenge. Consequently a value of *dose-response slope* (equivalent to b in the above equation) was calculated for each child tested at bronchial challenge.

viii. Binary Logistic Regression Analysis - This represents a type of linear regression model that possesses a single binary dependent variable and at least two explanatory variables. It allows one to determine which explanatory variables influence outcome by adjusting for possible confounding between explanatory variables. This technique was used for the analysis of independent risk factors for various wheezing phenotypes plus asthma, rhinitis and eczema at 10-years. In these cases risk factors that had shown a tendency towards significant effect at univariate analysis as indicated by $p<0.2$ were entered into the regression model. Where more than one risk factor could explain a particular exposure of interest the most relevant factor was entered into the model. Stepwise backward (likelihood ratio) logistic regression

analysis was used for this purpose with exclusion of variables at each stage with $p>0.05$. Results were then presented as adjusted odds ratios and their 95% confidence intervals.

CHAPTER 4

DEMOGRAPHIC DETAILS FROM THE FOLLOW-UP AT 10-YEARS

4.1 FOLLOW-UP RATE

A total of 1536 children were born on the Isle of Wight between 1 January 1989 and 28 February 1990. After exclusions because of refusal, adoption or perinatal death 1456 children were enrolled and available for subsequent prospective follow-up. At 1-year, 1167 children were seen again giving an 80.2% follow-up rate. At 2-years, this follow-up rate was maintained (80.6%) when 1174 children were seen. At 4-years, an even higher rate of follow-up of 83.7% was achieved when 1218 children were seen.

At 10-years, questionnaire information was updated in 1373 children giving a 94.3% follow-up rate for this phase of the study. Of children who participated in the 10-year follow-up 1043 (76.0%) attended at the *David Hide Asthma and Allergy Research Centre* for a 'full visit' entailing additional testing including video questionnaire, physical examination, skin prick testing, lung function testing, bronchial challenge and blood sampling (see **3.2** for details of methodology). The remaining 330 children only provided questionnaire information at 10-years. In most cases this latter situation arose where there was difficulty in attending for a 'full visit'. Often this was because the families had migrated off the Island (165 children) but sometimes it occurred where families still living on the Island were reluctant to do a 'full visit' but happy to complete a questionnaire at interview (165 children). Analysis of several demographic factors at 10-years for children who completed a 'full visit' or where only a questionnaire was completed did not show significant differences in proportions with domestic exposure to cats and dogs, domestic exposure to environmental tobacco smoke or male: female ratio (Table 4.1). However prevalence of *higher* social class (categories I-III non-manual) was significantly greater in those completing a questionnaire only.

A clear effect was observed by which children with *current wheeze* or lifetime history of allergic conditions such as *diagnosed asthma, eczema* or *hay fever* were more likely to attend for a 'full visit' at 10-years than just complete a questionnaire (Table 4.1).

Furthermore, comparing lifetime prevalence of parental asthma or allergy (*asthma, eczema, hay fever, urticaria, food allergy*) between children who did a 'full visit' or those completing only the questionnaire showed significantly higher prevalence for parental asthma or allergy in those attending for a 'full visit' (Table 4.1). This trend for greater full participation in an 'asthma and allergy study' amongst children with a personal or family history of such conditions is not altogether unexpected. It is worth reflecting that our original birth cohort was an unselected whole population sample. It would be entirely understandable that families directly affected by the problems being studied in our research would be more likely to show greater cooperation and more extensive participation than those who had no direct experience of allergy or asthma. However it is unlikely that this trend would have affected the prevalence results in our study at 10-years since these were determined purely from the questionnaires that were used regardless from other information gained at a 'full visit'.

The mean age of child at interview for 10-year follow-up was 10.01 years (95% Confidence Interval 10.00-10.03, with age range 9.03-11.20 years). Children who performed a 'full visit' had a significantly lower mean age at interview (9.97 years, standard deviation 0.25) than children for whom only a questionnaire was completed (10.12 years, standard deviation 0.34, $p < 0.001$). This probably reflects the fact that phone questionnaires were completed often as a last resort when it was not possible to obtain a 'full visit'. By contrast, 'full visits' typically occurred promptly within a few weeks of initial contact.

As described in **3.3.2** a total of 1034 children had available prospectively collected questionnaire information from all visits, being seen at infancy (1 or 2-years), 4 and 10-years. This subgroup was therefore used for prospective analyses with respect to natural history of disease in childhood.

Table 4.1: Characteristics of children seen at 10-years by participation

	Full Visit (n=1043)	Questionnaire Only (n=330)	P- Value (χ^2 Test - *statistically significant)
% Male (n=)	49.6% (517/1043)	54.5% (180/330)	0.115
% High social class (n=)	47.9% (450/939)	55.8% (154/276)	0.021*
% Smoking at home (n=)	44.9% (414/923)	49.7% (147/296)	0.149
%Domestic cat (n=)	44.7% (466/1043)	44.7% (182/329)	1.000
%Domestic dog (n=)	40.2% (419/1043)	35.3% (116/329)	0.111
%Current wheeze (n=)	20.9% (218/1043)	12.4% (41/330)	0.001*
%Asthma ever (n=)	21.7% (226/1042)	14.9% (49/328)	0.008*
%Eczema ever (n=)	43.3% (452/1043)	33.6% (111/330)	0.002*
%Hay fever ever (n=)	20.4% (213/1043)	13.0% (43/330)	0.003*
%Parental asthma (n=)	32.8% (324/989)	23.5% (77/328)	0.002*
%Parental allergy (n=)	63.4% (628/990)	54.3% (178/328)	0.003*

4.2 CHILDREN NOT SEEN AT 10-YEARS

Of the original 1456 children recruited at birth, 83(5.7%) were not seen in the 10-year follow-up. Twenty of the original 1456 children were known to have died by the age of 10-years (1.4%) whilst 18(1.2%) had been actively withdrawn from the study by their parents and were therefore not available for follow-up. By 10-years, 45 children recruited at

birth had never been seen at any subsequent follow-up. However at 10-years, 33 children were seen who had not been previously followed-up since their recruitment at birth.

Analysis from recruitment records revealed that there was no significant difference in gender between those who were seen at 10-years (50.7% male) and those who were 'missed' (54.3% male, p = 0.382). A trend for higher prevalence of social class I-III nm at birth was noted in those who returned for follow-up at 10-years than those who did not, although this did not reach statistical significance (46.4% v 35.4%, p = 0.063). The prevalence of diagnosed asthma at 1,2 and 4-year follow-ups was not significantly different amongst those seen at 10-years and those 'missed' (Table 4.2). Furthermore, prevalence of atopy at 4-year skin prick test was also similar for those seen or not seen at 10-years (Table 4.2). Thus it would seem that there was no specific sampling bias at 10-years whereby more previously allergic or asthmatic children returned for follow-up this time. Consequently the total 10-year follow-up group (n = 1373), just as the original group recruited at birth, could still be regarded as representing an unselected population sample.

4.3 MIGRATION AND ETHNIC COMPOSITION OF STUDY GROUP

At 10-years, out of the 1373 children followed up, 1172 (85.4%) were still resident on the Isle of Wight highlighting the low level of migration from the Island. Of Island children, 1007 (85.9%) attended at the Research Centre for a 'full visit' with the remainder of cases providing questionnaire information only, usually at telephone interview. One hundred and ninety five (14.2%) 10-year old children had left the Island and were resident elsewhere in mainland Britain (England, Scotland, Wales, Northern Ireland or the Channel Islands). In the majority of these cases questionnaire information only was completed during a telephone interview. However, 34 (17.4%) mainland children were seen for a 'full visit' at the Research Centre or during sessions held at Southampton General Hospital. Six children followed at 10-years (0.4%) were living overseas. Of these, one child was living in the Netherlands, one living in France, one in Greece, one in Libya and two in Australia. Two of these overseas children visited the Research Centre and participated in a 'full visit'. Analysis of the ethnic composition of our study population revealed that only 13 children

seen at 10-years (1.0%) were not of Caucasian ethnic origin. Three of these children were living on the mainland with the remainder still resident on the Island.

Table 4.2: Atopy and asthma characteristics from prior follow-ups of those seen and those 'missed' at 10-year follow-up

	Seen at 10-years (n=1373)	'Missed at 10-years' (n=163)	P-value [χ^2 Test]
% Asthma diagnosis at 1-years (n=)	9.8% (123/1259)	8.7% (10/115)	0.709
% Asthma diagnosis at 2-years (n=)	11.0% (125/1140)	7.7% (7/91)	0.332
% Asthma diagnosis at 4-years (n=)	15.2% (176/1160)	9.3% (5/54)	0.233
% Positive skin prick test at 4-years (n=)	19.7% (186/942)	18.4% (7/38)	0.841

4.4 SOCIO-ECONOMIC INDICES AT 10-YEARS

Several indices of socio-economic status were recorded at the 10-year visit.

4.4.1 Family Income

Total family income estimation at 10-years was provided by 1164 (84.8% of the sample) parents at interview. Analysis of this data identified that 83.3% of families had a total family income of less than £30,000 per annum. Five income bands were defined. The lowest band (less than £12,000) included 27.0% of families whilst the next band (£12,000 - £17,999) contained 24.9% of families. The largest proportion of families (31.4%) fell into the next income band (£18,000 - £29,000). Only 11.3% of families had incomes between

£30,000 and £41,999. Meanwhile the highest income band (more than £42,000) contained only 5.3% of families.

4.4.2 Tenure of Housing

Information on housing tenure was obtained for all 1373 children at 10-years. This identified that 70.1% (963) children lived in privately owned accommodation and 18.3% (251) children lived in Council/Housing Association properties. An additional 9.8% (134) of children lived in privately rented accommodation.

4.4.3 Maternal education

The year that the child's mother left full-time education was recorded as a further index of socio-economic status in 1227 cases. The median age was found to be 16-years with a range between 14 and 34-years.

4.4.4 Social class classification

The Standard Occupational Classification [178] was used to create a social class categorisation for 1215 children at 10-years (see Chapter 3.2.2 for details). An even distribution between the top three groupings (I, II, III non-manual) and lower three groupings (III manual, IV, V) was noted (49.7% v 50.3%) in our population. Class I contained 9.9% children, Class II contained 25.8% children, Class III (non-manual) contained 14.0% children, Class III (manual) contained 31.1% children, Class IV contained 13.0% children and Class V contained 6.2% children.

4.5 GENDER AND ANTHROPOMETRIC MEASUREMENTS

The group seen at 10-years had approximately equal gender composition with 697 (50.8%) males and 676 (49.2%) females.

The mean height for children seen at 10-years was 138.93 cm (standard deviation 6.18). The range in height was found to be between 120.2cm and 162.0cm. The mean weight of those seen at 10-years was 35.16 kg (standard deviation 7.46). The range in weight was found to be between 21.8 kg and 75.4 kg. Body Mass Index (BMI) was calculated for

children seen at 10-years using the equation (weight [kg]/ height^2 [m]) to provide an index of growth. The mean BMI at 10-years was therefore 18.11 (standard deviation 2.98). The range in BMI was found to be between 13.0 and 33.8. Reference values [192] as defined by Cole were used to define children in our population as being 'overweight' or 'obese' according to their BMI at 10-years. Thus the cut off points for 'overweight' were 19.84 for males and 19.86 for females at 10-years. The corresponding cut off points for 'obese' at 10-years were 24.00 for males and 24.11 for females. Using these definitions 22.3% (232/1040) of 10-year old children were 'overweight' whilst 4.9% (51/1040) of the population were 'obese'.

Analysis revealed no significant gender differences in height at 10-years (see Table 4.3). However at 10-years, females were found to be significantly heavier and to possess a significantly greater BMI than males. BMI was further categorised into quintiles. The highest quintile for BMI contained 208 children with BMI greater than 20.13. Comparing prevalence of gender distribution showed that a significantly greater proportion of children in the highest quintile for BMI were female than male (66.8% v 33.2%, $p < 0.001$). This finding further emphasises the fact that 10-year old females in our study showed a significant trend for being heavier than their male counterparts. This is confirmed by the fact that 'obesity' (7.2% v 2.5%, $p<0.001$) and 'overweight' (29.2% v 15.1%, $p<0.001$) states both showed significantly higher prevalence in females than males.

Analysis by social class showed no significant difference in weight (35.19 v 35.05kg, $p = 0.763$) or BMI (17.98 v 18.11, $p = 0.483$) at 10-years between those children in the three highest social classes and those in the lower three classes. In addition, prevalence of being 'obese' (3.8% v 5.9%, $p = 0.125$) or 'overweight' (20.7% v 22.5%, $p = 0.486$) did not vary significantly between those in Social Class I-III nm and III m-V at 10-years. Stratification by social class did reveal though that for girls prevalence of 'obesity' was significantly higher (10.6% v 4.0%, $p = 0.006$) amongst Social Class III m-V than Social Class I-III nm. An opposite but statistically insignificant relationship was noted for 'obesity' in boys (Social Class I-III nm 3.6% v Social Class III m-V 1.2%, $p = 0.095$). Thus there may be divergent interactions of social class with obesity for the two genders at this age. Height was found to be significantly greater in children from the highest three social classes compared to those within the lowest three groups (139.52 v 138.67cm, $p = 0.033$). Age at

visit might have confounded this finding since older children are likely to show greater height. However, taking into consideration possible confounding factors such as age at visit (actually significantly higher for lower social class, p = 0.040) or gender did not provide an alternative explanation for this finding. Thus it would appear that children from lower social classes might be suffering some element of growth impairment in childhood reflected by shorter stature at 10-years.

Table 4.3: Gender and anthropometry at 10-years

	Male (n=516)	Female (n=527)	P-value (Independent Samples T-test)
Height (cm) 95% CI	138.88 (138.37-139.39)	138.97 (138.42-139.53)	0.810
Weight (kg) 95% CI	33.98 (33.42-34.53)	36.32 (35.62-37.02)	<0.001*
BMI (kg /m^2) 95% CI	17.53 (17.31-17.74)	18.67 (18.39-18.96)	<0.001*

Notes: Values are arithmetic means with 95% Confidence Intervals for the means.

* Statistically significant at 5% level.

4.6 FAMILY DEMOGRAPHICS

Families participating in the 10-year follow-up were found to have an average of two children (median = 2.0, inter-quartile range = 2.0 to 3.0) at the time of 10-year interview. The range of family size found varied from 1 to a maximum of 10 (recorded for one family only). Families from the lower three social classes had significantly greater family size than children from the highest three classes. Comparison demonstrated a median family size of 3.0 for the lower social grouping compared to 2.0 children (p <0.001, *Mann Whitney U Test*) for the higher grouping. One hundred and thirty nine children (10.2%) in our population were 'only children' with no siblings. In 1229 families with more than one child, our 'study child' represented the firstborn within the family in 449 (36.5%) cases, the second born in 457 (37.2%) cases and the third born in 216 (17.6%) cases.

Fifteen sets of twins were seen during the 10-year follow-up. Of these, ten were same sex pairs (six female, four male) and five were mixed sex pairs.

Analysis at 10-years found that 234 (17.0%) children were from single parent families. Of these children, 214 had a mother as the sole parent whilst 20 had a father only.

4.7 SEASON OF BIRTH

Dates of birth for children followed up at 10-years were categorised into four seasons. Thus December, January, February births were classified as *Winter births*, March, April, May were classified *Spring births*, June, July, August as *Summer births* and September, October, November as *Autumn births*. Analysis of the whole10-year study population revealed 32.6% *Winter births*, 23.8% *Spring births*, 23.1 *Summer births* and 20.5% *Autumn births*. However, it should be noted that the original group recruited at birth extended over a 14-month period from January 1st 1989 to February 28th 1990. Consequently our sample contains two sets of children with January or February births, including 169 children who were born in January or February 1990 giving an artificial predominance of *Winter births*. If this group of *1990 children* were excluded from the seasonal analysis *Winter births* formed 23.2% of births, *Spring* 27.2%, *Summer* 26.3% and *Autumn* 23.3% showing that in fact births were evenly distributed throughout the calendar year for those study children born in 1989.

4.8 DOMESTIC PETS

Our findings at 10-years showed that domestic pet contact was extremely common. Thus 1184 (86.2%) 10-year old children had contact with domestic animals in their own home environment. When regular contact with animals elsewhere was also considered, 1291 (94.2%) children at 10-years experienced regular animal exposure at home or elsewhere. Ownership of *furry pets* was high with 1122 (81.7%) children having had a *furry pet* in the home within the preceding 2-years. The commonest domestic pets were cats being owned by 44.7% (613) children, dogs owned by 39.0% (535) children, hamsters owned by 24.3% (333) children and rabbits owned by 20.9% (287) children. Presence of birds within the

home was noted under the grouping *indoor birds* (parrots, cockatiels, budgerigars, canaries, zebra finches, lovebirds, sparrow and quail). With the semi-rural nature of the Isle of Wight several children also reported close contact with farm livestock in their home environment. These were classified as *livestock* (horses, ponies, cattle, sheep, goat, chickens). Details of the types of pet owned at 10-years are given in Table 4.4.

Analysis by social class revealed that children from the lower three social classes were significantly more likely to have *furry pets* in the home (86.4% v 78.8%, p <0.001). When the commonest domestic pets were considered separately different relationships with social class were observed. Thus whilst dog ownership (46.0% v 33.1%, p <0.001) was significantly greater amongst the lower three social groupings cat ownership did not vary between lower and higher social classes (45.8% v 45.0%, p = 0.781).

Table 4.4: Domestic pet ownership at 10-years

Type of Pet	Frequency of ownership (1373 households)
CAT	44.7% (613)
DOG	39.0% (535)
HAMSTER	24.3% (333)
RABBIT	20.9% (287)
FISH	14.2% (195)
INDOOR BIRDS	12.5% (171)
GUINEA PIG	11.6% (159)
LIVESTOCK	4.8% (66)
GERBIL	3.7% (51)
RAT	3.2% (44)
CHINCHILLA	1.4% (19)
MOUSE	0.9% (13)
SNAKE	0.9% (12)
LIZARD	0.6% (8)
FERRETT	0.5% (7)
TORTOISE	0.4% (5)

4.9 ENVIRONMENTAL TOBACCO SMOKE EXPOSURE AT 10-YEARS

At 10-years, 46.0% (561/1220) children regularly encountered tobacco smoke exposure from parents or others within the home environment.

Parental smoking was defined as average smoking of at least one cigarette per day in our study. Analysis revealed similar prevalence of smoking for mothers (28.8%) and fathers (29.3%) at 10-years. Fathers showed some trends for higher cigarette consumption than mothers. Thus smoking fathers were reported to have median cigarette consumption of 15.0 cigarettes per day (inter-quartile range 10.0-20.0). Smoking mothers were reported to have median cigarette consumption of 14.0 cigarettes per day (inter-quartile range 10.0-20.0). In 15.4% families both parents were smokers. Of parents who smoked at home, 56% described smoking predominantly inside the house with the remaining 44% smoking only outdoors. In addition to domestic tobacco smoke exposure our study identified that 20.2% (277/1371) children were regularly exposed to tobacco smoke at other locations such as relatives or family friends houses. If such exposures were considered in combination with domestic exposure then 54.5% (689/1264) children were regularly exposed to tobacco smoke either at home or elsewhere.

Analysis by social class classification showed clear trends with regard to smoking habits. *Any domestic tobacco smoke exposure* (including parental and any other smoking at home) was significantly commoner amongst the three lower social classes than the three higher classes (51.8% v 32.3%, $p < 0.001$). Prevalence of maternal smoking was also significantly greater amongst families from the lowest three social class groupings than those from the highest three social groups (31.7% v 19.5%, $p < 0.001$). The same trend was observed with regard to paternal smoking and social class groupings (37.4% v 18.7%, $p < 0.001$). Not surprisingly this trend was also repeated with regard to other smokers within the home and social class groupings (4.0% v 1.4%, $p = 0.005$). However the actual quantity of cigarettes consumed did not show any significant variation between mothers and fathers respectively in the three highest social classes and those within the lower three groupings. Thus median cigarette consumption for smoking mothers was 15.0 in the lower grouping and 10.0 in the higher social group ($p = 0.146$, *Mann Whitney U Test*). For smoking fathers median values

were 15.0 in the lower social grouping and 15.0 in the higher group (p = 0.96, *Mann Whitney U Test*).

In summary, children from the three lower social class groupings were found to face significantly greater tobacco smoke exposure at 10-years than their counterparts within the three higher social classes.

4.10 TESTING AT 10-YEARS

Of tests performed at 10-years ISAAC and supplementary written questionnaires were completed in 1373 cases. One thousand and forty-three (76.0% of 1373) children visited the Research Centre for a 'full visit'. Consequently physical examination and the ISAAC video questionnaire were performed on 1043 (100% of 1043) children. Skin prick testing to common allergens was performed in 1036 (99.3% of 1043) children whilst Total IgE analysis was obtained on samples from 953 (91.4% of 1043) children. Pulmonary function testing at spirometry was recorded in 981(94.1% of 1043) children and bronchial challenges to methacholine were conducted in 784 (75.2% of 1043) children. Mean spirometric results and Total IgE values for the population tested at 10-years are given in Table 4.5.

Table 4.5: Summary of mean 10-year testing results

	Mean +/- standard deviation
FVC Baseline (litres)	2.29 +/- 0.34
FEV_1 Baseline (litres)	2.03 +/- 0.30
FEV_1/ FVC Baseline	0.89 +/- 0.06
PEF (litres/sec)	4.14 +/- 0.78
Geometric mean total IgE (IU/ml)	80.52

4.11 DISCUSSION

With a 94% follow-up at 10-years our study has shown considerable retention of subjects. By comparison at 11-years, both the Tucson cohort study, USA [83] and Dunedin cohort study, New Zealand [100] updated information on approximately 77.0% of their original populations. Recently the MAS–Study Group [193] reported follow-up of 71.5% for their 7-year old German cohort. A highly unusual pattern was seen in our cohort with highest follow-up at 10-years rather than in the earlier study visits. Several factors might explain this phenomenon in our study. The presence of a highly organised research team and use of a highly structured recruitment process at 10-years (see **3.2.1**) undoubtedly played a significant role. The strong identity of the *David Hide Asthma and Allergy Research Centre* within the Island community was another important factor. The tendency for low migration from the Isle of Wight giving a very stable population base for follow-up was probably the single most important determinant for the very high rate of follow-up in our 10-year study. Furthermore, it is clear that there was no significant selection bias at 10-years that led to the population seen being unrepresentative of the whole population cohort that was originally recruited. However we did observe a consistent trend by which children with asthma or allergy or whose families had a history of such diseases performed a 'full visit' rather than just completing a questionnaire. Thus 'allergic families', perhaps not unsurprisingly, showed more motivation to participate fully at 10-years. This would not have affected the overall prevalence figures in our study since these were always determined by analysis of questionnaire responses. The single exception to this was the definition of *current asthma* at 10-years which incorporated bronchial hyper-responsiveness in its constitution. It is also possible that at 10-years we might have disproportionately conducted testing such as skin prick testing and bronchial challenges more often amongst subjects with a personal or family history of allergy since these children would have been more likely to attend for a 'full visit'.

Our study population also provides a very homogenous study group in terms of ethnicity with a marked predominance of Caucasian background amongst subjects seen at 10-years (99.1%). Thus our group provides a rare opportunity to observe a *pure* Caucasian population sample during an era when many populations within the UK are reflecting a more cosmopolitan and ethnically diverse make up.

Socio-economic classification has shown that there was a considerable prevalence of poverty in our population with a quarter of families falling into the lowest income band and over half the families falling into the lowest two (out of five) income bands. Accordingly the Isle of Wight could be described to some extent as being a region with considerable rural poverty. Social class classification identified highest prevalence amongst Class IIIm consisting of skilled manual workers. We identified strong links between lower social class groupings and larger family size, increased *furry p*et or dog ownership at 10-years as well as with increased prevalence of parental smoking. Such associations could have important implications for present and future health in these children. The fact that 10-year old children in the lower three social class groupings had significantly lower height than those in the highest groups may be a reflection of the health implications of lower socio-economic status. It certainly emphasises the importance of social factors towards optimal health during childhood.

Girls in our population were found to be significantly heavier than their male counterparts and possess a greater BMI as well. This may reflect the earlier commencement of growth acceleration associated with earlier puberty in girls, although it is worth noting that height was not significantly different between the sexes at 10-years. If pubertal growth was the sole determinant of our findings of heavier girls then a similar pattern in height might also have been expected. The fact that girls constituted a significantly greater proportion of children within the highest BMI quintile also suggests that obesity may be more of a problem amongst a subgroup of 10-year old girls than their male counterparts. Categorisation of obesity and being overweight using standard reference points confirmed that these indices were significantly commoner in girls at 10-years. That some interaction with social class might be important in these patterns was shown by the fact that girls of lower social class had higher prevalence of obesity than those in higher social classes. Interestingly an opposite (though not statistically significant) effect was observed in boys. Overall, we have identified a considerable prevalence of being overweight or obese amongst our 10-year population. The reasons for this and the long-term implications for both respiratory and general health in such subjects should be a matter of concern.

Very high prevalence of domestic pet ownership was identified in our 10-year study. The majority of such pets were *furry pets* to which exposure might be associated with a risk of allergic morbidity in predisposed individuals. A considerable proportion of our population (particularly from lower social classes) also experienced regular domestic environmental tobacco smoke exposure with strong implications for present and future health. Whether improved public health education might influence such patterns of behaviour is a matter of debate.

This chapter has identified and summarised the central demographic characteristics of the population seen at 10-years in our study. Furthermore it is evident from the follow-up achieved at 10-years that the Isle of Wight provides a highly conducive environment in which to conduct a prospective cohort study.

CHAPTER 5

THE NATURAL HISTORY OF WHEEZING DURING THE FIRST DECADE OF LIFE AND ITS ASSOCIATIONS WITH ATOPY AND BRONCHIAL HYPER-RESPONSIVENESS

An enhanced understanding of the natural history of childhood wheezing may provide an attractive framework for the future diagnosis and management of childhood asthma. In this chapter, a phenotypic classification for childhood wheezing based upon natural history is described along with factors that characterise these phenotypes.

5.1 ANALYSIS

At 10-years, information was obtained from 1373 of the original 1456 (94%) children recruited at birth. To minimise recall bias, analysis in this chapter is restricted to 1034 (71% of 1456) children seen prospectively with information at all study visits; 1 or 2-years (data from these visits was combined providing information in 'infancy'), 4 and 10-years. Of these 1034 children, SPT results were available for 875 (85%) 4-year olds. In addition at 10-years in this group SPT results, serum IgE measurements, baseline lung function and bronchial challenge results were also available for 861 (83%), 798 (77%), 859 (82%) and 647 (63%) children respectively. These 1034 children did not differ significantly in baseline characteristics from those observed at 10-years, but excluded from the present analysis because of prior missing follow-up (**Table 3.1**).

Children within this population were defined phenotypically as outlined below:

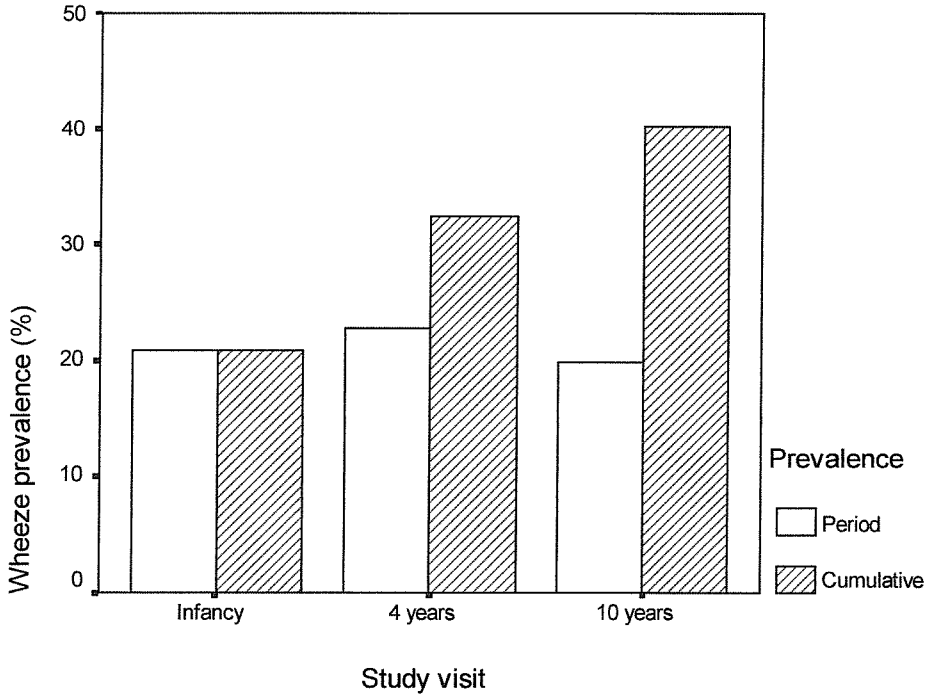
1 **Non-wheezers (NW)-** Children who never wheezed during the first decade of life.
2 **Early onset transient wheezers (ETW)-** Children with wheezing onset during the first 4 years of life which ceased and was not present within 12 months of being seen at 10-years.
3 **Early onset persistent wheezers (PW)-** Children with wheezing onset during the first 4 years of life who still wheezed at 10-years.

4 **Late onset wheezers (LW)-** Children with wheezing onset from 5-years onwards who still wheezed at 10-years.

5.2 RESULTS

Prospectively assessed prevalence of *ever wheezing* (cumulative prevalence) during the first decade of life was 40.3% (417 children). *Current wheeze* (period prevalence) covered 24 months for infancy and 4-years (the first and second 24 months of life), whereas at 10-years the term referred to symptoms within the previous 12 months. *Current wheeze* did not vary greatly during childhood (Figure 5.1) with highest prevalence at 4-years (22.8% - 236 children) and lowest prevalence at 10-years (19.9% - 206 children). Male predominance for *current wheeze* was noted throughout the first decade of life. Thus 56.8%, 56.4% and 57.3% of current wheezers at 'infancy', 4 and 10-years respectively were male.

Figure 5.1: Wheezing prevalence in the first decade of life



Note: 'Current wheeze' refers to the period prevalence of wheeze recorded at each study visit.

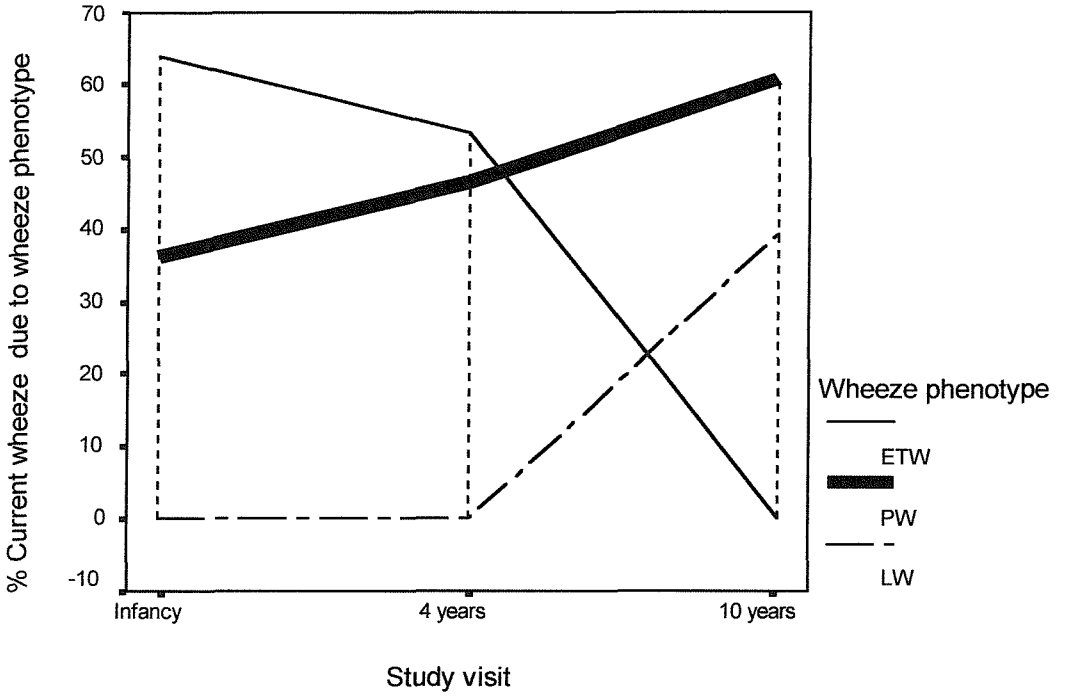
Of 417 children with a history of *ever wheezing*, 80.6% (336) had 'early onset wheezing' commencing by age 4-years. Amongst these 'early onset wheezers' 37.2% (125) had persistent symptoms to age 10-years with the remainder having transient wheeze. *Early transient wheeze* (ETW) was the commonest form of childhood wheezing seen in our population (Table 5.1). Male predominance was seen for all wheezing phenotypes especially *persistent wheeze* (PW). The changing prevalence of these phenotypes amongst 'currently wheezing' children at consecutive visits of our cohort study is illustrated in Figure 5.2.

Table 5.1: Classification of wheezing phenotypes during childhood

Wheeze Phenotype	No.	% Of 'Wheeze ever at 10-years' (n=417)	% Male
NW	617	0.0	46.5
ETW	211	50.6	56.9
PW	125	30.0	59.2
LW	81	19.4	54.3

Physician diagnosed asthma ever was reported in 19.9% (205) children at 10-years. Children with PW were significantly more likely to be given this diagnosis (76.0%) than either ETW (23.9%; $p < 0.001$) or *late onset wheeze* (LW) (51.9%; $p < 0.001$). LW also showed significantly higher prevalence of diagnosed asthma than ETW ($p < 0.001$).

Figure 5.2: The changing prevalence of wheezing phenotypes in 'currently wheezing' children at each study visit



Note: 'Current wheeze' refers to the period prevalence of wheeze recorded at each study visit. The proportion of 'current wheeze' attributable to each wheeze phenotype is shown for each study visit.

Prevalence of atopy at both 4 and 10-years, defined by positive skin prick test (SPT) to one or more common allergens, was significantly higher amongst PW or LW compared to *non-wheezers* (NW) and ETW. Similar trends were also noted for total serum IgE and positive IgE inhalant screen at 10-years (Table 5.2). Assessment of individual allergen sensitisation at 10-years clearly highlighted the importance of aero-allergen sensitisation amongst children with PW and LW (Table 5.3). House dust mite, grass pollen, cat and dog sensitisation were found to be the commonest sensitisations amongst PW and LW at 10-years occurring significantly more often for each phenotype than in comparison to NW. Other aero-allergen sensitivities however, including tree pollens, *cladosporium* and *alternaria* showed similarly low prevalence for each of these phenotypes in comparison with NW. For both PW and LW the highest odds ratios for sensitisation were observed for dog, cat and house dust mite with consistently lower but still significant values for grass pollen in each case. By contrast, such sensitisations amongst ETW were low and did not differ significantly in comparison to NW. Food sensitisation was very rare in any of these wheezing phenotypes at 10-years. Wheezing in all groups was associated with a higher

lifetime prevalence of *other allergic disorders* (eczema, food allergy or hay fever 'ever' as reported at 10-years) than non-wheezers (NW = 51.1%; ETW = 67.0%, $p < 0.001$; LW = 74.1%, $p < 0.001$; PW = 74.8%, $p < 0.001$). Lifetime prevalence for both eczema and food allergy was greatest in PW whilst hay fever prevalence was highest in LW (Table 5.2).

Table 5.2: Atopy, allergic disease and wheeze phenotype

	WHEEZING PHENOTYPE			
	NW	ETW	PW	LW
%Positive SPT 4-yrs n=	14.6% (75 / 515)	12.6% (23 / 182)	46.8% * ‡ (52 / 111)	34.3% * ‡ (23 / 67)
%Positive SPT 10-yrs n=	19.3% (96 / 497)	21.8% (39 / 179)	54.5% * ‡ (60 / 110)	54.7% * ‡ (41 / 75)
%Positive IgE Inhalant Screen 10-yrs n=	25.2% (116 / 460)	24.8% (41 / 165)	60.4% * ‡ (61 / 101)	63.4% * ‡ (45 / 71)
Mean $\log_{10}$ Total IgE 10-yrs (95% CI) n=	1.80 (1.73-1.86) (460)	1.80 (1.68-1.91) (165)	2.23 * ‡ (2.08-2.38) (101)	2.30 * ‡ (2.12-2.48) (72)
% ECZEMA EVER n=	38.2% (236 / 617)	49.3% † (104 / 211)	56.0% * (70 / 125)	53.1% (43 / 81)
% FOOD ALLERGY EVER n=	14.9% (92 / 617)	28.5% * (57 / 200)	40.3% * § (48 / 119)	21.0% (17 / 81)
% HAY FEVER EVER n=	13.3% (82 / 617)	14.7% (31 / 211)	39.2% * ‡ (49 / 125)	45.7% * ‡ (37 / 81)

Notes: 95% CI refers to 95% Confidence Interval for the mean. The Bonferroni correction approach has been applied to analyses.

Statistical significance compared to NW; * $p < 0.001$; † $p = 0.03$

Statistical significance compared to ETW; ‡ $p < 0.001$

Statistical significance compared to LW; § $p = 0.024$

Table 5.3: Individual allergen sensitisations for phenotypes at 10-years

ALLERGEN	ETW	PW	LW
%House Dust Mite	12.3%	46.4% *	46.7% *
OR	0.98	6.05	6.13
(95%CI)	(0.58-1.65)	(3.82-9.58)	(3.62-10.36)
%Cat	1.7%	25.5% *	20.0%*
OR	0.32	6.43	4.17
(95%CI)	(0.10-1.08)	(3.57-11.58)	(2.35-9.43)
%Dog	1.7%	14.5%*	16.0% *
OR	0.75 (¶)	7.51 (¶)	8.40
(95%CI)	(0.21-2.73)	(3.38-16.68)	(3.56-19.83)
%Grass	10.1%	28.2%*	24.0%†
OR	1.05 (¶)	3.67	2.95
(95%CI)	(0.59-1.85)	(2.20-6.12)	(1.61-5.42)
%Tree	1.7%	1.8%	2.7%
OR	1.04 (¶)	1.13 (¶)	1.67 (¶)
(95%CI)	(0.27-3.96)	(0.24-5.39)	(0.35-8.02)
%Cladosporium	0.6%	1.8%	1.3%
OR	0.46 (¶)	1.51(¶)	1.10 (¶)
(95%CI)	(0.06-3.84)	(0.30-7.60)	(0.13-9.30)
%Alternaria	2.2%	3.6%	1.3%
OR	1.24(¶)	2.04(¶)	0.73(¶)
(95%CI)	(0.38-4.07)	(0.62-6.76)	(0.09-5.86)
%Peanut	1.7%	3.7%	2.7%
OR	1.19(¶)	2.66(¶)	1.91(¶)
(95%CI)	(0.31-4.66)	(0.77-9.26)	(0.39-9.39)
%Milk	0.0%	1.8%§	1.3%
OR	-(¶)	-(¶)	-(¶)
(95%CI)	-	-	-
%Hens egg	0.6%	0.9%	1.3%
OR	2.78(¶)	4.58(¶)	6.69(¶)
(95%CI)	(0.17-44.70)	(0.28-73.85)	(0.41-108.10)
%Soya	0.0%	0.0%	1.3%
OR	-(¶)	-(¶)	6.69(¶)
(95%CI)	-	-	(0.41-108.10)
%Cod	0.6%	3.7%‡	1.3%
OR	2.78(¶)	18.86(¶)	6.69(¶)
(95%CI)	(0.17-44.70)	(2.09-170.43)	(0.41-108.10)

Table 5.3 Notes: Prevalence of individual allergen sensitisations at 10-year SPT amongst the three wheezing phenotypes (ETW, PW, LW) is illustrated. Odds ratios (with their 95% Confidence Intervals) refer to comparisons of individual allergen sensitisations between those found for each phenotype and those found for non-wheezer status. Chi-square risk analysis was used for this purpose with use of Fishers Exact Test (¶) where indicated (by situations where expected cell counts of less than 5 were encountered).
Statistical Significance Compared to NW;
* $p < 0.001$
† $p = 0.001$
‡ $p = 0.004$
§ $p = 0.032$

Lung function at 10-years was highest in NW (Table 5.4). PW had significantly lower FEV_1 than NW and FEV_1 / FVC ratio than both NW and ETW. ETW showed significantly lower PEF than NW, a finding that persisted if only ETW with wheezing confined to the first 4-years were analysed (PEF 4.21 v 4.00; $p = 0.048$; 95% Confidence Interval 0.001, 0.418; *ANOVA with Bonferroni Multiple Comparisons Test*).

Assessment of BHR by ATS classification (Figure 5.3) and *inverse slope* (Table 5.4) revealed greater levels of BHR amongst LW and PW than NW or ETW. *Definite BHR* (ATS categories, 'mild/positive' and 'severe') was compared for wheezing phenotypes. Significantly more PW (42.6%) had *definite BHR* than either NW (10.7%; $p < 0.001$) or ETW (15.1%; $p < 0.001$). LW (53.3% *definite BHR*) also showed a similar pattern in comparison to both NW ($p < 0.001$) and ETW ($p < 0.001$). Neither LW compared to PW ($p = 1.0$) nor ETW compared to NW ($p = 1.0$) showed significant differences in this category.

Table 5.4: Lung function and BHR *(inverse slope)* by wheeze type

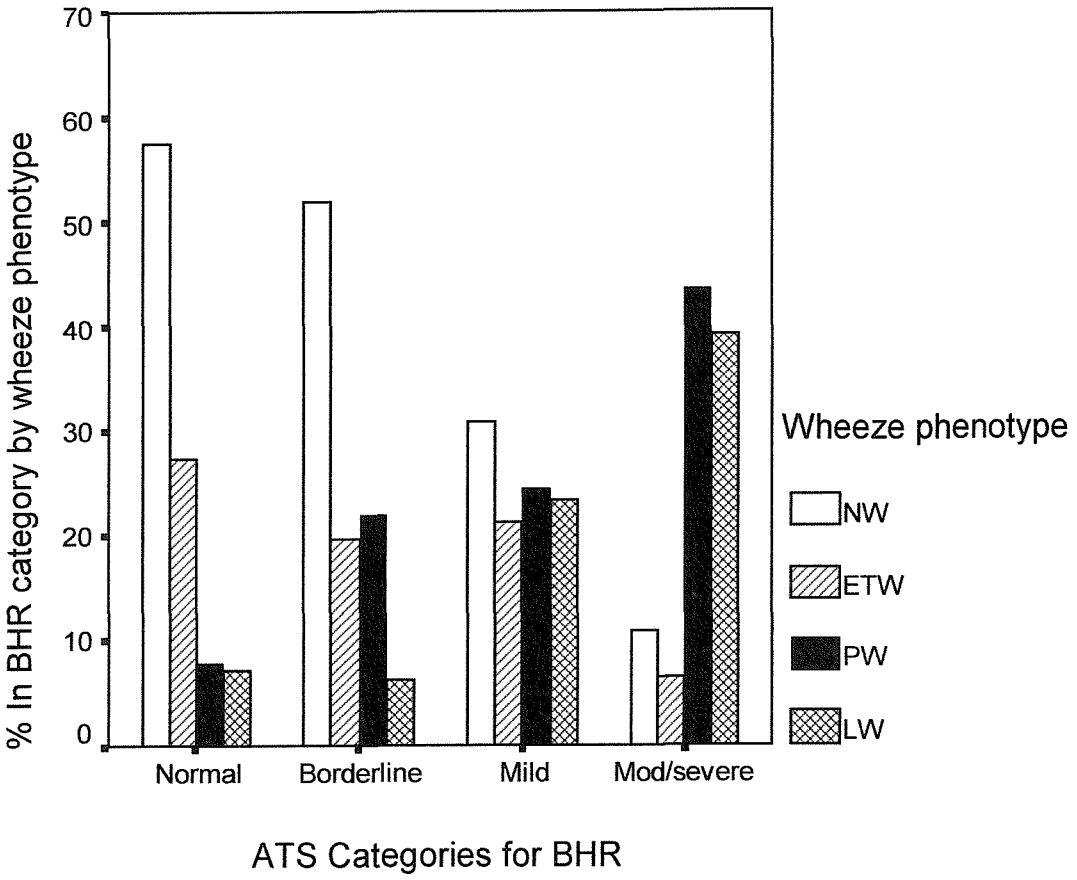
	WHEEZING PHENOTYPE			
	NW	**ETW**	**PW**	**LW**
FVC (Litres) (95% CI) n=	2.31 (2.28-2.34) (495)	2.26 (2.21-2.31) (178)	2.28 (2.22-2.35) (111)	2.28 (2.22-2.34) (76)
FEV_1 (Litres) (95% CI) n=	2.06 (2.03-2.08) (494)	2.00 (1.95-2.04) (178)	1.97 † (1.91-2.03) (111)	1.99 (1.94-2.05) (76)
FEV_1: FVC (95% CI) n=	0.89 (0.89-0.90) (494)	0.89 (0.88-0.90) (178)	0.86 * || (0.85-0.88) (111)	0.87 (0.86-0.89) (76)
PEF (Litres/sec) (95% CI) n=	4.21 (4.14-4.28) (495)	4.02 ‡ (3.91-4.13) (178)	4.02 (3.86-4.17) (111)	4.22 (4.05-4.39) (76)
1/ (10 - slope) (95% CI) n=	0.058 (0.054-0.062) (318)	0.057 (0.051-0.062) (152)	0.030 * § (0.025-0.036) (101)	0.033 * § (0.025-0.041) (75)

Notes: Values quoted are means with 95% Confidence Intervals (95% CI) for the means. Analysis is by ANOVA with the Bonferroni Multiple Comparisons Test.

Statistical significance compared to NW: * $p < 0.001$; † $p = 0.029$; ‡ $p = 0.036$

Statistical significance compared to ETW: § $p < 0.001$; || $p = 0.008$

Figure 5.3: The relationship between wheezing phenotype and BHR at 10-years



Note: The constitution of each BHR category is shown by wheezing phenotype.

American Thoracic Society Categorisation of BHR [191]

Normal BHR;	PC_{20}> 16 mg/ml.
Borderline;	PC_{20} = 4 to 16mg/ml.
Mild/ Positive;	PC_{20} = 1 to 4mg/ml.
Mod/ severe;	PC_{20}< 1mg/ml.

5.3 DISCUSSION

Recent studies have shown high prevalence of asthma, wheeze and atopy in Australia[41], New Zealand [194] and the UK [34,85]. With lifetime prevalence for wheezing of 40% and 'physician diagnosed asthma' of 20%, this cohort study confirms the magnitude of such problems amongst UK children.

That wheezing may be even greater in our sample is suggested by higher retrospectively determined *wheeze ever* (47%) at 10-years than the 40% prevalence of *cumulative wheeze* obtained using prospective data from each visit. It is possible that since *current wheeze* at each visit was our determining variable for prospective wheeze classification, our reported cumulative prevalence may slightly underestimate the problem. This is because given a 6-year interval between the last 2 follow-ups, some late onset wheezers were not 'detected' if they had wheezed transiently between the ages of 5 and 9-years. Retrospective information (collected at 10-years), indicate that this 'missed' group was too small (n=53) to have significantly altered the overall result patterns with regard to our wheezing phenotypes.

Common consensus is that most childhood wheezing occurs transiently in early life, associated with viral respiratory illness [44,85,167]. In this study, 81% of childhood wheezing began by the age of 4-years. However, a substantial proportion (37%) of early life wheezers in our unselected population sample still wheezed at 10-years. This extends previous findings by Martinez [44] and Brooke [85] who identified a similar degree of persistent wheeze at 6-years of age. Furthermore, our study reveals remarkably little change in prevalence of *current wheeze* during childhood. This was despite the fact that our definition of *current wheeze* at infancy and 4-years was over 24 months compared to just 12 months at 10-years. Significantly higher *current wheeze* at infancy and 4-years than at 10-years might have been expected if early transient wheeze was, as has often been suggested [81,167], the predominating childhood wheezing type. As shown in Figure 5.2 the relative predominance of particular wheezing phenotypes showed considerable change during the course of childhood.

Confirming previous work [34,42,44] we found *current wheeze* was commoner in boys. Phenotypic analysis found this particularly evident for those who started wheezing in early life (especially *persistent wheezers*), consistent with existing knowledge that boys have higher early life wheezing [34]. However, we found continuing male wheezing predominance at 10-years when, from previous work [34], it would have been expected that more girls would have commenced wheezing leading to equalisation of the male: female wheezing ratio. Whether this reflects factors peculiar to our population is unclear.

We used a phenotypic wheeze classification similar to the landmark study [44,83] of Martinez et al though our definition of 'early transient wheeze' is somewhat broader. Whilst various wheezing classifications have been previously used, this particular system appears most appropriate for studying the natural history of childhood wheeze.

Physician diagnosed asthma may be regarded as a crude indicator of disease morbidity in wheezing children. In our population the greatest proportion (46%) of diagnosed asthmatics were *persistent wheezers*. *Persistent wheezers* also showed highest prevalence of atopy at 4 and 10-year SPT. Intriguingly *late onset wheezers* had lower degrees of atopy at 4-years but comparably increased atopy by 10-years. It is worth recognising that *late onset wheezers* did not commence wheezing till age 5-years and thus were still 'non-wheezers' when seen at 4-years. Yet their prevalence of atopy at 4-years whilst less than that of *persistent wheezers* was significantly greater than both *early transient wheezers* and those destined never to wheeze. This raises the question whether atopy at 4-years in children who have not previously wheezed may have a predictive value for the subsequent development of wheezing during later childhood. By contrast, *early transient wheezers* had low prevalence of atopy at 4 and 10-years suggesting that early transient wheezing is largely non-atopic. In terms of atopy, therefore, one might define *persistent wheeze* as the true 'atopic condition' from early life, *late onset wheeze* as a later manifestation of atopy and *early transient wheeze* as a largely non-atopic condition. In examining this finding, we observed that both *persistent* and *late onset wheezers* showed significantly higher prevalence of aero-allergen sensitisation to house dust mite, grass pollen, cat and dog than *non-wheezers* at 10-years. This pattern was not repeated for *early transient wheezers*. Thus it could be hypothesized that aero-allergen sensitisation is an important factor for the presence of wheezing during the latter half of the first decade of life. Our results suggest that this would appear to be the

case regardless of wheezing phenotype in early life. Alternatively, food allergen sensitisation at 10-years was not strongly associated with any particular wheezing phenotype. Interestingly lifetime prevalence of both food allergy and eczema were significantly higher in those with early transient wheeze than those who had never wheezed. *Persistent wheezers* had highest prevalence of eczema and food allergy whilst *late onset wheezers* had highest hay fever prevalence but significantly less food allergy than *persistent wheezers*. These patterns mirror the natural history of such allergic conditions as outlined by the notion of an allergic march [15] in childhood. This theory suggests that food allergy and eczema arise frequently in early childhood with hay fever typically occurring later. Our observations suggest that timing of wheeze onset may influence co-existent allergic symptom expression – a novel perspective on the interactions of asthma and allergy and in turn on the nature of the allergic march. Certainly the association of these states appears more complex than a simple causal effect for allergy upon asthma.

Early transient wheezing was associated with lower PEF at 10-years. This was still the case if only those who wheezed exclusively in the first 4-years of life were considered. This extends previous findings [44,136,195] that reduced lung function in these children is inherent and probably a cause of viral associated wheeze in infancy. Our results suggest that elements of reduced lung function may endure into later childhood in such children despite their then being asymptomatic.

It has also been proposed that lung function deteriorates in *persistent wheezers* [85,169]. We found them to have a lower FEV_1 / FVC ratio and FEV_1 but not lower PEF or FVC, than *non-wheezers*. This is one of the first birth cohort studies to follow wheezing children entirely in an era when inhaled steroid usage is commonplace, particularly for those with persistent symptoms. It is possible that such treatment prevented the decline that might have been expected in those with persistent wheezing. Amongst all wheezing children, *late onset wheezers* although *current wheezers*, showed least impairment of lung function at 10-years. This may reflect their shorter illness duration compared to *persistent wheezers* such that any decline in their lung function had yet to manifest.

BHR showed clear associations with *current wheeze* at 10-years, with greatest severity in *persistent* and *late onset wheezers*. Therefore both atopy and BHR appear to be significant

factors in the persistence of early wheeze and wheeze onset in later childhood. There may be much similarity between these two phenotypes and the childhood 'atopic asthmatic' characterised as having ongoing airway inflammation by Stevenson et al [11]. Alternatively, *early life transient wheezers* showed scant difference to non-wheezers in terms of BHR and atopy. This probably reflects a different pathophysiology to such wheeze, associated with low lung function and airway calibre in the context of early life viral infection. Such a hypothesis would also be consistent with Stevenson's previous findings of little ongoing inflammation in children with viral associated wheeze [11].

In conclusion it is clear that early life wheezing is not always transient or benign in nature – rather the results presented in this chapter challenge the commonly accepted perception of the 'happy infant wheezer'. Children that wheeze transiently certainly do not fit the model of the 'asthmatic child' being similar in terms of atopy and BHR to non-wheezers. Yet they appear to constitute a distinct phenotype, showing a considerable 'life-time' prevalence of associated food allergy and eczema plus some evidence of continued low lung function even at the age of 10-years. In contrast, *persistent wheezers* constitute the largest proportion of diagnosed asthmatics indicating that childhood asthma originates in the early years.

This study demonstrates that there is a significant burden of *persistent wheezing* during the first decade of life. Factors found to be associated with this phenotype are physician diagnosed asthma, male gender, atopy (both at 4 and 10-years) and BHR. The search for early life factors capable of identifying and differentiating *persistent* from *transient wheezers* may prove of significant benefit in future management of childhood asthma.

CHAPTER 6

THE MORBIDITY OF WHEEZING ILLNESSES DURING THE FIRST DECADE OF LIFE

It is now clear that asthma is placing a considerable burden upon global healthcare resources. Assessments of asthma morbidity have identified increasing primary care consultations [58] as well as hospital admissions [60,61] although patterns appear to have stabilised in recent years [59]. Mortality rates for asthma in many countries have shown similar trends [62]. Phenotypic classification of childhood wheezing can help to create a better understanding as to why asthma is such a common problem. Many characteristics of wheezing phenotypes are now becoming apparent [44,85]. In Chapter 5 characteristics were described of a natural history based phenotypic classification for childhood wheezing. Patterns of disease morbidity for such wheezing phenotypes and their reliance upon various healthcare resources remain to be clarified. This chapter therefore sets out to examine measures of disease morbidity associated with the different wheezing phenotypes defined in Chapter 5.

6.1 RESULTS

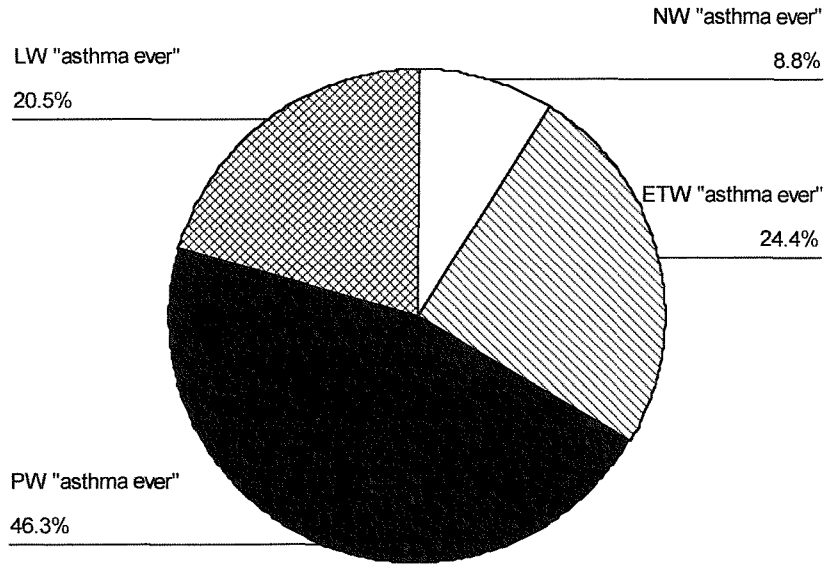
By 10-years, the cumulative prevalence of prospectively determined *wheeze ever* was 40.3% (417 children). Phenotypic classification of childhood wheezing according to natural history of symptoms showed that 211 wheezing children (50.6%) were *early transient wheezers* (ETW), 125 (30.0%) were *persistent wheezers* (PW) and 81 (19.4%) were *late onset wheezers* (LW). The remaining 617 children were categorised as *non-wheezers* (NW). Of ETW, 71.1% (150 children) had wheezing confined purely to the first 4-years of life. The remaining 61 children with ETW had further episodes of wheezing after age 4-years but did not wheeze within 12-months of being seen at 10-years.

The mean duration of wheezing illness (the interval from first to last reported wheezing episode) was significantly greater for PW (arithmetic mean 8.80 years; 95% Confidence Interval 8.61, 8.99) than ETW (3.81 years; 95% Confidence Interval 3.27, 4.35; $p < 0.001$) or LW (4.53 years; 95% Confidence Interval 3.93, 5.13; $p < 0.001$) compared by the

Mann-Whitney U test. ETW and LW did not differ significantly in length of wheezing illness ($p = 0.168$). Duration of wheezing was further divided into percentiles. The proportion of each phenotype with wheezing duration in the top 50th centile of duration (>5.75 years) was assessed. Thus 32.7% (37/113) ETW, 100.0% (125) PW and 35.0% (28/80) LW fell within this group of 'prolonged wheezers'.

At 10-years, *physician diagnosed asthma ever* was reported for 205 (19.9%) children in our study. PW formed a larger proportion of diagnosed asthmatics (46.3%) than ETW (24.4%) or LW (20.5%) as shown in Figure 6.1. Eighteen children classified as *non-wheezers* also had a reported *asthma diagnosis ever* at 10-years. Of these eighteen children, five had a history of symptoms of recurrent cough but no wheeze that led to an asthma diagnosis. The remaining thirteen children received an asthma diagnosis for wheezing that occurred between the ages of 5 and 9-years. Since *current wheeze* was the determining variable for wheeze type classification these *late transient wheezers* were not 'detected' as wheezing in our phenotypic classification.

Figure 6.1: Constitution of 'Physician diagnosed asthma ever' at 10-years by wheeze phenotype



At age 1-year, *diagnosed asthma* was present equally commonly amongst PW and ETW (29.6% v 25.1%; p = 0.370). By age 2-years, however, prevalence of *diagnosed asthma* was significantly higher in PW than ETW (46.5% v 30.7%; p = 0.005). At 4-years of age this trend was even stronger with 74.8% PW having *diagnosed asthma* compared to 32.9% ETW (p < 0.001). Questioning at 10-years confirmed these trends with *physician diagnosed asthma ever* in 76.0% PW but only 23.9% ETW (P<0.001). The terminology used at 10-years to assess asthma diagnosis (drawn from the ISAAC questionnaire) reflected a cumulative measurement and was different to the period prevalence used at earlier study visits. If period prevalence of *diagnosed asthma* had been assessed at 10-years one might have expected to encounter a much-reduced prevalence amongst ETW.

Prospectively reported chest infections in infancy were significantly less frequent in children classified NW or LW than those classified ETW or PW (Table 6.1). PW showed highest prevalence of such infections at 1 and 2-years with ETW showing intermediary patterns.

Table 6.1: Recurrent chest infection in infancy and wheeze phenotype

	WHEEZE PHENOTYPES			
	NW	ETW	PW	LW
Recurrent chest infection in 1st year (%)	1.8%	16.6%* ‡	21.6%* †	2.5%
n=	(11 / 617)	(35 / 211)	(27 / 125)	(2 / 81)
Recurrent chest infection in 2nd year (%)	2.8%	29.1%* †	42.1%* †	4.9%
n=	(17 / 617)	(58 / 199)	(48 / 114)	(4 / 81)

Notes: Chi-square analysis with Bonferroni correction approach was used.

Statistical significance compared to NW: * p < 0.001

Statistical significance compared to LW: † p < 0.001; ‡ p = 0.006

Recognised triggers for wheezing, described retrospectively at 10-years, were significantly less common for ETW (67.4%) than either LW (96.3%; p <0.001) or PW (92.7%; p

<0.001). Specific triggers such as exercise, pollen, house dust and stress were all significantly commoner in PW than ETW, whilst exercise and stress were significantly more frequent amongst LW than ETW (Table 6.2). The exception to this was wheezing with chest infections, which did not differ significantly between the phenotypes.

Table 6.2: Triggers for 'wheezing ever' reported at 10-years

	WHEEZING PHENOTYPE		
	ETW	PW	LW
%Chest Infection (n=)	55.6% (75/135)	66.9% (83/124)	58.0% (47/81)
%Exercise (n=)	10.9% (15/135)	50.8% * 63/124)	60.5% * (49/81)
%Pollen (n=)	3.0% (4/135)	23.4% * ‡ (29/124)	17.8% (8/81)
%Animals (n=)	1.5% (2/135)	9.7% † (12/124)	9.9%† || (8/81)
%House Dust (n=)	4.4% (6/135)	24.2% * § (30/124)	8.6% (7/81)
%Stress (n=)	2.2% (3/135)	16.9% * (21/124)	14.8% * (12/81)

Notes: Values given reflect prevalence of specific wheezing triggers for each phenotype. Chi-Square analysis with Bonferroni correction approach was used. || Denotes Fishers Exact Test.

Statistical significance compared to ETW; * $p < 0.001$; † $p = 0.012$

Statistical significance compared to LW; ‡ $p = 0.042$; § $p = 0.015$

Within the prospectively followed group of 1034 children 39.5% (374/948) children had ever been seen by their general practitioner because of wheezing whilst 7.4% (70/946) children had been admitted to hospital with wheezing illnesses during the first decade of life. Children with PW had the highest *lifetime requirements* for all levels of medical care with regard to their wheezing illness as indicated at 10-years by reported GP care, asthma specialist referral, hospital admission and casualty department attendance (Table 6.3). ETW and LW did not differ significantly in requirements for these levels of treatment.

Table 6.3: Use of healthcare resources by wheezing phenotypes

	WHEEZING PHENOTYPE		
	ETW	PW	LW
% GP Treatment (n=)	82.7% (115 / 139)	93.5% † (116 / 124)	91.4% (74 / 81)
% Specialist Care (n=)	8.6% (12 / 139)	21.8% * ‖ (27 / 124)	7.4% (6 / 81)
% Ever Admitted to Hospital (n=)	16.1% (22 / 137)	27.4% § (34 / 124)	11.1% (9 / 81)
% Ever Attended at Casualty (n=)	2.9% (4 / 134)	11.4% † (14 / 123)	4.9% (4 / 81)
% Multiple Hospital Admissions (n=)	2.9% (4 / 133)	11.3% ‡ (14 / 124)	3.7% (3 / 78)
% Multiple Casualty Attendances (n=)	0.7% (1 / 138)	3.3% (4 / 123)	0.0% (0 / 81)

Notes: Chi-Square analysis with Bonferroni correction approach was used.

Statistical significance compared to ETW; * p = 0.009; † p = 0.021; ‡ p = 0.024

Statistical significance compared to LW; § p = 0.015; ‖ p = 0.018

In our 1034 prospective group, 32.2% (307/952) children had ever received pharmacological treatment for wheezing by 10-years. Regular prophylactic medications were reportedly used at some point by 17.7% (166/940) children and oral steroids by 7.8% (74/946) children. At 10-years, *pharmacological treatment ever* for wheezing was significantly less frequent in ETW (62.2%) than PW (87.9%; p <0.001) or LW (82.7%; p = 0.003). PW and LW did not differ significantly in this context. *Treatment ever*, reported at 10-years, with each of inhaled bronchodilators, inhaled steroids, multiple prophylactic medications and oral steroids was commoner in PW than LW or ETW (Table 6.4). Significantly more PW than ETW required multiple courses of oral steroids during their life (64.0% v 21.1%; p = 0.003) but LW (58.3%) did not differ significantly in this context from PW (p = 1.0) or ETW (p =0.168) [*comparisons by Chi-square analysis with Bonferroni correction*].

Subgroup analysis of children within each wheezing phenotype was conducted to assess impact of wheezing duration upon morbidity. Amongst PW it was found that 80% had wheezing duration greater than 8.0 years with the remainder having duration between 6.0 and 8.0 years. Comparison of morbidity measures between these two groups revealed no evidence of increased healthcare utilisation in the group with longer disease duration. Amongst LW it was found that 20% had a wheezing duration less than 2.0 years. Comparison of this subgroup with those LW with greater wheezing duration demonstrated some evidence of decreased morbidity. Thus LW with lower wheezing duration had lower oral steroid usage (0% [23] v 21.1% [12/57]; p = 0.015 [*Fishers exact test*]) and lower prevalence of GP care (78.3% (18/23) v 96.5% [55/57]; p =0.019; OR = 0.37; 95%CI = 1.36,42.8; [*Fishers exact test*]). For ETW 40% of children had wheezing duration greater than 4.6 years. Comparison of this subgroup with ETW having wheezing duration shorter than 4.6 years demonstrated greater use of inhaled steroid usage in those with longer disease (34.9% (15/43) v 6.1% (4/66); p <0.001; OR = 8.30; 95%CI = 2.53, 27.29).

Measures of *current wheezing morbidity* at 10-years tended to be higher in PW than LW (Figure 6.2). However, only 'sleep disturbance by wheeze in the last year' was significantly greater in PW (60.2% v 41.3%; p = 0.024).

The number of other *allergic states ever present* was used for each child to provide an index of *allergic co-morbidity*. For this purpose eczema, food allergy and hay fever 'ever' reported at 10-years were totalled. Higher allergy counts (2 or 3 conditions) were present more often in PW (43.2%; p < 0.001), LW (37.0%; p < 0.001) and ETW (23.7%; p = 0.006) than NW (13.8%). PW also had significantly higher prevalence of 2 or 3 other allergic states than ETW (p< 0.001).

Table 6.4: Medication 'ever used' by wheezing phenotypes

	WHEEZING PHENOTYPE		
	ETW	PW	LW
% Bronchodilator Treatment (n=)	57.6% (80 / 139)	88.6% * (109 / 123)	79.0% * (64 / 81)
% Inhaled Steroid Treatment (n=)	15.2% (20 / 132)	58.5% * ‡ (72 / 123)	39.5% * (32 / 81)
% Multiple Prophylactic Treatments (n=)	6.1% (8 / 124)	14.6% ‖ (18 / 123)	3.7% (3 / 81)
% Oral Steroid Treatment (n=)	7.2% (10 / 138)	40.3% * † (50 / 124)	14.8% (12 / 81)

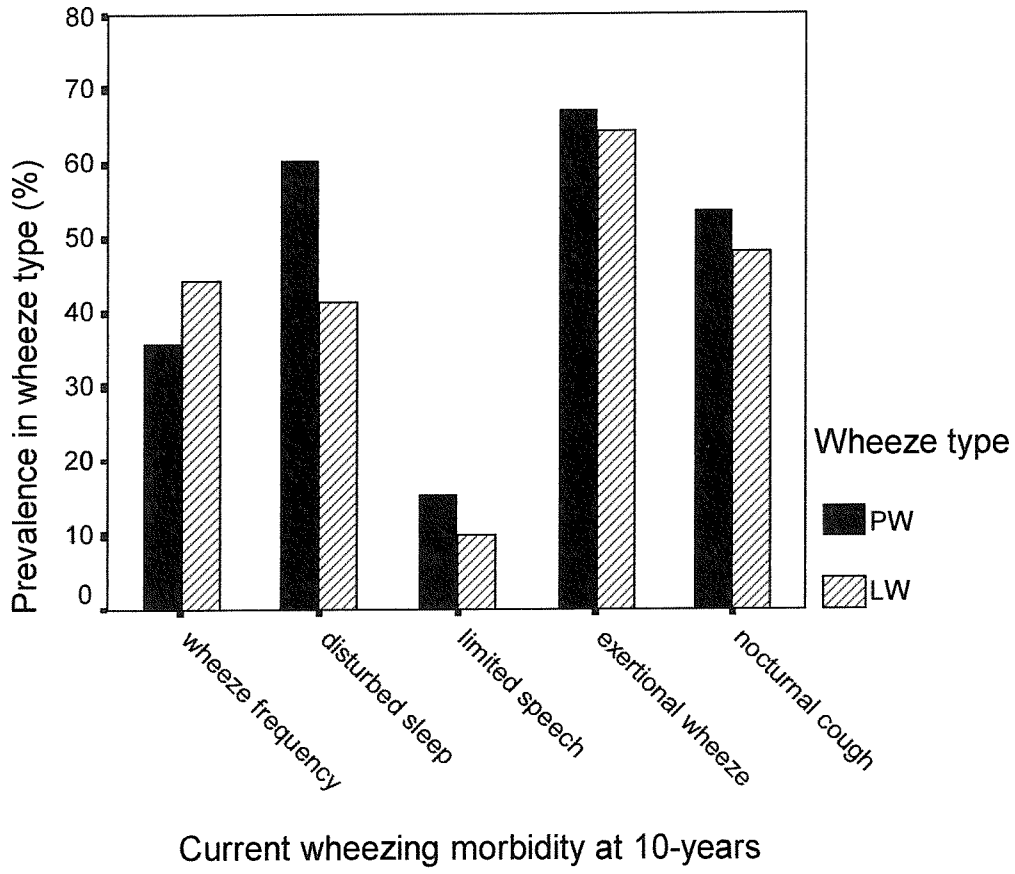
Notes:

Chi-Square analysis with Bonferroni correction approach was used.

Statistical significance compared to ETW; * $p < 0.001$;

Statistical significance compared to LW; † $p < 0.001$; ‡ $p = 0.024$; ‖ $p = 0.036$

Figure 6.2: Current wheezing morbidity at 10-years by wheeze phenotype



Notes:

Wheeze frequency:	4 or more episodes in the last year
Disturbed sleep:	Any nocturnal disturbance by wheezing in the last year
Limited speech:	Limitation of speech to 1 or more words at a time by wheeze in the last year.
Exertional wheeze:	Wheezing with exercise in the last year.
Nocturnal cough:	Dry cough at night in the last year (not associated with cold or flu).

6.2 DISCUSSION

This chapter clearly demonstrates that wheezing and asthma are major causes of morbidity amongst UK schoolchildren. It is worth reflecting that these findings were drawn from an unselected whole population sample rather than a hospital or clinic based sample where selection bias would have resulted in high morbidity indices. The heavy burden of childhood wheezing upon healthcare resources readily emerges from our findings. Over the first decade of life 40% of children in our sample had been seen by a general practitioner for a wheezing illness, whilst 18% had required regular prophylactic medication, 8% had required oral steroids and 7% had been admitted to hospital for wheezing.

As described in Chapter 5 we have adopted a phenotypic classification of childhood wheezing similar to that of the landmark study by Martinez et al [44], although our definition of *early transient wheezing* is somewhat broader.

In Chapter 5 it was demonstrated that 81% of childhood wheezing commences within the first 4-years of life. Whilst 60% of 'early life wheezers' in our sample were shown to have a transient condition, 40% wheezed persistently to age 10-years. Several factors characterised these *persistent wheezers* including male gender, high prevalence of atopy and other allergic diseases throughout childhood plus lower lung function and greater bronchial hyper-responsiveness (BHR) at 10-years. By contrast, *early transient wheezers* differed little from *non-wheezers* in terms of atopy and BHR, whilst showing some evidence of lower lung function at 10-years. *Late onset wheezers* with symptoms beginning after age 5 were found to have intermediary patterns of allergy and BHR, with relatively unimpaired lung function at 10-years. In this Chapter, these findings have been extended to show that clear patterns in disease morbidity and use of various healthcare resources accompany such wheezing phenotypes.

Prospectively collected information demonstrated that prevalence of chest infection during infancy (at 1 or 2-years) did not differ significantly between *early transient* and *persistent wheezers*. Interestingly *early transient* and *persistent wheezers* did have significantly more recurrent chest infections in infancy than children who did not wheeze during that period. Thus one might consider the apparent importance of common viral respiratory pathogens

for early life wheezing regardless of ultimate wheezing phenotype. This broadly agrees with Stein et al [133] who demonstrated increased development of both infrequent and frequent childhood wheezing illnesses in children who had evidence of *Respiratory Syncytial Virus* infection during infancy. Such infections might predispose to infantile wheezing through respiratory epithelial damage and denudation [133].

Physician diagnosed asthma is a crude indicator of disease morbidity in wheezing children. Over the first decade of life, *persistent wheezers* formed the largest proportion of asthmatics (46%). The early life origins of childhood asthma are highlighted in our study by the fact that, *early transient wheezers* formed a further 24% of those *ever diagnosed asthmatic*, a greater proportion than that of *late onset wheezers*. The prevalence of diagnosed asthma in early life also showed a markedly increasing trend amongst *persistent wheezers* from the age of 2-years onwards. This could be interpreted as suggesting a picture of increasing morbidity amongst *persistent wheezers* as they continue to wheeze. In this context, amongst all wheezing children, *persistent wheezers* were found to have the longest duration of wheezing illness. Thus as suggested in the CAMP study, USA [169], *persistent wheezers* might be expected to possess the greatest scope for development of uninterrupted airway inflammation with consequent airway structural damage and BHR. This notion is further supported by Stevenson et al [11] who have shown that ongoing 'persistent inflammation' may be detected in the airways of typically asthmatic children (such as our *persistent wheezers*) even when asymptomatic. In accordance with such thinking, we have previously demonstrated that by 10-years *persistent wheezers* display the lowest FEV_1 and FEV_1/ FVC ratio, whilst *late onset wheezers* show relatively normal lung function (**Table 5.4**). The juncture at which wheezing duration in *persistent wheezers* begins to exert influences upon morbidity remains unclear. Our subgroup analysis of morbidity measures amongst *persistent wheezers* did not show any significant difference between those with the shortest duration and those with more prolonged disease. By definition these children must have wheezed for at least 6-years to be defined *persistent wheezers*. These results suggest it is likely that significant damage had 'already been inflicted' on these children's airways by the time they had wheezed for 6-years.

The considerable morbidity of *persistent wheezing* is also reflected by figures showing that *persistent wheezers* had the highest lifetime requirements for medical consultations. This

was particularly so when considering consultations indicating greatest disease severity such as *asthma specialist referral* and *multiple hospital admissions*. *Early transient* and *late onset wheezers* did not differ significantly in requirements for such medical consultation. This is not surprising, if wheezing duration is indeed considered significant, since we found that *late onset* and *early transient wheezers* possessed similar wheezing duration. However, it does suggest that the notion of the 'happy infant wheezer', used to describe early transient wheezing as a benign condition, is mistaken. This is further illustrated in our sample by the fact that 16% of *early transient wheezers* were 'ever admitted' to hospital with wheezing. This latter finding may partly reflect an exaggerated tendency to admit wheezing infants than older children with wheezing due to extra caution by both physician and parent at that age. Nevertheless it emphasises the important burden upon healthcare resources created by early transient wheezing.

The BTS guidelines for management of asthma propose a stepwise approach to treatment of this condition [1]. Following these guidelines, *persistent wheezers* showed highest prevalence of treatment with regular inhaled corticosteroids, multiple prophylactic medications and oral steroid courses, indicating serious disease. Intermediary requirements for such medications were noted in *late onset wheezers* with lowest levels in *early transient wheezers*. The increased reliance of *persistent* and late onset wheezers on anti-inflammatory treatment probably reflects the distinctive inflammatory aetiology of these phenotypes. Several 'allergic' triggers such as pollen, animals and house dust were reported more frequently in *persistent* (and to a lesser extent *late onset*) wheezers than *early transient wheezers*. This corresponds to our prior findings (**Tables 5.2 and 5.3**) of significantly higher atopy amongst these phenotypes than *early transient wheezers*. This concept of the 'atopic' *persistent* and *late onset wheezer* is further supported by the finding of highest *allergic co-morbidity* amongst these wheezing phenotypes in our study. Ultimately, *persistent* and *late onset wheezers* may constitute two variants of the same 'atopic' asthmatic state - one condition manifesting in infancy, the other in later childhood.

The importance of psychosocial factors in asthma is demonstrated by our findings that stress was reported significantly more often as a trigger for wheezing in *persistent* or *late onset wheezers* than *early transient wheezers*. In this context the impact of moderate to severe childhood wheezing illness upon behaviour and school performance [196] has

previously been documented in a New Zealand study. Therefore, although often ignored, psychosocial triggers should be actively borne in mind when treating the asthmatic child.

Whilst many indicators of overall disease morbidity were significantly greater amongst *persistent* than *late onset wheezers* this trend was not confirmed for indicators of current morbidity at 10-years (with the exception of nocturnal disturbance). This would be consistent with the theory that wheezing duration has a bearing on morbidity; by 10-years many *late onset wheezers* may have begun to develop significant long-term sequelae of persisting airways inflammation. Consequently the disparity in current morbidity between *persistent* and *late onset wheezers* might follow suit and narrow by age 10-years. In accordance with this theory we observed some significant differences in healthcare utilisation amongst *late onset wheezers* with greatest wheezing duration compared to those with shorter duration.

In summary, all forms of wheezing illness during the first decade of life are associated with substantial morbidity and have considerable impact upon healthcare resources. *Early transient wheezers* may have a condition that is not 'true asthma' but associated more with recurrent chest infections rather than atopy or BHR. Nevertheless, they still show considerable morbidity reflected by use of medications and hospital admissions. *Late onset wheezers* show some features similar to persistent wheezers in terms of atopy, *allergic co-morbidity* and BHR. However, they show less morbidity than *persistent wheezers* during the first decade of life with lower indices of medical consultation and pharmacological treatment. This may partly reflect that *late onset wheezers* have wheezed for a shorter period than *persistent wheezers*. Their potential for future morbidity as their airways disease continues should not therefore be underestimated.

Persistent wheezers were found to correlate closely with the concept of the typical 'childhood asthmatic' at several levels. They show high atopy and *allergic co-morbidity* throughout childhood as well as impaired lung function and BHR at 10-years. They also showed greatest disease morbidity reflected by most medical consultations and pharmacological treatments and having received an asthma diagnosis most frequently. Their greater morbidity may reflect the effects of longer wheezing duration, since we have identified that this group of children start wheezing early in life. The significant morbidity

associated with *persistent wheeze* should be a cause of major concern for parents and physicians alike. The search for factors capable of identifying such children in early life should be a matter of priority for researchers in this field. Such knowledge may yield strategies that could prevent this cause of much childhood morbidity. In the next two chapters risk factor analysis for childhood wheezing phenotypes identified in this study will be described.

CHAPTER 7

RISK FACTORS FOR THE IDENTIFICATION AND DIFFERENTIATION OF EARLY LIFE WHEEZING PHENOTYPES

Over the past decade it has been increasingly recognised that childhood wheezing is a heterogeneous condition [167]. The development of a natural history based phenotypic classification for childhood wheezing by Martinez et al [44] has allowed considerable insight into the outcome of wheezing in early life. Whilst it is clear [44,81,85] that most early life wheezing may be transient in nature, it is also now apparent that a substantial proportion of early life wheezing may persist into later childhood [44,85,88,168]. In Chapters 5 and 6 we demonstrated that *persistent wheezers* correlate closely with those diagnosed as *childhood asthmatics* possessing high levels of personal atopy, impaired lung function and bronchial hyper-responsiveness. We also found them to show significant disease morbidity. A combination of both genetic and environmental risk factors [64,197,198] has long been thought to influence the development of atopic asthma. Family history of allergy, early life eczema and parental smoking have all been linked to the *persistent wheezing* phenotype [88,167]. A clear understanding of factors that lead to the *persistent wheezing* phenotype and importantly differentiate it from the *early transient wheezing* phenotype is crucial to the management of childhood asthma.

In this chapter, early life risk factors for identification and differentiation of *persistent* and *early transient wheeze* amongst children in this whole population birth cohort study are examined.

7.1 ANALYSIS

To minimise recall bias, analysis in this chapter (as in Chapters 5 and 6) is restricted to the 1034 (71% of 1456) children seen prospectively with information at all study visits; 1 or 2-years, 4 and 10-years.

Separate univariate risk factor analysis for persistent wheeze (PW) and early transient wheeze (ETW) was performed in comparison to children who never wheezed (NW) during the first decade of life. Chi-square analysis (with Fishers exact test where indicated by low expected cell counts) was used for this purpose. Risk factor analysis to identify persistence of early life wheezing was done in a similar fashion comparing factors between PW and ETW. To obtain the independent effect of risk factors showing trends for significance ($p<0.2$), logistic regression models were created for each outcome variable. Stepwise backward (likelihood ratio) logistic regression was used for this purpose. In order to identify factors of relevance for identifying these phenotypes during early life only factors obtained in the first 4-years of life were included in multivariate analysis. Prior asthma diagnoses were not included in any of these models.

7.2 RESULTS

Of 417 children with a lifetime history of wheezing in this population, 80.6% (336) had 'early onset' wheezing commencing by age 4-years while the remainder only wheezed from the age of 5-years onwards. Six hundred and seventeen children gave a history of never wheezing (NW) in the first decade of life. Of early life wheezers, 37.2% (125) had persistent symptoms (PW) to age 10-years with the remaining 62.8% (211) having a transient wheezing condition (ETW).

7.2.1 Risk Factors For Persistent Wheezing (PW) Compared to Never Wheezing (NW)

Factors showing trends for significance at univariate analysis for development of PW compared to NW are shown in Table 7.1. Male gender carried an increased risk at univariate analysis for having PW in the first decade of life. Personal histories of diagnosed allergy at 1-year (asthma, eczema, rhinitis, food allergy), 2-years (asthma, eczema, rhinitis, food allergy) and 4-years (asthma, eczema, rhinitis, food allergy) were also significant risk factors at univariate analysis for PW. Recurrent chest infections at 1 and 2-years showed similarly strong significance for PW. Atopic sensitisation at 4-year SPT was also highly significant for PW. Family history of allergic disease too showed significant risk. Thus maternal and sibling asthma, conferred significantly increased risk for PW along with

paternal eczema and maternal urticaria. Similar non-significant trends for increased risk of PW were found for paternal asthma, maternal eczema and sibling urticaria.

Higher Social Class at birth (Classes I-IIInm) was associated with significant risk reduction of PW. Exclusive breastfeeding in the first 3 months of life was associated with significantly reduced risk of having PW. Early introduction of solids (within the first 3 months of life) was conversely associated with increased risk for PW. Parental smoking at birth, 1, 2 and 4-years also conferred increased univariate risk of PW.

Non-significant trends for reduced risk of having PW were noted for cat ownership at birth and 4-years, as well as dog ownership at birth, 2-years, and 4-years.

Cord IgE at birth did not differ significantly between PW and NW (median 0.1 v 0.1, $p = 0.818$ [*Mann Whitney U- Test*]).

In order to obtain the independent effect of early life risk factors for having PW compared to NW, logistic regression analysis was used. In the final regression model, parental smoking at 2-years, chest infections at 1 or 2-years, eczema at 2-years, food allergy at 4-years, atopy at 4-year SPT, maternal urticaria, maternal asthma and sibling asthma all showed independent significance for PW (Table 7.4). Alternatively high Social Class at birth retained a significant protective effect against PW. Recorded cat ownership at birth nearly demonstrated a similar protective effect in the final model ($p = 0.059$, OR = 0.31, 95%CI = 0.09-1.05).

Table 7.1: Univariate risk analysis for development of persistent wheeze (p<0.2)

Factor	P-value	OR	95% CI
Atopic SPT 4yr	<0.001*	5.17	3.31-8.08
Asthma 1yr	<0.001*	28.40	13.26-60.86
Eczema 1yr	<0.001*	5.54	3.32-9.22
Rhinitis 1yr	<0.001*	3.08	1.67-5.68
Food Allergy 1yr	<0.001*	3.82	2.11-6.90
Asthma 2yr	<0.001*	177.83	53.96-586.02
Eczema 2yr	0.001*	2.45	1.41-4.26
Rhinitis 2yr	<0.001*	3.87	2.15-6.96
Food Allergy 2yr	<0.001*	4.85	2.04-11.51
Asthma 4yr	<0.001*	1828.13	246.59-13553.33
Eczema 4yr	<0.001*	3.12	1.89-5.14
Rhinitis 4yr	<0.001*	7.12	3.63-13.94
Food Allergy 4yr	<0.001*	5.32	2.16-13.06
Maternal Asthma	<0.001*	2.58	1.63-4.10
Sibling Asthma	<0.001*	2.06	1.38-3.08
Paternal Eczema	0.042*	1.90	1.02-3.56
Parental Eczema	0.007*	1.80	1.17-2.77
Maternal Urticaria	0.011*	2.20	1.18-4.09
Parental Urticaria	0.016*	2.03	1.13-3.63
Parental Allergy	0.011*	1.72	1.13-2.63
Paternal Asthma	0.090	1.55	0.93-2.60
Maternal Eczema	0.111	1.50	0.91-2.48
Sibling Urticaria	0.061	1.70	0.97-2.97
Male Gender	0.010*	1.67	1.13-2.47
Social Class I-III at Birth	0.040*	0.59	0.35-0.98
Early Solids	0.020*	1.77	1.09-2.88
Exclusive Breastfeeding 1st 3/12	<0.001*	0.38	0.24-0.62
Exclusive Formula Feeding 1st 3/12	0.006*	1.74	1.17-2.58
Parental Smoking Birth	0.001*	1.88	1.27-2.77
Parental Smoking 1yr	<0.001*	2.05	1.39-3.02
Parental Smoking 2yr	0.001*	2.00	1.33-3.00
Parental Smoking 4yr	<0.001*	2.25	1.52-3.32
Chest Infections 1yr	<0.001*	15.18	7.29-31.59

Chest Infections 2yr	<0.001*	25.67	13.96-47.18
Pet Cat at Birth	0.053	0.65	0.43-1.01
Pet Dog at Birth	0.152	0.72	0.46-1.13
Dog 2yr	0.077	0.59	0.32-1.07
Cat 4yr	0.137	0.73	0.49-1.11
Dog 4yr	0.136	0.71	0.45-1.12

Notes:

Only factors showing trends for significance at univariate analysis ($p<0.2$) are shown. Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).

* Denotes statistical significance ($p<0.05$) compared to NW.

Unfortunately, Social Class at birth was only obtained for 685 children so that including this factor limited the size of the regression model. Excluding this factor from the model however gave broadly similar results with independent significance for eczema at 1-year ($p = 0.003$, OR = 3.72, 95%CI = 1.58-8.72), food allergy at 2-years ($p = 0.012$, OR = 5.73, 95%CI = 1.46-22.50) plus recurrent chest infections at 1-year ($p = 0.001$, OR = 8.19, 95%CI = 2.26-29.60) and 2-years ($p<0.001$, OR = 18.53, 95%CI = 7.88-43.56). Significance was also found for both parental smoking ($p = 0.020$, OR = 2.11, 95%CI = 1.12-3.97) and personal atopy at 4-years ($p<0.003$, OR = 6.08, 95%CI = 3.15-11.72). In this latter model early weaning ($p = 0.008$, OR = 3.20, 95%CI = 1.35-1.60) and formula feeding ($p = 0.011$, OR = 2.58, 95%CI = 1.24-5.36) also showed independent significance whilst maternal asthma no longer did ($p = 0.084$, OR = 1.90, 95%CI = 0.92-3.93). Sibling asthma retained marginal independent significance ($p = 0.05$, OR = 1.85, 95%CI = 1.00-3.43)

7.2.2 Risk Factors For Early Transient Wheezing (ETW) Compared to Never Wheezing (NW)

Factors showing trends for significance at univariate analysis for development of ETW compared to NW are shown in Table 7.2. Male gender was associated with significant increased risk of ETW at univariate analysis. Diagnosed allergic conditions at 1-year (asthma, eczema, rhinitis, food allergy), 2-years (asthma, eczema, rhinitis, food allergy), 4-years (asthma, rhinitis, food allergy) were also significant factors for having ETW. However atopic sensitisation at 4-years did not show any effect. An increased risk of ETW was also found at univariate analysis for recurrent chest infections at 1 and 2-years. Significant effects of allergic family history were noted for ETW. Thus maternal and

sibling asthma, maternal and sibling eczema and maternal urticaria showed univariate significance for having ETW. Similar non-significant effects were noted for sibling urticaria and food allergy along with a family history of rhinitis.

High Social Class at birth was associated with a significantly reduced risk of having ETW. Exclusive breastfeeding in the first 3 months of life was also associated with significant risk reduction of ETW. Conversely early introduction of solids carried an increased risk of ETW. Low birth weight (<2.5kg) was also significantly commoner in those with ETW. Parental smoking at 1 and 2-years was also significant for ETW. A similar non-significant trend for parental smoking at birth and 4-years was observed. No associations with pet ownership in early life and ETW were found. Cord IgE showed no significant difference between ETW and NW (Median 0.1 v 0.1, p =0.320 [*Mann Whitney-U Test*]).

In order to obtain the independent effect of early life risk factors for having ETW compared to NW, logistic regression analysis was used. Recurrent chest infections at 1 or 2-years, diagnosed rhinitis at 1 or 2-years, maternal urticaria, sibling asthma, parental smoking at 2-years, and early introduction of solids all showed independent significance for ETW at multivariate analysis (Table 7.4).

Exclusion of Social Class from the regression model gave similar results with independent significance for chest infections at 1-year (p = 0.004, OR = 5.01, 95%CI = 1.68-14.97) and 2-years (p<0.001, OR = 13.68, 95%CI = 6.31-29.64) plus parental smoking at 2-years (p = 0.005, OR = 1.88, 95%CI = 1.21-2.91) as well as diagnosed rhinitis at 1-year (p<0.001, OR = 4.71, 95%CI = 2.47-8.96). Meanwhile food allergy at 1-year (p = 0.007, OR = 2.79, 95%CI = 1.32-5.87), rhinitis at 4-years (p = 0.046, OR = 2.60, 95%CI = 1.02-6.67) and male gender (p = 0.012, OR = 1.74, 95%CI = 1.13-2.69) assumed independent significance for ETW. Maternal urticaria continued to show significance (p = 0.033, OR = 2.17, 95%CI = 1.06-4.43) whilst sibling eczema assumed independent significance (p = 0.009, OR = 1.83, 95%CI = 1.16-2.87). Finally breastfeeding developed a significant protective role against ETW in this latter model (p = 0.014, OR = 0.55, 95%CI = 0.34-0.89).

Table 7.2: Univariate risk analysis for early transient wheeze (p<0.2)

Factor	P-value	OR	95% CI
Asthma 1yr	<0.001*	22.66	10.94-46.93
Eczema 1yr	<0.001*	2.46	1.48-4.07
Rhinitis 1yr	<0.001*	5.24	3.24-8.48
Food Allergy 1yr	0.006*	2.20	1.24-3.89
Asthma 2yr	<0.001*	90.47	27.98-292.57
Eczema 2yr	0.012*	1.85	1.14-3.01
Rhinitis 2yr	<0.001*	5.30	3.29-8.53
Food Allergy 2yr	0.046*	2.39	0.99-5.76
Asthma 4yr	<0.001*	301.45	41.51-2188.94
Rhinitis 4yr	0.022*	2.33	1.11-4.87
Food Allergy 4yr	0.004*	3.35	1.40-8.01
Maternal Asthma	0.003*	1.86	1.23-2.82
Sibling Asthma	0.040*	1.44	1.02-2.04
Maternal Eczema	0.026*	1.60	1.06-2.44
Sibling Eczema	0.005*	1.62	1.15-2.27
Maternal Urticaria	0.013*	1.98	1.14-3.40
Sibling Urticaria	0.104	1.50	0.92-2.44
Sibling Food Allergy	0.139	1.44	0.88-2.35
Sibling Allergy	0.057	1.37	0.99-1.91
Family History Rhinitis	0.179	1.25	0.90-1.73
Male Gender	0.009*	1.52	1.11-2.08
Social Class I-III at Birth	0.015*	0.62	0.42-0.91
Early Solids	0.030*	1.58	1.04-2.39
Exclusive Breastfeeding 1st 3/12	0.007*	0.62	0.43-0.88
Parental Smoking Birth	0.061	1.36	0.99-1.87
Parental Smoking 1yr	0.032*	1.42	1.03-1.96
Parental Smoking 2yr	0.010*	1.54	1.11-2.14
Parental Smoking 4yr	0.057	1.37	0.99-1.88
Low Birth Weight	0.016*	2.44	1.15-5.16
Chest Infections 1yr	<0.001*	10.96	5.45-22.02
Chest Infections 2yr	<0.001*	14.52	8.20-25.69

Notes: Only factors showing trends for significance at univariate analysis (p<0.2) are shown. Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).

*Denotes statistical significance (p<0.05) compared to NW.

7.2.3 Risk Factors For Persistence of Early Life Wheezing (PW compared to ETW)

Factors showing trends for significance at univariate analysis for development of PW compared to ETW are shown in Table 7.3. No trends with either gender or Social Class at birth were observed for PW compared to ETW at univariate analysis.

Personal history of eczema at 1-year, asthma and recurrent chest infections at 2-years plus asthma, eczema and rhinitis at 4-years were significant for PW at univariate analysis. Atopic sensitisation at 4 and 10-years also showed significantly increased risk for PW. Non-significant trends for increased risk of PW were seen for food allergy at 1 and 2-years. In contrast, a non-significant trend for reduced risk of PW was found for rhinitis at 1-year. Family history of asthma conferred a significantly increased risk of PW whilst paternal eczema gave a non-significant effect in the same direction. Conversely sibling eczema showed a non-significant trend for lower risk of PW.

PW was significantly higher with maternal smoking at birth and parental smoking at 4-years. Similar non-significant trends were seen for parental smoking at 1-year. Cat and dog ownership at birth showed non-significant trends for reduced PW. Cord IgE did not differ significantly between PW and ETW (median 0.1 v 0.1, p = 0.298 [*Mann Whitney U-Test*]).

In order to obtain the independent effect of early life risk factors for persistence of early life wheezing, logistic regression analysis was used. Social Class at birth was not included in regression models, as it did not show significance at univariate analysis. Multivariate analysis (Table 7.4) identified independent significance for PW with family history of asthma, recurrent chest infections at 2-years and atopic SPT at 4-years. A similar non-significant trend for formula feeding was also observed (p = 0.094, OR = 1.67, 95%CI = 0.92-3.06). Conversely, significantly reduced risk of wheezing persistence was found for diagnosed rhinitis at 1-year. Similar non-significant trends for reduced persistence were found for cat ownership at birth (p = 0.091, OR = 0.58, 95%CI =0.30-1.09) and sibling eczema (p = 0.074, OR = 0.56, 95%CI = 0.29-1.06).

Table 7.3: Univariate risk for persistence of early life wheezing (p<0.2)

Factor	P-Value	OR	95% CI
Atopic SPT 4yr	<0.001*	6.09	3.43-10.82
Eczema 1yr	0.003*	2.25	1.30-3.91
Rhinitis 1yr	0.077	0.59	0.32-1.07
Food Allergy 1yr	0.091	1.74	0.91-3.30
Food Allergy 2yr	0.130	2.03	0.80-5.15
Asthma 2yr	0.005*	1.97	1.22-3.16
Asthma 4yr	<0.001*	6.07	3.68-9.99
Eczema 4yr	<0.001*	3.47	1.81-6.62
Rhinitis 4yr	0.002*	3.06	1.47-6.36
Family History Asthma	0.001*	2.24	1.38-3.63
Parental Asthma	0.051	1.58	1.00-2.52
Sibling Asthma	0.132	1.43	0.90-2.28
Paternal Eczema	0.089	1.95	0.89-4.25
Sibling Eczema	0.164	0.71	0.44-1.15
Exclusively Breastfed 1st 3/12	0.088	0.62	0.36-1.08
Exclusive Formula Feeding 1st 3/12	0.078	1.51	0.95-2.38
Maternal Smoking Birth	0.039*	1.68	1.02-2.75
Parental Smoking Birth	0.155	1.38	0.88-2.16
Parental Smoking 1yr	0.106	1.44	0.92-2.25
Parental Smoking 4yr	0.028*	1.65	1.05-2.57
Chest Infections 2yr	0.020*	1.77	1.09-2.86
Cat Birth	0.170	0.71	0.44-1.16
Dog Birth	0.158	0.70	0.42-1.15

Table 7.3 Notes:

Only factors showing trends for significance at univariate analysis (p<0.2) are shown. Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).

* Denotes statistical significance (p<0.05) comparing PW to ETW.

Table 7.4: Multivariate analysis for persistent wheeze, early transient wheeze and the persistence of early life wheezing

	Risk Factors	P-Value	OR	95%CI
PERSISTENT WHEEZE	Parental Smoking at 2yr	0.039	2.72	1.05-7.04
	Social Class I-III at Birth	0.005	0.24	0.09-0.65
	Atopy at 4yr SPT	<0.001	12.70	4.63-34.82
	Recurrent Chest Infections at 1yr	0.022	9.40	1.38-64.03
	Recurrent Chest Infections at 2yr	<0.001	90.50	21.76-376.42
	Eczema at 2yr	0.014	4.30	1.35-13.73
	Food Allergy at 4yr	0.034	6.03	1.14-31.87
	Maternal Asthma	0.003	5.51	1.76-17.25
	Sibling Asthma	0.002	4.41	1.71-11.37
	Maternal Urticaria	0.006	10.49	1.95-56.41
EARLY TRANSIENT WHEEZE	Early Solids	0.030	2.10	1.08-4.10
	Parental Smoking at 2yr	0.002	2.39	1.40-4.14
	Recurrent Chest Infections at 1yr	0.010	6.40	1.56-26.21
	Rhinitis at 1yr	0.001	3.92	1.79-8.61
	Recurrent Chest Infections at 2yr	<0.001	9.91	3.74-26.26
	Rhinitis at 2yr	0.019	2.80	1.18-6.64
	Maternal Urticaria	0.015	3.53	1.27-9.77
	Sibling Asthma	0.034	1.91	1.05-3.46
PERSISTENCE OF EARLY LIFE WHEEZING	Recurrent Chest Infections at 2yr	0.034	1.99	1.05-3.77
	Family History of Asthma	0.010	2.31	1.22-4.37
	Atopic SPT at 4yr	<0.001	5.73	2.95-11.12
	Rhinitis at 1yr	0.039	0.43	0.19-0.96

Notes: Results presented are adjusted Odds Ratios (OR) and their 95% Confidence Intervals (95%CI). Only factors that showed a significant effect at the final step of each regression model are shown. Risk factors for persistent wheeze and early transient wheeze in each case refer to comparison with children who had never wheezed. Risk factors for persistence of early life wheezing refer to comparison of risk factors for persistent with those for early transient wheezing. Models presented for persistent and early transient wheezing include Social Class at Birth.

7.3 DISCUSSION

This chapter clearly demonstrates that the different early life wheezing phenotypes outlined in Chapters 5 and 6 carry distinctive risk factor profiles. Thus *persistent wheeze* showed significant independent associations with a personal history of allergy and atopic sensitisation in early life along with allergic family history, recurrent chest infections and lower Social Class. Transient wheezing also showed significant independent associations to recurrent chest infections plus diagnosed rhinitis in early life. However, transient wheezing did not show independent associations with early life atopic sensitisation or personal/family history of allergy. Therefore one might regard *persistent wheezing* as showing a largely 'allergic' risk profile whilst *early transient wheeze* shows a 'non-allergic' profile.

Our findings confirm and extend existing understanding about early life wheezing phenotypes. We showed that food allergy and eczema in early life carried independent significance for the development of *persistent wheeze*. Thus early food allergy should be added to Martinez's previous finding that early eczema was important in this regard [44]. This also substantiates previous studies [15,16] linking early life food allergy and eczema to subsequent airways disease. Strong associations between developing *persistent wheeze* and presence of allergic disease were noted. We found this to be particularly the case for family history of asthma, paralleling findings of the importance of maternal asthma found for this state in the Tucson Study [44].

Interestingly, low Social Class at birth emerged as an independently significant factor for developing *persistent wheeze* in our study. This is contradictory to findings from the 1970 British Cohort Study [81] where increased symptom persistence to 16-years was found with higher Social Class. Our more recent study may reflect changes in disease patterns over the last 30-years within the UK.

Unexpectedly at univariate analysis we found that *early transient wheeze* development was significantly associated with diagnosis of several allergic conditions. However this was only weakly retained at multivariate analysis for sibling asthma and maternal urticaria. Therefore our findings suggest that *early transient wheezing* is not strongly associated with

early personal allergy, atopy or a family history of allergy. This is wholly consistent with earlier findings from Tucson [44].

The independent association of *early transient wheezing* to recurrent chest infections and diagnosed early life rhinitis is interesting. It is certainly possible that there was some diagnostic overlap between these risk factors in early life since both nasal and chest symptoms might have been manifestations of viral respiratory infection at that age. Thus the diagnosed rhinitis during infancy recorded in our study is highly likely to have included children with infective rather than allergic nasal symptoms. The notion that *early transient wheezing* occurs predominantly with viral respiratory infections appears to gain credence from our findings. However it is worth reflecting that we also found recurrent chest infections in infancy to have independent significance for the development of *persistent wheeze*. This may illustrate the importance of common viral respiratory pathogens in early life wheezing regardless of ultimate wheezing phenotype. This would broadly agree with Stein et al [133] who demonstrated increased development of both infrequent and frequent childhood wheezing illnesses in children who showed *Respiratory Syncytial Virus* infection in infancy. Such infections may predispose to *persistent* infantile wheezing through respiratory epithelial damage and denudation [133]. We demonstrated that amongst children with early life wheezing, recurrent chest infections at 2-years were independently associated with symptom persistence. Conversely it was found that rhinitis at 1-year was independently associated with a *transient* outcome for early life wheezing. Rhinitis at 1-year was likely to have reflected infective nasal symptoms rather than atopic disease. It is conceivable therefore, as recently suggested by the MAS-Study [199], that upper respiratory tract viral infections may predict a *transient* outcome to early life wheezing whilst lower respiratory tract infections may predict a more *persistent* outcome.

Univariate analysis also identified other risk factors that were common to both *early transient* and *persistent wheeze* in early life. Thus exposure to parental smoking, formula feeding, early weaning, lower Social Class and male gender appear to be important for developing early wheezing in general. Several of these factors are interrelated – it has been previously demonstrated in this cohort that lower Social Classes smoke more and breastfeed less [117]. However we demonstrated that parental smoking at 2-years retained an independent risk for developing both *persistent* and *early transient wheezing phenotypes* in

early life. The finding of an association between parental smoking and early wheezing is consistent with those of the Tucson cohort [44,122] and may be explained by Young's [71] findings of increased airway hyper-responsiveness in 4-week old infants with smoking parents. The significant effects of feeding method at univariate analysis may to some extent reflect confounding by the effects of Social Class and smoking. Apart from early weaning in children with *early transient wheeze*, they did not show independent significance at multivariate analysis for each phenotype. If Social Class was excluded from regression analysis then feeding methods showed independent effects illustrating the close association of feeding patterns with Social Class. A recent Australian study [116] demonstrated significant protective effect against asthma at 6–years for exclusive early breastfeeding. Our results cannot confirm that such feeding methods are independent risk factors for the development of *persistent wheezing*.

It is evident that wheezing in early life is a common phenomenon. In our cohort, 33% of all children had wheezed in the first 4-years of life. Whilst most of these children will lose their symptoms we have shown that 37% will have persistent symptoms to 10-years. In Chapter 6 we showed that this phenotype suffers considerable morbidity associated with their condition throughout childhood. Therefore finding factors that are associated with symptom persistence in children with early life wheezing may allow early intervention with prophylactic treatments like inhaled steroids in those at highest risk of symptom persistence. Amongst early life wheezers we have shown that a family history of asthma as well as recurrent chest infections at 2-years and atopic sensitisation at 4-years are independent predictors of persisting childhood wheeze. Rhinitis at 1-year (probably reflecting nasal infection at that age) showed a significant protective effect against wheezing persistence in these children. There may be two explanations for this finding. Firstly that such nasal infections might be secondary to viral disease and thus be commonly associated with viral induced transient wheeze. Secondly that specific infection in early life may have a protective role against atopy and asthma. That factors such as parental smoking did not show an effect for wheezing persistence probably reflects that they are relevant for early life wheezing regardless of outcome. However, Csonka et al [200] recently showed parental smoking in the first 3-years of life was associated with persistence of wheeze to school age. Use of a much broader definition of parental smoking in that study may explain these differences.

We did not identify any increased risk of developing early life wheezing phenotypes in association with pet exposure. Interestingly we showed non-significant trends for reduced development of *persistent wheezing* in early life with early life cat and dog ownership. Cat ownership at birth nearly showed independent significance for lower development of *persistent wheeze* at multivariate analysis. This may reflect the fact that *persistently wheezing* children were more likely to come from allergic families who might therefore be more likely to already practice allergen avoidance and not keep such pets. Alternatively it may infer some protective quality for such ownership reflecting one aspect of the evolving concept of a hygiene hypothesis in allergy development [156,201]. We can only speculate on this finding but some studies [202] have suggested reduced allergy development with cat exposure.

This chapter highlights that development of *persistent wheezing* in early childhood is strongly associated with early life eczema, food allergy and atopic sensitisation, as well as lower Social Class, family history of asthma, early life smoking exposure and recurrent chest infections. Conversely development of *early transient wheeze* does not show independent associations with personal or family history of allergy, instead being significantly associated with early life smoking exposure, early weaning plus recurrent chest and nasal infections. Amongst all children wheezing in early life, family history of asthma, atopic sensitisation in early life and recurrent chest infections at 2-years are important factors for symptom persistence.

CHAPTER 8

RISK FACTORS FOR THE DEVELOPMENT OF LATE ONSET WHEEZING IN CHILDHOOD

It is now apparent [168] that the majority of childhood asthma may originate in early childhood. Thus natural history based classifications of childhood wheezing have identified a group of *persistent wheezers* who commence symptoms in early life and continue to be troubled by their disease during childhood [44,167]. In Chapter 5 it was demonstrated that such children appear to show high levels of atopy, bronchial hyper-responsiveness and deterioration in baseline lung function by later childhood. In association with these findings it was revealed in Chapter 6 that they also suffered significant disease morbidity during childhood. Risk factors for *persistent wheezing* such as maternal asthma, early life eczema, food allergy and parental smoking have previously been reported [44,88,202-204]. In Chapter 7 we confirmed and added to this understanding of the aetiology of persistent childhood wheezing by showing associations with early life eczema, food allergy and atopic status as well as lower Social Class, asthmatic family history and recurrent chest infections in infancy.

In their original phenotypic classification, Martinez et al [44] also demonstrated the presence of a distinct phenotype of *late onset wheezers*. In that study such children commenced symptoms after the age of 3-years and were found to bear similar characteristics to *persistent wheezers* in terms of personal history of rhinitis and family history of asthma [44]. In Chapter 5 we showed that at 10-years, our *late onset wheezers* showed similar atopic sensitisation and bronchial hyper-responsiveness to *persistent wheezers*. This group of children is important since for the first years of life they are asymptomatic and may be indistinguishable from children who never wheeze. From data presented in Chapter 6 it is apparent that this state is nevertheless associated with significant morbidity by 10-years of age. Therefore being able to identify children who are at high risk of developing such wheezing could prevent significant disease morbidity in later childhood. In this chapter we

describe risk factors for the development of *late onset wheezing* within this whole population birth cohort.

8.1 ANALYSIS

To minimise recall bias, analysis in this chapter (as in Chapters 5, 6 and 7) was restricted to those 1034 (71% of 1456) children seen prospectively with information at all study visits: 1 or 2-years, 4 and 10-years.

Univariate risk factor analysis for late onset wheeze was undertaken in comparison to children who never wheezed during childhood. Potential risk factors from the full duration of the study were used for this analysis. Chi-square analysis (with Fishers exact test where indicated by low expected cell counts) was used for this purpose. To obtain the independent effect of risk factors showing trends for significance ($p<0.2$), logistic regression models were created for each outcome variable. Stepwise backward (likelihood ratio) logistic regression was used for this purpose. In order to identify factors of relevance in early life for identifying these phenotypes only factors obtained in the first 4-years of life were included in multivariate analysis.

8.2 RESULTS

Of 417 children with a lifetime history of wheezing in this population, 19.4% (81) had *late onset wheezing* (LW) commencing from age 5-years onwards (and still present at 10-years) while the remainder had wheezing that commenced in the first 4-years of life. Six hundred and seventeen children gave a history of never wheezing (NW) in the first decade of life. Consequently 11.6% (81/698) *non-wheezing* children in the first 4-years of life would go on to become *late onset wheezers*.

Risk factors showing trends for significance with regard to LW development in comparison to NW development are shown in Table 8.1. Thus eczema in early life (1,2 or 4-years) was a significant risk factor for having LW. Increased risk of LW was also found for presence of eczema and rhinitis at 10-years. A similar non-significant trend for increased risk with urticaria at 10-years was also observed. Atopic sensitisation at 4 and 10-years conferred

significantly increased risk of LW. Analysis of individual allergen sensitivities at 4-years showed that house dust mite ($p < 0.001$, OR = 4.50, 95%CI = 2.28-8.89), cat ($p < 0.001$, OR = 5.14, 95%CI = 2.25-11.76 [*Fishers exact test*]) and grass pollen sensitisation ($p = 0.03$, OR = 2.81, 95%CI = 1.26-6.25 [*Fishers exact test*]) all had significant univariate risk for increased LW at 10-years. Similar analysis at 10-years found that house dust mite ($p < 0.001$, OR = 6.13, 95%CI = 3.62-10.36), cat ($p < 0.001$, OR = 4.71, 95%CI = 2.35-9.43), dog ($p < 0.001$, OR = 8.40, 95%CI = 3.56-19.83), and grass pollen sensitisation ($p = 0.001$, OR = 2.95, 95%CI = 1.61-5.42) had significant univariate risk for having LW.

Both maternal and paternal asthma showed significance for increased risk of LW, whilst sibling asthma showed a similar non-significant trend. Family history of rhinitis also emerged as a significant risk factor, although individual maternal ($p = 0.107$), paternal ($p = 0.133$) and sibling rhinitis ($p = 0.127$) did not reach statistical significance. Family histories of urticaria and food allergy also showed non-significant trends for increased risk of LW.

No significant effect of Social Class measured at birth or 10-years was observed for development of LW. Similarly no effect of breast or formula feeding was observed. However, early introduction of solids (within the first 3 months of life) showed a non-significant trend for reduced risk of LW. Being an only child at 10-years showed no effect for having LW (OR = 1.08, 95%CI = 0.52-2.26). Male gender showed a non-significant trend for increased risk of LW. Early life pet exposure showed no trends for development of LW, although dog ownership at 10-years was associated with a non-significant trend for increased risk. Cord IgE did not demonstrate any significant risk for developing LW compared to NW (median 0.1 v 0.1, $p = 0.166$ [*Mann Whitney U Test*]).

Multivariate analysis was used to obtain the independent effect of significant univariate risk factors. Individual allergen sensitivities at 4-years were not used because of low numbers – instead atopy at 4-year SPT to any allergen was used. In the final regression model using purely early life factors, eczema at 4-years, family history of rhinitis, atopic sensitisation at 4-years, and maternal and paternal history of asthma all showed independent significance for developing LW (Table 8.2). A further regression model was created including 10-year

factors that showed trends for significance (p<0.2). In this model, eczema at 4-years, rhinitis at 10-years, atopic sensitisation at 10-years, plus a maternal history of asthma all showed independent significance for having LW (Table 8.2).

Table 8.1:Univariate risk analysis for development of late onset wheeze (p<0.2)

Factor	P-value	OR	95% CI
Atopic SPT 4yr	<0.001*	3.07	1.75-5.37
Atopic SPT 10yr	<0.001*	5.04	3.04-8.36
Eczema 1yr	0.046*	2.09	1.00-4.36
Eczema 2yr	0.010*	2.27	1.20-4.32
Eczema 4yr	0.002*	2.52	1.36-4.64
Current Eczema 10yr	0.003*	2.34	1.32-4.13
Current Rhinitis 10yr	<0.001*	6.12	3.67-10.20
Current Urticaria 10yr	0.088	1.87	0.90-3.89
Maternal Asthma	0.003*	2.27	1.29-3.97
Paternal Asthma	0.008*	2.12	1.20-3.74
Sibling Asthma	0.152	1.44	0.87-2.37
Maternal Rhinitis	0.107	1.51	0.91-2.51
Paternal Rhinitis	0.133	1.54	0.87-2.73
Sibling Rhinitis	0.127	1.52	0.89-2.60
Family History Urticaria	0.196	1.45	0.82-2.56
Family History Food Allergy	0.196	1.45	0.82-2.56
Male Gender	0.186	1.37	0.86-2.18
Early Solids	0.142	0.53	0.22-1.25
Dog at 10yr	0.075	1.52	0.96-2.42

Notes:

Only factors showing trends for significance (p<0.2) are listed. Results describe comparison between LW and children who had never wheezed with Odds Ratios (OR) and their 95%CI (95% Confidence Intervals).

* Denotes statistical significance (p<0.05).

Table 8.2: Multivariate analysis of early life and full 10-year risk factors for the development of late onset wheeze

	Risk Factor	P-value	OR	95%CI
Early Life Factors	Eczema at 4yr	0.006	2.95	1.36-6.38
	Atopic SPT at 4yr	0.005	2.74	1.36-5.52
	Family History of Rhinitis	0.035	2.11	1.05-4.23
	Maternal Asthma	0.010	2.71	1.27-5.80
	Paternal Asthma	0.026	2.40	1.11-5.16
Full 10-Year Factors	Eczema at 4yr	0.018	2.66	1.18-5.98
	Atopic SPT at 10yr	<0.001	4.37	2.15-8.90
	Rhinitis at 10yr	0.004	3.01	1.43-6.35
	Maternal Asthma	0.011	2.85	1.27-6.43

Notes: Only significant results at the final step of the regression model (backward stepwise likelihood ratio testing) are shown. In each case results are adjusted Odds Ratios (OR) and their 95% Confidence Intervals (95%CI) comparing risk factors between LW and NW.

8.3 DISCUSSION

Factors such as early life eczema, allergic family history and maternal smoking have been identified as relevant to the development of persistent early life wheezing [44,88,200]. Data presented in Chapter 7 confirmed and expanded this understanding of risk factors for *persistent wheezing*. In this chapter we have clearly identified that there are also characteristic factors in early life that are associated with the development of *late onset wheezing* – that is amongst children who have not wheezed during the first 4-years of life. In this regard, we found that 'allergic risk factors' emerged as significant predictors for developing this state whilst environmental factors such as parental smoking and pet exposure in early life carried little influence. Furthermore we showed that there was no independently increased risk of developing *late onset wheeze* with allergic states in infancy (unlike the case with *persistent wheeze*). However, allergic conditions and atopic sensitisation at 4-years did emerge as independently significant risk factors for *late onset*

wheeze. Thus we both confirm and extend previous knowledge about factors associated with *late onset wheezing* in childhood.

It has been suggested [15] that early life allergic conditions such as food allergy and eczema may lead to respiratory allergy in later childhood. Thus Bergmann [14] has demonstrated that as many as 40% of children with atopic dermatitis in infancy may develop symptoms of asthma by later childhood. We found that having eczema at 4-years was a significant independent predictor of developing late onset wheeze.

Previously in the Tucson Cohort study [44], any significant relationship between eczema in the first year of life and *late onset wheeze* was not found. Our findings show that eczema during a 'later phase of early life' is nevertheless of relevance to the development of *late onset wheeze*. In line with this finding we demonstrated an independently significant effect for development of *late onset wheeze* with atopic sensitisation at 4-year skin prick test. Analysis of individual allergen sensitisation showed that aeroallergen sensitivities to house dust mite, cat and dog were of significance at univariate analysis. No food allergen sensitivities showed such significance at 4-years. It has however been suggested [16] that earlier sensitisation to food allergens in infancy may be associated with later allergic disease. Unfortunately relatively little skin prick testing was performed in infancy in our study (only for symptomatic children) and therefore meaningful interpretation of early food sensitisation with regard to subsequent *late onset wheeze* development is not possible. However it is worth noting in this regard that early life diagnoses of food allergy did not show any significant effect for development of *late onset wheeze*.

In our study family history of respiratory allergies had independent significance for the development of *late onset wheeze*. In this context, maternal and paternal asthma demonstrated strong independent significance for *late onset wheeze*. Similarly, family history of rhinitis also conferred increased risk of *late onset wheeze*. Interestingly family history of non-respiratory allergic diseases such as eczema, food allergy and urticaria showed no association with *late onset wheezing* at univariate analysis.

If risk factors present at 10-years were also included in the analysis further insights into the development of *late onset wheeze* appear. Thus whereas early life risk analysis revealed

that family history of rhinitis was an important risk factor; analysis including 10-year data showed that current rhinitis was also a significant factor. This further demonstrates the close relationship between childhood rhinitis and wheezing found in other cohort studies [23]. It would certainly appear feasible that late onset wheezing and rhinitis show shared mechanisms of inheritance since onset of childhood rhinitis has often been observed to occur in later childhood [24]. Multivariate analysis including 10-year data showed a very strong independent effect for atopic sensitisation at 10-year skin prick test as a risk factor for *late onset wheeze*. It is known that rhinitis also shows similar strong associations with aeroallergen sensitisation during childhood [24]. Such common features of rhinitis and *late onset wheeze* might conceivably result in disease co-expression during later childhood.

We did not find any significant effect of pet ownership upon *late onset wheeze*. The concept of the hygiene hypothesis [156] of allergy development might even suggest a protective effect for such exposures in the development of allergy and wheezing in childhood. Some recent work [202] has suggested a protective effect for cat ownership in this context. We found no such relationship with the development of *late onset wheezing*. Family size might also be thought to have a role in conferring protection against the development of allergic symptoms. It has been demonstrated that number of siblings [158] may be inversely related to atopic sensitisation. However we found no such effect upon the presence of *late onset wheeze*.

Environmental tobacco smoke exposure demonstrated no particular effect upon the development of *late onset wheeze* in childhood. This was the case for smoking exposures in early childhood as well as at 10-years. This is in contrast to the case of persistent wheezers where exposures to tobacco smoke have been shown to be important associated factors [44,88].

In Chapter 7 it was seen that recurrent chest infections in infancy were significant independent factors in the development of early life wheezing phenotypes. In addition, such infections at 2-years were significantly associated with persistence of early life wheezing. However *late onset wheezers* showed no such associations with early life chest infections indicating that somewhat different mechanisms underlie this condition in comparison to *persistent wheezing*.

In summary we have identified that children with *late onset wheeze* show a characteristic risk factor profile that may help to identify them in early life before they become symptomatic. In this respect a similar 'allergic' risk factor profile to that of children with early life persistent wheezing was observed. Whilst allergic conditions in the first two years of life were identified in Chapter 7 to be of independent significance for *persistent wheezing* the same was not true for *late onset wheeze*. Instead a significant independent effect for allergic conditions and atopic sensitisation in later childhood (at 4-years) was demonstrated in our study for developing wheezing from the age of 5-years onwards. In this context we have shown that eczema at 4-years of age, atopic sensitisation at 4-years (to aero-allergens), family history of rhinitis and maternal/paternal history of asthma are all important factors for the subsequent development of *late onset wheeze*. Thus environmental factors appear to have little influence upon development of this phenotype. This may signify the greater importance of an allergic genetic predisposition towards development of late onset wheezing.

CHAPTER 9

THE PREVALENCE OF WHEEZING AND ASTHMA AT 10-YEARS OF AGE

During the latter decades of the twentieth-century studies consistently identified a high prevalence of childhood wheezing illness and asthma [34,41,42,44,54]. Worryingly, serial observations within the same geographical locations [55,56] have also suggested a real increase in prevalence for childhood asthma over this period. A consistent trend for higher prevalence of wheezing and asthma in more affluent westernized societies has been shown repeatedly [47]. Of these, the worst affected countries appear to have been New Zealand [43,194], Australia [41] and the UK [33,34,38,47,171].

A major difficulty in the past with interpretation of prevalence data for childhood wheezing and asthma has been the wide range of definitions used for these conditions by various studies. Thus comparison of data between studies has often been impossible. The inception of ISAAC [47] (International Study of Asthma and Allergies in Childhood) using standardized questionnaire material has helped to reduce this problem. Another shortcoming of many prevalence studies has been the lack of objective data [38,171] such as skin prick testing, IgE measurement, lung function testing and bronchial hyper-responsiveness assessment to corroborate questionnaire data.

In this chapter the prevalence of wheezing illnesses and asthma at 10-years of age is described from the Isle of Wight Whole Population Birth Cohort Study where both ISAAC questionnaire materials and objective assessments of asthma were used.

9.1 RESULTS

At 10-years, information was obtained from 1373 (94%) of the original 1456 children recruited into the study at birth. Of these 1043 (76.0%) visited the Research Centre to complete questionnaire (n = 1043), SPT (n = 1036), total IgE measurement (n = 953), spirometry (n = 981) and methacholine bronchial challenge (n = 784). Only a questionnaire was updated in the remaining 330 children. Children attending the Research Centre were

more likely to have a personal or family history of allergy than those for whom only a questionnaire was obtained (see **4.1**).

At 10-years, *current wheeze* (as defined by the ISAAC questionnaire) was present in 18.9% (259) children. *Current asthma* (a combination of *current wheeze* and a PC_{20} FEV_1 < 8mg/ml) was present in 14.4% (113/784) children undergoing bronchial challenge testing. Furthermore 13.0% (178 children) of the whole 10-year population had *Currently Diagnosed Asthma* (*CDA* - a combination of *asthma ever* and *current wheeze* at 10-years). In total 55.7% (113/203) of *current wheezers* who performed a bronchial challenge met the criteria for having *current asthma* whilst 68.7% (178/259) of *current wheezers* fulfilled the definition of *CDA*. Amongst children with *CDA* who underwent bronchial challenge, 62.8% (86/137) also satisfied criteria for *current asthma*.

Male predominance was seen for all three wheezing categorizations. Significantly higher prevalence for *current wheeze* (21.4% v 16.2%, p = 0.015) and *CDA* (15.3% v 10.7%, p = 0.012) was found in boys than girls. A similar trend was found in *current asthmatic* children (boys 9.8% v girls 7.3%, p = 0.107) although this did not reach statistical significance.

At 10-years, parents were asked to retrospectively state when their child first experienced any wheezing episodes. To minimize recall bias this response was incorporated with data obtained earlier in the course of the study. Analysis indicated an early origin for wheezing at 10-years. The median age of first symptom for *current wheeze* was 2.0 years (interquartile range 4.25), for *current asthma* was 2.0 years (interquartile range 4.0) and *CDA* was 2.0 years (interquartile range 3.50).

Morbidity indices for these three separate wheezing categorizations showed a trend for higher values in those with *current asthma* or *CDA* than those with *current wheeze* (Table 9.1). Pharmacological treatment for wheezing was used by 85.7% *current wheezers,* 97.2% *CDA* and 90.3% *current asthmatics.* Bronchodilators were used by 84.4% *current wheezers,* 97.2% *CDA* and 90.3% *current asthmatics.* Similarly inhaled steroids were used by 51.0% *current wheezers,* 69.7% *CDA* and 58.4% *current asthmatics.*

Table 9.1: Morbidity measures for *current wheeze, CDA status and current asthma*

	Current wheeze	CDA	*Current asthma*
% 1-3 wheezing episodes in last year	59.0%	54.7%	55.9%
(n=)	(147)	(93)	(62)
% 4-12 wheezing episodes in last year	29.7%	32.4%	28.8%
(n=)	(74)	(55)	(32)
% >12 wheezing episodes in last year	11.2%	12.9%	15.3%
(n=)	(28)	(22)	(17)
% Sleep disturbance (in the last year)	53.5%	60.9%	60.7%
(n=)	(136)	(106)	(68)
% Speech limitation (in the last year)	12.6%	17.3%	18.9%
(n=)	(32)	(30)	(21)
% Nocturnal cough (in the last year)	50.8%	58.2%	54.9%
(n=)	(131)	(103)	(62)
% Exercise symptoms (in the last year)	65.6%	72.5%	69.9%
(n=)	(170)	(129)	(79)

Atopy was significantly commoner when each of *current wheeze, current asthma* or *CDA* were present than when these states were absent (Table 9.2). Aeroallergen sensitisation predominated for each state, especially to house dust mite, cat, dog and grass (Table 9.3). In each case, children with *current wheeze* (2.24 v 1.82, $p<0.001$), *CDA* (2.32 v 1.84, $p<0.001$) or who had *current asthma* (2.53 v 1.82, $p<0.001$ – Figure 9.1) had significantly higher mean $\log_{10}$ total IgE than those without that condition.

Table 9.2: Prevalence of atopy for *Current Wheeze, CDA status and Current Asthma*

Condition	Disease status	% Atopic at 10-year SPT (n=)	% Positive inhalant screen (n=)	Statistical Significance
Current wheeze	Present	52.8%* (113/214)	59.3%* (118/199)	*p<0.001
	Absent	20.2% (166/822)	26.0% (196/753)	
CDA	Present	63.6%* (91/143)	68.7%* (92/134)	* p<0.001
	Absent	21.1% (188/892)	27.2% (222/817)	
Current asthma	Present	73.0% * (81/111)	79.0% * (83/105)	* p<0.001
	Absent	21.4% (195/912)	27.2% (228/838)	

Note:

Pairwise comparison performed using Chi-Square Test to compare prevalence of atopy and positive inhalant screen in the presence and absence of each wheezing condition.

Figure 9.1: Log_{10} total IgE in presence and absence of *current asthma*

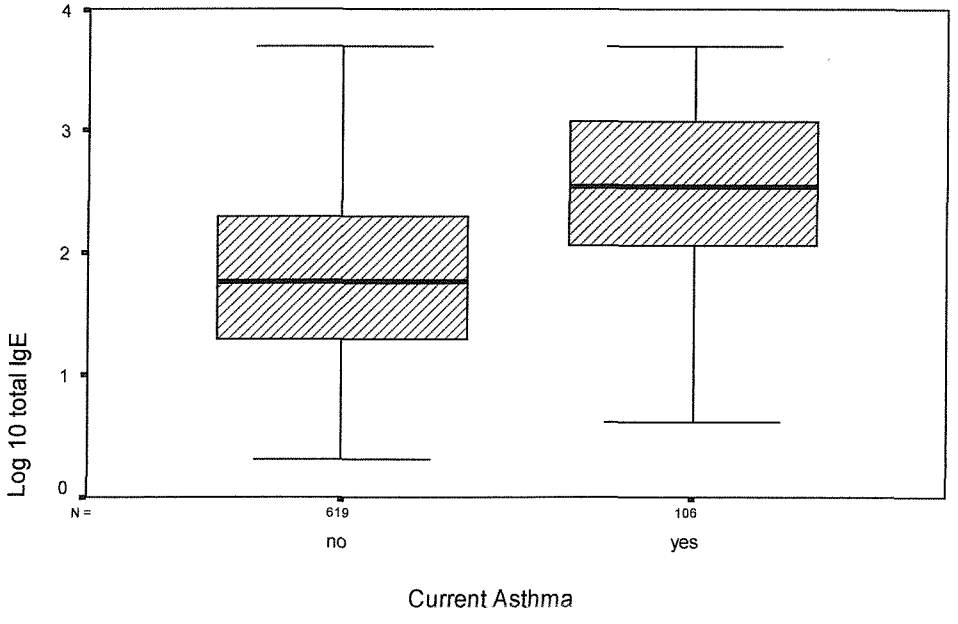


Table 9.3: Individual allergen sensitivities for *current wheeze, current asthma, CDA*

ALLERGENS	*Current Wheeze*	*Current Asthma*	*CDA*
HOUSE DUST MITE	43.9% *	64.0%*	51.7%*
OR (95%CI)	5.34 (3.81-7.50)	11.16(7.25-17.18)	6.57(4.50-9.60)
CAT	22.0% *	29.7%*	26.6%*
OR (95%CI)	6.32(3.96-10.10)	7.61(4.61-12.54)	6.97(4.32-11.25)
DOG	14.0% *	20.7%* #	17.5%*
OR (95%CI)	8.20(4.38-15.36)	10.56(5.66-19.72)	8.78(4.76-16.17)
GRASS	25.7% *	31.5%*	32.2%*
OR (95%CI)	3.25(2.22-4.78)	3.91(2.49-6.16)	4.33(2.86-6.56)
TREE	2.3% #	2.7%#	3.55 #
OR (95%CI)	1.38(0.49-3.87)	1.55(0.45-5.42)	2.27(0.81-6.40)
CLADOSPORIUM	1.9% #	3.6%** #	2.8% #
OR (95%CI)	2.22(0.64-7.64)	4.83(1.39-16.76)	3.63(1.05-12.58)
ALTERNARIA	3.3% #	2.7% #	4.2% #
OR (95%CI)	1.82(0.73-4.51)	1.38(0.40-4.76)	2.40(0.92-6.23)
MILK	1.4% || #	0.9% #	2.1%‡ #
OR (95%CI)	-	8.26(0.51-133.05)	-
EGG	0.9% #	1.8% #	1.4%#
OR (95%CI)	3.88(0.54-27.72)	8.33(1.16-59.73)	6.35(0.89-45.45)
PEANUT	3.3% #	4.5% # ††	4.9% § #
OR (95%CI)	2.50(0.96-6.53)	3.26(1.14-9.31)	4.15(1.58-10.89)
COD	2.3%¶ #	2.7% # ‡‡	3.5%† #
OR (95%CI)	6.55(1.55-27.65)	5.03(1.19-21.33)	10.80(2.55-45.72)
SOYA	0.5%#	0.9%#	0.0% #
	3.87 (0.24-62.09)	8.26(0.51-133.05)	-

Notes:

Results show prevalence of skin test positivity for individual allergens in Current Wheeze, Current Asthma, and CDA. Also presented are Odds Ratios (OR) and 95%Confidence Intervals (95%CI) for pairwise comparisons (Chi-Square Test) of prevalence in the presence of each state compared to when that state was absent.

# Denotes use of Fishers exact test.

Statistical significance for these comparisons were denoted by:

* p <0.001, † p = 0.002, ‡ p = 0.003, § p = 0.007, || p =0.009, ¶ p = 0.012, ** p = 0.024, †† p = 0.037, and ‡‡ p = 0.047.

For the whole population seen at 10-years, *symptoms of current allergy* (wheeze, nasal symptoms not associated with a cold, itchy rash coming and going for at least 6 months or urticarial episodes) were found in 44.8% children. Similarly the overall prevalence of *current rhinitis* was 15.1%, *current eczema* 13.7% and *current urticaria* 8.7%. The

prevalence of other *current allergic states* was generally higher in children with current wheezing or asthma than amongst the whole population at 10-years. Thus the prevalence of *current eczema* was 23.0% in those with *current wheeze,* 32.7% with *current asthma,* 24.4% with *CDA* and 11.5% with *non-wheezers*. *Current rhinitis* was found in 34.3% with *current wheeze*, 42.5% with *current asthma*, 39.9% with *CDA* and 10.6% with *non-wheezers*. *Current urticaria* occurred in 13.8% with *current wheeze*, 16.1% with *current asthma*, 8.2% with *CDA* and 7.5% with *non-wheezers*.

Recognized triggers for wheezing episodes were identified for 96.5% (109) children with *current asthma*. In such children, chest infections were reported in 72.5% (79) children whilst exercise induced wheeze occurred in 58.7% (64) children. For children with current asthma triggers reported were as follows: house dust 26.6% (29) children, stress 22.0% (24) children, pollens 22.0%(24) children and animals 13.8% (15) children.

Varying evidence of lower baseline lung function was noted in each case for children with *current wheeze, current asthma* or who had *CDA* compared to when that particular condition was absent (Table 9.4). This tended to be statistically significant for indices associated with an obstructive pattern of spirometry (FEV_1, FEV_1/FVC ratio). Analysis by gender for the whole population revealed, significantly lower baseline lung function for girls than boys (Table 9.5). This remained the case when children without *current wheeze* were considered separately. However, despite higher absolute values, an obstructive pattern (lower FEV_1 /FVC ratio) was more prominent in boys for both the whole population and those without *current wheeze*. Surprisingly, there was no significant variation by gender for lung function in those with *current wheeze* (Table 9.5).

BHR assessed by *inverse slope* analysis was significantly greater in the presence of both *current wheeze* and *CDA* than when that state was absent. Presence of PC_{20} FEV_1 <8.0mg/ml formed part of the definition of having *current asthma* and such children therefore possessed highly significant BHR judged by *inverse slope* analysis (Table 9.4). *Inverse slope* did not vary significantly by gender amongst either the whole population tested (male 0.05 v female 0.05, $p = 0.599$) or children with *current wheeze* (male 0.03 v female 0.03, $p = 0.692$).

Table 9.4: Baseline lung function and BHR for children with and without *Current Wheeze, CDA* and *Current Asthma* status at 10-years

	WHEEZING CONDITION AT 10-YEARS						
Spirometry	*Current wheeze*		*CDA*		*Current Asthma*		Statistical Significance ‡
	Present	Absent	Present	Absent	Present	Absent	
FVC (litres) 95% CI	2.29 (2.25-2.34)	2.29 (2.29-2.32)	2.30 (2.24-2.35)	2.29 (2.27-2.31)	2.29 (2.24-2.34)	2.28 (2.25-2.31)	
FEV_1 (litres) 95% CI	1.99 (1.95-2.03)	2.04 (2.02-2.06)	1.99 (1.94-2.04)	2.03 (2.01-2.05)	1.94† (1.90-1.99)	2.02 (2.00-2.05)	†p=0.010
FEV_1 /FVC 95% CI	0.87* (0.86-0.88)	0.89 (0.89-0.89)	0.87* (0.86-0.88)	0.89 (0.89-0.89)	0.85* (0.84-0.86)	0.89 (0.89-0.89)	*p<0.001
PEF (litres/sec) 95% CI	4.14 (4.03-4.24)	4.15 (4.09-4.20)	4.21 (4.08-4.34)	4.13 (4.08-4.19)	4.13 (3.99-4.26)	4.11 (4.05-4.17)	
Inverse Slope 95% CI	0.03* (0.03-0.04)	0.06 (0.05-0.06)	0.03* (0.02-0.03)	0.06 (0.05-0.06)	0.01* (0.01-0.01)	0.06 (0.06-0.06)	*p<0.001

Notes:

Lung function and BHR in the presence and absence of each respective state are given. Values represent means with their 95% confidence intervals (95%CI).

‡ Independent Samples T-tests were used to compare lung function in the presence and absence of each wheezing condition. Significant differences are highlighted by the symbols * and †.

Table 9.5: Baseline lung function by gender at 10-years

	Spirometry (litres)	Male	Female	P-value * Statistically Significant
Whole Population (95% CI)	FVC	2.35 (2.32-2.38)	2.23 (2.21-2.26)	<0.001*
	FEV_1	2.06 (2.03-2.08)	2.00 (1.97-2.02)	0.001*
	FEV_1 /FVC	0.88 (0.87-0.88)	0.90 (0.89-0.90)	<0.001*
	PEF (Litres/sec)	4.21 (4.14-4.27)	4.08 (4.01-4.15)	0.012*
Not *Current Wheeze* (95% CI)	FVC	2.36 (2.33-2.40)	2.23 (2.20-2.26)	<0.001*
	FEV_1	2.08 (2.04-2.11)	2.00 (1.97-2.03)	<0.001*
	FEV_1 /FVC	0.88 (0.87-0.89)	0.90 (0.90-0.91)	<0.001*
	PEF (Litres/sec)	4.21 (4.13-4.29)	4.09 (4.01-4.17)	0.027*
Current Wheeze (95% CI)	FVC	2.32 (2.26-2.37)	2.27 (2.20-2.34)	0.267
	FEV_1	2.01 (1.95-2.06)	1.98 (1.91-2.04)	0.526
	FEV_1 /FVC	0.87 (0.85-0.88)	0.87 (0.86-0.89)	0.447
	PEF (Litres/sec)	4.19 (4.06-4.32)	4.06 (3.87-4.25)	0.229

9.3 DISCUSSION

In our study we have identified a considerable prevalence for wheezing illnesses and asthma at 10-years of age for a whole population sample in the UK. Almost one fifth of the population had experienced a wheezing illness at the age of 10-years. Furthermore we found that 13.0% of children had *currently diagnosed asthma* as defined by having both *current wheeze at 10-years* and *asthma ever*. This may represent a more accurate reflection of the extent of this problem amongst 10-year old children since not all wheezing in childhood is necessarily associated with true asthma [163]. However such a definition of asthma is reliant upon accurate diagnosis of asthma (*asthma ever* in the ISAAC questionnaire) and could therefore even underestimate the problem in some situations where physician recognition of asthma may not be consistent. Nevertheless the prevalence of *currently diagnosed asthma* at 10-year demonstrates that despite a rather conservative definition of asthma we found it to be a substantial problem. By comparison, previous UK studies have reported slightly lower period prevalence for asthma of 9.3% at 7-years [33] and 9.5% at 11-years [34]. An alternative classification of *current asthma* using a combination of *current wheeze* and bronchial hyper-responsiveness (BHR) at bronchial challenge has become increasingly used as the 'gold standard' [41,104] for asthma diagnosis in epidemiological surveys. This approach has the advantage that an element of objective measurement is introduced into the definition rather than just relying upon simple questionnaire reporting that may be open to misinterpretation. However it is also worth reflecting that evidence of BHR is not always synonymous with presence of asthma. Thus Lee [33] has demonstrated BHR in a third of asymptomatic 7-year old children and also shown that a similar proportion of such children with recurrent wheeze do not react to histamine. Furthermore Sears [205] has demonstrated that 8.0% of 9-year old children with no history of wheeze showed methacholine responsiveness, whilst 35.0% of symptomatic children failed to show BHR at challenge.

In our survey, methacholine bronchial challenge was performed in all children who visited the Research Centre and had a history of *ever wheezing* (n = 484) as well as a control group of 300 children who visited the Centre and had never wheezed. Unfortunately time and financial constraints prevented us from performing bronchial challenges in all available subjects. Using the 'gold standard' definition of symptomatic BHR *current asthma* was found in 14.4% of 784 children undergoing bronchial challenge and 10.8% of the 1043

children visiting the Research Centre. These are substantial figures that bear comparison to findings by Peat et al [41] of *current asthma* ranging from 7.1% to 13.0% amongst 8-11 year old Australian populations. It should be noted that some studies [41,104] have taken any BHR (regardless of PC_{20}) in their definition of BHR for *current asthma*. However this approach might tend to overestimate asthma prevalence. Therefore we have used a PC_{20} <8mg/ml as evidence of BHR in defining *current asthma* for our population. That not all wheezing is associated with asthma is reflected by the fact that only 55.7% of current wheezers who underwent methacholine bronchial challenge in our study satisfied our definition of *current asthma*.

In considering the question of asthma definitions it is worth noting that in using a purely questionnaire-derived definition of *currently diagnosed asthma* we have identified similar characteristics to those found when using an objective definition including BHR measurement. Interestingly trends for higher prevalence of bronchodilator and inhaled steroid usage were seen when *currently diagnosed asthma* rather than *current asthma* was used as a definition. This may well reflect the pre-existing physician diagnosis element to the *currently diagnosed asthma* definition. After all a group that is identified as asthmatic by a physician might be expected to be more likely to be prescribed treatment for that condition. Not unexpectedly children with *current asthma* showed a trend for greater BHR since by definition they must have had a $PC_{20}FEV_1$ less than 8.0 mg/ml. We also demonstrated trends for greater obstructive patterns of lung function in *current asthma* than with the other states considered. In this context it was recently shown [193] that impaired baseline lung function can serve as a risk factor for BHR. Furthermore *current asthmatics* showed trends for higher atopic sensitisation and prevalence of other allergic conditions possibly reflecting an association between presence of such diseases and greater BHR. This notion is supported by recent findings from the MAS-Study [193] suggesting that atopy, indoor allergen sensitisation and high IgE are all risk factors for significant BHR in childhood. The use of objective measurements within the definition of asthma, as occurs with the incorporation of BHR, may allow better identification of 'core asthmatic' subjects. Nevertheless where bronchial challenge testing is not readily available the use of a composite questionnaire based definition of asthma such as the *currently diagnosed asthmatic* in our survey may provide a useful research tool.

We found early life origins of *current wheeze, current asthma* and the *currently diagnosed asthmatic* state at 10-years with an average age of onset at 2 to 3-years depending upon the precise definition used. It is important to realise that in order to have one of these states the child had to be wheezing at 10-years thereby excluding *early transient wheezers*, to revert to a phenotypic definition. Such *transient wheezers* might be expected to possess an earlier average wheezing onset than our *current wheezers / asthmatics* who were phenotypically either *persistent* or *late onset wheezers*. Indeed Dodge [168] has demonstrated an average onset for persistent childhood asthma of 3 to 4-years. These findings therefore add to the body of evidence presented in Chapters 5 and 6 suggesting that significant wheezing in childhood is a persistent condition originating in early life.

This study has shown that *current wheeze* and *currently diagnosed asthma* were significantly commoner in boys at 10-years. This is consistent with findings from several other childhood studies [34,38,42,44,81]. Most indices of wheezing morbidity did not differ greatly by gender at 10-years indicating that severity of wheezing at this age may not be very different for boys and girls. BHR measurement also did not differ by gender. Baseline lung function, however, was significantly lower for girls both amongst the whole population as well as children who were not *current wheezers*. The association of gender with lung function in childhood is a complex one with other factors such as height also having an important influence. It is therefore worth reflecting that there was no significant difference in height by gender within our study population although girls were significantly heavier. It is known that lower airway size to lung parenchyma ratio leads to lower airway calibre in boys during early life [84] and may influence an increased wheezing tendency in boys during infancy. It is possible that during growth boys may show more pronounced changes in thoracic dimensions and hence show better lung function than girls by 10-years. However despite better overall lung function at 10-years, the boys in our population without *current wheeze* still showed a significantly more obstructive pattern of lung function than their female counterparts. This suggests that there are persisting elements of obstructive lung function still evident amongst 10-year old boys independently of symptom expression. Interestingly, amongst children with current wheeze no such variations in lung function by gender were noted suggesting that in the presence of wheezing symptoms gender has little further impact upon lung function at 10-years. It has previously been noted that an equalization of the male: female asthma ratio is reached by puberty [54] with peak

prevalence for asthma occurring earlier in boys than girls [34]. It may well be that in seeing our population at 10-years of age we have assessed our children during a transition period when major changes in gender ratio not only for asthma but also in baseline lung function are occurring.

Strong associations between atopy and other allergic disorders were identified in children with wheezing or asthma at 10-years. This was especially the case for the group we categorized as having *current asthma* by virtue of their showing significant BHR at 10-years in combination with wheezing. Three quarters of this group were atopic at SPT. Not surprisingly sensitisation to aeroallergens was very common in children with wheezing or asthma. House dust mite sensitisation consistently emerged as the commonest of these allergens, occurring in 64% of children with *current asthma*. The MAS-Study [193] showed similar importance for HDM sensitivity as a risk factor for significant BHR amongst 7-year olds. *Current wheeze, current asthma* and *the currently diagnosed asthmatic state* were all associated with significantly higher $\log_{10}$ total IgE than in the absence of each respective condition. Thus IgE mediated allergen sensitisation is likely to play an important role in the presence of BHR and asthma at 10-years.

The fact that recognized triggers for wheezing episodes were frequently reported in children with *current asthma* suggests that identification of such triggers, whether allergic or physical, may help to facilitate better symptom control in such children.

Allergic co-morbidity was also found to be substantial amongst children with wheezing or asthma at 10-years. This was particularly the case for *current rhinitis*, which probably reflects the nature of the 'allergic march' by which allergic sensitisation to aeroallergens rather than food allergens [15] becomes more problematic during later childhood. Thus children with *current asthma* had a 2.8 fold increased prevalence of *current rhinitis* compared to the general population. Similarly these children also had a 2.4 fold increased prevalence of *current eczema* and 1.9 fold increased prevalence of *current urticaria* compared to the whole population. Clearly the potential for other allergic conditions to cause significant co-morbidity in asthmatic 10-year old children should not be ignored.

In summary, this chapter has highlighted a substantial prevalence of *current wheeze* and *asthma* for 10-year old children in the UK. This has been with both an objective 'gold standard' definition of *current asthma* as well as an ISAAC questionnaire based definition of *currently diagnosed asthma* that may serve as an adequate alternative where bronchial challenge testing is not feasible. It is clear that most asthma at 10-years appears to originate in early life. Furthermore strong associations to atopy and allergic states are observed for asthma at this age. Identification of risk factors for the presence of asthma at 10-years of age will permit a better understanding of the development of this state. These will be described in Chapter 13.

CHAPTER 10

THE PREVALENCE OF ATOPY AND ALLERGIC DISEASES AT 10-YEARS OF AGE

Studies of childhood asthma and allergy prevalence have revealed particularly high frequency of such conditions in affluent westernized societies [38]. In recent years, paediatric studies within the United Kingdom have demonstrated that this nation possesses some of the highest prevalence figures for atopy and allergic diseases on a global basis [34,38,85]. In this chapter, prevalence figures are presented for atopy and the major allergic conditions (eczema, rhinitis, urticaria and food allergy) at 10-years of age from the Isle of Wight Whole Population Birth Cohort Study.

10.1 ATOPY AT 10-YEARS

Skin prick testing (SPT) to a battery of common food and aeroallergens was performed in 1036 children at 10-years. Atopy was defined as the presence of at least one positive skin test response having a minimum mean wheal diameter of 3mm. Following these criteria 26.9% (279) children skin prick tested at 10-years were atopic. An inhalant screen for IgE antibody to inhalant allergens was also performed on serum samples collected at 10-years. Analysis of this test revealed that 33.0% (314/953) children tested had a *positive inhalant screen* indicating the presence of IgE antibodies to one of a panel of common inhalant allergens (see **3.2.5**). Atopy defined by both SPT and by *positive inhalant screen* was significantly commoner in 10-year old boys than girls (Table 10.1).

Table 10.1: Prevalence of atopy and allergic disorder by gender at 10-years

	MALE (n=)	FEMALE (n=)	P-value * Statistically significant
% Atopy at SPT	31.0% (160/516)	22.9% (119/520)	0.003*
% Positive inhalant screen	37.9% (181/478)	28.1% (133/474)	0.001*
Log $_{10}$ total IgE (IU/ml)	1.94	1.87	0.146
% Current allergy	38.2% (262/686)	35.2% (233/662)	0.254
% Current eczema	13.4% (92/687)	14.0% (94/671)	0.741
% Current rhinitis	15.3% (106/692)	14.8% (99/670)	0.780
% Current urticaria	7.8% (54/693)	9.6% (64/668)	0.241

Notes: For definitions of allergic states see **3.3.1**

Table 10.2: Skin test sensitisation at 10-years to individual allergens

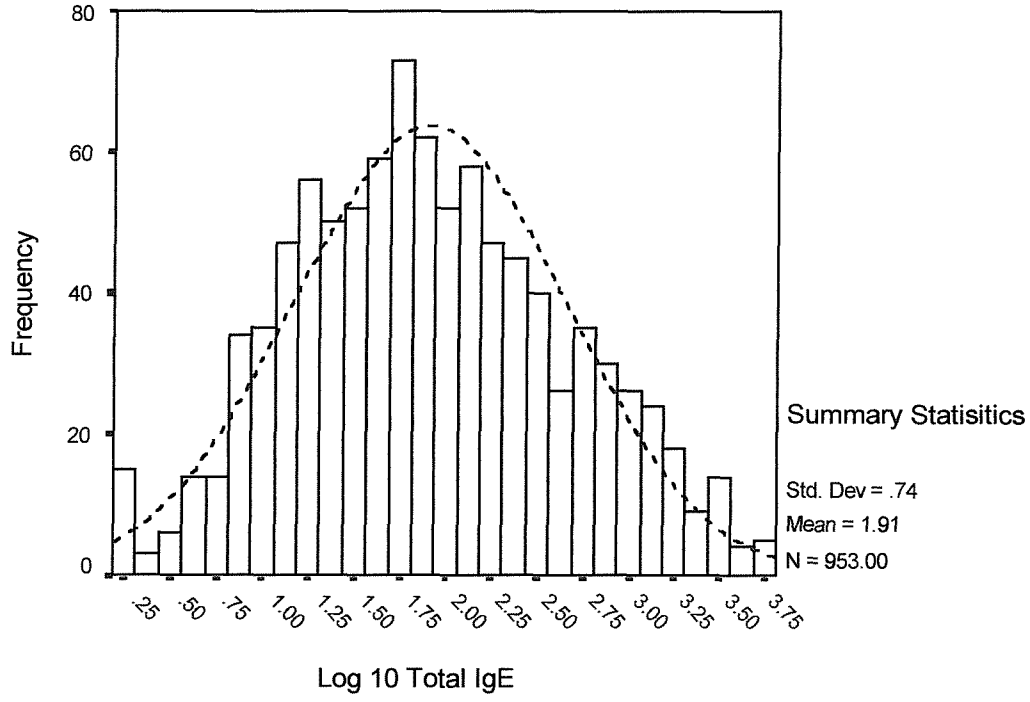
ALLERGEN	Number Positive	% Amongst Sample (n = 1036)	% Amongst Atopics (n = 279)
HOUSE DUST MITE	199	19.2%	71.3%
GRASS POLLEN	134	12.9%	48.0%
CAT	82	7.9%	29.4%
DOG	46	4.4%	16.5%
ALTERNARIA	22	2.1%	7.9%
TREE	19	1.8%	6.8%
PEANUT	18	1.7%	6.5%
CLADOSPORIUM	11	1.1%	3.9%
COD	8	0.8%	2.9%
EGG	4	0.4%	1.4%
MILK	3	0.3%	1.1%
SOYA	2	0.2%	0.7%

Prevalence of individual allergen sensitisation at SPT was greatest to aeroallergens such as house dust mite (*Dermatophagoides Pteronyssinus*), grass pollen, cat and dog (Table 10.2).

House dust mite proved the commonest allergen with almost one fifth of the test population showing sensitivity. In contrast, sensitisation to at least one common food allergen (milk, egg, soya, peanut or cod) was present in only 2.6% (27) children skin tested at 10-years. Of these, peanut was the commonest food sensitivity found at 10-year SPT, being present in 1.7% (18) children tested.

Total serum IgE measurements were available in 953 children at 10-years with a whole population median IgE value of 71.2 IU/ml. Total IgE measurements were found to follow a *lognormal* distribution for the whole 10-year population (Figure 10.1). Total IgE did not vary significantly by gender (Table 10.1). Log_{10} IgE was significantly higher in those who were atopic at SPT (mean 2.47 v 1.70, $p < 0.001$) or with a *positive inhalant screen* (mean 2.48 v 1.62, $p < 0.001$).

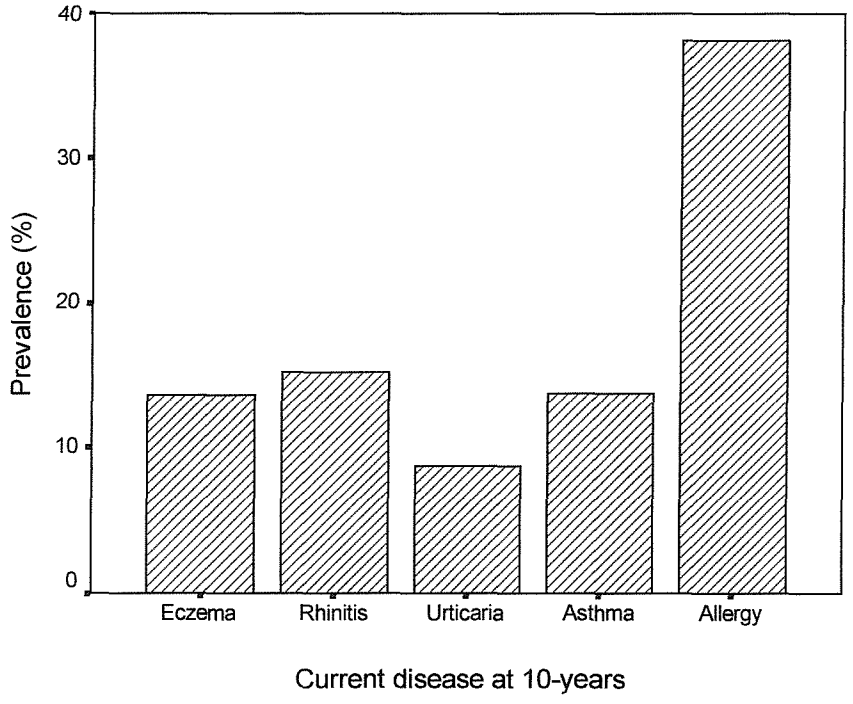
Figure 10.1: Whole population distribution of log $_{10}$ total IgE at 10-years



10.2 CURRENT ALLERGY AT 10-YEARS

The prevalence of *any symptoms* suggestive of current allergy at 10-years was 44.8% (605/1350). Atopy at 10-year SPT was significantly greater in the presence of any allergic symptoms than in their absence (41.1% v 13.1%, p<0.001). *Current allergy* at 10-years however was defined as the presence of *current eczema, current rhinitis, current urticaria* or *currently diagnosed asthma* (details of individual definitions are given in **3.3.1**). Using this definition, 36.7% (495/1350) children had *current allergy* at 10-years. There was no significant gender variation for *current allergy* (Table 10.1). *Currently diagnosed asthma, current rhinitis* and *current eczema* were present together in 2.0% (27/1350) children. Such children had higher prevalence of atopy at SPT than those without all three conditions together (87.0% v 25.6%, p <0.001). The prevalence of the various allergic states at 10-years is illustrated in Figure 10.2.

Figure 10.2: Prevalence of allergic conditions at 10-years



10.3 ECZEMA

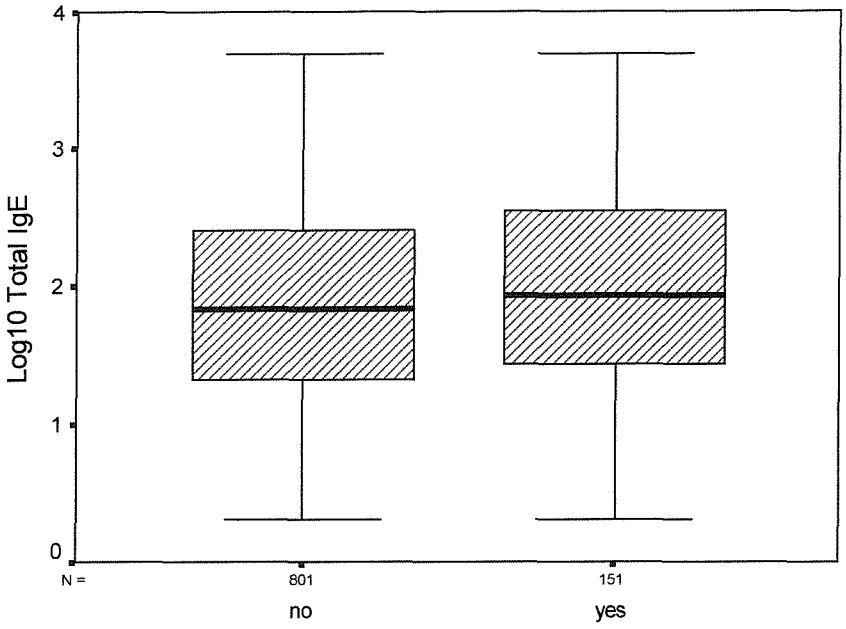
The period prevalence of diagnosed eczema varied little during the first decade of life. Thus prospectively diagnosed eczema was present in 11.3% (132/1167), 10.8% (127/1174) and 11.9% (145/1214) at 1-, 2- and 4-years respectively. *Current itchy rash* ('chronic itchy rash occurring within the last 12 months') was reported in 14.3% (194/1358) children at 10-years whilst *eczema ever* was reported in 41.0% (563/1373) children. *Current eczema*, defined as a combination of both these outcomes at 10-years, occurred in 13.7% (186/1358) children with no significant variation in prevalence by gender (Table 10.1). The prevalence of *current eczema* in those with *current itchy rash* was 95.9%. Conversely the prevalence of *current eczema* amongst those with *eczema ever* was only 33.9%. At 10-years, most *current eczema* was retrospectively reported to have commenced in early life. Thus 55.4% (103/186) children with *current eczema* had symptom onset by age 2-years, 15.6% (29) had onset between 2 and 4-years and only 29.0% (54) children began symptoms after 5-years. In our population we identified a subgroup of 132 children with diagnosed eczema at 4-years who were seen again at 10-years. Amongst such children 56.3% (72/128) had *current eczema* at 10-years. Most children with *current eczema* - 86.5% (160/185) children experienced a classical expression of eczema affecting the flexures, buttocks and around the neck, ears or eyes. A relapsing/remitting course was identified for most cases of *current eczema* at 10-years. In this context, 71.4% (132/185) children with *current eczema* reported that their rash 'had cleared completely at any time during the last 12 months'. Furthermore morbidity caused by *current eczema* was found to be low with only 3.2% (6/185) such children being kept awake at night more than once a week by their eczema. Most, 78.4% (145/185), children with *current eczema* experienced no nocturnal disturbance from their disease during the preceding year.

Prevalence of atopy (whether defined by positive SPT or inhalant screen) in children with *current eczema* was significantly higher than in children without the condition (Table 10.3). Atopy at 10-year SPT was also significantly greater with *current itchy rash* (37.7% v 24.9%, p = 0.001, OR = 1.83, 95%CI = 1.29-2.59) and to a lesser extent *eczema ever* (30.7% v 24.1%, p = 0.018, OR = 1.40, 95% CI = 1.06-1.84). However, $\log_{10}$ total IgE (mean 2.00 v 1.89, p = 0.107) did not vary significantly between those with or without *current eczema* (Figure 10.3). The commonest allergen sensitivities at 10-year SPT in

children with *current eczema* were house dust mite (29.6%), grass (22.6%), cat (13.2%), dog (11.3%), peanut (3.8%) and cod (2.5%). Comparison with children who *did not have current eczema* showed these specific sensitivities to be significantly commoner in the presence of *current eczema* – house dust mite ($p < 0.001$, OR = 2.00, 95%CI = 1.36-2.93), cat ($p = 0.007$, OR = 2.03, 95%CI = 1.20-3.44), dog ($p<0.001$, OR = 3.86, 95%CI = 2.08-7.17), grass ($p<0.001$, OR = 2.32, 95%CI = 1.52-3.56), peanut ($p = 0.044$, OR = 2.84, 95%CI = 1.05-7.68 [*Fishers exact test*]) and cod ($p = 0.022$, OR = 5.66, 95%CI = 1.40-22.85 [*Fishers exact test*]). Overall food allergen sensitisation at 10-year SPT was significantly higher in the presence of *current eczema* (5.7% v 2.1%, $p = 0.014$, OR = 2.88, 95%CI = 1.27-6.52 [*Fishers exact test*]). Significantly greater *current eczema* at 10-years was seen in the presence of atopy at 4-year (24.6% v 12.1%; $p<0.001$; OR = 2.36; 95% CI = 1.56-3.53). Furthermore prevalence of *current eczema* was higher with the combination of atopy and diagnosed food allergy at 4-years (70.6% v 13.6%, $p<0.001$,OR = 15.19, 95%CI = 5.26-43.84, [*Fishers exact test*]). Prevalence of *current eczema* in relation to individual allergen sensitisation in infancy was also assessed. *Current eczema* was significantly greater amongst those sensitised to egg allergen at 1-year (48.1% v 21.0% in those not sensitised; $p = 0.002$; OR = 3.49; 95%CI = 1.53-7.95) or 2-years (62.5% v 23.4% in those not sensitised; $p = 0.002$ [*Fishers exact test*]; OR = 5.45; 95%CI = 1.90-15.65). Contrary to expectation milk sensitisation in infancy showed no significant association with *current eczema*. Other allergen sensitivities in infancy demonstrating an association with significantly higher prevalence of *current eczema* were house dust mite sensitisation at 2-years (45.5% v 17.4% in those not sensitised; $p<0.001$; OR = 3.96; 95% CI = 1.88-8.32) and cat sensitisation at 1-year (60.0% v 21.6% in those not sensitised; $p = 0.001$ [*Fishers exact test*]; OR = 5.46; 95% CI = 1.82-16.43).

Current rhinitis (25.4% v 13.6%, $p<0.001$), *currently diagnosed asthma* (23.1% v 11.4%, $p<0.001$) and *current urticaria* (18.9% v 7.1%, $p<0.001$) were all significantly commoner in the presence of *current eczema*. The same pattern was seen in the presence *of eczema ever – current rhinitis* (20.4% v 11.3%, $p<0.001$), *currently diagnosed asthma* (17.8% v 9.6%, $p<0.001$) and *current urticaria* (11.1% v 7.0%, $p= 0.008$). Slightly lower prevalence was found amongst the 369 children who had outgrown their eczema by 10-years – (*current rhinitis* 18.6%, *currently diagnosed asthma* 15.3% and *current urticaria* 7.5%).

Figure 10.3: Log_{10} total IgE for those with and without *current eczema*



10.4 RHINITIS

At 10-years, *current nasal symptoms* (nasal symptoms occurring in the absence of cold or flu within the last 12 months) were present in 22.6% (308/1362) children. *Hay fever ever* was reported for 18.6% (256/1373) children. *Current rhinitis,* representing a combination of both of these outcomes at 10-years, was present in 15.1% (205/1358) children. Thus *current rhinitis* was present in 66.6% of children with *current nasal symptoms*. The prevalence of *current rhinitis* amongst those with *hay fever ever* was 83.7%. It is worth reflecting that this definition of *current rhinitis* was dependent on a response about *hay fever ever*. Although conventionally hay fever may be interpreted as being seasonal in nature in our study parents completing the questionnaires tended to interpret this term synonymously with rhinitis. Hence both perennial and seasonal disease was recorded in response to this question. Prevalence did not vary significantly with gender (Table 10.1). Retrospective reporting at 10-years gave a median age of onset for *current rhinitis* symptoms of 7.0-years (interquartile range 4.0). The majority of children with *current*

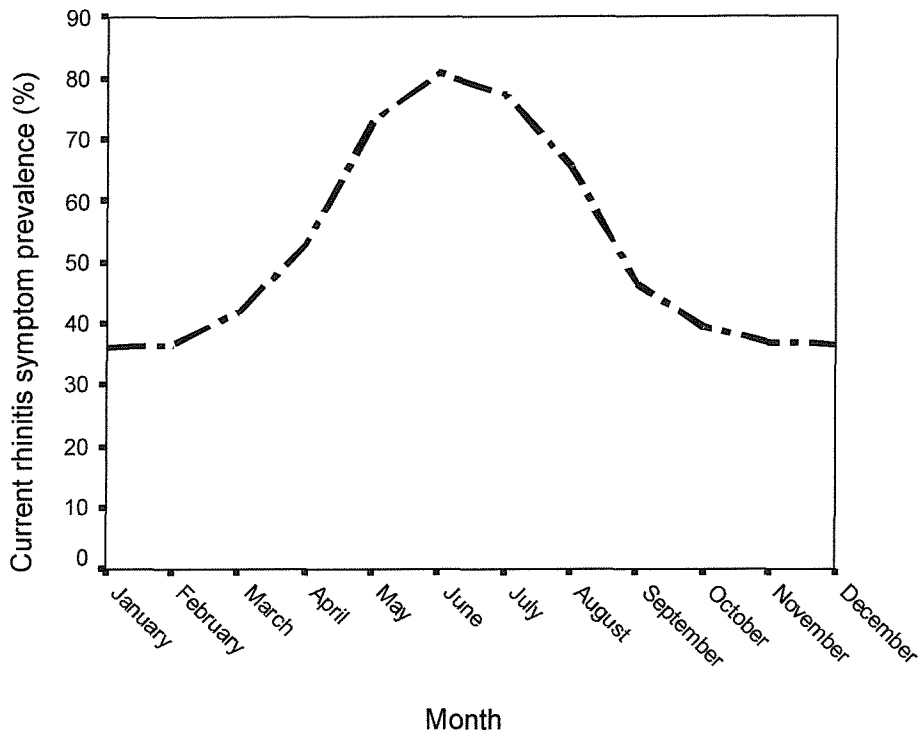
rhinitis described a predominantly seasonal condition 60.3%(123/204), whilst 30.3% (62) described a perennial condition without seasonal exacerbation and 9.3% (19) experienced a perennial condition with seasonal exacerbation. Children with *current rhinitis* had highest symptom prevalence during June and July (Figure 10.4).

Most, 67.8% (139/205) children with *current rhinitis* suffered with associated conjunctivitis symptoms. Disease sufficient to interfere to some extent with daily activity was present in 30.7% (62/202) children with *current rhinitis*. However, only 9.4% (19/202) of those with *current rhinitis* experienced moderate impairment of activity whilst a further 4.4% (9/202) were felt to have experienced a lot of impairment of activity because of their condition. Fifty six percent (112/200) of children with *current rhinitis* used some manner of pharmacological treatment. Oral antihistamines were most frequently used as single agent therapy 31.0% (62/200) children whilst nasal steroids were used alone or in combination in 10.5% (21/200) children with *current rhinitis*. Topical sodium cromoglycate therapy was used alone, or in combination, by 10.0% (20/200) of these children. Only 7.5% (15/200) children with *current rhinitis* required multiple drug therapy for their symptoms.

Sixty four percent (128/200) children with *current rhinitis* were reported to have identifiable triggers for their symptoms at 10-years. The commonest single trigger reported was pollen contact in 48.5% (97/200) children. House dust, alone or in combination with other triggers, was reported in 9.5% (19/200) children and animals similarly reported in 8.0% (16/200) children.

Prevalence of atopy at 10-years (at either SPT or positive inhalant screen) was significantly greater in those with *current rhinitis* than those without (Table 10.3). Similarly, atopy at 10-year SPT was significantly greater in the presence of both *current nasal symptoms* (51.3% v 18.4%, $p<0.001$, OR = 4.68, 95%CI = 3.46-6.32) and *hay fever ever* (60.4% v 18.3%, $p<0.001$, OR = 6.79, 95%CI = 4.90-9.42). Mean $\log_{10}$ total IgE was also significantly higher (2.35 v 1.81, $p< 0.001$) in those with *current rhinitis* than those without it (Figure 10.5).

Figure 10.4: Seasonal variation of symptom prevalence in *current rhinitis*

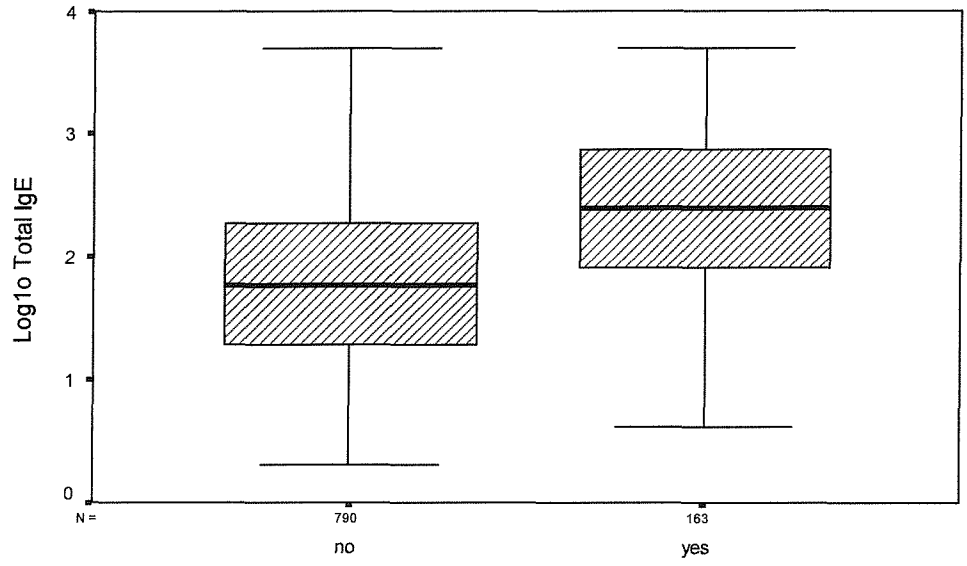


The commonest allergen sensitivities for *current rhinitis* at 10-years were house dust mite (43.3%), grass (42.2%), cat (22.8%), dog (13.9%), tree (5.6%), alternaria (5.6%), peanut (5.6%), cladosporium (3.9%) and cod (2.2%). Comparison with children who *did not have current rhinitis* revealed that these sensitivities were significantly commoner in the presence of *current rhinitis* – house dust mite ($p<0.001$, OR = 4.64, 95%CI = 3.26-6.60), grass ($p<0.001$, OR = 2.04, 95%CI = 1.68-2.49), cat ($p<0.001$, OR = 5.86, 95%CI = 3.67-9.36), dog ($p<0.001$, OR = 6.41, 95%CI = 3.50-11.73), tree ($p<0.001$, OR = 5.53, 95%CI = 2.21-13.81 [*Fishers exact test*]), cladosporium ($p = 0.001$, OR = 8.61, 95%CI = 2.49-29.73 [*Fishers exact test*]), alternaria ($p = 0.002$, OR = 4.13, 95%CI = 1.76-9.72 [*Fishers exact test*]), peanut ($p <0.001$, OR = 6.27, 95%CI = 2.44-16.11 [*Fishers exact test*]) and cod ($p = 0.034$, OR = 4.86, 95%CI = 1.21-19.63 [*Fishers exact test*]). Any food allergen sensitisation at 10-years was significantly commoner in the presence of *current rhinitis*, (8.9% v 1.3%, $p <0.001$, OR = 7.53, 95%CI = 3.43-16.53 [*Fishers exact test*]).

Current eczema (22.9% v 12.1%, $p<0.001$), *currently diagnosed asthma* (33.7% v 9.0%, $p<0.001$) and *current urticaria* (13.2% v 7.9%, $p = 0.014$) were all significantly commoner

in the presence of *current rhinitis*. Similar findings were found for co-morbidity in the presence of *hay fever ever – current eczema* (21.6% v 11.9%, p<0.001), *currently diagnosed asthmatic* (31.6% v 8.7%, p<0.001) and *current urticaria* (12.3% v 7.8%, p = 0.023).

Figure 10.5: Log_{10} total IgE for those with and without *current rhinitis*



Use of current asthma medications was significantly greater for children with *current wheeze* in the presence of *current rhinitis* than in its absence (76.5% v 59.9%, p = 0.013). There was no variation in baseline lung function in the presence of *current rhinitis* for children both with and without *current wheeze*. However *Definite BHR* (PC_{20} < 4 mg/ml) at methacholine challenge was found to be significantly commoner when *current rhinitis* was present than absent amongst children with *current wheeze* (56.0% v 40.6%, p = 0.034). Furthermore, the presence of *current rhinitis* was also associated with significantly greater prevalence of *Definite BHR* (24.4% v 11.2%, p = 0.001) in children who did not have *current wheeze*.

10.5 URTICARIA

Current urticaria, defined by criteria in the supplementary questionnaire at 10-years, was present in 8.7% (118/1361) children. Prevalence did not vary significantly by gender (Table 10.1). Median age of symptom onset for *current urticaria* was retrospectively reported to

be 6.0 years (interquartile range 3.0). The majority of cases of *current urticaria* were part of a chronic recurrent condition with 50.8% (60/118) of such children having experienced more than 5 episodes in their lifetime whilst only 16.1% (19) children had just a single episode of urticaria. Furthermore, most children with *current urticaria* (80.5%, 95 children) had typical duration of less than 3 days for an episode of urticaria. The majority of cases of *current urticaria* were idiopathic in aetiology with known triggers for urticarial episodes reported in only 39.0% (46) children. In those reporting disease triggers the commonest specific triggers identified were pollens in 26.1% (12/46) cases, physical causes (heat or solar exposure) in 19.6% (9) cases, soaps or washing powders in 10.9% (5) cases, animals in 8.7% (4) cases and foods in 8.7% (4) cases.

The prevalence of atopy (at SPT or positive inhalant screen) was significantly higher in those with *current urticaria* than those without it (Table 10.3). However, mean $\log_{10}$ total IgE was not significantly greater (2.03 v 1.89, p = 0.093) in those with current urticaria (Figure 10.6).

The commonest sensitisations at 10-year SPT for those with *current urticaria* were house dust mite (25.5%), grass (16.7%), cat (13.7%) and dog (8.8%). Comparison with children who *did not have current urticaria* found that only cat (p = 0.023, OR = 2.02, 95%CI = 1.09-3.74) and dog (p = 0.035, OR = 2.41, 95%CI = 1.12-5.15 [*Fishers exact test*]) sensitisation was significantly greater in the presence of current urticaria. Food allergen sensitisation at 10-years was not significantly greater in the presence of current urticaria (3.9% v 2.5%, p = 0.332, OR = 1.61, 95%CI = 0.55-4.75 [*Fishers exact test*]). *Current eczema* (29.7% v 12.2%, p<0.001) and *current rhinitis* (22.9% v 14.4%, p = 0. 014) were significantly commoner in the presence of current urticaria. A similar trend was observed with *currently diagnosed asthma* for *current urticaria* although this did not reach statistical significance (17.8% v 12.2%, p = 0.079).

Figure 10.6: Log_{10} total IgE for those with and without *current urticaria*

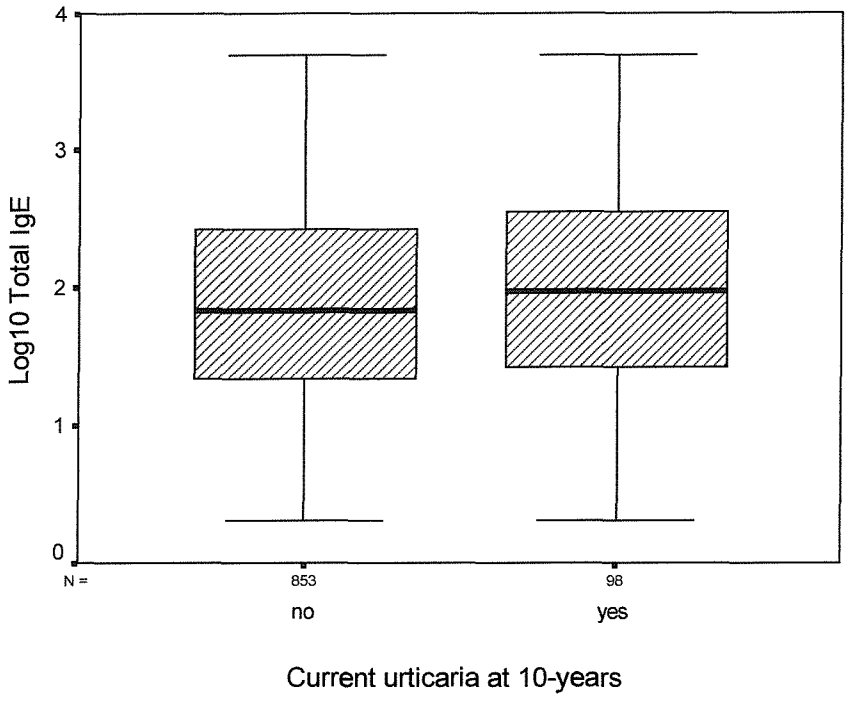


Table 10.3: Prevalence of atopy for current allergies at 10-years

Condition	Disease status	% Atopic at 10-year SPT (n=)	% Positive inhalant screen (n=)	Statistical Significance
Current eczema	Present	38.4%* (61/159)	44.4%† (67/151)	* p<0.001 † p= 0.001
	Absent	24.9% (218/876)	30.9% (247/800)	
Current rhinitis	Present	61.1%* (110/180)	69.9%* (114/163)	* p<0.001
	Absent	19.7% (169/856)	25.3% (200/789)	
Current urticaria	Present	37.3%‡ (38/102)	41.8%§ (41/98)	‡ p= 0.013 § p= 0.048
	Absent	25.8% (240/930)	31.9% (272/853)	

Table 10.3 Notes:

Pairwise comparison performed using Chi-Square Test to compare prevalence of atopy and positive inhalant screen in the presence and absence of each state.

10.6 FOOD ALLERGY

Current food allergy was very rarely reported at 10-years. However at 10-years, 8.5% (117/1373) children gave a history of food related reactions (including both food allergy and hyperactivity) since the age of 4-years. In this context, hyperactivity was described for 2.3% (32/1373) children. Of children with a history of reaction since age 4-years, 41.6% (42/101) were atopic as defined by positive SPT at 10-years with 8.1% (8/99) actually showing a positive reaction to a food allergen at this SPT. Fifty percent of children with a food reaction history gave a positive inhalant screen to IgE antibody at 10-years. It is important to note that in the whole population at 10-years, 27 children gave a positive reaction to a food allergen at SPT. This indicates that 70.4% (19/27) of children who had a positive SPT to a food allergen at 10-years gave no history of reacting to foods in the previous 6-years. Thus a high prevalence of latent sensitisation appears to have been present amongst those showing food related skin test positivity at 10-years.

The commonest food reactions reported over this 6-year period were to dairy produce (milk, cream, cheese or butter) occurring in 1.5 % (20/1373) of all children. Egg was mentioned as a cause of reactions in 0.7% (10) of all children since the age of 4-years. Peanut comprised the single most common food reported for food related reactions being described for 1.0% (14) of all children over the 6-year period. Equal proportions of boys and girls were reported to have suffered such peanut related reactions. Atopy at 10-year SPT was present in 76.9% (10/13) children with a history of peanut related reactions; however sensitisation to peanut was present amongst only 61.5% (8/13) peanut reacting children at 10-year SPT. At 10-years sensitisation to peanut was actually found in a total of 18 children indicating that some children with a positive SPT to peanut at 10-years had a *latent sensitisation*. Other common sensitivities amongst children reported to have reacted to peanut were house dust mite (53.8%), grass (53.8%), cat (30.8%), dog (30.8%), cod (23.1%), egg (7.7%) and cladosporium (7.7%). Such children also had high prevalence of other 'allergic' indices. Thus 90.9% (10/11) peanut reacting children had a positive IgE inhalant screen at 10-years, whilst 42.9% (6/14) had *current eczema*, 50.0% (7/14) had *current hay fever*, 21.4% (3/14) had *current urticaria* and 42.9% (6/14) had *current wheeze*. Possibly because of stringent avoidance measures no *current reactions* to peanut (within the past 12 months) were actually reported amongst such children at the age

of 10-years. The commonest reported reactions to peanut since 4-years of age were vomiting in 36.4% (4/11) children, urticaria in 27.3% (3/11), eczema in 18.2% (2/11), angioedema in 7.1% (1/11), oral tingling in 7.1% (1/11) and breathlessness 7.1% (1/11). Anaphylaxis was not reported in association with any peanut reactions between the ages of 4 and 10-years.

Overall, the commonest reported food related reactions since age 5-years were urticaria in 20% (22/110) of cases, vomiting in19.1% (21/110) cases and eczema in 14.5% (16/110) cases. Most food related reactions (67.0%) were within 1 hour of ingesting the foods in question with 95.0% of all reactions occurring within 12 hours of ingestion.

10.7 OTHER ALLERGIES

In addition to the major allergic states described above several children were reported to have experienced other allergic type reactions since the age of 4-years. Thus 0.22% (3/1373) children were reported to have had reactions to insect venom after stinging episodes (two to bee, one to wasp). Allergic reactions to antibiotics were described in 0.58% (8/1373) children (penicillin, amoxycillin or cefaclor). One child was reported to have had an anaphylactic episode since the age of 4-years although the cause of this reaction was not identified. Furthermore one child was known to have a form of *hereditary angioedema.*

10.8 DISCUSSION

This study demonstrates that allergic conditions are still very common ailments amongst 10-year old children in the UK. Over one third (36.7%) of our general population sample at 10-years was adjudged to have *current allergy* of some form – eczema, urticaria, rhinitis or asthma. The definitions used for these conditions need to be considered when interpreting the results of a study like this [47]. Our definitions of current disease states incorporated a combination of both *current symptoms* suggestive of the condition as well as reporting *ever having had* that condition. Relying purely on known diagnoses has the potential to give a misleading picture of disease prevalence. However, purely using symptom reporting to

identify prevalence may also be flawed. Our combined approach was likely to have yielded lower prevalence figures than if only current symptoms suggestive of each condition were assessed. Indeed if just current suggestive symptoms alone were considered then *current allergic symptoms* would have been present in 45% of our population, findings comparable to those from the 12-14 year old UK arm of the ISAAC study [171]. ISAAC UK [171] used a combination of current nasal and eye symptoms to define current rhinoconjunctivitis. That approach yielded a prevalence figure of 18.2% (compared to 15.1% for *current rhinitis* in our study). The combination of intermittent itchy rash and rash affecting flexures used to define *current eczema* in that study gave a prevalence of 16.4% (compared to 13.7% for *current eczema* in our study). Our approach may be a more conservative one but does offer an alternative interpretation for ISAAC data.

Our reported findings of ISAAC defined symptoms suggestive of rhinitis (23%) or eczema (14%) confirms that UK children suffer amongst the highest prevalence for such symptoms on a global basis [47]. Comparison with ISAAC UK [171] at 12-14 years shows some unexpected findings. Our reported prevalence of *eczema ever* at 10-years (41%) was considerably higher than that reported at 12-14 years for ISAAC UK [171] (22.5%). This might suggest that eczema prevalence during the first decade of life is higher in our population. However it may also reflect recall bias with poor recollection of infantile disease in the ISAAC survey. In our prospective cohort study families were seen at regular intervals during childhood and this may have militated against this effect to some extent. As might be expected, comparison with data at 12-14 years from ISAAC UK [171] showed that our (younger) children had substantially lower prevalence of *hay fever ever* (18.9% v 34.9%). In addition reporting of current symptoms suggestive of rhinitis was also similarly lower (22.6% v 37.9%) in our study. This latter finding would support a hypothesis that this disease rises in prevalence during the teenage years and into early adulthood. Indeed comparison with ISAAC data [38] on 6-7 year olds from North-east England showed very similar prevalence (20.5%) of current symptoms of rhinitis to that in our 10-year olds, suggesting that this rise in prevalence had not yet begun in our children.

We demonstrated that a quarter (26.9%) of all those skin tested were atopic whilst one third (33.0%) of children had a positive IgE antibody inhalant screen. Comparison with studies elsewhere show that prevalence of atopy at SPT was much lower in our population than

those previously reported from Australia (42.4% of 9-11 year olds) [41], New Zealand (45.8% of 13-year olds) [87] and the USA (64% of 12-14 year olds) [45]. To some extent this may be due to our use of 3mm as the definition for positive wheal diameter at SPT whilst other studies have sometimes used 2mm [87]. It may also reflect the range of allergens used in our survey. It is worth considering that whatever the allergic condition, in our study slightly higher prevalence of atopy was consistently noted for testing by positive inhalant screen than by positive SPT. This was probably because the inhalant screen covered a wider range of inhalant allergens than the SPT and could be taken as further evidence that our SPT may have slightly underestimated the prevalence of 10-year atopy. However, another point to consider is that children who underwent skin prick testing at 10-years in our study were more likely to have a personal or family history of atopy than those who completed only a questionnaire. Therefore these results for atopy at skin prick testing and inhalant screen might even slightly overestimate that state for our whole population.

Atopy, the tendency to produce IgE antibody and demonstrate type I hypersensitivity, is often used synonymously with allergy in a clinical setting. At 10-years atopy determined by positive SPT or positive inhalant screen was significantly commoner in boys than girls. However, prevalence of *current allergic conditions* did not vary significantly by gender at 10-years. This disparity between atopy and clinical allergy is further emphasized by findings of atopy at SPT in only 38.4% *current eczema* and 37.3% *current urticaria*. This suggests that the extent to which atopic sensitisation contributes to these conditions at 10-years may be limited. Certainly total IgE was not significantly raised in children with current eczema or urticaria. Conversely as shown in the Tucson Children's Respiratory Study [23] very strong associations between atopy and allergy appeared to be present for *current rhinitis*, 61.1% of who were atopic at SPT in our population. In this respect we found that a wide range of allergen sensitivities were significantly commoner at this age in the presence of *current rhinitis*. In addition, *current rhinitis* was the only allergic state where the presence of that state was associated with significantly higher total IgE value than in the absence of that state.

Prevalence studies have identified different patterns of allergen sensitisation depending upon local environment. Thus in the dry conditions of Arizona sensitivity [73] to alternaria is pre-eminent, at the high altitude of Los Alamos [45] cat sensitivity is important and in the

humid coastal areas of New South Wales [41] house dust mite sensitivity is common. Our study confirms the high prevalence of house dust mite and grass pollen sensitisation amongst UK schoolchildren. It also demonstrates the relative predominance of aeroallergen sensitisation over food allergen sensitisation in atopic individuals at 10-years. Interestingly this was both the case in children with respiratory allergy as well as eczema and urticaria.

Our findings of no significant gender difference in *current allergic conditions* are in contrast to those of ISAAC UK [171] where prevalence of atopic symptoms at 12 to14-years was generally higher in girls. This may reflect the younger age of our children since it has been proposed that atopy changes from early male predominance to female predominance at some point in later childhood [171,206]. It is possible that at 10-years we have observed our population during the transition period for atopic sex ratio and thus failed to detect significant prevalence variations between boys and girls. This might explain why total IgE did not vary significantly by gender at 10-years. Some evidence to support this theory is provided by ISAAC data on younger children [38] where 7-year old boys were found to have greater prevalence of rhinitis (but not eczema) symptoms whilst data on older children has shown higher prevalence of such allergic symptoms in 12 to 14-year old girls [171].

The notion of an 'allergic march' to describe the manner in which an atopic individual may experience a characteristic evolution of different allergic states as childhood progresses has been described. Thus sensitisation to food allergens[15] in infancy may give way to later sensitisation to predominantly inhalant allergens, reflected by a shift from predominant food allergy and eczema in infancy to asthma and rhinitis in later childhood. Food allergen sensitisation in infancy, particularly to egg, is thought to be significant in this regard [16,22]. Our study also confirmed this link for *current eczema* at 10-years with significantly greater disease prevalence if the child had both atopic skin prick test and diagnosed food allergy at 4-years. We also demonstrated the importance of egg sensitisation in infancy for *current eczema* at 10-years. Retrospective analysis at 10-years gave an onset of symptoms within the first 2-years for the majority of children with *current eczema* whilst the average age of onset for rhinitis symptoms was 7-years. Furthermore most children with *eczema ever* did not have *current eczema* by our definition, whilst most children with *hay fever ever* had *current rhinitis*. Thus whilst most childhood eczema had occurred at an earlier age in our population, rhinitis/hay fever was very much a current condition at 10-years. However, it is

worth noting that 56% of those with eczema at 4-years showed evidence of disease at 10-years indicating persisting disease in a substantial proportion.

We demonstrated that children with *eczema* or *hay fever ever* as well as *current eczema, rhinitis* and *urticaria* at 10-years had strong tendency to show higher prevalence of other current allergic conditions than the general population, confirming the tendency for such diseases to cluster within an individual. High allergic co-morbidity at 10-years was also seen in children who had outgrown early life eczema supporting the concept that early life allergic conditions may remit only to be replaced by others later.

Particular interactions between rhinitis and asthma were observed at 10-years by which children with *current rhinitis* had a 2.5-fold increased prevalence of *currently diagnosed asthma* compared to the general population. This may reflect the dual importance of aeroallergen sensitisation to the presence of both asthma and rhinitis at 10-years. Further objective evidence of this relationship was shown by findings that current asthma treatment and bronchial hyper-responsiveness in *currently wheezing* children were significantly greater in the presence of *current rhinitis*. That *current rhinitis* may have an independent influence upon BHR was shown by the fact that BHR was higher in children with *current rhinitis* even when *current wheeze* was absent. Recognition of the relationship of childhood asthma and rhinitis as 'one airway, one disease' will enhance management of both states.

Amongst the whole population at 10-years, highest period prevalence was found for rhinitis (15.1%) with lower values for eczema (13.7%) asthma (13.0%) and urticaria (8.7%). *Current food allergy* at 10-years was seldom reported whilst sensitivity to any food allergens at 10-years was found in only 2.6% children. Furthermore 70% of children showing sensitivity to food allergens at 10-years had an apparently latent sensitisation with no history of a food related reaction in the preceding 6-years. An alternative explanation for this figure however may be that reactions were not experienced by some children because of avoidance of foods previously known to cause problems from experiences during the first 4-years of life. This might particularly be the case for children with nut related reactions that were amongst the commonest named foods. Peanut allergy was the single commonest food implicated in food related reactions since the age of 4-years. However, in line with the above argument, no such reactions were reported currently at 10-years and no

episodes of anaphylaxis due to peanut ingestion were noted since the age of 4-years. Nut allergy [177,207] has been the subject of much research on the Island in recent years, attracting considerable media attention and leading to increased recognition amongst the public. Thus our findings of few recent reactions to peanut may reflect increased parental awareness of the possible dangers of nut allergy and hence more stringent peanut avoidance. That only 61% of children reported to have reacted to peanut were skin test positive at 10-years gives further insight into the low frequency of recent reactions to peanut. It is possible that some children may have lost their sensitivity to peanut by 10-years or equally well that the initial labelling of reacting to peanuts was incorrect for some children. Food challenges to peanut were not employed in our study but would have helped to elucidate the nature of this problem and clearly identify the prevalence of latent sensitisation amongst these children.

Although often regarded as not being *truly allergic* we found that atopy at SPT and other allergic conditions were significantly commoner with the presence of urticaria. Thus it is likely that atopy exerts an influence upon childhood urticaria in certain individuals. Exploration of this relationship may offer avenues of opportunity in an often difficult to treat condition. We also observed that only a minority of children with urticaria had isolated episodes with most having more than five episodes in their lifetime. Most cases were also idiopathic in nature suggesting that much childhood urticaria may conform to the picture of chronic idiopathic urticaria often observed in adults.

In summary, this chapter highlights the significant presence of allergic states amongst 10-year old children in the UK. Co-morbidity of allergic diseases in childhood is strong and such conditions should not be considered in isolation. The search for risk factors that mediate development of these states can improve understanding of these diseases. In Chapters 11 and 12 risk factors for eczema and rhinitis at 10-years of age are described.

CHAPTER 11

RISK FACTORS FOR ECZEMA IN 10-YEAR OLD SCHOOLCHILDREN

Along with childhood asthma and rhinitis, childhood eczema forms a considerable burden of allergic disease in many populations [47]. It is known that this condition often appears as one of the earliest manifestations of allergy in the atopic infant and may be the opening event in a subsequent cascade of allergic diseases during childhood [14,15]. Often regarded by parents as a transient condition of infancy, it has been found that 40% of infants with atopic eczema may show asthmatic symptoms by age 4-years [14]. Recently, global comparisons have revealed particularly high lifetime prevalence for symptoms of this condition in affluent westernized societies [38,47,171]. In this context high prevalence of childhood eczema symptoms (up to 20% at 13-years) has been consistently shown in British, Scandinavian and New Zealand populations [47]. Similar high prevalence was shown for our own 10-year old population in Chapter 10. The reasons for these patterns of disease remain to be elucidated but are likely to reflect an interaction of genetic and environmental influences [117]. Better understanding of risk factors involved in this process could therefore help alleviate substantial morbidity in childhood. In this chapter, risk factors for *eczema ever* during the first decade of life as well as for *current eczema* at 10-years are examined.

11.1 ANALYSIS

Separate univariate risk factor analysis for *eczema ever* and *current eczema* was performed by chi-square analysis (with Fishers exact test where indicated). Backward stepwise (likelihood ratio) logistic regression analysis was used for each definition of eczema to assess the independent effect of risk factors with $p<0.2$ at univariate testing. To provide information useful in early life for determining subsequent presence of eczema, inclusion in regression models was restricted in each case to factors obtained from the first 4-years of life. Where more than one factor explained the same exposure the most relevant was chosen for inclusion in the regression model. Results were expressed as adjusted odds ratios (OR) and their 95% confidence intervals (CI).

11.2 RESULTS

Risk factors displaying trends for significance at univariate analysis for developing *current eczema* ($p<0.2$) are shown in Table 11.1. Thus physician diagnosed allergic conditions at 1-year (asthma, eczema, food allergy), 2-year (eczema), 4-years (asthma, eczema, rhinitis) and 10-years (rhinitis, asthma, urticaria) as well as positive SPT at 4 and 10-years were all significant risk factors for having *current eczema* at 10-years. Maternal and paternal eczema were also significant risk factors along with maternal asthma. Weaker associations ($p>0.05$ but <0.2) to family histories of other allergic diseases including sibling eczema, rhinitis, food allergy and urticaria, as well as maternal and paternal urticaria were found. Similar statistically non-significant influence for higher Social Class (I-IIInm) at birth upon *current eczema* was observed. Accordingly, low family income (less than £18,999 per annum) at 10-years showed a non-significant trend for lower prevalence of *current eczema* at 10-years.

Cat ownership at 10-years too showed a non-significant trend for lower prevalence of *current eczema* whereas dog ownership at this age alternatively showed a non-significant trend for increased risk of *current eczema*. Exclusive formula feeding in the first 3 months of life, maternal smoking at birth and parental smoking at 2 and 4-years all showed trends for lower risk of *current eczema* but none of these reached statistical significance. However parental smoking at 10-years did show a significant association with reduced *current eczema*. It should be noted that previously it has been shown for this population that there is considerable interaction between Social Class, infant feeding and smoking behaviour such that higher social classes formula feed less and smoke less [117]. The apparent protective effect of parental smoking at 10-years noted at univariate analysis for *current eczema* may simply reflect the fact that children with *current eczema* were more likely to have also had high Social Class at birth and therefore less smoking exposure. An alternative explanation would be that atopic parents of children with *current eczema* smoked less for their own health reasons anyway.

Table 11.1: Univariate risk analysis for *current eczema* (p <0.2)

Factor	P-Value	OR	95% CI
Atopic SPT 4yr	<0.001*	2.32	1.55-3.46
Atopic SPT 10yr	<0.001*	1.88	1.32-2.68
Asthma 1yr	0.022*	1.73	1.08-2.78
Eczema 1yr	<0.001*	5.85	3.89-8.80
Food Allergy 1yr	<0.001*	2.87	1.71-4.80
Rhinitis 1yr	0.148	1.45	0.88-2.39
Eczema 2yr	<0.001*	6.20	4.09-9.40
Asthma 4yr	0.005*	1.80	1.19-2.71
Eczema 4yr	<0.001*	13.68	9.06-20.65
Rhinitis 4yr	<0.001*	2.43	1.35-4.35
Food Allergy 4yr	<0.001* †	11.29	5.53-23.05
Current Rhinitis10yr	<0.001*	2.17	1.50-3.14
Current Asthma 10yr	<0.001*	2.34	1.59-3.45
Current Urticaria 10yr	<0.001*	3.03	1.97-4.67
Maternal Asthma	<0.002*	1.79	1.24-2.58
Maternal Eczema	0.024*	1.56	1.06-2.29
Paternal Eczema	0.004*	2.01	1.24-3.28
Sibling Eczema	0.063	1.36	0.98-1.89
Sibling Rhinitis	0.073	1.40	0.97-2.03
Maternal Urticaria	0.153	1.48	0.86-2.53
Paternal Urticaria	0.186	1.96	0.71-5.42
Sibling Urticaria	0.188	1.36	0.86-2.17
Sibling Food Allergy	0.188	1.35	0.86-2.11
Cat 10yr	0.101	0.77	0.56-1.05
Dog 10yr	0.094	1.31	0.96-1.78
Social Class I-III Birth	0.072	1.49	0.96-2.31
Exc. Formula Fed 1st 3/12	0.136	0.77	0.55-1.09
Parental Smoking 2yr	0.173	0.78	0.55-1.11
Parental Smoking 4yr	0.117	0.75	0.53-1.07
Parental Smoking 10yr	0.010*	0.64	0.46-0.90
Low Income 10yr	0.176	0.80	0.58-1.11

Notes:

Results are Odds ratios (OR) and their 95% Confidence Intervals (95% CI).

† Fishers exact test. * Statistically significant (p<0.05).

If *current itchy rash coming and going for at least 6 months* was used as the outcome variable rather than *current eczema* an almost identical pattern of univariate risk factors was observed for allergic family history, early life allergic history, environmental factors and atopy at 4-year SPT (results not presented). However if *eczema ever* was used as the outcome variable some differences were noted at univariate analysis (Table 11.2). A wider range of allergies at 1 and 2-years was found to be significant for *eczema ever* whilst family histories of asthma and rhinitis were also significant for this outcome. Furthermore for *eczema ever*, Social Class at birth showed no significance but large family size at 10-years (more than 2 children) did show significantly increased risk.

In order to obtain the independent effect of risk factors for *current eczema* and *eczema ever*, logistic regression models were created using all factors from the first 4-years of life that showed trends towards significance at univariate analysis ($p<0.2$). Cord IgE was not a significant predictive factor for *current eczema* at 10-years (median 0.1 v 0.1, $p = 0.78$ [*Mann-Whitney U Test*]) and therefore not included in relevant regression models. Eczema diagnoses at prior visits were not included as risk factors in the final regression model – analysis including these factors showed that diagnosed eczema at 4-years ($p < 0.001$, OR = 6.31, 95% CI = 2.78-14.32) was independently associated with *current eczema.*

In the final regression model for *current eczema,* maternal asthma, presence of diagnosed rhinitis and food allergy at 4-years plus positive SPT at 4-years were all independently associated with having *current eczema* at 10-years. Parental smoking at 4-years was associated with a significant reduction in risk of having *current eczema* at 10-years (Table 11.3). Unfortunately Social Class at Birth was only available for 685 children in our population. Thus inclusion of this factor limited the size of the regression model. However if this factor was taken out of the regression model similar independent significance for maternal asthma, food allergy and atopy at 4-years were observed whilst parental smoking at 4-years still showed a reduced risk for *current eczema*. The only differences were that rhinitis at 4-years no longer showed independent significance whereas paternal eczema did. In the final regression model for *eczema ever* sibling eczema, paternal eczema, diagnosed asthma at 1-year, rhinitis at 2-years and food allergy at 4-years were all independently associated with *eczema ever*. Parental smoking at birth was independently associated with

lower risk of *eczema ever* (Table 11.3). Social Class at Birth was not included in this latter model, as it did not show significance at univariate analysis.

Table 11.2: Univariate risk analysis for *eczema ever* (p <0.2)

Factor	P-Value	OR	95% CI
Atopic SPT 4yr	0.005*	1.58	1.15-2.19
Atopic SPT 10yr	0.018*	1.40	1.06-1.84
Asthma 1yr	<0.001*	2.19	1.50-3.20
Food Allergy 1yr	<0.001*	2.74	1.71-4.41
Rhinitis 1yr	0.002*	1.83	1.25-2.69
Asthma 2yr	0.026*	1.52	1.05-2.21
Rhinitis 2yr	0.004*	1.75	1.19-2.59
Food Allergy 2yr	0.003*	3.04	1.43-6.49
Asthma 4yr	<0.001*	2.17	1.56-3.00
Rhinitis 4yr	<0.003*	2.16	1.29-3.63
Food Allergy 4yr	<0.001*	6.71	2.76-16.33
Urticaria 4yr	0.022* †	5.52	0.38-0.72
Maternal Asthma	0.002*	1.55	1.17-2.06
Sibling Asthma	0.009*	1.37	1.08-1.73
Maternal Eczema	<0.001*	1.72	1.29-2.30
Paternal Eczema	<0.001*	2.11	1.40-3.17
Sibling Eczema	<0.001*	2.01	1.58-2.54
Maternal Urticaria	0.006*	1.79	1.18-2.71
Maternal Food Allergy	0.012*	1.83	1.14-2.96
Sibling Food Allergy	0.002*	1.67	1.20-2.33
Paternal Asthma	0.065	1.34	0.98-1.84
Paternal Rhinitis	0.135	1.25	0.93-1.68
Sibling Rhinitis	0.135	1.23	0.94-1.62
Paternal Urticaria	0.136	1.92	0.80-4.59
Sibling Urticaria	0.061	1.39	0.98-1.97
Exc. Formula Fed 1st 3/12	0.085	0.82	0.65-1.03
Parental Smoking Birth	0.002*	0.70	0.56-0.88
Parental Smoking 2yr	0.022*	0.75	0.59-0.96
Parental Smoking 4yr	0.077	0.80	0.63-1.02

Parental Smoking 10yr	0.002*	0.69	0.55-0.87
Recurrent Chest Infections 1yr	0.022*	1.64	1.07-2.51
Recurrent Chest Infections 2yr	0.002*	1.72	1.21-2.44
Cat 10yr	0.135	0.85	0.68-1.05
Large Family 10yr	0.010*	1.33	1.07-1.65

Notes: Results are Odds ratios (OR) and their 95% Confidence Intervals (95% CI).

† Fishers Exact Test

* Statistically Significant ($p<0.05$)

Table 11.3: Multivariate analysis of early life risk factors for *current eczema* and *eczema ever* at 10-years

	Risk factor	P-value	OR	95% CI
Current Eczema	Atopic SPT at 4yr	0.013	2.300	1.195-4.426
	Rhinitis at 4yr	0.038	2.673	1.056-6.769
	Food allergy at 4yr	0.010	4.336	1.411-13.331
	Maternal asthma	0.034	2.157	1.061-4.383
	Parental smoking at 4yr	0.020	0.430	0.211-0.877
Eczema Ever	Asthma at 1yr	0.015	1.961	1.139-3.379
	Rhinitis at 2yr	0.018	1.813	1.109-2.963
	Food allergy at 4yr	0.001	8.612	2.330-28.594
	Sibling eczema	<0.001	1.855	1.345-2.559
	Paternal eczema	0.020	1.916	1.108-3.313
	Parental smoking at birth	0.012	0.673	0.494-0.917

Notes:

Results presented are adjusted Odds Ratios (OR) and their 95% Confidence Intervals (95%CI). Only factors that showed a significant effect at the final step of each regression model are shown. Early life risk factors for current eczema and eczema ever in each case refer to comparison with children who did not have that condition. Social Class at birth was included in the model for current eczema but not for eczema ever shown here.

In Chapter 10 we identified a significant degree of persistent eczema during the first decade of life amongst a subgroup of 132 children with diagnosed eczema at 4-years who were followed up again at 10-years. Little is known about factors influencing such disease persistence. Univariate testing showed significantly increased risk of persistent disease with diagnosed food allergy at 4-years ($p = 0.01$; OR = 4.65; 95%CI = 1.27-16.97). Rhinitis at 4-

years marginally failed to show similar significance at univariate analysis (p = 0.05; OR = 3.08; 95%CI = 0.95-9.95). However at multivariate testing diagnosed rhinitis at 4-years (p = 0.04; OR = 5.25; 95%CI = 1.07-25.67) emerged as being independently significant for persistence of eczema from 4 to 10-years.

11.3 DISCUSSION

Risk factor analysis for both *current eczema* at 10-years and *eczema ever* identified strong independent associations with early life allergic disorders and atopic sensitisation. Family history of allergic conditions, especially eczema and asthma, were also significantly higher in the presence of *current eczema* or *eczema ever*. Indeed maternal asthma emerged as an independent predictor for *current eczema*. Interestingly family history of eczema itself emerged as a strong independent risk factor in the case of *eczema ever* but not *current eczema*. In this regard paternal eczema showed a stronger effect than maternal disease for *eczema ever* – an opposite finding [75] to that which might be expected. The apparent differences in patterns of risk factor for these two definitions of disease may reflect the fact that only one third of children with *eczema ever* still had *current eczema* at 10-years (see **10.3**). Thus slightly different risk factors may be relevant to the initial development of eczema as compared to the continuing presence of the condition in later childhood. In this context, we also found that a wider range of early life allergic conditions showed independent significance for *eczema ever* than *current eczema*. Therefore allergic co-morbidity in early life may be more important for symptom expression of eczema at that time than it is for symptom presence in later childhood. Our analysis of a subgroup with persistent eczema from age 4 to 10-years yields further insight into this matter. Persistent disease was independently associated with diagnosed rhinitis at 4-years. Therefore whether aeroallergen sensitisation in later childhood not only leads to respiratory allergy but also perpetuates pre-existing allergic disease such as eczema remains to be seen. In this context it is also worth noting that both house dust mite and cat allergen sensitisation in infancy demonstrated significant associations with subsequent *current eczema* at 10-years (see **10.3**).

Environmental factors in early life did not emerge as strong independent predictors of disease for either definition of eczema. The apparent protective effects of smoking and to a

lesser extent formula feeding were probably results of confounding by higher social class at birth, since this did show trends for significance as a risk factor and would have been associated with lower prevalence of both smoking and formula feeding. Nevertheless, parental smoking at 4-years still showed independent significance for reduced *current eczema* at multivariate analysis. The same was true for parental smoking at birth and reduced risk of *eczema ever*. The reasons for this persisting protective effect of smoking at regression analysis are not clear. We did not find a significant effect for pet ownership at any stage of childhood upon *current eczema* or *eczema ever*. Dog ownership at 10-years showed a non-significant trend for increased risk but conversely cat ownership showed a similar non-significant effect in the opposite direction. If viewed in the light of the 'hygiene hypothesis'[156] this relationship with cat ownership might be viewed as showing some form of protective effect against *current eczema*. However it could also reflect that parents of eczematous children had banished cats from the household as a measure of allergen avoidance. Some [158] have shown that large family size is inversely related to allergic sensitisation and thus it might be expected that *current eczema/eczema ever* were lower in children with large sibships. We did not confirm this pattern at 10-years for *current eczema* and indeed showed the opposite effect for *eczema ever*.

In summary, we have identified that both family and personal history of allergy during early childhood appear to be highly significant for the presence of eczema both at any point in childhood and specifically at 10-years of age. This was especially so in the case of *eczema ever*. However we failed to detect evidence for significant associations between development of childhood eczema and early life environmental factors. This suggests that the contribution of such factors towards development of childhood eczema is not as great as the influence of a genetic predisposition towards atopy and eczema.

CHAPTER 12

RISK FACTORS FOR RHINITIS IN 10-YEAR OLD SCHOOLCHILDREN

In recent years a high prevalence of childhood rhinitis has been described in many populations [23,47,58]. Particularly high frequencies have often been found in affluent westernized societies [23,38,47,58,171]. For instance presence of rhino-conjunctivitis symptoms in 20% [47] of 12-14 year olds has been described for children in the UK, Australia and the USA. In Chapter 10 we confirmed that these patterns existed within our own 10-year population. The reasons for such trends remain to be elucidated but are likely to reflect an interaction of genetic and environmental influences [208]. Thus allergic family histories, heavy maternal cigarette smoking in the first year of life and co-existent asthma have all been implicated [23,24]. Better understanding of these risk factors has the potential to alleviate substantial disease morbidity in childhood. In this chapter early life risk factors for *hay fever ever* and *current rhinitis* at 10-years are described.

12.1 ANALYSIS

Univariate risk analysis for rhinitis was done using chi-square analysis (with Fishers exact test where indicated). Backward stepwise (likelihood ratio) logistic regression analysis was used to assess the independent effect of risk factors with $p<0.2$ at univariate testing. To provide information useful in early life for determining subsequent presence of rhinitis at 10-years, selection was restricted in each model to factors obtained from the first 4-years of life. Where more than one factor explained the same exposure the most relevant was chosen for inclusion in the regression model. Results were expressed as adjusted odds ratios (OR) with their 95% confidence intervals (CI).

12.2 RESULTS

Risk factors showing trends for significance ($p<0.2$) at univariate analysis with regard to *current rhinitis* development at 10-years are given in Table 12.1. Diagnosed allergic conditions at 1-year (eczema, food allergy), 2-years (eczema), 4-years (asthma, eczema, rhinitis) and 10-years (eczema, asthma, urticaria) as well as positive SPT at 4 and 10-years all demonstrated statistical significance at univariate analysis. Maternal, paternal and to a lesser extent sibling rhinitis ($p = 0.050$) also showed significant effect along with paternal asthma and food allergy, maternal urticaria and sibling eczema and urticaria. Higher social class at birth was also a significant risk factor for *current rhinitis*. By contrast, some factors showed a significantly reduced univariate risk for *current rhinitis* including large family size at 10-years (more than 2 children) and parental smoking at birth and 1-year. Similar statistically non-significant trends for reduced risk of *current rhinitis* were observed for cat ownership at 10-years and parental smoking at 10-years. The apparent protective effect of smoking observed here in early life probably reflects the confounding effect of *high social class* at birth as a risk factor for *current rhinitis*. Previously in this cohort [117] it was found that the higher social classes smoked less, a trend still shown at 10-years (see **4.9**).

If *current nasal symptoms* was used as the outcome variable a very similar pattern of risk factors was noted at univariate analysis (results not presented). If *hay fever ever* was analyzed in this way, again similar patterns were shown although a stronger effect of social class was observed along with a significantly lower risk of *hay fever ever* with cat ownership at 1-year (Table 12.2).

In order to obtain the independent effect of risk factors for *current rhinitis* or *hay fever ever*, logistic regression models were created using all factors that showed $p<0.2$ at univariate analysis. Cord IgE did not show a significant effect for *current rhinitis*, (median 0.1 v 0.1, $p = 0.420$ [*Mann-Whitney U Test*]) and was not included in any models. Rhinitis diagnosis at 4-years was not included as a risk factor in the final model – analysis including this factor showed it to be a significant independent risk factor for *current rhinitis* at 10-years ($p = 0.002$, OR = 3.88, 95%CI = 1.65-9.13). In the final model for *current rhinitis* maternal and paternal rhinitis, sibling eczema, presence of diagnosed asthma at 4-years and positive SPT at 4-years were all independently associated with *current rhinitis* at 10-years

(Table 12.3). Unfortunately Social Class information at birth was available in only 685 children. Thus inclusion of this factor in the regression model led to a smaller model size. However, exclusion of this factor from the regression model still showed similar independent significance for maternal / paternal rhinitis and atopic sensitisation at 4-years. With exclusion of Social Class at birth, eczema at 4-years rather than asthma at 4-years also showed independent significance.

Multivariate analysis for *hay fever ever* found independent significance for paternal asthma, maternal and paternal rhinitis, sibling eczema, presence of diagnosed food allergy at 4-years and positive SPT at 4-years (Table 12.3). Again if Social Class at birth was excluded from the regression model, similar independent significance for maternal / paternal rhinitis, sibling eczema and atopy at 4-years were seen. However in this latter model, rather than food allergy at 4-years, eczema at that age also showed independent significance as did sibling urticaria.

Table 12.1: Univariate analysis for *current rhinitis* at 10yrs (p <0.2)

Factor	P-Value	OR	95%CI
Atopic SPT 4yr	<0.001*	4.78	3.30-6.39
Atopic SPT 10yr	<0.001*	6.39	4.53-9.01
Eczema 1yr	0.001*	2.12	1.37-3.28
Food Allergy 1yr	0.047*	1.74	1.00-3.01
Eczema 2yr	0.001*	2.08	1.33-3.25
Asthma 4yr	<0.001*	2.43	1.66-3.55
Eczema 4yr	<0.001*	3.11	2.07-4.66
Rhinitis 4yr	<0.001*	4.05	2.36-6.99
Food Allergy 4yr	0.002*	3.00	1.46-6.18
Current Eczema 10yr	<0.001*	2.17	1.50-3.14
Current Asthma 10yr	<0.001*	5.12	3.60-7.29
Current Urticaria 10yr	0.014*	1.76	1.11-2.78
Paternal Asthma	0.008*	1.69	1.14-2.50
Sibling Eczema	0.016*	1.47	1.07-2.02
Maternal Rhinitis	0.002*	1.70	1.22-2.37
Paternal Rhinitis	<0.001*	3.13	2.22-4.43
Maternal Urticaria	0.004*	2.04	1.24-3.35
Paternal Urticaria	0.020* †	3.18	1.25-8.08
Sibling Urticaria	0.006*	1.80	1.18-2.78
Paternal Food Allergy	0.023*	2.77	1.18-6.51
Maternal Food Allergy	0.191	1.50	0.82-2.75
Social Class I-III at Birth	0.018*	1.62	1.08-2.42
Parental Smoking Birth	0.010*	0.66	0.49-0.91
Parental Smoking 1yr	0.014*	0.66	0.48-0.92
Parental Smoking 10yr	0.104	0.76	0.55-1.06
Cat 10yr	0.081	0.76	0.56-1.04
Large Family 10yr	0.003*	0.64	0.47-0.86

Notes: Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).

† Fishers exact test.

* Statistically significant (p<0.05).

Table 12.2: Univariate analysis for *hay fever ever* (p <0.2)

Factor	P-Value	OR	95%CI
Atopic SPT 4yr	<0.001*	5.28	3.70-7.53
Atopic SPT 10yr	<0.001*	6.79	4.90-9.42
Eczema 1yr	<0.001*	2.10	1.39-3.18
Food Allergy 1yr	0.002*	2.19	1.33-3.59
Eczema 2yr	0.005*	1.83	1.19-2.83
Asthma 4yr	<0.001*	2.53	1.78-3.60
Eczema 4yr	<0.001*	3.40	2.32-4.99
Food Allergy 4yr	<0.001*	3.40	1.70-6.81
Paternal Asthma	<0.001*	1.95	1.36-2.78
Sibling Eczema	<0.001*	1.69	1.27-2.25
Maternal Rhinitis	<0.001*	1.82	1.35-2.46
Paternal Rhinitis	<0.001*	2.95	2.13-4.08
Sibling Rhinitis	0.001*	1.69	1.22-2.34
Maternal Urticaria	<0.001*	2.34	1.50-3.67
Paternal Urticaria	0.008* †	3.40	1.42-8.16
Sibling Urticaria	<0.001*	2.23	1.52-3.27
Paternal Food Allergy	0.034*	2.53	1.11-5.80
Maternal Eczema	0.107	1.34	0.94-1.90
Paternal Eczema	0.065	1.55	0.97-2.48
Sibling Asthma	0.083	1.29	0.97-1.73
Sibling Food Allergy	0.141	1.35	0.91-2.02
Social Class I-III at Birth	0.009*	1.63	1.13-2.34
Excl. Formula Fed 1st 3/12	0.064	0.75	0.55-1.02
Parental Smoking Birth	0.006*	0.67	0.51-0.89
Parental Smoking 1yr	0.004*	0.64	0.47-0.87
Parental Smoking 10yr	0.053	0.75	0.55-1.00
Cat Birth	0.051	0.74	0.55-1.00
Cat 1yr	0.022*	0.68	0.49-0.95
Cat 10yr	0.084	0.78	0.60-1.03
Large Family 10yr	0.021*	0.72	0.55-0.95

Notes: Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).

† Fishers exact test.

* Statistically significant (p<0.05)

Table 12.3: Multivariate analysis of early life risk factors for *hay fever ever* and *current rhinitis*

	Risk factor	P-value	OR	95% CI
Hay fever ever	Atopic SPT at 4yr	<0.001	5.32	2.99-9.47
	Food allergy at 4yr	0.038	3.31	1.07-10.22
	Paternal asthma	0.012	2.47	1.22-5.02
	Maternal rhinitis	<0.001	2.94	1.64-5.26
	Paternal rhinitis	0.004	2.56	1.34-4.88
	Sibling eczema	0.002	2.53	1.41-4.52
Current Rhinitis	Atopic SPT at 4yr	<0.001	4.05	2.25-7.32
	Asthma at 4yr	0.040	1.98	1.03-3.79
	Sibling eczema	0.047	1.80	1.01-3.23
	Maternal rhinitis	0.029	1.94	1.07-3.50
	Paternal rhinitis	0.001	2.75	1.48-5.14

Notes: Results presented are adjusted Odds Ratios (OR) and their 95% Confidence Intervals (95%CI). Only factors that showed a significant effect at the final step of each regression model are shown. Risk factors for current rhinitis and hay fever ever in each case refer to comparison with children who did not have that condition. Models presented include Social Class at Birth.

12.3 DISCUSSION

In the search to identify risk factors for rhinitis we have identified a strong association between childhood rhinitis and atopy during the early years of life. Atopic sensitisation at 4-years emerged as an independently significant risk factor for both *current rhinitis* and *hay fever ever*. Univariate analysis also revealed that both eczema and food allergy in infancy were significantly associated with increased risk of *current rhinitis* and *hay fever ever*. In the case of *hay fever ever*, diagnosed food allergy at 4-years of age also showed independent significance as a risk factor. Therefore these findings provide substantial support for the notion of an allergic march [15,16,29] in childhood progressing from food related allergy in the early years to aero-allergen related disease in later childhood. The close relationship between childhood asthma and rhinitis was also illustrated by the fact that having an asthma diagnosis at 4-years was an independent predictor of *current rhinitis* at 10-years. This finding mirrors those of Wright et al [23] for physician diagnosed rhinitis at 6-years of age in the Tucson study. That slight differences were observed in the independent significance of early life allergic disorders for *current rhinitis* and *hay fever ever* may reflect the fact that not all children with *hay fever ever* also had *current rhinitis*. Thus somewhat different risk factors may operate for rhinitis occurring in earlier life than at 10-years.

Family history of allergic conditions emerged as very significant risk factors for childhood rhinitis. This was particularly so for family history of rhinitis where paternal rhinitis emerged as a very strong independent predictor in the case of *current rhinitis*. However, history of other allergic diseases also had an important influence as demonstrated by the fact that sibling eczema showed independent significance for both *current rhinitis* and *hay fever ever*. In the case of *hay fever ever*, paternal asthma also showed independent significance. It is interesting that paternal asthma and rhinitis demonstrated such a strong independent effect for rhinitis in our study. It has been previously shown that maternal disease may confer a greater risk of hay fever and atopy in general in the offspring [69]. Thus our findings add further insight into existing evidence that personal allergy in early life [117] and allergic family history [23,24,69,75] are crucial components for the presence of rhinitis in later childhood.

Importantly this study also shows that children with rhinitis during early life are at risk of symptom persistence as highlighted by the fact that if diagnosis of rhinitis at 4-years was introduced into regression analysis it then emerged as a strong independent predictor for still having that condition at 10.

Contrary to the findings of Wright et al [23] we found no evidence of a link between parental smoking in early life and subsequent rhinitis. We found that higher Social Class at birth was a very significant risk factor at univariate analysis for both *current rhinitis* and *hay fever ever*. This may explain the apparent reduced risk of rhinitis with parental smoking in early life found at univariate analysis since smokers were more likely to come from a lower Social Class [117]. Thus strong interactions with Social Class might explain why we failed to show any enhanced risk with parental smoking.

Much interest in recent years has surrounded the concept of the hygiene hypothesis [156] in allergy development. Thus it has been found that children raised in a rural farming environment [144,145] with regular contact with animals have less hay fever and atopy in general. Family size [158] may play a role in this effect since the larger the family the greater the risk of shared infections and consequent immune deviation away from the atopy driving TH_2 mechanisms to TH_1 mechanisms instead. In this context we found that large family size at 10-years (more than 2 siblings) was a significant protective factor at univariate analysis for *current rhinitis*. However we have shown that at 10-years, lower Social Classes have larger family size (see **4.6**) and thus it is likely that this finding may be heavily confounded by the effect of Social Class. Certainly large family size did not retain an effect in multivariate analysis. Frequent animal contact may also increase the risk of infections and immune deviation away from the atopic phenotype. Interestingly we found that cat ownership at one year was associated with significant reduction of *hay fever ever* at univariate analysis with similar non-significant trends observed at birth and 10-years. However this significance did not remain at multivariate analysis. Social Class did not show a significant interaction with cat ownership in our study and therefore would not have acted as a confounding factor in these results. Whilst the protective role of cat exposure may be speculative we certainly found no evidence to support a hypothesis that domestic pet exposure was associated with an increased risk of childhood rhinitis. Our results may indicate some protection against rhinitis development with pet exposure although an

alternative explanation might be the deliberate removal of a potential allergen from households with a known strong family history of allergy. In our study families with a negative family history of allergy did not show significantly reduced cat (43.8% v 45.3%; p = 0.658) or dog ownership (34.9% v 40.0%; p = 0.128) compared to those with a positive family history. In some cases, though, such as family history of rhinitis there was a significant reduction in pet ownership amongst affected families. Thus dog ownership was found in significantly fewer families with a positive family history of rhinitis (36.2% v 41.7%; p = 0.038). Thus allergen avoidance may in some circumstances have played a part in our findings relating pet ownership and rhinitis development.

In summary, this chapter demonstrates that both family and personal history of allergy in early childhood are significant risk factors for rhinitis at 10-years of age and indeed for rhinitis at any point during the first decade of life. Furthermore we again could not demonstrate a significant independent effect for common environmental risk factors suggesting that genetic predisposition to atopy and rhinitis may ultimately be more important for determining development of childhood rhinitis.

CHAPTER 13

RISK FACTORS FOR THE PRESENCE OF ASTHMA IN TEN YEAR OLD CHILDREN

The reasons for the recent increasing prevalence of asthma have yet to be conclusively demonstrated, although both genetic and environmental factors have been implicated [64]. Family histories of allergy and asthma have shown significant risk for developing childhood asthma [69,112,197]. Whilst the scope of modifying genetic risk factors is still limited much attention has focussed on possible environmental risk factors that might be amenable to intervention strategies. Close links between childhood asthma and atopy [112] have been shown. This has led to attempts at allergen avoidance to modify disease development [91]. Increased risk of asthma with cigarette smoke exposure [112,122,197] has been observed. Conversely, breastfeeding [116] has been shown to be protective against asthma development in some studies. The evolving concept of a hygiene hypothesis [156] for allergy development has led to findings that large family size [158], rural living [144,145], anthroposophic lifestyle [142] and close animal contact [202] may offer protection against allergy and asthma development. Attempts to clarify risk factors for childhood asthma remain an important area of ongoing research.

A consistent difficulty in studies of childhood asthma has been a lack of standardised definitions for this condition. The use of symptomatic bronchial hyper-responsiveness to define *current asthma* has been increasingly used as the gold standard [41,104] in epidemiological surveys. In Chapter 9 the prevalence of such *current asthma*, along with ISAAC questionnaire defined *current wheeze* and a questionnaire-derived definition of *Currently Diagnosed Asthma* was examined. In this chapter we report early life risk factors for these states in 10-year old children.

13.1 ANALYSIS

Univariate risk factor analysis for *current wheeze, current asthma* and *CDA* was performed separately in comparison to children who did not have that respective state. Chi-square analysis (with Fishers exact test where indicated by low expected cell counts) was used for

this purpose. To obtain the independent effect of risk factors showing trends for significance ($p<0.2$), logistic regression models were created for each outcome variable. Stepwise backward (likelihood ratio) logistic regression was used for this purpose. In order to identify factors of relevance for identifying these states during early life only factors obtained in the first 4-years of life were included in this multivariate analysis. Prior asthma diagnoses were excluded from the models.

13.2 RISK FACTORS FOR *CURRENT WHEEZE* AT 10-YEARS

Risk factors showing trends for significance at univariate analysis ($p<0.2$) for *current wheeze* development are shown in Table 13.1. Thus significantly increased risk of having *current wheeze* was conferred by male gender, allergic disease at 1-year (eczema, asthma, food allergy), 2-years (eczema, asthma), 4-years (eczema, asthma, rhinitis, food allergy) and 10-years (eczema, rhinitis, urticaria). Atopic sensitisation at 4 and 10-years both gave increased risk of *current wheeze*. Recurrent chest infections at 1 and 2-years also conferred increased risk of *current wheeze*. Statistically non-significant trends for increased risk were found with rhinitis and food allergy at 2-years.

Maternal, paternal and sibling asthma all showed significant univariate risk for *current wheeze* along with maternal urticaria. Non-significant trends for increased *current wheeze* were also seen with paternal eczema, maternal rhinitis, paternal rhinitis, sibling urticaria and maternal food allergy.

Parental smoking at 4-years was associated with significant increased univariate risk of *current wheeze*. Similar but statistically non-significant effects for smoking at 1-year, 2-years and 10-years were found.

Exclusive formula feeding in the first 3 months of life carried a significant risk for *current wheeze*. A non-significant trend for increased risk of current wheeze was found with low birth weight. Neither Social Class at birth ($p = 0.656$) nor 10-years ($p = 0.389$) showed any associations with *current wheeze*.

Table 13.1: Univariate risk analysis for *current wheezing* at 10-years (p<0.2)

Factor	P-Value	OR	95% CI
Atopic at 4yr SPT	<0.001*	4.38	3.07-6.25
Atopic at 10yr SPT	<0.001*	4.42	3.22-6.08
Eczema 1yr	<0.001*	3.04	2.05-4.51
Asthma 1yr	<0.001*	2.71	1.82-4.06
Food Allergy 1yr	0.001*	2.21	1.35-3.61
Eczema 2yr	<0.001*	2.08	1.37-3.17
Asthma 2yr	<0.001*	4.03	2.73-5.97
Rhinitis at 2yr	0.101	1.46	0.93-2.30
Food Allergy at 2yr	0.069	2.00	0.93-4.29
Eczema 4yr	<0.001*	3.04	2.06-4.47
Asthma 4yr	<0.001*	8.60	6.04-12.22
Rhinitis 4yr	<0.001*	3.72	2.21-6.27
Food Allergy 4yr	0.004*	2.72	1.34-5.51
Eczema 10yr	<0.001*	2.29	1.62-3.23
Rhinitis 10yr	<0.001*	4.37	3.17-6.03
Urticaria 10yr	0.001*	1.98	1.30-3.02
Maternal Asthma	<0.001*	2.06	1.49-2.85
Paternal Asthma	0.017*	1.56	1.08-2.24
Sibling Asthma	0.001*	1.60	1.20-2.12
Maternal Urticaria	0.048*	1.60	1.00-2.57
Paternal Eczema	0.058	1.07	0.75-1.54
Maternal Rhinitis	0.085	1.31	0.96-1.78
Paternal Rhinitis	0.149	1.30	0.91-1.85
Sibling Urticaria	0.061	1.47	0.98-2.20
Maternal Food Allergy	0.198	1.43	0.83-2.49
Male Gender	0.015*	1.40	1.07-1.85
Exclusive Formula Feeding	0.021*	1.41	1.05-1.88
Parental Smoking at 1yr	0.069	1.30	0.98-1.73
Parental Smoking at 2yr	0.159	1.24	0.92-1.68
Parental Smoking at 4yr	0.004*	1.54	1.15-2.07
Parental Smoking at 10yr	0.054	1.33	0.99-1.77

Recurrent Chest Infections 1yr	<0.001*	2.37	1.50-3.75
Recurrent Chest Infections 2yr	<0.001*	3.11	2.14-4.53
Cat at Birth	0.041*	0.73	0.54-0.99
Cat at 1yr	0.154	0.79	0.58-1.09
Dog at 10yr	0.048*	1.32	1.00-1.73
Low Birth weight	0.164	1.56	0.83-2.91

Notes: Only factors showing trends for significance ($p<0.2$) are given. Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).
* Statistical significance.

A significant reduction in risk of *current wheeze* was found with cat ownership at birth. A similar but statistically non-significant trend was also observed with cat ownership at 1-year. The only association with dog ownership was found at 10-years with significant increased risk of current wheeze.

Cord IgE did not vary significantly with presence of *current wheeze* (median 0.1 v 0.1, $p = 0.257$ [*Mann Whitney U Test*]).

Logistic regression analysis using significant univariate early life risk factors showed that maternal and paternal asthma, recurrent chest infections at 2-years, atopic sensitisation at 4-years, parental smoking at 4-years and eczema at 4-years were all independently significant for current wheeze (Table 13.4). Inclusion of 10-year data in the model showed additional independent significance for atopic sensitisation and current rhinitis at 10-years.

13.3 RISK FACTORS FOR *CURRENT ASTHMA*

Risk factors displaying significant trends for *current asthma* development at univariate analysis ($p<0.2$) are shown in Table 13.2. Personal history of allergy at 1-year (eczema, asthma), 2-years (eczema, asthma), 4-years (eczema, asthma, rhinitis, food allergy) and 10-years (eczema, urticaria, rhinitis) all demonstrated significantly increased univariate risk for *current asthma*. Atopic sensitisation at 4 and 10-years also gave significantly increased univariate risk of *current asthma*. Statistically non-significant trends for increased *current asthma* were seen with recurrent chest infections at 1 and 2-years as well as food allergy at 2-years and urticaria at 4-years.

Maternal and sibling asthma significantly increased *current asthma* risk. Statistically non-significant trends for increased risk were found for sibling eczema, paternal asthma, maternal rhinitis, paternal rhinitis, sibling rhinitis, maternal urticaria, and sibling urticaria.

Cord IgE did not vary significantly with presence of *current asthma* (median 0.1 v 0.1, $p = 0.397$ [*Mann Whitney U Test*]).

Statistically non-significant trends for higher *current asthma* with male gender and exclusive formula feeding were also noted. Cat ownership at birth showed a non-significant effect for reduced *current asthma*. Dog ownership at 10-years, however, showed a marginally non-significant increased risk.

Parental smoking at birth and 4-years demonstrated statistically non-significant trends for increased risk of *current asthma.*

Multivariate analysis using significant univariate early life risk factors found independent significance for atopic sensitisation at 4-years and maternal asthma (Table 13.4). If 10-year data was included in the model, current rhinitis and atopic sensitisation at 10-years also showed independent significance.

Table 13.2: Univariate risk analysis for *current asthma* (p<0.2)

Factor	P-Value	OR	95% CI
Atopic SPT at 4yr	<0.001*	9.27	5.80-14.81
Atopic SPT at 10yr	<0.001*	9.93	6.34-15.54
Eczema at 1yr	<0.001*	2.70	1.62-4.51
Asthma at 1yr	0.006*	2.13	1.23-3.69
Eczema at 2yr	0.028*	1.86	1.06-3.26
Asthma at 2yr	0.021*	1.92	1.09-3.37
Food Allergy at 2yr	0.050†	2.56	1.02-6.39
Eczema at 4yr	<0.001*	2.88	1.74-4.76
Asthma at 4yr	<0.001*	6.12	3.92-9.54
Rhinitis at 4yr	<0.001*	4.07	2.17-7.63
Food Allergy at 4yr	0.001 *†	4.29	1.93-9.55
Urticaria at 4yr	0.054	4.42	1.12-17.35
Eczema at 10yr	<0.001*	3.54	2.30-5.44
Urticaria at 10yr	0.004*	2.20	1.27-3.79
Rhinitis at 10yr	<0.001*	5.36	3.55-8.09
Maternal Asthma	<0.001*	2.23	1.45-3.43
Sibling Asthma	0.013*	1.65	1.11-2.45
Sibling Eczema	0.146	1.35	0.90-2.01
Paternal Asthma	0.070	1.58	0.96-2.59
Maternal Rhinitis	0.073	1.47	0.96-2.24
Paternal Rhinitis	0.066	1.55	0.97-2.49
Sibling Rhinitis	0.062	1.53	0.98-2.39
Maternal Urticaria	0.119	1.66	0.87-3.15
Sibling Urticaria	0.065	1.65	0.96-2.83
Male Gender	0.107	1.38	0.93-2.03
Exclusive Formula Feeding 1st 3/12	0.109	1.40	0.93-2.12
Parental Smoking at Birth	0.184	1.30	0.88-1.92
Parental Smoking at 4yr	0.137	1.36	0.90-2.06
Recurrent Chest Infections at 1yr	0.153	1.62	0.83-3.16
Recurrent Chest Infections at 2yr	0.196	1.45	0.82-2.57
Cat at Birth	0.149	0.73	0.47-1.12
Dog at 10yr	0.051	1.47	1.00-2.16

Table 13.2 Notes: Only factors showing trends for significance (p<0.2) are shown. Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).
† Fishers exact test.
* Statistical significance.

13.4 RISK FACTORS FOR *CURRENTLY DIAGNOSED ASTHMA (CDA)*

Risk factors displaying significant trends for *currently diagnosed asthma* development at univariate analysis (p<0.2) are shown in Table 13.3. Male gender conferred significantly increased univariate risk for *CDA*. Personal history of allergy at 1-year (asthma, eczema, food allergy), 2-years (asthma, eczema, food allergy), 4-years (asthma, eczema, rhinitis, food allergy), and 10-years (eczema, rhinitis) all showed similar significance for *CDA*. Atopic sensitisation at 4 and 10-years carried strong univariate risk for *CDA*. Recurrent chest infections at 1 and 2-years also showed significance. Urticaria at 10-years showed a statistically non-significant trend for increased risk.

Maternal and sibling asthma, as well as paternal eczema significantly increased risk of *CDA*. Statistically non-significant trends for increased risk were also identified for paternal asthma, maternal eczema, maternal rhinitis, maternal urticaria, sibling urticaria, and sibling food allergy. Cord IgE showed a non-significant trend for higher values in *CDA* (median 0.1 v 0.1, p = 0.064 [*Mann Whitney U Test*]).

Social Class at birth (p = 0.889) or 10-years (p = 0.222) showed no association with *CDA*. A non-significant trend for increased *CDA* with formula feeding was found whilst exclusive breastfeeding demonstrated a non-significant protective effect. Low birth weight showed a non-significant trend for increased *CDA*. Meanwhile *only child status* at 10-years showed a marginally statistically non-significant effect for increased risk of *CDA*.

Parental smoking at 1 and 4-years showed significantly increased univariate risk for *CDA*. Statistically non-significant trends for increased risk were also found with smoking at 10-years.

Table 13.3: Univariate risk analysis for *currently diagnosed asthma (CDA)* (p<0.2)

Factor	P-Value	OR	95% CI
Atopic SPT 4yr	<0.001*	6.96	4.67-10.37
Atopic SPT 10yr	<0.001*	6.55	4.50-9.55
Asthma 1yr	<0.001*	3.18	2.05-4.92
Eczema 1yr	<0.001*	3.99	2.61-6.11
Food Allergy 1yr	<0.001*	3.04	1.80-5.13
Asthma 2yr	<0.001*	4.78	3.12-7.33
Eczema 2yr	<0.001*	2.60	1.64-4.13
Food Allergy 2yr	0.011 *†	2.94	1.33-6.49
Asthma 4yr	<0.001*	12.67	8.60-18.66
Eczema 4yr	<0.001*	3.93	2.59-5.96
Rhinitis 4yr	<0.001*	5.87	3.45-10.01
Food Allergy 4yr	0.003 *†	3.36	1.60-7.05
Current Eczema 10yr	<0.001*	2.34	1.59-3.45
Current Rhinitis 10yr	<0.001*	5.12	3.60-7.29
Current Urticaria 10yr	0.079	1.56	0.95-2.58
Maternal Asthma	<0.001*	2.16	1.50-3.12
Sibling Asthma	0.001*	1.70	1.22-2.36
Paternal Eczema	0.021*	1.81	1.09-3.01
Paternal Asthma	0.096	1.43	0.94-2.19
Maternal Eczema	0.163	1.33	0.89-1.99
Maternal Rhinitis	0.053	1.42	0.99-2.01
Maternal Urticaria	0.177	1.46	0.84-2.53
Sibling Urticaria	0.106	1.46	0.92-2.33
Sibling Food Allergy	0.088	1.48	0.94-2.32
Gender	0.008*	1.54	1.12-2.13
Exclusively Breast Fed 1st 3/12	0.067	0.70	0.48-1.03
Exclusively Formula Fed 1st 3/12	0.076	1.36	0.98-1.92
Parental Smoking 1yr	0.046*	1.41	1.01-1.97
Parental Smoking 4yr	0.015*	1.53	1.08-2.15
Parental Smoking 10yr	0.070	1.37	0.97-1.92
Chest Infections 1yr	<0.001*	2.60	1.57-4.32
Chest Infections 2yr	<0.001*	3.41	2.24-5.18
Dog at 10yr	0.158	1.26	0.91-1.73

Only Child 10yr	0.068	1.54	0.97-2.45
Low Birth weight	0.151	1.67	0.82-3.41

Notes: Only factors showing trends for significance ($p<0.2$) are given. Results are Odds Ratios (OR) and their 95% Confidence Intervals (95% CI).
† Fishers exact test.
* Statistical significance

The only association with pet exposure for *CDA* was with dog ownership at 10-years which showed a statistically non-significant trend for increased risk.

Multivariate analysis purely employing early life risk factors showed independent significance for maternal/paternal/sibling asthma, recurrent chest infections at 1 and 2-years, eczema at 4-years, atopic sensitisation at 4-years, parental smoking at 1-year and male gender (Table 13.4). If 10-year data was included in the model, independent significance was also found for atopic sensitisation, current rhinitis and dog ownership at 10-years. However this latter 'whole data' model surprisingly showed that raised cord IgE had an independent effect for reduced *CDA* at 10-years.

Table 13.4: Multivariate analysis of early life risk factors for wheezing and asthma at 10-years

	Risk Factor	P-value	OR	95%CI
Current Wheeze	Maternal asthma	0.004	2.08	1.27-3.41
	Paternal asthma	0.003	2.12	1.29-3.51
	Recurrent chest infections at 2yr	<0.001	3.98	2.36-6.70
	Atopic SPT at 4yr	<0.001	3.69	2.36-5.76
	Parental smoking at 4yr	0.006	2.18	1.25-3.81
	Eczema at 4yr	0.006	2.15	1.24-3.73
Current Asthma	Maternal asthma	0.005	2.39	1.30-4.38
	Atopic SPT at 4yr	<0.001	8.14	4.81-13.80
Currently Diagnosed Asthma (CDA)	Maternal asthma	0.011	2.26	1.20-4.24
	Paternal asthma	0.016	2.30	1.17-4.52
	Sibling asthma	0.013	2.00	1.16-3.43
	Recurrent chest infections at 1yr	0.027	2.67	1.12-6.40
	Recurrent chest infections at 2yr	<0.001	4.11	2.06-8.18
	Eczema at 4yr	<0.001	3.27	1.71-6.28
	Atopic SPT at 4yr	<0.001	7.22	4.13-12.62
	Parental smoking at 1yr	0.014	1.99	1.15-3.45
	Male gender	0.047	1.72	1.01-2.95

Notes: Only early life risk factors showing trends for significance at univariate testing were entered into the regression models. Factors showing statistical significance ($p<0.05$) at the final stage of each regression model are shown (using backward stepwise logistic regression). Results are adjusted Odds Ratios (OR) and their 95% Confidence Intervals (95% CI). Cord IgE was included in the model for CDA presented but not for Current Asthma or Current Wheeze.

13.5 DISCUSSION

In this Chapter we have reported early life risk factors for having wheezing and asthma at 10-years using prospectively collected information. In doing so we have used an ISAAC questionnaire definition of *current wheeze* and a definition of *current asthma* (using symptomatic bronchial hyper-responsiveness) that has been used in other epidemiological surveys [41,104]. We also report factors for an ISAAC questionnaire-derived definition of *currently diagnosed asthma (CDA)* that may be informative where bronchial challenge testing is not feasible.

It is clear that similar risk factors act for development of current wheeze and asthma at 10-years. Thus personal and family history of allergic disease in early life showed independent effects as risk factors. In this regard, family history of asthma emerged as highly significant. For wheezing and *CDA*, independent significance was observed for both paternal and maternal asthma. However, *current asthma*, which may represent better the core asthmatic child at 10-years showed independent significance only for maternal asthma in this regard, confirming previous findings of the importance of maternal disease for atopic conditions [75].

Eczema in early life was shown to be independently significant for *current wheeze* and *CDA*. This confirms earlier work that suggests a link between atopic eczema and subsequent allergic airways disease [14]. Atopic sensitisation at 4-years also emerged as a highly significant independent predictor for *current wheeze, CDA*, and *current asthma* at 10-years.

The strong independent effects of asthmatic family history and personal atopy and allergy in early life suggest that genetic predisposition is highly significant for the presence of wheezing or asthma at 10-years. Analysis of environmental risk factors in early life demonstrated some effects at univariate analysis but these did not tend to remain at multivariate assessment. Male gender showed univariate significance for both *current wheeze* and *CDA* but only retained independent significance for the latter state. In relying by definition upon a physician diagnosis of asthma, *CDA* may represent those more longstanding *current wheezers* and thus be more likely to bear a male preponderance. To

some extent this confirms previous results [197] showing higher risk for childhood wheezing with male gender.

Parental smoking in early life showed some significant independent risk for *current wheeze* and *CDA*. Interestingly this was not the case for those with *current asthma.*

No independently significant protective effect of breastfeeding was observed. Similarly no independently increased risk of early weaning or formula feeding was demonstrated. Thus we could not confirm recent findings from an Australian study [116] that showed such effects for asthma at 6-years of age.

Pet ownership in early life did not demonstrate any significant risk for having wheezing or asthma at 10-years. Conversely cat ownership at birth showed significant reduced univariate risk for *current wheeze*. This may be consistent with findings from other studies that such exposures may be protective [202]. However it may also suggest that such families were more likely to practice allergen avoidance because of strong allergic family histories and therefore banish such pets from the household. Indeed a non-significant trend for reduced cat ownership in families with a positive family history of asthma (42.7% v 47.4%; $p = 0.086$) was observed in our population. Interestingly dog exposure at 10-years showed a significant univariate association with *current wheeze* suggesting that timing of such exposures in life may be important for their effect as triggers for asthma.

We identified that recurrent chest infections in infancy were significant independent risk factors for *current wheeze* and *CDA*. This supports evidence from Stein [133] that respiratory pathogens such as *Respiratory Synctial Virus* may cause structural damage to bronchial epithelium and be associated with persistent childhood disease. Interestingly though, children with *current asthma* did not show significant univariate risk from such factors again suggesting that different factors may be relevant for this asthmatic categorization. This group by definition had symptomatic bronchial hyper-responsiveness (BHR). Our results therefore might be taken as evidence that chest infections in early life predispose to wheezing symptoms but not necessarily to BHR. Accordingly we showed no relationship between *Definite BHR* (PC_{20}<4 mg/ml) and chest infections at 1-year (9.5% *Definite BHR* v 8.5% *Not Definite BHR*; $p = 0.704$) and 2-years (15.4% *Definite BHR* v 16.3% *Not Definite*

BHR; p = 0.807). It is known that BHR and wheezing are not always synonymous – whether differences in pathogenesis at the structural level are responsible for this fact remains to be seen.

In many ways, our children defined as having *current wheeze* and *currently diagnosed asthma* showed very similar risk factor profiles with independent associations to parental asthma, early life eczema, atopic sensitisation at 4-years, parental smoking in early life, and recurrent chest infections in infancy. However, the incorporation of significant bronchial hyper-responsiveness into the definition (*current asthma*) produced a slightly different risk factor profile that may best predict the *core asthmatic child.* Thus for *current asthma* a predominantly atopic profile was highlighted with maternal asthma and atopic sensitisation at 4-years only retaining independent significance. This may reflect the close relationship between inheritance for atopy and bronchial hyper-responsiveness that has been shown in some studies [97]. Alternatively this discrepancy between our wheezing categorizations may reflect severity of disease with milder disease defined by symptoms alone having a broader range of risk factors whilst *current asthmatics* suffering a severer disease for which atopy is of paramount importance. It appears likely that environmental exposure such as tobacco smoke play only adjuvant roles in the state of symptomatic bronchial hyper-responsiveness. Consequently the quest to better understand asthmatic states may benefit from focussing further upon genetic aspects.

CHAPTER 14

DISCUSSION

A whole population birth cohort study is capable of providing much insight into the natural history of childhood diseases. Such studies are often fraught with difficulty – they possess considerable organisational and administrative demands, suffer high running costs not to mention the problems of subject retention over time. The 10-year follow-up of the Isle of Wight 1989 Whole Population Birth Cohort was no exception in this regard, taking place 6-years after the last contact with any participating children. However our cohort provides a unique and rich resource for prospective follow-up since it is drawn from a close-knit community. Consequently it was possible to maintain a very high follow-up rate at 10-years with information being updated on 94% of the original cohort. In turn this has made it possible to draw firm conclusions from our data upon the prevalence, natural history and risk factors for asthma and allergic diseases during childhood.

The elusive nature of precise definitions for asthma and allergic states such as eczema, rhinitis and food allergy has been a point of considerable concern when conducting research in this field. Therefore the introduction of standardised research materials and definitions in the ISAAC study [47] has helped to provide a welcome degree of conformity in this regard. Using such definitions at 10-years we identified a substantial cumulative prevalence for allergic states such as *asthma ever* (20%), *hay fever ever* (20%) and *eczema ever* (40%). Comparison of our results with other ISAAC data [47] confirms that British populations suffer amongst the highest burden of childhood allergic disease on a global basis. This trend for high prevalence of allergic disease within our population was maintained if current symptoms of these allergic states at 10-years were considered. Whilst providing standardised definitions for *diseases ever* and *current symptoms* ISAAC study material fails to provide single definitions for *current disease* such as *current asthma*, *current eczema* and *current rhinitis*. In response to this we created composite definitions for *current disease* states by combining *disease ever* with *current symptom* expression. Thus we demonstrated *currently diagnosed asthma* in 13.0%, *current eczema* in 13.7%, *current rhinitis* in 15.1% and *current urticaria* in 8.7% at 10-years. This approach may provide a

more accurate reflection of the extent of such problems amongst 10-year old children since reliance purely upon known diagnoses may not reflect their current status. On the other hand usage of purely *current symptom* expression to define the problem may overestimate the extent of disease. Thus our approach offers a useful compromise between *disease ever* and *current symptoms*.

The increasing usage of techniques such as bronchial challenge testing in epidemiological surveys has allowed more objective measurements to substantiate questionnaire definitions of asthma [179,180]. Thus the term *current asthma* to define symptomatic bronchial hyper-responsiveness (BHR) [41,104] has gained widespread acceptance as being an accurate indicator of the asthmatic state. Applying this definition we demonstrated *current asthma* in 14.4% children performing a bronchial challenge at 10-years. *Current asthmatics* showed evidence of obstructive patterns of lung function, significant BHR and high disease morbidity. This state was also associated with allergic co-morbidity, atopic sensitisation and high IgE at 10-years. Interestingly a similar risk profile for significant BHR amongst 7-year olds has been identified in the MAS-Study [193]. Confirming strong relationships to atopy [154,209] multivariate risk analysis for *current asthma* demonstrated that atopic status at 4-years and maternal asthma were independent risk factors for its development.

An alternative method of study rather than relying upon defining asthma as an entity is to focus upon the symptom of wheezing [210]. Martinez [44,167] pioneered a natural history based classification of childhood wheezing in the landmark Tucson Children's Respiratory Study. Such an approach has the potential to considerably enhance understanding of the nature of this condition during early life. It has the advantage of not relying upon diagnostic terms such as asthma that require strict definition but of purely using symptom reporting to comprehend the problem. Therefore a better understanding of wheezing symptoms may ensue since it is evident [163] that not all childhood wheezing necessarily reflects presence of asthma. This classification may, however, 'miss' children with a *cough variant* form of asthma, although this group [211] is known to be relatively small. In this study we have used a similar (but slightly broader) classification to study the natural history of wheezing during the first decade of life and identify relevant risk factors for various forms of childhood wheezing. Consequently children were defined as being *persistent*, *early transient*, *late onset* or *non wheezers* during the first decade of life. To avoid recall bias prospectively

collected information was used to build this classification and only children seen at every visit were included in it.

It is a popularly held belief amongst both parents and physicians that much childhood wheezing is transient in nature occurring in the context of viral respiratory illnesses, confined to the early years and bearing little long-term consequence. Studies have tended to confirm this notion – over 80% of childhood wheezing was shown to have remitted by 16-years in the British Cohort Study [81]. Our study confirms that the majority of early life wheezing is indeed a transient entity. Yet it is worth considering that despite having a transient nature this state was associated with considerable disease morbidity in terms of hospital admissions and medical treatment. Thus the notion of the 'happy infant wheezer' who will suffer little from their disease [173] appears something of a misnomer. These children constitute a distinctive wheezing phenotype that shows little in terms of atopy or BHR that would typify the childhood asthmatic state. We confirmed the apparently important role of respiratory infections in the aetiology of such transient wheezing; such illnesses were reported in 56% of this group. Prospectively reported chest infections in infancy emerged as independently significant risk factors for developing this phenotype. Furthermore rhinitis in infancy also emerged as an independently significant risk factor for *transient wheeze* development. However rhinitis at that age was likely to have reflected viral upper respiratory tract infections rather than atopy. Findings of impaired lung function in early infancy [44,106,135,136] amongst *early transient wheezers* have previously suggested that impaired airway calibre in infancy may be a cause of the wheezing seen in this group in response to chest infections at that age. Unfortunately in our study it was not possible to perform lung function measurement in early life upon participating children. Intriguingly, though, we demonstrated evidence of impairment in lung function at 10-years of age amongst *early transient wheezers*. Previously Martinez [44] showed similar patterns of lung function at 6-years in the Tucson study. Our findings suggest that this impaired lung function is an inherent and continuing feature in children who wheeze transiently in infancy and that this finding may continue into later life.

In common with work by Brooke [85] and Martinez [44] we have also identified that a substantial minority (37%) of children wheezing during the first four years of life possess a persistent condition that is still present at 10-years. It is worth noting that ours is a whole

population sample that is unlikely to overestimate the prevalence of this state unlike studies drawn from hospital or clinic based communities [166]. In contrast to *early transient wheezers* intrinsically close links with atopic sensitisation and significant allergic co-morbidity throughout childhood was revealed in this phenotype. We have shown that these *persistent wheezers* correlate closely with the concept of the asthmatic child. Thus we found them to constitute the largest proportion (46%) of diagnosed asthmatics in childhood, highlighting the early life origins of this condition. In line with this finding we also demonstrated that *persistent wheezers* had the greatest requirements for prophylactic pharmacological treatment during childhood in terms of both inhaled steroids and sodium cromoglycate. In addition they experienced the highest frequency of hospital admissions during childhood as well as the largest needs for treatment with oral steroids. Such findings are substantiated by the demonstration of high degrees of BHR at 10-years of age in this group. In turn *persistent wheezers* also showed significantly impaired elements of baseline lung function at 10-years illustrating the potential long-term consequences of this form of disease given evidence from the MAS-Study [193] that impaired lung function may serve as a risk factor for BHR. It is very important to recognise that our study is one of the first to report findings entirely from an era when steroid usage for childhood asthma has been commonplace. Certainly the impairment in lung function shown by *persistent wheezers* in our study was not as much as might have been expected given the high degree of morbidity that they also showed. One might speculate that this reflected the high usage of inhaled steroid treatment amongst children we found to be in this group – a factor that may have attenuated the expected decline in lung function.

Considerable homology between *persistent* and *late onset wheezers* was observed in our study. In this respect, *late onset wheezers* showed similar atopic sensitisation, allergic co-morbidity and BHR to *persistent wheezers* at 10-years. In contrast to *persistent wheezers* this group remained asymptomatic during early life and were indistinguishable at that time of life from children who ultimately never wheezed. Our data provides information that may help to identify such *late onset wheezers* whilst still asymptomatic in early life. In this context multivariate regression analysis identified significant risk for developing *late onset wheeze* with eczema and atopic SPT at 4-years, plus family history of rhinitis or asthma. Confirming the close associations between this state and aeroallergen sensitisation,

development of rhinitis at 10-years was also shown to be a significant associated factor for *late onset wheeze*.

Late onset wheezers were found to have comparable current morbidity at 10-years but lower lifetime treatment requirements than *persistent wheezers*. They also did not show any impairment of lung function at 10-years. The fact that *late onset wheezers* maintain normal baseline lung function at 10-years may be a reflection of the fact that they have wheezed for a relatively shorter period than *persistent wheezers*. In other words their disease may not have been present sufficiently long to have made an impact upon lung function. This could also explain why lifetime morbidity measurements for *late onset wheezers* tended to show lower values than their *persistent* counterparts whilst current morbidity indices at 10-years did not show much difference between these two groups. Thus in observing these children at 10-years we may have begun to see the point at which their disease starts to take hold in terms of significant morbidity.

The strong association of both *persistent* and *late onset wheeze* with atopy and BHR would suggest that similar mechanisms underlie both wheezing phenotypes. Do these states therefore represent two aspects of the same atopic asthmatic condition? Study of children with *current asthma* at 10-years confirmed similar patterns of atopy and BHR to those found for these two phenotypes. The question then arises as to why one group of children expresses symptoms from infancy onwards whilst the other only develops problems during later childhood. Examination of the risk factor profiles we determined for each phenotype may give some insight into this question. A genetic predisposition for asthma and atopy appears to be common to both states. Thus maternal urticaria plus maternal and sibling asthma were found to carry increased risk of developing *persistent wheeze* whilst family history of rhinitis plus maternal and paternal asthma conferred a significant risk of *late onset wheeze*. Whereas allergic states in infancy showed independent significance for *persistent wheeze* only conditions during a later phase of early childhood (at 4-years) showed such effects for *late onset wheeze.* Unfortunately in our study insufficient skin prick testing was performed during infancy for meaningful analysis to be possible. However results emerging from the German MAS-Study [16] suggest that early life development of food allergen sensitisation is of importance for subsequent significant wheezing and asthma. The results from our study show similar trends with significant

associations between early life food allergy and eczema and the appearance of *persistent wheezing* in early life. Our findings suggest that timing of co-existent allergic disease expression may therefore influence the timing of onset of wheezing symptoms in atopic individuals or vice-versa. This offers an interesting variation upon the evolving notion of an 'Allergic March' during childhood whereby conditions like eczema [14,18,19] and food allergy [15,16,120] are thought to predispose to subsequent respiratory allergy in later childhood. Other early life factors such as recurrent chest infections, low Social Class and parental smoking also showed independent associations with *persistent* but not *late onset wheeze* development. The role of Social Class in developing *persistent wheeze* shown in this work is contrary to findings from prior work in this country [81]. This may partly reflect changing patterns of disease over the last thirty years in this country. It may also partly reflect confounding by other related factors such as parental smoking and infant feeding method, since in this cohort [117] it was previously demonstrated that lower social groupings smoked more and breastfed less. It is interesting to observe that neither smoking nor Social Class during later childhood had any significant bearing upon *late onset wheeze* development. It is quite possible that these factors in association with other allergic states during early life may superimpose upon an overwhelming underlying genetic predisposition to atopic asthma and result in the expression of the *persistent wheeze* state during early life. Alternatively where this constellation of genetic and environmental factors fails to materialise in a genetically predisposed individual during early childhood, the *late onset wheeze* phenotype may subsequently appear. Whether correction of factors such as early life smoking exposure, recurrent chest infections and social deprivation therefore merely delays the inevitable onset of the atopic asthmatic (as a *late onset* rather than a *persistent wheezer*) or may offer real preventive benefit is open to speculation.

Our study identifies that together *late onset* and *persistent wheezers* appear to comprise the true atopic asthmatic of childhood. However, whilst these two groups show considerable homology, *persistent wheezers* seem to form a central core of the most problematic asthmatic children based upon morbidity and lung function data. This would be consistent with findings from the CAMP Study USA [169] that have suggested that the severity of childhood asthma may be a function of the overall length of illness. Dodge [168] who showed an association between respiratory symptoms at 3-years of age and the subsequent diagnosis of childhood asthma has also provided suggestion of this trend. In many ways

such findings are of considerable interest as they suggest that the asthmatic children who suffer the most from their disease in the first decade of life are those with an early origin for their disease. This naturally leads to suggestions that intervention strategies [9,212] in children wheezing during infancy may hold some promise in attenuating the unrelenting course of ensuing *persistent* disease. The efficacy of early intervention with inhaled corticosteroids [13] in newly diagnosed asthma has previously been demonstrated. However, much concern has arisen about the potential long-term side effects of unnecessary treatment with agents such as inhaled corticosteroids in early childhood [12,174]. As has been demonstrated in several studies [44,81,85] including this one the majority of infantile wheezing is a transient state. Why treat a condition that will naturally resolve? Balanced against this argument is the knowledge that although less common than *transient* wheezing, *persistent* wheezing carries substantial morbidity. Consequently if it were possible to reliably identify those early life wheezers at highest risk of symptom persistence it might be possible to target early intervention appropriately.

This study has identified a characteristic risk factor profile that may herald persistence of early life wheeze. In this context the genetic predisposition to being atopic would again appear to be paramount, confirming recent work by Csonka [200], as indicated by significant risk for wheezing persistence in those with atopy at 4-year SPT or with a positive family (parent or sibling) history of asthma. Recurrent chest infections at 2-years of age also conferred an increased risk of persistence amongst early life wheezers. The presence of recurrent infantile chest infections as a significant predictor of wheezing persistence extends prior work by Stein et al [133] that such infection in infancy may show associations not only with *transient* but also with *persistent wheezing*. The long-term consequences of such infections on bronchial epithelium have been speculated upon [133,134]. Our results indeed suggest that such infections have a significant contributory role with the *persistent wheezing* phenotype. Conversely early life rhinitis symptoms (possibly reflecting upper respiratory tract viral infections) signalled an increased risk of *transient wheezing*. This may be viewed as being consistent with recent findings from the MAS-Study [199] that 1-year olds with recurrent symptoms of nasal infection were less likely to have wheeze, asthma and atopy in later childhood. Thus it could indeed be that whilst lower respiratory tract infections may contribute to *persistent wheeze*, upper respiratory tract infections may offer a protective effect.

Our risk factor results could form the basis of an algorithm for use in early life wheezers that is capable of detecting those at highest risk of wheezing persistence. Thus a child wheezing in the setting of recurrent chest infections during infancy upon a background of an asthmatic family history, who is then found to be atopic at SPT when 4-years old appears to be at highest risk of wheezing persistence throughout the first decade of life. Lesser variations of this constellation might be seen to confer lower risks of wheezing persistence. This study confirms and extends earlier findings of risk factors for childhood wheezing phenotypes reported by Martinez [44,167,213] in the Tucson cohort. Given the unselected nature of our whole population cohort the predictive capacity and relevance of risk factors identified in this study is likely to be more applicable than for results derived from studies of 'high-risk' cohorts [214]. Such information may facilitate strategies to minimise the burden of developing *persistent wheeze*. In this regard, targeting of parents with strong personal and family histories of asthma and allergy might provide an important 'high risk' group upon which to focus efforts. The strategies that might be employed in these families are open to speculation. Avoidance of parental smoking during the early years of life may be one avenue of opportunity given numerous studies [71,124,128,129] that have shown associations between childhood smoke exposure and BHR. In this study we identified that such smoking contact was a significant risk factor for early life wheezing regardless of ultimate *transient* or *persistent* phenotype. Tobacco smoke exposure was not however a significant risk factor for persistence of early life wheezing to 10-years nor for *late onset wheeze* or *current asthma* at 10-years. Therefore the degree of long-term benefit afforded by smoking avoidance measures may be limited. It is worth remembering that our cohort was an unselected whole population sample and reflecting on whether smoking avoidance measures may be of more value in specific 'high allergy risk' groups.

At univariate analysis both *persistent* and *transient* early life wheezing phenotypes showed significantly increased risk with early weaning and reduced risk with breastfeeding. To some extent this lends support to other studies [115,116,118] that have displayed a protective effect of breastfeeding against wheezing and asthma. However in our study these results were not retained at multivariate analysis indicating a likely confounding effect of Social Class [117] upon feeding method. In addition we could not establish a significant protective effect against persistence of early life wheezing for breastfeeding in preference to formula feeding or early weaning. Neither could we demonstrate any significant effect at

multivariate analysis for method of infant feeding and developing *late onset wheeze*, *current wheeze*, *current asthma*, or *currently diagnosed asthma* at 10-years. We cannot therefore claim on the basis of these results that breastfeeding provides a genuine protective effect amongst the whole population with regards to significant childhood wheezing and asthma. In this light it is worth considering work by Wright [119] that has revealed differential effects of breastfeeding upon IgE in childhood depending upon maternal IgE. Thus in subjects with high maternal IgE breastfeeding was associated with increased IgE in the offspring whereas in mothers with lower IgE breastfeeding was related to reduced IgE in the child. We did not assess the impact of other dietary factors upon wheezing phenotype in this study. Some studies [215,216] have suggested possible links between childhood diet and asthma and this may provide a basis for further future investigation.

Given the apparent importance of recurrent chest infections during infancy for persistence of early life wheezing another measure worthy of consideration is whether promptly treating chest infections in wheezing infants may help reduce the risk of *persistent wheeze* in those with strong personal or family histories of allergy. Given the likely viral aetiology of many such infections just how treatment could be achieved remains to be seen.

The concept of a 'hygiene hypothesis' for asthma and allergy development has gained increasing favour in recent years [149,156]. In this context it has been postulated that a shift in immune responses in favour of allergy creating TH_2 rather than microbial tackling TH_1 lymphocyte reactions may facilitate expression of allergic disease. Thus increased exposure to sources of infection could stimulate TH_1 responses and suppress TH_2 responses thereby protecting against allergy development. We did not confirm any protective effect of early life chest infections against significant childhood wheezing or asthma. Neither could we demonstrate any significant protective effect of large family size (through increased frequency of infection) or significant increased risk with being an only child (through reduced exposure to infections) for either wheezing or asthma. The same was true with eczema. However large family size was associated with significantly reduced risk of *current rhinitis* or *hay fever ever* at univariate analysis providing some support for prior work [201] showing that situations increasing exposure to potential infection may reduce incidence of respiratory allergy. Household pet contact was seen to be very common in our study population and again might have acted as a source of microbial exposure that

protected against allergy and asthma development. In this context a significant protective effect for cat ownership at birth with *current wheeze* at 10-years was observed at univariate analysis. A similar protective effect of cat ownership at 1-year was found for *hay fever ever* at univariate analysis. This might be taken as evidence that some pet exposures, particularly cat, can be associated with a reduced risk of certain allergic states confirming recent findings[219] from other work. A more likely view might be that children with these states were from families that already possessed strong histories of allergy in other family members and therefore which may have been more likely to practice allergen avoidance in the form of not keeping domestic pets. We demonstrated some evidence to support this notion in families with a history of rhinitis. Furthermore whilst cat ownership was typically associated with trends for lower prevalence of all allergies, asthma and major wheezing phenotypes in our study no such consistent patterns were detected with regard to dog ownership. Thus whether such animal exposures are capable of making any significant impact upon the development of *persistent* or *late onset wheeze* remains to be seen.

Given the clear significance of atopy and allergy in development of both *persistent* and *late onset wheeze*, it might be expected that the use of allergen avoidance measures during infancy in 'high allergy risk' children may prove beneficial in disease prevention. Allergen avoidance has shown short-term efficacy in some trials [20,91-93]. However these practices have not showed continued effect after they have been discontinued and whether they can influence long-term outcome remains to be seen. An alternative approach in children perceived to be at highest risk of developing *persistent* or *late onset wheeze* would be the use of anti-inflammatory strategies to address the underlying inflammatory mechanisms [4] of these states. Oral antihistamine usage in early life amongst those with strong personal or family histories of allergy is one tool to prevent subsequent significant wheezing and asthma. In this regard some efficacy for agents like ketotifen [26,27] and certirizine [25] has already been demonstrated. Whether inhaled corticosteroids may have a similar role remains to be established although understandable cautions about using these medications in young children exist given the possibility of side effects [9,12] and the present lack of knowledge of the long-term consequences of such treatment [174]. Leukotriene antagonists may offer a viable alternative.

In this study the natural history of childhood wheezing, asthma and allergy during the first decade of life has been described. An enhanced understanding of those factors in early life that are related to the appearance of these conditions in childhood has been defined. In this respect the fundamental importance of inheriting an allergic tendency for the development of significant wheezing forms like *persistent* and *late onset wheeze* is supported by similar findings with regard to *current asthma* at 10-years. This is not surprising since *current asthmatics* in our study by definition will have come from one or other of these two phenotypes. However we have also demonstrated that other allergic states at 10-years of age also show this close association with inherited risk factors. Thus we found very similar patterns for the importance of genetic factors with *current rhinitis* and *current eczema* as well as *eczema ever* and *hay fever ever*. This would suggest that genetic predisposition is the fundamental underlying factor that may govern expression of allergic disease during the first decade of life. Common environmental factors appeared to show some effect of variable significance in our study but this was consistently overshadowed by the dominating effect of heritable factors with regard to each of the allergic states considered. Nevertheless further scrutiny of environmental influences both in utero [217] and in early life [218] is warranted since heredity alone is unlikely to be the sole explanation for childhood allergic disease. Meanwhile although clearly not a straightforward proposition [219], clarification of the genetic characteristics of these states should also be pursued in order to better understand the nature of childhood wheezing, asthma and allergy.

APPENDIX I – Study Personnel at 10-year Visit

The members who participated in the 1989 Study Research Team during the 10-year visit of the cohort study are listed below:

Research Fellow:	Dr Ramesh Kurukulaaratchy (RJK)
Research Nurses:	Mrs Monica Fenn (MF)
	Mrs Linda Waterhouse (LW)
	Mrs Sharon Matthews (SM)
	Mrs Cathy Wilby (CW)
	Mrs Heidi Savory (HS)
	Miss Tessa Booth (TB)
Secretary/Administration:	Mrs Linda Terry (LT)
Secretary/Tracing:	Mrs Gail Poulton (GP)
Laboratory IgE Analysis:	Mr Roger Twiselton (RT)
Cohort Study Supervisor:	Dr Hasan Arshad (SHA)

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RELATED PUBLICATIONS AND PRESENTATIONS

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Abstracts

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CONFERENCE PRESENTATIONS

ERS Annual Congress, Berlin September 2001. Poster Discussions;

1.Identifying and differentiating persistent from transient wheezing in early life.

2.Early life risk factors for late onset wheezing in childhood.

3.Asthma prevalence.

4.Early life risk factors for wheezing and asthma in 10-year old children.

World Congress on Lung Health, Florence, September 2000. Poster Presentations;

1.Characteristics of wheezing illness at the age of 10 years – results from a 10 year birth cohort.

2.The prevalence of rhinitis in childhood and its relationship to atopy, asthma and bronchial hyperactivity.

3. The outcome of wheezing illnesses in early childhood – results from a 10 year birth cohort study.

ATS 2000, Toronto, May 2000. Oral Presentation;

Wheezing from infancy to age ten years and its relationship to bronchial responsiveness and atopy.

ERS Annual Congress, Madrid, October 1999. Poster Discussion;

Measuring bronchial hyper-reactivity by bronchial challenge with histamine and methacholine in nine year old children.

ACCOMPANYING MATERIALS

Study Materials Used at 10-years

Samples of the study materials used in the 10-year study visit are provided in the following section as outlined below:

Patient Information Sheet
Consent Form
ISAAC Written Questionnaire
Childhood Immunisation History
Physical Examination Record
Family History Questionnaire
Modified Postal Questionnaire
ISAAC Video Questionnaire
Supplementary Atopic Disease Questionnaire
Skin Prick Test Results Form
Baseline Spirometry Report
Methacholine Bronchial Challenge Report

Patient Information Sheet

THE DAVID HIDE ASTHMA AND ALLERGY RESEARCH CENTRE

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Dr S H Arshad DM MRCP

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Patient Information Sheet

STUDY: THE PREVALENCE OF AND RISK FACTORS FOR ATOPY IN EARLY CHILDHOOD: A whole population birth cohort and study

Your child is being invited to attend a follow-up visit for the 1989 birth cohort study. This information leaflet describes what the visit involves, the purpose of the visit and the tests which would be performed. Please read through this leaflet carefully and listen to the explanation of the study given by the doctor, before making your decision. Feel free to ask the medical staff about anything that is not clear. You can contact them at the address given at the end of this leaflet.

What is the study about?

The purpose of this study is to identify important risk factors for the development of asthma and allergies with a potential for intervention at an early age.

We will invite all 1456 children who participated in the original study to return for the follow-up visit.

How long is the study?

This study will only involve one visit to the David Hide Asthma and Allergy Research Centre.

What will happen during the visit and what type of tests will be performed?

We will ask you questions regarding your child's health, lifestyle and medication so that we can complete a questionnaire. We will also ask you to watch a video and fill in another questionnaire. Your child will be given a physical examination by the doctor and a skin prick test to various foods and air-borne allergens will be performed. Your child may also be asked to undergo a methacholine challenge test.

The skin prick test is to determine what your child is allergic to. It would involve placing small drops of solution on the inside of the forearm and making a small prick on the skin. If your child is allergic to any of the substances the surrounding skin will redden and itch.

The methacholine challenge is a procedure which is routinely carried out in respiratory laboratories. It involves inhaling increasing doses of methacholine which is used to cause controlled narrowing of the airways in the lungs. The narrowing is monitored by carrying out breathing tests. The test takes up to one hour to perform and the effect of methacholine wears off after about 30 minutes. A blood test – approximately 20 ml will be taken during the visit → 10 ml will be taken for various tests and the remaining 10 ml sample will be frozen for genetic analysis in an attempt to discover genes responsible for asthma and allergy. Some children will be asked to provide a sample of sputum after breathing in a mist of salt water.

This visit will entail spending 1-2 hours in the Centre.

What are the risks and discomforts my child might experience?

As this study involves no new drugs or experimental techniques, your child is put under no extra risk at all. The maximum discomfort they may experience is that of a skin prick test and before blood is taken a local anaesthetic cream will be put on the arm so your child should not feel anything. Their chest may feel tight towards the end of the challenge test but we can easily give them medication to relieve this feeling if they require it.

What instructions should I follow regarding my child's asthma medications?

We would ask your child to refrain from using their bronchodilator inhaler for four hours prior to the visit. Use of their inhaler can change the results of the tests so could you please advise the study doctor before you attend the clinic if your child needed to use the inhaler in the preceding four hours.

What are the benefits of participating in this study?

As this study is looking into the natural history of allergies and asthma in childhood and the risk factors contributing to its development we may, in the future, be able to provide guidelines for lessening and perhaps even preventing the development of asthma and allergies.

The benefit your child is likely to derive from this follow-up visit is the chance for a medical check-up.

How will my child's identity be protected as a patient in this study?

All information collected during the study will be stored in a computer. Only your study personnel will know who the information is about. Your child will not be individually identified in any reports or publications resulting from the study.

Your GP will be informed that your child is participating in the follow-up.

How long will I be given to decide whether my child should take part and can I decide to withdraw from this study at any time?

The decision to allow your child to participate in this study is entirely voluntary and you should take as much time as you need to reach your decision. Once you have decided and you would like your child to participate in the study, you will be asked to sign the attached consent form before taking part in this study. This is to ensure that you have been fully informed regarding this study.

Would my child be compensated for any injury?

It is highly unlikely that any significant injury can be caused directly by your child's participation in this study. But in the unlikely event of any injury, compensation will be paid through insurance cover provided by the Isle of Wight Healthcare Trust.

Who can I contact to get more information?

If you would like more information on this study, please contact Dr Ramesh Kurukulaaratchy on telephone number (01983) 534898. Alternatively you can write to him at:

The David Hide Asthma and Allergy Research Centre
St Mary's Hospital, Newport, Isle of Wight PO30 5TG

Consent Form

THE DAVID HIDE ASTHMA AND ALLERGY RESEARCH CENTRE

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The prevalence of and risk factors for atopy in early childhood:
A whole population birth cohort study

CHILD CONSENT FORM

I (print name).....

of (address).....

.....

understand my parents/guardians and I will complete a questionnaire. I will have a skin prick test and blood will be taken after application of anaesthetic cream. I may also have a 'Methacholine' challenge breathing test which may cause slight tightness of the chest that is easily removed by a rescue inhaler. I may also have sputum collected after breathing in a mist of salt water. These tests have been explained to me by:

.....

and I have talked about it with this person and my parents/guardians.
I understand that I can withdraw from the study should I wish.

SIGNED.....

I (print name).....
parent/guardian of (print child's name).....
understand that all results will be treated in the strictest confidence and used to promote medical knowledge. The blood samples may be used at a later stage to study specifically for new asthma genes.
I agree that my general practitioner ..... is notified of my child's participation in the study. I have informed an investigator of any drug that my child is presently taking.
I understand that I may withdraw my child at any stage in the investigation and this will not affect his/her treatment in any way.

Signed: .....

Date: .....

INVESTIGATOR to sign that he/she explained the study, provided an information sheet and consent was given freely and voluntarily.

.....

ISAAC Written Questionnaire

1989 STUDY

NINE YEAR FOLLOW UP

Date seen	/ /

NAME & ADDRESS

DATE OF BIRTH

Height | | | | . | |

Weight | | | | . | |

PHONE:	
GP:	

Male	Female

Firstly I would like to ask you some questions about your home and family

Is your house.....?
- owned -privately[1]
- rented -privately[2]
- rented -council/housing asscin[3]
- other[4]

Do you cook on.....? gas[1]
- electricity[2]
- other[3]

Father/partner's occupation

Mother's occupation

Mother's age on leaving full time education

Child no. of Mum [ ] of [ ]

Total annual family income (estimate)
- less than 12.000 [1]
- 12.000 - 17.999 [2]
- 18.000 - 29.000 [3]
- 30.000 - 41.999 [4]
- greater than 42.000 [5]

SMOKING
inside the house:
- Mother: [ ][ ] /day
- Father: [ ][ ] /day
- Other: [ ][ ] /day

outside the house (garden or porch): Yes[1] No[2]

other place of care Yes[1] No[2]

PETS
in house in the last 2 years:
- Cat Yes[1] No[2]
- Dog Yes[1] No[2]
- Other Yes[1] No[2] What?

regular exposure elsewhere:
- Cat Yes[1] No[2]
- Dog Yes[1] No[2]
- Other Yes[1] No[2] What?

Atopic disease since review at *age 4 years*

Asthma/wheezing episodes	Yes[1]	No[2]
Nocturnal/recurrent cough	Yes[1]	No[2]
Eczema	Yes[1]	No[2]
Perennial/seasonal rhinitis	Yes[1]	No[2]
(Hayfever seasonal/all year)		
Urticaria	Yes[1]	No[2]
(rash like nettle rash)		
Food intolerance or allergy	Yes[1]	No[2]

Here are some questions about your child's chest

1 Has your child ever had wheezing or whistling in the chest at any time in the past?
Yes[1] ☐ No[2] ☐
IF 'NO' SKIP TO Q. 6

2 Has your child had wheezing or whistling in the chest in the last 12 months?
Yes[1] ☐ No[2] ☐
IF 'NO' SKIP TO Q. 6

3 How many attacks of wheezing has your child had in the last 12 months?
None[1] ☐ 1 to 3[2] ☐ 4 - 12[3] ☐ >12[4] ☐

4 In the last 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?
Never woken with wheezing[1] ☐ Less than one night per week[2] ☐
One or more nights per week[3] ☐

5 In the last 12 months, has wheezing ever been severe enough to limit your child's speech to one or two words at a time between breaths? Yes[1] ☐ No[2] ☐

6 Has your child ever had asthma? Yes[1] ☐ No[2] ☐

7 In the last 12 months, has your child's chest sounded wheezy during or after exercise?
Yes[1] ☐ No[2] ☐

8 In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection? Yes[1] ☐ No[2] ☐

Here are some questions about your child's nose and eyes.

9 Has your child ever had a problem with sneezing , or a runny ,or a blocked nose when he/she DID NOT have a cold or the flu? Yes[1] ☐ No[2] ☐
IF 'NO' SKIP TO Q. 14

10 In the past 12 months, has your child had a problem with sneezing, or a runny or a blocked nose when he/she DID NOT have a cold or the flu? Yes[1] ☐ No[2] ☐
IF 'NO' SKIP TO Q. 14

11 In the past 12 months, has this nose problem been accompanied by itchy-watery eyes? Yes[1] ☐ No[2] ☐

12 In which of the past 12 months did this nose problem occur?

January[1] ☐ February[2] ☐ March[3] ☐ April[4] ☐
May[5] ☐ June[6] ☐ July[7] ☐ August[8] ☐
September[9] ☐ October[10] ☐ November[11] ☐ December[12] ☐

13 In the past 12 months, how much did this nose problem interfere with your child's daily activities?
Not a lot[1] ☐ A little[2] ☐ Moderate amount[3] ☐ A lot[4] ☐

14 Has your child ever had hayfever? Yes[1] ☐ No[2] ☐

Here are some questions about your child's skin

15 Has your child ever had an itchy rash which was coming and going for at least 6 months?
Yes[1] ☐ No[2] ☐

IF 'NO' SKIP TO Q. 21

16 Has your child had this itchy rash at any time in the last 12 months?
Yes[1] ☐ No[2] ☐

IF 'NO' SKIP TO Q. 21

17 Has this itchy rash at any time affected any of the following places: The folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?
Yes[1] ☐ No[2] ☐

18 At what age did this itchy rash first occur? < 2 ys[1] ☐ 2-4 ys[2] ☐ >5 ys[3] ☐

19 Has this rash cleared completely at any time during the last 12 months? Yes[1] ☐ No[2] ☐

20 In the last 12 months, how often, on average, has your child been kept awake at night by this itchy rash? Never[1] ☐ less than one night/week[2] ☐ One or more nights/week[3] ☐

21 Has your child ever had eczema? Yes[1] ☐ No[2] ☐

Childhood Immunisation History and Physical Examination Record

Has the child had the following immunisations?

DPT and polio	Y[1]	N[2]
DPT and polio without pertussis	Y[1]	N[2]
HIB	Y[1]	N[2]
BCG	Y[1]	N[2]
MMR	Y[1]	N[2]
Other vaccinations	Y[1]	N[2]

What .....

On examination: Any abnormalities in the following systems?

Respiratory	Yes[1]	No[2]	Specify
Cardiovascular	Yes[1]	No[2]	Specify
Gastrointestinal	Yes[1]	No[2]	Specify
Skin	Yes[1]	No[2]	eczema urticaria other
Ear, nose, throat	Yes[1]	No[2]	allergic rhinitis allergic conjunctivitis other
Any other problems			Specify

Family History Questionnaire

Has anybody else in the family ever had the following:

	Mother	Father	Siblings		
Asthma			M / F	M / F	M / F
Nocturnal/Recurrent Cough			M / F	M / F	M / F
Eczema			M / F	M / F	M / F
Hayfever			M / F	M / F	M / F
Urticaria			M / F	M / F	M / F
Food Allergy			M / F	M / F	M / F

Modified Postal Questionnaire

THE DAVID HIDE ASTHMA AND ALLERGY RESEARCH CENTRE

St Mary's Hospital
Newport
Isle of Wight PO30 5TG
Telephone: (01983) 534898

Director:
Dr Hasan Arshad

1989 STUDY QUESTIONNAIRE

We are currently completing the latest update of the "Isle of Wight 1989 Study" which involved all children born on the Island back in 1989. This study has already provided valuable information about children's health as they grow up – particularly with reference to asthma and allergies. We are very keen to **update our information about all the children** who originally took part in the study and would be very grateful if you can fill in this questionnaire about ..... and return it to us in the pre-paid envelope. By doing this you will be helping this world famous study tremendously. I would like to take this opportunity for thanking you for taking the time to help us with this important study.

DR RJ KURUKULAARATCHY {Research Fellow}

NAME	DATE OF BIRTH / /
ADDRESS	
TELEPHONE	
FAMILY GP AND SURGERY	

QUESTION ONE Please tick if your child has **EVER HAD** any of the following

	WHEEZING / ASTHMA
	NIGHT-TIME/ RECURRENT COUGH
	ECZEMA
	HAYFEVER / RHINITIS
	URTICARIA {a blotchy rash like a nettle rash}
	FOOD ALLERGY

IF **YES** TO ANY ABOVE PLEASE ANSWER **Q.TWO**

OTHERWISE **GO STRAIGHT TO Q.THREE**

QUESTION TWO Please tick if your child has had any of the following **since they were FOUR YEARS OLD.**

	WHEEZING / ASTHMA
	NIGHT-TIME / RECURRENT COUGH
	ECZEMA
	HAYFEVER/ RHINITIS
	URTICARIA {a blotchy rash like a nettle rash}
	FOOD ALLERGY

QUESTION THREE Please tick if your child has had the following **Vaccinations**

	DPT- Diptheria, Pertussis {whooping cough}, Tetanus
	DT – Diptheria & Tetanus but NOT whooping cough
	HIB – Haemophilus Influenzae Type B for meningitis
	MMR – Measles, Mumps & Rubella
	OTHER ; Please state what.....

QUESTION FOUR Please state below where ..... comes in the order of the children in your family {eg 2nd child out of 3}.

CHILD.....OUT OF .....

QUESTION FIVE The next question is about the rest of your immediate family. Please circle in the table at the top of the next page to show us if anybody else in the family has ever had the following;

Eg: If the mother and second child (who is a girl) have had wheezing or asthma the table would be completed as below:

WHEEZING OR ASTHMA	MOTHER	FATHER	Child 1 Boy/girl	Child 2 Boy/girl	Child 3 Boy/girl	Child 4 Boy/gir

WHEEZING OR ASTHMA	MOTHER	FATHER	Child 1 Boy/girl	Child 2 Boy/girl	Child 3 Boy/girl	Child 4 Boy/girl
NIGHT-TIME OR RECURRENT COUGH	MOTHER	FATHER	Child 1 Boy/girl	Child 2 Boy/girl	Child 3 Boy/girl	Child 4 Boy/girl
ECZEMA	MOTHER	FATHER	Child 1 Boy/girl	Child 2 Boy/girl	Child 3 Boy/girl	Child 4 Boy/girl
HAYFEVER/ RHINITIS	MOTHER	FATHER	Child 1 Boy/girl	Child 2 Boy/girl	Child 3 Boy/girl	Child 4 Boy/girl
URTICARIA {a blotchy rash like a nettle rash}	MOTHER	FATHER	Child 1 Boy/girl	Child 2 Boy/girl	Child 3 Boy/girl	Child 4 Boy/girl
FOOD ALLERGY	MOTHER	FATHER	Child 1 Boy/girl	Child 2 Boy/girl	Child 3 Boy/girl	Child 4 Boy/girl

QUESTION SIX — The following are some general questions about your home & family. Please tick or complete below.

A. Is your home

	Privately Owned
	Privately Rented
	Rented from Council / Housing association
	Other

B. What do you cook on at home?

	Gas
	Electricity
	Other

C. Parents Occupations – Please state below your occupation

Father	
Mother	

D. Please indicate below if anybody smokes at home by ticking the "smoke" box. If you can, please also give an estimate of how much each person smokes per day in the next box.

Example:

	Smoke	How many
Mother	√	10
Father		
Other		

	Smoke	How many
Mother		
Father		
Other		

E. If people do smoke at home, do they smoke mainly {circle as appropriate}

INSIDE THE HOUSE	**YES**
OUTSIDE THE HOUSE	**YES**

F. Is your child regularly exposed to cigarette smoke elsewhere? **YES / NO** {please circle}.

G. Have you had any pets at home in the last 2 years? **YES / NO** {please circle}
If yes, what sort of pets?

.....

H. Is your child regularly exposed to pets elsewhere? **YES / NO** {please circle}
If yes, what sort of pets?

.....

IF YOUR CHILD HAS EVER HAD WHEEZING PLEASE NOW FILL IN THE ADDITIONAL "WHEEZING" QUESTIONNAIRE.

THANK YOU FOR HELPING COMPLETE THE 1989 STUDY

PLEASE NOW RETURN THIS QUESTIONNAIRE IN THE PREPAID ENVELOPE. IF YOU WISH TO TALK TO ANYONE ABOUT THE 1989 STUDY PLEASE CONTACT US ON 01983 534898 OR WRITE TO US AT "THE DAVID HIDE ASTHMA & ALLERGY RESEARCH CENTRE, ST.MARY'S HOSPITAL, NEWPORT, ISLE OF WIGHT".

1989 STUDY WHEEZING QUESTIONNAIRE

Please complete these additional questions if ..... **HAS EVER HAD** wheezing or asthma.

Question 1. How old was your child when they first had wheezing/asthma ?.....

Question 2. Has your child had wheezing/ asthma in the last 12 months? YES / NO {please circle}
If NO when did it stop?.....

If you answered NO to Question 2 please go straight to Question 8.

If you answered YES to Question 2 please now answer Questions 3 to 7.

Question 3. How many attacks of wheezing has your child had in the last 12 months? {please circle}

NONE	1 to 3	4 to 12	More than 12

Question 4. In the last 12 months has your child's sleep been disturbed by wheezing? {please circle}

NEVER	Less than 1 night per week	1 or more nights per week

Question 5. In the last 12 months has the wheezing ever been severe enough to limit your child's speech to one or two words at a time? YES / NO {please circle}

Question 6. In the last 12 months has your child been wheezy during or after exercise? YES / NO {please circle}

Question 7. In the last 12 months has your child had a dry cough at night except with a cold or chest infection? YES / NO {please circle}

Question 8. Has your child ever been diagnosed with ASTHMA? YES / NO {please circle}

Question 9. How many times has your child been admitted to hospital with wheezing/ asthma?.....

Question 10. How many times has your child been taken to Casualty with wheezing / asthma?.....

Question 11. Please indicate below who has looked after your child's wheezing/ asthma {please circle}

Hospital specialist	GP/ Nurse	Other

Question 12. Has your child ever taken treatment for wheezing/ asthma? YES/ NO {please circle}
If yes please state what
medications.....

Question 13. Was this treatment PAST or is it CURRENT {please circle}

Question 14. Has your child ever had steroid tablets for their wheezing /asthma? YES / NO {please circle}
If yes HOW MANY SEPARATE COURSES?.....

Question 15. Does anything in particular trigger your child's wheezing /asthma? YES / NO {please circle}
If yes please state
what.....
.....

THANKYOU FOR HELPING COMPLETE THE 1989 STUDY

ISAAC Video Questionnaire

1989 STUDY

NINE YEAR FOLLOW UP

VIDEO SURVEY

NAME & ADDRESS

DATE OF BIRTH STUDY NO.

Date Seen / /

M/F

1 Has your breathing ever been like this at any time in your life? Yes[1] ☐ No[2] ☐

If yes in the last year? Yes[1] ☐ No[2] ☐

If yes, one or more times a month? Yes[1] ☐ No[2] ☐

2 Has your breathing been like the girl's in the video following exercise?

At any time in your life? Yes[1] ☐ No[2] ☐

If yes, in the last year? Yes[1] ☐ No[2] ☐

If yes one or more times a month? Yes[1] ☐ No[2] ☐

3 Have you ever been woken like this at night?

At any time in your life? Yes[1] ☐ No[2] ☐

If yes, in the last year? Yes[1] ☐ No[2] ☐

If yes one or more times a month? Yes[1] ☐ No[2] ☐

4 Have you been woken like this at night?

At any time in your life? Yes[1] ☐ No[2] ☐

If yes, in the last year? Yes[1] ☐ No[2] ☐

If yes one or more times a month? Yes[1] ☐ No[2] ☐

5 Has your breathing been like this?

At any time in your life? Yes[1] ☐ No[2] ☐

If yes, in the last year? Yes[1] ☐ No[2] ☐

If yes one or more times a month? Yes[1] ☐ No[2] ☐

Supplementary Atopic Disease Questionnaire

If atopic symptoms are present

NINE YEAR FOLLOW UP

DATE SEEN	/ /

Name & Address

d.o.b. **Study No.**

1. **ASTHMA/Recurrent wheeze**

At what age did asthma/recurrent wheeze first appear. ☐ Years old

Have you had asthma/recurrent wheeze in the last 12 months ☐ Yes[1] ☐ No[2]

If no, at what age did it stop ☐ Years old

No of overnight hospital admissions ☐☐ No of A&E/Ward-attender contacts ☐

Asthma cared for by: Hospital spclst[1] ☐ GP/Nurse[2] ☐ Other[3]_____ ☐

Asthma treatment Current[1] ☐ Past[2] ☐

Bronchodilators Yes[1] ☐ No[2] ☐ What? _____

Prophylactic Inhaled steroids[1] ☐ cromoglycate[2] ☐ Steroids & cromoglycate[3] ☐ theophylline[4] ☐ other[5] ☐ _____

oral steroids Yes[1] ☐ No[2] ☐ no of courses ☐☐

Recognised triggers Yes[1] ☐ No[2] ☐

Exercise[1] ☐ infection[2] ☐ Pollen[3] ☐ animals[4] ☐ house dust[5] ☐ stress[6] ☐ Other[7] _____

2. **ATOPIC DERMATITIS** (eczema)

At what age did the atopic dermatitis first appear. ☐ Years old

Have you had atopic dermatitis in the last 12 months ☐ Yes[1] ☐ No[2]

If no at what age did it stop ☐ Years old

3. **RHINITIS**

At what age did the rhinitis first appear. ☐ Years old

Have you had rhinitis in the last 12 months ☐ Yes[1] ☐ No[2]

If no at what age did it stop ☐ Years old

Timing seasonal[1] ☐ perennial[2] ☐ seasonal & perennial[3] ☐

eye symptoms Yes[1] ☐ No[2] ☐ itching[1] ☐ redness[2] ☐ discharge[3] ☐

Recognised triggers Yes[1] ☐ No[2] ☐
infection[1] ☐ house dust[2] ☐ animals[3] ☐ pollen[4] ☐

Treatment nasal steroids[1] ☐ Na cromoglycate[2] ☐ antihistamines[3] ☐ other[4] ☐

4. **URTICARIA**

At what age did the urticaria first appear. ☐ Years old

Have you had urticaria in the last 12 months Yes[1] / No[2]

If no at what age was the last episode ☐ Years old

Frequency

once[1] ☐ 2-5[2] ☐ >5 episodes[3] ☐

Duration < a day ☐ 1-3 days ☐ >3 days ☐

Suspected triggers ☐

5. **FOOD ALLERGY/INTOLERANCE since 4 yrs**

Suspected food (s) ☐

reaction

vomiting[1] ☐ angio-oedema[6] ☐
diarrhoea[2] ☐ oral symptoms[7] ☐
colic[3] ☐ wheezing/SOB[8] ☐
eczema[4] ☐ throat tightness[9] ☐
urticaria[5] ☐ systemic[10] ☐

temporal relationship <1hr[1] ☐ 1-12hrs[2] ☐ >12 hrs[3] ☐

Comments

INVESTIGATORS NAME:_____ SIGNATURE: _____

Skin Prick Test Results Form

1989 STUDY SPT

NAME [redacted]

STUDY NUMBER

DOB: 18/6/89 Study No: [redacted] /

DATE 10 / 3 / 99 TESTER (initials) RK.

ALLERGEN	WHEAL	MEAN DIAM.
Histamine	0	7x5mm
N. Saline		
HDM 5·5mm x 4mm		
Cat 4·5mm x 4mm		
Dog 5mm 6x4mm		
Grass 7·mm x 5mm		
Tree 2·5m 3x2mm		
Cladosporium Herbarum	—	
Alternaria alternata	—	
Milk	—	
Egg	—	
Wheat	—	
Peanut	—	
Cod	—	
Soya	—	

6mm JG 5·2·01

5·2·01 JG

ATOPIC ☑ NON ATOPIC ☐

sptrec.doc/forms/brenda

Baseline Spirometry and Methacholine Bronchial Challenge Results Printout

KoKo Spirometer System
Pulmonary Data Service Instrumentation, Inc.
901 Main Street, Louisville, Colorado 80027 (800) 431-7733

CHALLENGE REPORT

Name: [redacted]
ID #: 89-[redacted]
Age: 9 Sex: m Height: 136 cm. Weight: 30 kg.
Doctor: rk Tech: mf
Test set started: 03-10-1999 13:25:43 Report date: 07-30-2001 14:22:22
Diagnosis: asthma
Comments:
Test performed on Pulmonary Data Service Instrumentation "KoKo" Spirometer

~~~~~~~~~~~ Challenge (gtc asthma) ~~~~~~
(Test performed 03-10-1999 14:00:02)

		FVC	%Prd	FEV1	%Prd	FEV1/FV	%Prd	PEFR	%Prd	FEF25-7	%Prd
Saln (ref)		2.40		2.21		0.92		4.41		2.84	
Pred		2.19	110	1.92	115	0.88	105	4.79	92	---	--

	Time	FVC	%Chg	FEV1	%Chg	FEV1/FV	%Chg	PEFR	%Chg	FEF25-7	%Chg
Base	00:00:00	2.22	-8	2.16	-2	0.97	6	4.84	10	3.21	13
		2.26	-6	2.12	-4	0.94	2	4.69	6	2.93	3
		2.14	-11	1.97	-11	0.92	-0	4.69	6	2.58	-9
Saln	00:05:07	2.40	0	2.21	0	0.92	0	4.41	0	2.84	0
		2.40	0	2.17	-2	0.90	-2	4.41	0	2.77	-3
		2.27	-5	2.06	-7	0.91	-1	4.69	6	2.53	-11
Stg1	00:08:20	2.37	-1	2.17	-2	0.92	-1	4.41	0	2.90	2
		2.37	-1	2.15	-3	0.91	-1	4.27	-3	2.69	-5
		2.22	-8	2.07	-6	0.93	1	4.55	3	2.41	-15
Stg2	00:10:42	2.36	-2	2.15	-3	0.91	-1	4.27	-3	2.92	3
		2.34	-3	2.14	-3	0.92	-1	4.41	0	2.86	1
		2.16	-10	1.98	-10	0.92	-0	4.41	0	2.62	-8
Stg3	00:13:30	2.40	0	2.15	-3	0.90	-3	4.27	-3	2.76	-3
		2.37	-1	2.06	-7	0.87	-6	4.41	0	2.52	-11
		2.20	-8	1.95	-12	0.89	-4	3.98	-10	2.25	-21
Stg4	00:16:02	2.35	-2	2.06	-7	0.88	-5	4.41	0	2.59	-9
		2.26	-6	1.97	-11	0.87	-5	4.12	-7	2.37	-17
		2.06	-14	1.93	-13	0.94	2	4.55	3	2.47	-13
Stg5	00:18:52	2.17	-10	1.85	-16	0.85	-7	4.41	0	2.10	-26
		1.98	-18	1.77	-20	0.89	-3	4.12	-7	2.15	-24
		2.16	-10	1.77	-20	0.82	-11	4.41	0	1.63	-43
Stg6	00:21:06	2.06	-14	1.63	-26	0.79	-14	3.84	-13	1.44	-49
		2.00	-17	1.57	-29	0.79	-15	3.98	-10	1.37	-52
		1.71	-29	1.48	-33	0.87	-6	3.84	-13	1.57	-45
Post	00:40:45	2.38	-1	2.22	0	0.93	1	4.55	3	2.64	-7
		2.33	-3	2.09	-5	0.90	-3	4.27	-3	2.85	0
		2.32	-3	2.07	-6	0.89	-3	4.27	-3	2.72	-5
~~~~~~~~~~~

KoKo Spirometer System
Pulmonary Data Service Instrumentation, Inc.
901 Main Street, Louisville, Colorado 80027 (800) 431-7733

Name: [redacted] ID #: 89-[redacted]

~~~~~~~~~~~ Challenge (gtc asthma) ~~~~~~
(Test performed 03-10-1999 14:00:02)

	Conc	Brths	Dsg(du)	Dsg(mg)	BP	HR	Comments	2nd
Base	--	--	--	--				Cons
Saln	--	5	--	--				Cons
Stg1	.06	5	0.3	0.0027				Cons
Stg2	.12	5	0.9	0.0082				Cons
Stg3	.25	5	2.15	0.0195				Cons
Stg4	.5	5	4.65	0.0423				Cons
Stg5	1	5	9.65	0.0877				Incn
Stg6	2	5	19.65	0.1786				Cons
Post	--	--	--	--				Incn

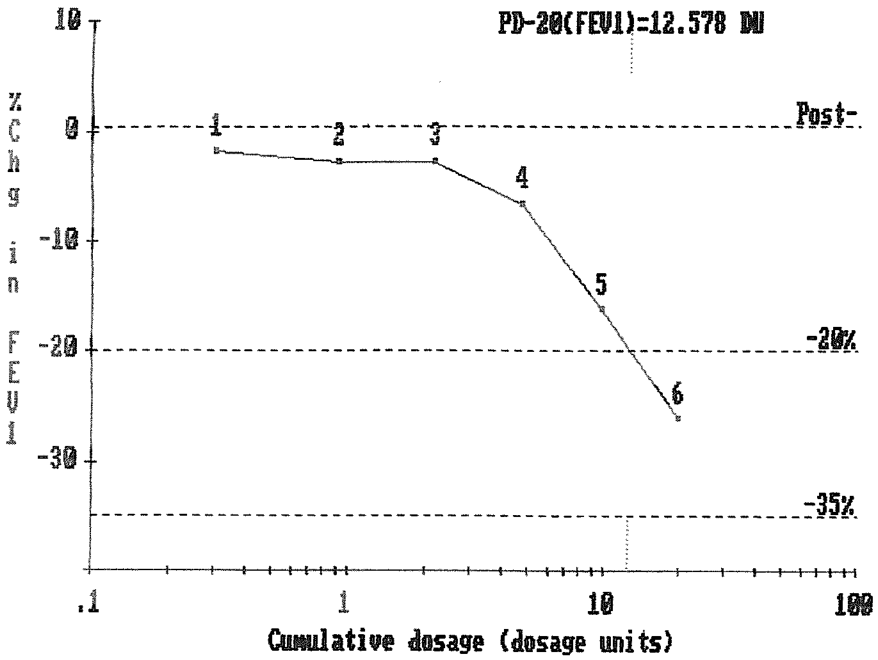
PD-20(FEV1): 12.578 du, 0.114 mg
PC-20(FEV1): 1.295 mg/ml, 0.059 mg
Area under curve (FEV1): 477.83
Nebulizer output: 0.9090 ml/min Challenge agent: methacholine
Inhalation: Onset: 0.10 L Rate: 0.50 L/s Time: 0.60 sec

Conc = concentration of challenge agent in mg/ml, Brths = current breaths
Dsg(du) = cumulative dosage in Dosage Units, Dsg(mg) = cumulative dosage in mg
(1 Dosage Unit = 1 breath of 1 mg/ml concentration of provocation agent)
PD-20(FEV1) du = Cumulative dosage units which causes a 20% fall in FEV1
PD-20(FEV1) mg = Cumulative dose in mg which causes a 20% fall in FEV1
PC-20(FEV1) mg/ml = Concentration being delivered when a 20% fall in FEV1 occu
PC-20(FEV1) mg = Dose in mg being delivered when a 20% fall in FEV1 occurs
~~~~~~~~~~~

KoKo Spirometer System
Pulmonary Data Service Instrumentation, Inc.
901 Main Street, Louisville, Colorado 80027 (800) 431-7733

CHALLENGE REPORT

Name: [redacted] ID #: 89-[redacted]



~~~~~~~~~~~ Interpretation~~~~~~
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