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University College Cork, Ireland
Coláiste na hOllscoile Corcaigh

An exploration of the positive and negative relationships associated with the development of asthma and atopic disorders in primary school children in Cork

April, 2013

Eileen Mary Duggan

MA (Health Promotion)

Thesis submitted to the Faculty of Medicine and Health, University College Cork for the degree of Doctor of Philosophy

Based on the work carried out at the Department of Paediatrics and Child Health and the Department of Epidemiology and Public Health, University College Cork

Under the supervision of Professor Jonathan Hourihane M.D. and Dr. Anthony Fitzgerald PhD

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Declaration

I hereby certify that the thesis I am presenting for examination for the degree Doctor of Philosophy in Medicine in the College of Medicine and Health, University College Cork, is solely my own work, other than where I have clearly indicated that it is the work of others.

I consider the work to be a complete thesis fit for examination.

Signed__________________________

Date___________________________

Dedication

To Mum, Dad, Declan and Jimmy

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I wish to thank my supervisors, Professor Jonathan Hourihane, and Dr. Tony Fitzgerald for sharing their time and expertise throughout this PhD. You both were very generous with your skills and experience; your guidance and support was most appreciated.

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Naturally, meeting the children in schools was fantastic; and my Irish improved along the way. For taking the questionnaires home and asking your Mum or Dad to fill them in….*go raibh míle maith agaibh*!

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List of Abbreviations

ALADDIN	Assessment of Lifestyle and Allergic Diseases During Infancy
ALSPAC	Avon Longitudinal Study of Parents and Children birth cohort
AR	Allergic Rhinitis
ARIA	Allergic Rhinitis and its Impact on Asthma
BASME	Children, Allergy, Milieu, Stockholm, Epidemiological Survey
BCG	Bacille Calmette-Guérin
BHR	Bronchial Hyperresponsiveness
CAMP	Childhood Asthma Management Program
COAST	Childhood Origins of ASThma
COPSAC	Copenhagen Study on Asthma in Childhood
DC	Dendritic Cell
DEPs	Diesel Exhaust Particulates
EASI	Eczema Area and Severity Index
ECA	Environment and Childhood Asthma study
ELISA	Enzyme Linked ImmunoSorbent Assay study
ENRIECO	The ENvironmental health Risks In European birth Cohorts collaboration
FLG	Filaggrin
Foxp3	Forkhead box protein 3
GA^{2}LEN	Global Allergy and Asthma European Network
GALT	Gut-Associated Lymphoid Tissue
GINA	Global Initiative for Asthma
GIS	Geographical Information System
GP	General Practitioner
GWAS	Genome-Wide Association Study
IgE	Immunoglobulin E
IAR	Intermittent Allergic Rhinitis
ISAAC	International Study of Asthma and Allergy in Childhood
LISA	The influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany and the development of allergies in childhood.

LISAplus	The influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany Plus the influence of traffic emissions and genetics study
LUR	Land Use Regression Model
MAAS	Manchester Asthma and Allergy Study
MAS	German Multicentre Allergy Study
MACS	The Melbourne Atopy Cohort Study
NICE	The National Institute for Health and Clinical Excellence
NO_2	Nitrogen dioxide
O_3	Ozone
PAR	Perennial Allergic Rhinitis
PASTURE	Protection Against Allergy Study in Rural Environments study
PER	PERsistent Allergic Rhinitis
PIAMA	The Prevention and Incidence of Asthma and Mite Allergy study
PM	Particulate Matter
RSV	Respiratory Syncytial Virus
RV	Respiratory Virus
SAR	Seasonal Allergic Rhinitis
SCARPOL	Swiss Surveillance Program of Childhood Asthma and Allergies with respect to Air Pollution
SCORAD	Severity Scoring of Atopic Dermatitis
SNP	Single Nucleotide Polymorphism
SP-D	Surfactant Protein D
T4SS	Total 4 Symptom Score
Th cell	T helper cell
TGF-β	Transforming Growth Factor-beta
TLR	Toll Like Receptor
T_{reg}	T regulatory cell
VAS	Visual Analogue Score
WAO	The World Allergy Organisation

Thesis Abstract

Background: Childhood asthma, allergic rhinitis and eczema are complex heterogenic chronic inflammatory allergic disorders. They constitute a major burden to children, their families and society, hugely affecting physical, social and psychological quality of life. The prevalence of childhood allergic disorders is increasing worldwide and merely rudimentary understanding exists regarding causality, or the influence of the environment on disease expression. Phase Three of the International Study of Asthma and Allergy in Childhood (ISAAC) reported that Irish adolescents had the 4th highest eczema and rhinoconjunctivitis prevalence and 3rd highest asthma prevalence in the world. There are no ISAAC data pertaining to young Irish children. In 2002, using the ISAAC methodology and protocol, Sturley reported a high prevalence of current asthma in Cork primary school children aged 6-9 years.

Aims: The overall aims of this thesis are:

1. To establish the 2007 prevalence and trends of prevalence of allergic disorders in Cork schoolchildren aged 6-9 years and in Irish adolescents (aged 11-13 vs. 13-14 years) and to stratify prevalence results by sex.
2. To examine the natural history of allergic disorders in a cohort of children from 6-9 years to 11-13 years.
3. To investigate putative protective and risk factors associated with prevalence of childhood allergic disorders in young school children from rural and urban locations (age 6-9 years).

Methods: This thesis comprises of three cross-sectional studies and a quasi-retrospective cohort study. Although not part of ISAAC, data was attained by parentally completed ISAAC-based questionnaires, using the ISAAC protocol.

Study1: Prevalence data from two identical cross-sectional studies performed in 2002 and 2007, pertaining to children aged 6–9 from the same 24 Cork City schools, were compared (Sturley, 2002 n=1474, response rate=74.8% vs. Duggan, 2007, n=1535, response rate=76.2%), to examine trends of prevalence in young children aged 6-9 years.

Study 2: In 2007, a cross-sectional study was performed in 110 randomly selected, rural and urban, state-funded primary schools, to assess prevalence of allergic disease and putatively associated factors, in children (n=3464, age 6-9, response rate=75.8%), living in rural and urban environments in Cork.

Study 3: In 2007, a quasi-retrospective cohort study examined the prevalence of allergic disease in children aged 6-9 years until 11-13 years, to examine the natural history of allergic disease in this population. The cohort study re-examined children from year 3 of school (1st class) in 2002 (Sturley, n=1474, age 6-9, response rate 74.8%), in the 8th and final year of primary school in 2007 (Duggan, n=706, age 11-13, response rate=70.8%).

Study 4: Prevalence data from adolescents in the Duggan, 2007 study (n=706, age 11-13) were compared against prevalence data from the Manning 2002, Irish ISAAC Phase 3 study (n=3089, age 13-14), to examine the trends of prevalence of allergic disease in Irish adolescents.

Results: Study 1 revealed that the prevalence of asthma had plateaued at 23.5%, but remained high in relation to many other countries. Significant increases were found in the prevalence of rhino-conjunctivitis (7.6 to 10.6%, $p=0.005$) and current eczema (8.9 to 13.5%, $p<0.001$). The prevalence of lifetime eczema had significantly reduced (21.6% to 15.0%, $p<0.001$). An alteration in the sex-specific profile of current asthma and lifetime allergic rhinitis towards equalization in distribution was also evident.

Study 2 observed many positive and negative associations with parental and child exposures. Early childhood antibiotic consumption was positively associated with allergic rhinitis ($p<0.001$) and in a dose-dependent manner with the development of current asthma ($p<0.001$). Early respiratory infection was a risk factor for current asthma (OR 1.9; 95% CI 1.55, 2.4) and lifetime asthma (OR 2.1; 95% CI 1.74, 2.64), current allergic rhinitis (OR 1.3; 95% CI 1.04, 1.55) and lifetime eczema (OR 1.3; 95% CI 1.02, 1.58). Gastrointestinal infection, prior to 3 years of age, was a risk factor for current asthma (OR 1.3; 95% CI 1.07, 1.67) and current allergic rhinitis (OR 1.5; 95% CI 1.12, 1.91). Passive smoking was a risk factor for current asthma (OR 1.4; 95% CI 1.07, 1.73), while maternal smoking in the child's first year of life was found to protect against lifetime eczema (OR 0.8; 95% CI 0.58, 0.97) and current eczema prevalence (OR 0.7; 95% CI 0.57, 0.94). An inverse association was observed between current exposure to farm animals and both current asthma (OR 0.6; 95% CI 0.4, 0.98) and lifetime asthma (OR 0.6; 95% CI 0.43, 0.9). Current barn exposure was protective against the development of current allergic rhinitis (OR 0.6; 95% CI 0.35, 0.95), while positive associations between lifetime eczema and the mother being farm reared were observed (OR 1.4; 95% CI 1.06, 1.83). Pregnancy barn exposure (OR 2.0; 95% CI 1.27, 3.04) and year 1 stable exposure (OR 3.7; 95% CI 1.55, 8.93) were risk factors for current eczema. An inverse association was found between exposure to furry pets during pregnancy and lifetime eczema (OR 0.8; 95% CI 0.61, 0.95) and current furry pet exposure was positively associated with current rhinoconjunctivitis (OR 1.3; 95% CI 1.02, 1.75). Damp bedroom exposure during the first year of life was positively associated with lifetime asthma (OR 1.4; 95% CI 1.07, 1.89). Full time crèche attendance in the first year of life was inversely associated with current asthma (OR 0.7; 95% CI 0.53, 0.94).

Study 3 demonstrated many variations in allergic disease prevalences from 2002-2007 in this cohort of children (aged 6-9 until 11-13). The prevalence of asthma decreased (21.7% to 17.1%), lifetime asthma remained stable. Current rhino-conjunctivitis prevalence (7.6% to 13.7%) and lifetime hayfever prevalence (9.0% to 14.9%) increased, while current allergic rhinitis prevalence remained stable (26.1%). Current eczema prevalence stabilised (8.9% to 10.5%), whereas, lifetime eczema reduced dramatically (21.6% to 12.1%) in this cohort of children. Co-morbidity of allergic disease remained high. There was a shift from male dominance to equalisation in the ratio of asthma symptom prevalence, although severe symptoms were more prevalent in females.

Study 4 revealed a decrease in the prevalence of current asthma (26.7% to 17.1%) and a stabilisation in the prevalence of lifetime asthma (21.6% to 24.6%). Lifetime hayfever had decreased (31.5% to 14.9%), while allergic rhino-conjunctivitis prevalence remained stable (15.5% to 13.7%). The prevalence of current eczema had increased (8.6% to 10.5%), while lifetime eczema prevalence had stabilised (14.3 to 12.0%).

Conclusions: The prevalence, natural history and risk factors of childhood allergy in Ireland, as described in this thesis, echo those in worldwide allergy research. The variations of prevalence in different populations worldwide and the recurring themes of associations between childhood allergy and microbial exposures, from farming environments and/or gastrointestinal infections, as shown in this thesis, strengthen the mounting evidence that microbial exposure on GALT may hold the key to the mechanisms of allergy development. In this regard, probiotics may be an area of particular interest in allergy modification. Although their effects in relation to allergy, have been investigated now for several years, our knowledge of their diversity, complex functions and interactions with gut microflora, remain rudimentary. Birth cohort studies which include genomic and microbiomic research are recommended in order to examine the underlying mechanisms and the natural course of allergic diseases.

Chapter 1

Introduction

1.1 BACKGROUND TO THESIS

Childhood asthma, allergic rhinitis and eczema are chronic, inflammatory, heterogenic allergic disorders. They constitute a major burden to children, their families and society, hugely affecting physical, social and psychological quality of life (1-4). Asthma is an allergic airway disorder involving recurrent episodes of wheezing, breathlessness, chest tightness, and coughing (5). Allergic rhinitis also involves the upper airways and is characterised by nasal congestion, rhinorrhoea, sneezing, and nasal itching (2). Eczema is a chronic inflammatory skin disorder which presents with itchy skin lesions on the cheeks, forehead and flexural areas (6).

The prevalence of childhood allergic disorders is increasing worldwide, especially in developing countries (7). The *International Study of Asthma and Allergy in Childhood* (ISAAC) is a four-phase worldwide initiative, developed to investigate prevalence, elucidate associations and monitor prevalence trends of childhood asthma, allergic rhinoconjunctivitis and eczema, (using validated and standardised questionnaires and protocols), while aiming to develop a database of evidence-based best practice guidelines to improve childhood allergy diagnosis and management (8-10). Phase Three of ISAAC (examining trends of prevalence) reported that, despite recent reductions, Irish adolescents had the 4th highest eczema and rhinoconjunctivitis prevalence and 3rd highest asthma prevalence in the world (7). There are no ISAAC data pertaining to young Irish children. Few Irish data examine the prevalence of asthma and allergy in young Irish children. In 2002, using the ISAAC methodology and protocol, Sturley examined primary school children aged 6-9 years from Cork city and suburbs and found the prevalence of current asthma was 21.5% (11), which was significantly higher than that of 15.5% found in a similar age group of children in Galway in 1996 (12).

Despite extensive research focus, only rudimentary understanding exists regarding causality and disease expression (13-16). Many environmental factors have been investigated in an effort to increase our understanding of these complex diseases. A theory called the *Hygiene Hypothesis* has been the focus of much investigation since it was first proposed by Strachan in 1989, in response to the increasing prevalence of childhood atopic disease. The hypothesis asserts that growing up in a more hygienic environment with less microbial exposure is associated with allergic sensitisation and the development of atopy, especially rhinitis (17, 18). Substantiating this theory, some early life exposures to certain allergens have been found to have a protective effect on the development of childhood atopy. For example, children reared on farms demonstrate a lower prevalence of asthma and atopy than their non-farming peers (19). Contact with livestock and unpasteurised milk consumption appear to be the mediating exposures which convey protection (20). Other markers of bacterial and viral encounters which have been investigated include day-care attendance, immunisation and sibship size but results have been inconsistent regarding their association (21). Research evidence has resulted in a new interpretation of the hygiene hypothesis, that allergy is not only mediated by microbial stimuli, but also by gene-environment interactions, gene-gene interactions and predisposition to atopy (21, 22). Furthermore, increased knowledge of the critical role of T regulatory cells (T_{regs}), in immunoregulation has moved the understanding of allergy development away from the original concept of T helper cell (Th)1-Th2 imbalance (23, 24).

The potential effect of gastrointestinal infections on allergy development has been extensively researched, as infections potentially enhance immune maturation by stimulation of the vast lymphoid tissue containing T_{regs} in the gut (25). Exposures to foodborne infections and Hepatitis A virus (markers of unhygienic exposure to orofaecal and foodborne microbes) have been found to protect against the development of allergy (26-28). However, the literature is inconsistent, as other studies have found a positive association (29), or no association (30) with allergy development.

The association between antibiotic consumption in early childhood and the development of childhood allergic disease has also been extensively examined. The association is biologically plausible considering the immunomodulatory capacity of the gut. Antibiotics reduce the commensal gut flora biodiversity and potentially disrupt immunoregulation (31). However, the examination of the effect of antibiotics on allergy development has produced conflicting results (32-36). For the most part, when the association with asthma development has been examined, positive associations have been predominant when studies were confined to early exposure (prior to 2 years of age) (32). In ISAAC, antibiotic use in the first year of life was associated with childhood current asthma throughout most regions in the world (37). They found a weaker association between antibiotics and the development of rhino-conjunctivitis and eczema in 6-7 year old children.

Another linked factor of considerable focus is the association between viral respiratory infections and the development of asthma. Respiratory infections such as bronchiolitis commonly occur in young babies, are usually viral in origin and present with wheezing, tachypnoea, airway inflammation and respiratory distress, similar to symptoms of asthma. Approximately one third of children with acute wheezing from viral infections such as bronchiolitis progress to develop asthma (38). Similarly, frequent upper respiratory infections are also positively associated with allergic rhinitis (39). The relationship between early viral infection and asthma and rhinitis is complex; it has been found to present most risk for children who are already pre-disposed to atopy (39-42).

Ireland is an ideal setting in which to examine the prevalence of asthma and allergy, as it underwent huge economic changes in the “Celtic Tiger” period, between 1995 and 2008. To put the changes into context, in 1988, *The Economist* described Ireland as “the poorest of the rich”; with a gross domestic product only 64% of the EU average (43). Within a decade, in 1997, Ireland was pronounced as “Europe’s shining light”, with an economy which was among the most prosperous in Europe (44, 45). The economic success was accompanied by many environmental and lifestyle changes including increased standards of living, higher levels of education, less unemployment and increased private car ownership with significantly higher greenhouse gas emissions (46, 47).

The population in the Sturley study was primarily urban and suburban; therefore, it is important to extend the examination to children from rural areas. Cork city and county provide a diverse setting in which to compare populations from urban and rural locations. Cork is the largest county in Ireland covering an area of 7,454 sq. km, with a coastline of 1,100 km. It has a lower population density than the EU average (39 vs. 115 persons per square kilometre). The hinterlands of main towns in the north and west of the County are predominantly rural; here the population density reduces to an average of 23 persons per square kilometre (48).

Cork city, being the principal population centre in the Southwest region of Ireland, is a relatively busy urban area, with a variety of industries located in the surrounding environs (49). In the 2006 Census, the population of Cork City and suburbs was 190,384 with 290,911 people living in the rural towns, villages and farms (50). In Cork, there are over 14,000 active farms (51) of which 4293 specialise in dairy farming (52). Typically in Ireland, the average farm size is small (81 acres), not intensive and family run. In total, 91% of land is given to grass production (silage, hay and grazing) for feeding livestock. For the most part (93%), Irish farming is devoted to dairy and livestock production (51, 53). In Irish small holdings, family consumption of raw (unpasteurised) milk is common. In 1998, a study of farms in 8 Irish counties, (including Cork), found that raw milk was consumed in 84% of farms, many of which were home to young children (54). This practice persists as farm families consider the consumption of raw milk to be cost-effective, convenient, safe, healthier and, of higher quality than pasteurised milk (55, 56).

The question remains, why is the prevalence of allergic disease in Irish children so high? No genetic evidence exists that Irish children are more susceptible to atopic conditions than their counterparts worldwide. The alteration in the economic climate and resultant different exposures, coupled with the high asthma prevalence in young Cork schoolchildren (11), warrants continued investigation of the trends of prevalence allergic conditions in this young population. Altered allergen exposures during the economic boom may have resulted in different gene-environment interactions, and gene-gene interactions, causing varying sensitisation effects. Previous studies have demonstrated that interactions between exposures and antibody responses are specific to the allergens found in each environment (57). The diversity of exposures in Cork City and County facilitates investigation of a range of rural and urban putative associated protective elements and risk factors in this young population.

1.2 SUMMARY OF THESIS

Overall, this Thesis is comprised of 4 studies which explore prevalence trends and factors associated with childhood asthma, allergic rhinitis and eczema in the Irish context. Using the ISAAC core questionnaire and protocol, it examines school children from two age groups, namely, 6-9 years and 11-13 years living in Cork City and County. The broad aims of the thesis include:

1.2.1 Aims

1. To establish the 2007 prevalence and trends of prevalence of asthma and allergic disorders in Cork schoolchildren.
2. To explore the natural history of asthma and allergy in Cork young schoolchildren until they reach early adolescence.
3. To examine the trends of prevalence of allergic diseases in Irish adolescents.
4. To examine the protective elements and risk factors associated with the development of asthma and allergic disorders in Cork schoolchildren.
5. To explore the relationship between exposure to a farming and/or rural environment and the development of childhood allergic disease.
6. To study the effect of antibiotic consumption on the development of childhood atopic conditions.
7. To examine the effects of early childhood infections on the development of childhood allergic disease.

1.2.2 Objectives

1. To measure the prevalence of symptoms indicative of childhood allergic diseases within the sample populations of younger and older children in the study.
2. To examine the trends of prevalence of symptoms of allergic diseases within the sample populations of younger and older children in the study.
3. To examine the natural history of childhood allergy in Cork schoolchildren aged 6-9 until 11-13 years.
4. To stratify the prevalence of all allergic symptoms by sex.

5. To investigate the symptoms of childhood allergic disease prevalence in relation to protective associations and/or risk factors. Specifically:
    a. To study the effects of the exposures of a rural or farming environment on the development of childhood allergic disease.
    b. To examine the effects of early childhood infections on the development of childhood allergic disease.
    c. To investigate the effects of early childhood antibiotic consumption on the development of childhood allergic disease.

1.2.3 Thesis study components

This thesis contains 4 studies. The population involved in each study are presented in Figure 3.1 (Chapter 3, page 72). Studies 1 and 2 examine children aged 6-9 years, while studies 3 and 4 are concerned with older children aged 11-13 years. The ISAAC core questionnaire and protocol were used to obtain data for all four studies. The studies are explained in more detail in the following section.

1.2.3.1 *Children aged 6-9 years*

Study 1

Study 1 aims to examine the prevalence trends of childhood asthma and allergy in children aged 6-9 years from 2002 to 2007. Previously, Sturley (2002), in a prevalence study of 1474 urban/suburban children (aged 6-9), reported higher prevalence rates of asthma than previous Irish studies of similar age groups. No trend data for this age group exists in the Irish context. Study 1 aims to fill this gap in the literature by performing a follow-up to the Sturley 2002 study. In 2007, children (n=1535, aged 6-9), from the same 24 schools as the 2002 Sturley study (n=1474, age 6-9), were examined using the same ISAAC methodology. This study was motivated by the huge changes in the Irish socio-economic climate in the 5 years between 2002 and 2007, resulting in a higher standard of living and altered environmental exposures. Therefore, given that ISAAC deemed five years as the acceptable time interval for trend studies (7), the study was pragmatically designed to avail of the opportunity to concurrently perform the trends study along with a retrospective cohort study in older children within the same schools. Otherwise, this opportunity would have been missed, as the older children were leaving school and would be untraceable. Research evidence demonstrates that gene-environmental interactions mediate the prevalence of childhood allergic disease. Study 1 examines the prevalence trends of childhood allergic disease and explores possible effects of alterations during the economic changes during the intervening years from 2002 to 2007.

Hypothesis – "The hygiene hypothesis"

Underpinned by the hygiene hypothesis, study 1 hypothesises that the prevalence of childhood allergic disease will have increased between 2002 and 2007, in line with the increased standards of living and associated increased levels of hygiene in the intervening years.

Study 2

The Sturley (2002) study examined factors associated with of allergic disorders in children from urban/suburban schools (n=24 schools, 1474 children). Study 2 repeats the examination of children from these 24 schools and, to facilitate the comparison between the exposures from urban and rural environments; it also examines children from an additional 87 schools in rural locations. In total, the study population of Study 2 includes 3464 children from 110 schools throughout Cork city and County. Study 2 examines the potential factors associated with the development of allergic disorders in this age group. It examines three main hypotheses:

Hypothesis A – "The farming effect"

Hypothesis A is underpinned by the hygiene hypothesis and associated supporting international evidence. It proposes that the increased microbial exposures associated with living in a rural and/or farming environment in Cork protect against the development of childhood allergy. The specific elements of the hypothesis include:

1. Cork schoolchildren who are regularly exposed to farm animals are protected against the development of allergy.

2. Cork schoolchildren who are regularly exposed to barns/stables are protected against the development of allergy.
3. Cork schoolchildren who consume unpasteurised milk in early childhood are protected against the development of allergy.
4. Cork schoolchildren living in the countryside, who drink water from a home well water source, are protected against the development of allergy.
5. Parental childhood exposure to a rural or farming environment is protective against the development of childhood allergy in the offspring.
6. Maternal prenatal exposure to a rural or farming environment is protective against the development of childhood allergy in the offspring.

Hypothesis B – Childhood infections

Also, theoretically grounded by the hygiene hypothesis, Hypothesis B examines the role of early childhood infections on the development of childhood allergic disease. The specific hypotheses include:

1. Early childhood gastrointestinal infections protect against the development of childhood allergy in Cork schoolchildren.
2. Early childhood respiratory infections are positively associated with the development of childhood allergy in Cork schoolchildren.

Hypothesis C - Antibiotics

Underpinned by the understanding of the importance of gut microflora in the maintenance of normal immunoregulation (development from the hygiene hypothesis), Hypothesis C examines the effect of receiving antibiotics in early childhood on the prevalence of childhood allergic disease. The hypothesis is that consumption of antibiotics in early childhood is positively associated with the development of childhood allergic disease in Cork schoolchildren.

1.2.3.2 *Children aged 11-13 years*

Study 3

The high ISAAC adolescent rates of asthma, rhinitis and eczema merit on-going examination of this age group in the Irish context. Yet, no cohort study exists in the Irish context to examine the natural history in this population. Therefore, when faced with the unique opportunity to attain data from the same cohort of children over two time periods, a quasi-retrospective cohort study was performed. This cohort study is a repeat study of children who were aged 6-9 during the Sturley 2002 study and were aged 11-13 in 2007 (their last year in primary school). It investigates the natural history of asthma and allergy in children from Cork city and suburbs from 6-9 years until 11-13 years (Sturley, 2002, age 6-9, n=1474 and Duggan, 2007, age 11-13, n=706).

Hypothesis – Natural history of childhood allergy

The hypothesis is that the natural history of asthma and allergy in Irish adolescents may be different to their international counterparts because of different gene-environmental interactions.

Study 4

It is important to assess trends in Irish adolescents, because of the high prevalence in comparison to international rates. Therefore, the purpose of Study 4 is to examine prevalence trends of allergic diseases in Irish adolescents (2003-2007). In 2003, Manning published the prevalence of childhood allergic disease in ISAAC Phase 3 (age 13-14, n= 3089). These results were compared to the prevalence rates of the children in the 2007 aspect study 3 described above (Duggan, 2007, age 11-13, n=706).

Hypothesis – Trends of prevalence in adolescents

The hypothesis is that the trends of prevalence of allergic disease in Irish adolescents may be different to those internationally, because of different environmental exposures and genetic make-up.

1.3 SCOPE OF THESIS

This study examines the atopic diseases of asthma, allergic rhinitis and eczema in childhood. It is primarily epidemiological in nature and therefore the literature review and thesis will focus on the prevalence and potential modifying factors associated with these diseases. Genetic and immunological factors are also discussed, as they support the biological plausibility of associations found in the study.

Although asthma, allergic rhinitis and eczema are referred to as allergic conditions throughout the thesis, it is accepted that without biological markers, one cannot differentiate between allergic and non-allergic presentations (58). Nevertheless, this study uses the ISAAC questionnaire and protocol, which is a standardised, validated tool used to elucidate the prevalence of these three allergic disorders; it is therefore deemed acceptable practice to refer to the conditions as allergic (59). There are many putative risk and protective factors linked with the development of childhood allergic disorders; however, it is beyond the scope of the study to investigate all of them.

1.4 OUTLINE OF THESIS

Chapter 1 is an introductory chapter. It commences with a brief background to the childhood allergic diseases of asthma, allergic rhinitis and eczema. It outlines the main putative associated factors which are examined in the study and the context of the location of study is described. Finally, the aims, objectives, rationale, hypothesis, scope and outline of the thesis are summarised. Chapter 2 is a review of the current literature pertaining to the childhood allergic conditions of asthma, allergic rhinitis and eczema. It concludes with the expected contributions of this thesis to the body of knowledge. Chapter 3 describes the study design, tools and research methods employed in thesis. It also describes and rationalises the use of statistical analyses and data management. In Chapter 4, the results of the thesis are presented. Results commence with the socio-demographic and descriptive data pertaining to the study participants, followed by the results of the four studies within the thesis. In Chapter 5, the results are discussed in relation to the current evidence.

The novel aspects and implications, strengths and limitations are also debated. It concludes with recommendations for future research. The contributions of the author and others involved in the Thesis are presented in Table 1.1.

Table 1.1 *Contributions to the thesis*

	Author's personal contributions	Assistance received
Study concept and design	Performed a literature review Adapted the modifying factors aspect of the questionnaire Prepared research protocol. Applied for and received ethical approval.	Expert advice from the Research Team: ○ Professor Jonathan Hourihane, Department of Paediatrics UCC ○ Professor Ivan Perry, and Dr Tony Fitzgerald, Department of Epidemiology and Public health, UCC ○ Dr J. Sturley, Department Early Childhood Care and Education, Mary Immaculate College, Limerick.
Questionnaire design and layout	Designed questionnaire layout into suitable format for upload to *Teleform*® Scanner Software Uploaded the questionnaire to *Teleform*®	Educated regarding the use of the *Teleform*® software and scanner by: ○ Ms. Vera McCarthy (Dept. of Epidemiology and Public Health).
Study process	Contacted previously involved schools and recruited 87 further schools in rural areas	
Data collection	Collected data from 110 schools in Cork City/County	Kindly facilitated by: ○ School headmasters/mistresses ○ Teachers ○ Parents and children
Data entry	Entered 4170 questionnaires into *Teleform*® software for export to Microsoft Excel, via sidekick scanner	Eight hours of student assistance to enter data, provided by: ○ The Department of Paediatrics and Child Health, UCC
Data analysis	Analysed data for all studies	Statistical advice received from: ○ The research team ○ Dr Anthony Fitzgerald ○ Ms. Jennifer Lutomski (Department of Epidemiology and Public Health)
Publication and Dissemination	Presented research findings in the form of a Thesis Published 1 research article Two articles in preparation	Guidance, proof-reading and corrections provided by: ○ All members of the research team.

Chapter 2

Literature Review

2.1 INTRODUCTION

This literature review commences with an overview of atopy and the atopic diseases of asthma, eczema and allergic rhinitis. Epidemiological evidence surrounding allergy development in relation to smoking, breastfeeding and the hygiene hypothesis will be reviewed. Although this is an epidemiological study, the literature pertaining to the genetic and immunological pathophysiology of allergic disease is included in the literature review, as it is often essential in order to support the biological plausibility of the study findings. The chapter concludes with the expected contributions of this thesis to the body of knowledge.

2.2 ATOPY

The term 'atopy' has been used since the 1930s to describe conditions associated with the clinical and biological responses (skin-prick test hypersensitivity and high serum levels of specific associated immunoglobulin E (IgE) molecules) when exposed to inhaled or digested or environmental allergens (60). According to the revised nomenclature for allergy for global use, atopy is defined as *...a personal and/or familial tendency usually in childhood or adolescence to become sensitised and produce IgE antibodies in response to ordinary exposures to allergens, usually proteins, as a consequence, these persons can develop typical symptoms of asthma, rhinoconjunctivitis or eczema* (58). The childhood atopic allergic disorders of asthma, allergic rhinitis and eczema are a major burden to children and their families, as they often impair a child's ability to partake in normal childhood activities, can severely impair the quality of life if left untreated, and are often responsible for many hospitalisations/healthcare visits, absenteeism from school/day-care resulting in missed days from work by parents (1-4, 61, 62). Childhood allergic diseases are extremely complex and heterogeneous disorders, which are both genetically and environmentally mediated. Several phenotypes exist which differ with age of onset, sensitisation, gene-environment interactions, severity, comorbidities and development over time (63).

2.3 ASTHMA

Childhood asthma is a complex inflammatory allergic airway disease resulting in bronchospasm and bronchial hyperresponsiveness which cause episodes of wheezing, breathlessness, chest tightness and coughing (64). Despite being the most common chronic disease in children, a diagnostic definition remains elusive, because of its heterogeneity (64). Asthma may be of allergic (IgE mediated) or non-allergic origin (58) and its pathophysiology depends upon complex genetic-environmental interactions (65). It produces structural airway remodelling involving a plethora of structural changes (including epithelial damage, elastin destruction, thickening of the sub-basement membrane and mucous gland hyperplasia), resulting in smooth muscle hyperplasia and hypertrophy and impaired lung growth and development (66). Consequentially, the epithelium in asthmatic airways is more fragile and permeable, allowing increased entry of inhaled allergens, pollutants and irritants (66).

The global burden of childhood asthma is considerable; it affects approximately 7 million (9.4%) children in America (67). Up to 9.3 million children are affected in Europe, costing as much as €5200 million per year (68). The burden of asthma on children’s quality of life is also extensive. In a qualitative study to develop a quality of life questionnaire for children with asthma, the themes which emerged from focus groups were that asthma negatively influenced children’s lives on many levels. Children reported that they were not just affected by the physical aspects such as shortness of breath and cough, but there were many emotional and social implications. They complained of feeling dependant on medication, and being bullied as they stood out as being different and often unable to participate in activities (69).

2.3.1 Diagnosis of asthma

In recognition of the difficulty with diagnosis and management of childhood asthma, (owing to the heterogeneity of clinical presentations) and the associated mortality and morbidity, the *Global Initiative for Asthma* (GINA, a World Health Organisation initiative) devised child-specific criteria for asthma diagnosis and management (5). The overall aims of GINA are improved assessment, monitoring, and control of asthma, through which, the enormous burden may be reduced for many children, so that they may enjoy the normal activities of life. The GINA guidelines recommend that a diagnosis of asthma ought to be considered if any of the following signs or symptoms are present:

- Frequent episodes of wheezing – more than once a month
- Activity induced cough or wheeze
- Cough particularly at night during periods without viral infections
- Absence of seasonal variation in wheeze
- Symptoms that persist after the age of 3
- Symptoms occur or worsen in the presence of:
    - Allergens (house dust mites, companion animals, cockroach, fungi)
    - Exercise
    - Pollen
    - Respiratory (viral) illness
    - Strong emotional expression
    - Tobacco smoke
- Child's colds repeatedly "go to the chest" or take more than 10 days to clear
- Symptoms improve when asthma medication is given

2.3.1.1 *Night cough*

Night cough is a recognised associated symptom of asthma and shares many of the long-term effects of classic wheezing asthma e.g. airway remodelling (70). However, while cough variant asthma is well recognised in adults (71), there is a paucity of related empirical data in children (72). Caution is advised when diagnosing and treating asthma in children based only on the presence of a persistent cough (73-76), as other possible aetiologies exist (77-79) and unnecessary treatment from incorrect diagnosis can have adverse effects (80). Recognition and treatment of cough variant asthma is included in the GINA guidelines (5).

2.3.2 Natural history of asthma

Asthma symptoms have been recorded far back in history, but, despite much research, the classification and natural course of this complex disease still remains an issue for investigation (81). Anecdotally, there was always an awareness that many children "grew out of asthma" and as asthma prevalence is lower in adults than in children, there is an acceptance that remission occurs in many children (7, 67, 81). Initially, long term cohort studies were set up to examine the natural history of asthma, however, they have developed to provide a framework within which to understand the complex nature and prognosis of different presentations of asthma in early years of life (82).

Some long-term trajectories of the natural course of asthma have been reported from older long running cohort studies. The *Australian Melbourne Asthma Study* found an association between severe childhood asthma and asthma persistence into adulthood. They recruited 295 children with a history of wheezing and 106 without (aged 7 years in 1964, 3 years later they added 83 children with severe asthma). On examination at 42 years old (87% cohort retention), 20% who had asthma at 7 years of age reported asthma symptoms aged 42 years, compared to 50% of the cohort of children recruited at age 10 with severe asthma symptoms in childhood (83). There were limitations to this study's methodology and also treatments have altered significantly since the study commenced.

However, treatment has been demonstrated not to have an effect on the long-term outcome of disease. The *Childhood Asthma Management Program* (CAMP) initially started as a randomised controlled trial (4.3 years) comparing two treatments (anti-inflammatory drugs – budesonide or nedocromil, each versus placebo, followed by 4 additional years of observation) in order to establish if treatment had an impact on remission. The trial was followed by a four year observation period. They concluded that the progression or remission of asthma does not appear to be decided by treatment choice rather than by issues such as sensitization and exposure, lung function, and airway hyper responsiveness (84). The presentation of asthma is heterogeneous in childhood, making it very difficult to examine the pathways of asthma development.

2.4 ALLERGIC RHINITIS

Allergic rhinitis (AR) is a chronic disease affecting the upper airways which is characterised by nasal itching, sneezing, watery rhinorrhoea and nasal obstruction (85). When AR includes the ocular symptoms of eye itch, tearing, redness and lid puffiness, it is termed “rhino-conjunctivitis” (86). AR is IgE-mediated, involving mast cell degranulation, release of mediators and subsequent release of inflammatory cells (85). The major aggravating allergens are from pollens (grass, tree and weeds), pets (cats, dogs, rabbits, horses) and house dust mite (14).

Allergic rhinitis frequently occurs in children with asthma, typically presenting after the second year of life (87) and has been found to predict asthma incidence and persistence into middle age (88). The prevalence of AR in young children (age 6-7) increased in most countries globally in ISAAC Phase Three and was found to be as high as 40% in some centres (7). The *German Multicentre Allergy Study* (MAS, birth cohort study, 0-10 years, n=1314) reported a rising prevalence from early childhood to adolescence, with a higher risk associated in children with allergic predisposition who were sensitised to aero-allergens (89). MAS also reported that children with *severe persistent AR* suffered proportionately more wheezing symptoms than children with *mild persistent* or *intermittent AR*. Asthma and AR commonly co-exist and there are many similarities in their pathogenesis, giving rise to the concept of “one airway, one disease” (85).

The impact of childhood allergic rhinitis is substantial, often affecting children’s cognitive performance and overall quality of life (62, 90, 91). In America, Meltzer et al. conducted a telephone survey of parents and children (n=500 children with allergic rhinitis, n=504 without rhinitis) to elucidate the burden of allergic rhinitis on children’s and families lives (2). The cardinal physical symptoms of AR were reported to be moderately to severely bothersome and frequently extended to headaches, facial pain, ear pain and dry irritable cough, practically on a daily basis during exacerbations. Many children suffered sleep deprivation and resultant tiredness, misery and irritability. Children with allergic rhinitis were twice as likely to suffer impaired involvement in their daily activities of living and 4 in 10 children with allergic rhinitis reported that it affected their performance at school. Parents complained about the lack of efficacy of the medication and children found it to be unpleasant both in taste and sensation (running down the back of their throat).

The *Environment and Childhood Asthma* (ECA, birth cohort study 0 – 10 years, allergic sensitisation tests, parental interviews, clinical examination, lung function tests, n=1019) study, in Norway found that 87.4% of children with rhinitis had at least one co-morbid allergic condition (92). The reported prevalence of co-morbid conditions was very high (conjunctivitis = 75.5%, current asthma = 31.7%, current atopic eczema = 30.3%). Children with allergic sensitisation and rhino-conjunctivitis had more frequent and severe bronchial hyperresponsiveness (BHR). Children who suffered AR symptoms associated with exposure to pollen and furry pets were more likely to suffer from concomitant asthma than those who suffered symptoms of AR from just pollen exposure. Overall, symptoms triggered by exposure to pollen resulted in higher impairment of the activities of daily living (92).

2.4.1 Allergic rhinitis and its impact on asthma (ARIA)

In recognition of the high prevalence of AR patients with concomitant asthma and the negative impact of undiagnosed, untreated or mismanaged AR on asthma, the *Allergic Rhinitis and its Impact on Asthma* (ARIA) workshop was set up by the World Health Organisation (85, 86). The ARIA classification and guidelines provide an evidence based, systematic stepwise approach to the diagnosis and management of AR, aiming to improve patients', clinicians' and policy makers' knowledge in order to improve management of AR and in turn, asthma. They have been validated in the paediatric population (86). The ARIA definitions of allergic rhinitis are as follows:

Intermittent –symptoms are present < 4 days a week or < 4 consecutive weeks

***Persistent* -** symptoms are present > 4 days a week and > 4 consecutive weeks

***Mild* -** none of the following items are present: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, symptoms are present but not troublesome.

Moderate/severe - one or more of the following items are present: sleep disturbance, impairment of daily activities, leisure and/or sport, impairment of school or work, troublesome symptoms.

2.5 ECZEMA

Eczema is a highly pruritic chronic inflammatory skin condition which is often the first manifestation of allergy in children (93). It is characterised by skin dryness and the presence of lesions which appear as pruritic red plaques which ooze when scratched (94). Eczema usually presents in infancy and early childhood with remission after adolescence in many cases, although it may recur in some adults at a later stage (95). It can present anywhere in the body, but in children it usually affects flexural areas and the face (96). Clinical diagnosis of eczema can be difficult, as other differential diagnoses exist, (for example, seborrhoic dermatitis or scabies) (95). To counteract misdiagnosis, guidelines were developed, such as those by Hanifin and Rajka (97) or the UK working Party (98-100). The UK working party diagnostic criteria which are the most validated are as follows:

The child must have: An itchy skin condition (or parental report of scratching or rubbing) in the past 12 months AND three or more of the following:

- History of involvement of the skin creases (fronts of elbows, behind knees, fronts of ankles, around neck or around eyes)
- Personal history of asthma or hay fever (or history of atopic disease in first-degree relative if child aged < 4 years)
- History of generally dry skin in the past year
- Onset before the age of 2 years (not used if child aged < 4 years)
- Visible flexural dermatitis (including dermatitis affecting cheeks or forehead and outer areas of limbs in children aged < 4 years)

The severity of eczema may be assessed using validated scores, such as *Eczema Area and Severity Index* (EASI) or *Severity Scoring of Atopic Dermatitis* (SCORAD) (101). Without diagnosis confirmed by IgE antibody determination or a skin test, the World Allergy Organisation (WAO) recommend that the terms atopic eczema/dermatitis should be replaced by the term eczema (58). The prevalence of childhood eczema is at times difficult to ascertain, as it depends upon the definition used by the researchers; for epidemiological purposes ISAAC defined current eczema as having a persistent flexural rash which was coming and going for at least 6 months, in the previous 12 months. ISAAC Phase Three found a worldwide increase in the prevalence of eczema with a large range of variability in prevalence rates (1.5% to 20.9%) in 6-7 year old children (102).

Childhood eczema impacts hugely on the quality of life of the child and their parents. A recent review of the effects of the symptoms describes the misery of living with the effects of itching, soreness, sleeplessness and the resultant exhaustion, lack of concentration, impaired cognitive and psychosocial functioning (together with many more negative impacts) (4). The impaired quality of life also extends to other family members as parents express feelings of exhaustion, guilt, anger and depression (4).

There is a strong link with eczema and atopy, as it often coexists with, or predicts the other two atopic conditions of asthma and rhinitis (61) and a systematic review of 13 prospective cohort studies reported that 1 in 3 children with eczema will go on to develop asthma (103). The natural history of eczema can be divided into 3 stages which are defined by the age of manifestation; namely, infantile (appears in the first year of life with itchy red bumps on cheeks, forehead, scalp, sometimes spreading to trunk and in more severe cases skin on hand and feet are dry), childhood (occurs from age 4-10 and is associated with itchy eruptions on face, trunk and flexural areas of arms or legs - scaly, dry and thickened skin) and adolescent/adult stage (develops post-puberty and may persist into adulthood. It is characterised by lichenified eczematous areas in face, neck, wrists, hand and flexural areas) (93, 104). Risk factors for the continuance of eczema symptoms and progression to the atopic march are severe childhood eczema, family history, filaggrin mutation, early wheeze and atopic sensitisation (93, 104).

2.6 PATHOPHYSIOLOGY OF ALLERGIC DISEASE

The childhood allergic conditions of asthma, rhinitis and eczema are characterised by inflammation, which is usually IgE mediated. They are the result of a complex interplay between inflammatory cells and synergistically orchestrated by several transcription factors and epigenetic modulation (105).

2.6.1 Immunological processes and allergy

The normal immune response to environmental allergens is that the immune system works in a synchronised manner to maintain homeostasis (23). Allergic diseases are the manifestation of an abnormal immune response, resulting in the development of IgE antibodies against common environmental allergens, in genetically predisposed children (106). The IgE orchestrated inflammatory process involves synergistic complex interplay between mast cells, basophils, lymphocytes, dendritic cells, eosinophils and, in severe cases neutrophils (105).

Mast cells exist in tissues throughout the body and when exposed to allergen release inflammatory mediators such as proteases, cytokines, and chemokines (105). Following allergen exposure, they initiate allergic inflammation in the mucosa by cytokines IL-9 and stem-cell factor (SCF) and in the skin by the cytokine (TSLP) (107). This is rapidly followed by release of synthesised mediators (Table 2.1) which cause result in bronchoconstriction, vasodilation, and plasma exudation causing asthma symptoms or, nasal secretions and inflammation causing allergic rhinitis symptoms (105). In the skin, mast cells appear to act as sensors of environmental and emotional stress (108), which, when activated, result in the inflammatory symptoms of the skin in eczema (109).

T-cell tolerance is the key mechanism promoting a normal immune response to what are known as *self* and *non-self* antigens (24). Antigen presenting cells called dendritic cells (DCs) play a key role in the differentiation of naïve $CD4^+$ T lymphocytes into subsets of T-helper cells (Th), namely Th1, Th2, Th9, Th17 and Th22 (110). The differentiation and processing of allergens by the highly specialised DCs is influenced by costimulatory signals, cytokines, chemokines and regulatory T cells (T_{regs}). T_{regs} are currently the only known population of lymphocytes mediating dominant tolerance; their suppressor function is vital for the maintenance of immune homeostasis (111). Basophils work with DCs to promote optimal Th2 activation (112). Th1 cells are responsible for delayed-type hypersensitivity reactions (secreting cytokines IL-2, IFN-γ, and TNF-α and TNF-β) and Th2 cells mediate against parasitic infections and produce the allergic inflammatory reactions to allergens, (secreting cytokines IL-4, IL-5, IL-9 and IL13) (113). Eosinophil production is induced by Th2 cells (mediated by release of IL-5) and is linked with airway remodeling in asthma (105). Another T cell lineage was recently discovered called Th17 cells (differentiate under the influence of IL-6, IL-21 and IL-23 and TGF-β), which are also associated with allergy (especially eczema) (114) and with neutrophilia in severe allergic asthma (105).

Experimental evidence demonstrates that the neonatal immune system displays a Th2 cell phenotype, which, through environmental exposures, matures towards a balanced interaction of Th1 and Th2 cells (115-117). Atopy occurs when there is Th2 skewed response to allergen exposure, leading to secretion of Th2-type cytokines and the subsequent development of allergen-specific IgE antibodies. Previously, allergy was thought to occur solely as a result of dysregulation in the Th1/Th2 balance. However, T_{regs} with their distinct phenotypes and mechanism of action to suppress or induce the production of IgE, are now known to play a key role in immune homeostasis (24).

Figure 2.1 *Effects of the release of mediators on allergic airway inflammation*

Cells differentiated and infiltrated in the lung	Cytokines/mediators	Biological effects
Cells that exacerbate inflammation and asthma		
Mast cells	IL-9, Stem cell factor (SCF)	Bronchoconstriction, vasodilation, plasma exudation
Eosinophils	Toxic granules; MBP, EDN, EPO, cytokines	Prolonged bronchoconstriction, damaged epithelium, airway remodelling
TH2 cells	IL-4, IL-5, IL-13	Humoral antibody production, chemotaxis and survival of eosinophils
Th17 cells	IL-17, IL-17F, IL-22, IL-26	Neutrophilia, AHR, airway remodelling
Dendritic cells	IL-4, GM-CSF (cholera toxin, PGE2, histamine may potentiate the effect)	Induction of TH2 cells; suppression of TH1 cells
CD8+ T cells	IL-5, IL-13	AHR, eosinophilia
Cells that suppress allergic and asthmatic response		
Regulatory T cells	IL-10, TGF-β	Prevention of T-cell expansion
CD8+ T cells	IFN-γ	Suppression of allergic immune response
TH1 cells	IL-2, IFN-γ, lymphotoxin	Enhanced cellular response; suppression of TH2 cells
Plasmacytoid DCs and Regulatory Dendritic cells	IL-10, IL-12 (LPS, bacterial CpG, CpR oligonucleotides)	Induction of TH1 cells and T cell suppression

AHR–airway hyperresponsiveness; CpG–cytosine-phosphorothiolated guanine; CpR–cytosine-phosphorothiolated 2′-dioxy-7-deazaguanosine; EDN–eosinophil-derived neurotoxin; EPO–erythropoietin; GM-CSF–granulocyte-macrophage colony-stimulating factor; IFN–interferon; IL–interleukin; MBP–myelin basic protein; TGF–transforming growth factor; TH–T helper

Adapted from Agrawal et al. (111)

2.6.2 Genetic factors and allergy

Immune function is modified by genetically determined cellular surface structures. Naturally-occurring $CD4^{+}CD25^{+}$ T_{regs} (NT_{regs}) are generated in the thymus and express $CD25^{+}$ and transcription factor *Foxp3*, which prevent deviation of T_{regs} into effector T cells (118). Transcription factors are master regulators which commit cells to a specific cell lineage, i.e. cell differentiation (119). The constant expression of *Foxp3* in mature T_{reg} cells is necessary for them to maintain their phenotype of suppression of the immune response (120, 121). Suppression of immune responses occur in many ways, for example through the production of anti-inflammatory cytokines, direct cell-cell contact, and by modulating the activation state and function of antigen presenting cells (111). Loss or reduced expression of *Foxp3* in T_{reg} cells leads to T_{regs} gaining effector T cell properties and subsequent production of immune response-promoting cytokines such as IL-2, IL-4, IL-17, and IFN-γ (119, 120). As well as developing in the thymus, *Foxp3*$^{+}$ T_{regs} can also be differentiated in the periphery, in which case they are called induced T regulatory cells (iT_{regs}) (23). iT_{reg} cell differentiation favours particular environments, such as the gut mucosal system in gut-associated lymphoid tissue (GALT) (25). Currently, factors which influence the expression of *Foxp3* are largely unknown (118).

Childhood allergic diseases are complex geno-environmentally mediated disorders (122). A child's predisposition to allergy is as a result of genetic variations, caused by inheriting several mutant genes. For example, polymorphisms (mutations) in filaggrin (*FLG*, the filament-aggregating protein which is of direct key importance to epidermal barrier function) were found to be a risk factor for eczema development and moreover as a risk factor for asthma and atopy (123). This knowledge may prove to be a critical predictor of which children are likely to progress on the allergic march (124). Geneticists have now identified three new risk loci for eczema, confirming the involvement of the *FLG* locus and the importance of deviations in skin barrier function in the development of eczema (125).

Gene-environment interactions can be protective or causative. Pattern recognition receptors *CD14* and toll-like receptor (*TLR) 4* are important in recognising and eliminating endotoxin by activating the innate immune response (65). The pathway of gene modification from environmental exposure was evident in the PARSIFAL study where, in children whose mothers were exposed to farm animals prenatally, *TLR2* and *TLR4* and *CD14* upregulated in a dose-response fashion to each farm animal encountered (126). The specificity of the roles of genes in the pathogenesis of asthma is highlighted in the *Copenhagen Prospective Study on Asthma in Childhood* (COPSAC). They found variants on the 17q21 asthma locus, (which encode the *ORMDL3* and *GSDML* genes) are associated with increased risk of non-atopic asthma (hazard ratio: 1.88; 95% CI, 1.15-3.07, $p = 0.01$), but not atopic asthma or any other atopic condition (127). Table 2.2 outlines some of the discovered genetic associations with different stages of asthma and atopy. Although advances in genetic studies have increased our understanding of the pathogenesis of asthma, they currently are poor predictors of disease progress.

Polymorphisms in gene-gene interaction are also associated with the development of allergy. Genetic studies in 3 birth cohorts revealed polymorphisms in gene-gene interactions in *IL2RA*, *TLR2*, *TGFBR2*, and *Foxp3*, all of which are involved in regulatory T-cell development and function (128). Investigation continues into the genetic complexities in allergic disease.

2.7 PREVALENCE OF ALLERGIC DISORDERS IN CHILDREN

Using a standardised questionnaire, the International Study of Asthma and Allergies in Childhood (ISAAC) measured the prevalence of asthma, allergic rhinitis and eczema in children and demonstrated a worldwide increase in their prevalence (129). The main outcome measures used in the ISAAC study are the 12 month prevalence of symptoms of asthma (current wheeze), allergic rhinitis (current allergic rhinitis) and atopic eczema (current eczema). Phase One reported an increase in worldwide prevalence of all three allergic conditions, with variations according to location (129). Ireland ranked within the top 4 in the World in this phase, for each condition (7). Phase Two performed clinical examinations and collected objective biomarkers (e.g. skin prick testing for sensitisation and bronchial challenge tests) from a subsample of children to investigate putative associations and validity of questionnaires. This phase confirmed that childhood allergic disorders involve a complex panorama of gene-environment interaction while also validating the ISAAC questionnaires as epidemiological tools in many populations (7, 130). Phase Three examined trends, and found rising prevalence in developing countries, with reductions in areas of high Phase One prevalence (such as Ireland). The Irish element of this study highlighted that Ireland has the fourth highest 12-month prevalence of asthma in 13 -14 year old children in the world (131). The Northern Ireland ISAAC protocol study findings concurred with those of the Republic (132). The combination of the findings of both studies revealed that between 21 – 27 % of children who reported disturbed nights and/or moderate or greater disturbance of daily activity were neither diagnosed as, nor treated for, asthma. This highlights the demand for empirical evidence within the Irish setting to increase both professional and non-professional awareness of the prevalence and symptoms of asthma, thus facilitating its detection and treatment.

2.7.1 Secular trends of prevalence

Trends of prevalence are crucial to healthcare management and planning. Worldwide time trend analyses using the ISAAC protocol have yielded inconsistent results. Many studies suggest that the prevalence of symptoms indicative of asthma and atopic conditions may have plateaued from the late nineties (133-135). In Switzerland, although the prevalence of asthma and hay fever plateaued, symptoms of atopic dermatitis continued to rise, especially in girls (136). Sex predominance was also evident in Germany, where the prevalence and severity of childhood and adolescent asthma and atopic conditions had increased from 1995 to 2000 (137). In Spain, the prevalence of asthma was found to have stabilised in adolescents but increased in the younger age-groups (138). In Hong Kong, rates of asthma were found to be decreasing in adolescents and stabilizing in 6 – 7 year olds, but increasing rates of allergic rhinitis and eczema were found the latter age group (139). A Norwegian 10 year cohort study found that the prevalence of childhood asthma had doubled over a 10 year period to a prevalence of 20.2% (140).

2.7.2 Sex-specific prevalence of atopic conditions

The sex-specific prevalence of asthma has been widely reported with inconsistent results. Male preponderance to asthma in young children had traditionally been the accepted norm (141-144). This has partly been attributed to differences in the physiological development of the lungs between the sexes. From the prenatal period, although males have larger lungs than females, they have narrower airways (airways are made up of parenchymal tissue) (145), boys' airways also grow at a slower rate than girls (dysanaptic growth) (146).

There is a switch to female dominance in the prevalence of asthma in adulthood (142, 147). The main hypothesis for the reversal in prevalence following puberty is that sex hormones play a major role in the pathogenesis of asthma (148). Oestrogens enhance the production of antibodies and the subsequent immune response, while testosterone and progesterone seem to suppress immunity and inflammation (149, 150). Testosterone has been suggested as a treatment, at levels which would not produce virilisation (151-153).

The male dominance in the prevalence of childhood asthma has been challenged. It has been questioned as being attributable to bias in health professional diagnosis (154-156) or the fact that girls are less likely to report their symptoms of asthma (155). The "Yentyl" syndrome in relation to asthma diagnosis has been described as being a possible contributor to the under-diagnosis of asthma (156); this refers to the phenomenon whereby females need to present similarly and with the same severity as males to be diagnosed as having a disease. Girls present differently to, and are often less atopic than, boys (157-159). As some doctors may perceive asthma to be purely atopic, they may be less likely to diagnose females as asthmatic and they may remain untreated (160).

In young children, differing patterns of sex-specific prevalence of allergic disorders are emerging from ISAAC centres. In Munster, Germany (137), Maziak et al. reported that the prevalence of current asthma had moved from male predominance to equal sex distribution from ISAAC Phase I to phase III (age 6-7). Rhinitis showed male preponderance, while eczema moved from sex equalisation to female dominance. Conversely, in Lithuania, current asthma was more prevalent in boys during both timeframes of ISAAC ($p<0.05$), while lifetime asthma had moved from equal distribution to male predominance (($p<0.01$). They reported that eczema symptoms were equally distributed between the sexes during both timeframes. Of allergic rhinitis, only lifetime rhinitis was found to be more prevalent in boys during both studies ($p<0.05$) (161). ISAAC in England reported male preponderance to asthma in Phases I and III, although the gap had narrowed during the intervening years (162). The increases in female asthma prevalence and the subsequent move towards sex equalisation in asthma distribution was apparent in younger children (age 6-9) in many ISAAC centres where stratification by sex was reported, although, overall, higher male prevalence remained evident, (137, 161-163). As the sex-specific prevalence of eczema and allergic rhinitis are less reported, no clear pattern has emerged (137, 162).

The M:F gap also appeared to diminish in slightly older children, as studies reported substantial increases in asthma prevalence in female children, aged 9-12 years (164-166). This alteration in the sex profile of asthma and allergic disease was particularly apparent in a study in Aberdeen where, Osman et al. performed four cross-sectional studies in the same schools in 1989 (n=3,390, response rate 86%), 1994 (n=4,047, response rate 96.4%), 1999 (n=3,540, response rate 84%) and 2004 (1,920, response rate 57.2%). Parent completed questionnaires were used to obtain information regarding the prevalence of symptoms of asthma and allergy in children aged 9-11 years. They reported a decline in male predominance for wheeze, diagnosed asthma and AR and a complete reversal in the prevalence of eczema which now had moved to female predominance.

The altering sex-specific profile of equalising distribution has come under scrutiny; the question being, whether it is artefact, improvement in diagnosis or genuine (166). One theory is that complex interactions of environmental influences may have altered the fine hormonal balance that traditionally made young boys more susceptible than girls to asthma (166). Oestrogen-like endocrine disrupting chemicals (ubiquitously found in many man-made products e.g. pesticides, baby feeding bottles and toys) have been identified as a possible cause, by potentially decreasing age of puberty, thereby decreasing the age of disadvantage for young males, while in turn, contributing to the relatively higher increases in asthma prevalence in girls than in boys (166).

2.7.3 Co-morbidity of allergic disease

A high percentage of young Irish children suffer symptoms of more than one atopic disorder. Sturley reported 3.2% current symptom prevalence for all three conditions in 2002 (11), significantly higher than ISAAC Phase Three findings of only 1% internationally of 6-7 year old children and 1.2% of adolescents suffering symptoms of all three conditions (7). Punekar and Sheikh (2009) in a retrospective cohort study (n=43,477, birth – 18 yrs.) examined co-prevalence of multiple atopic disorders and found a high co-prevalence of 2.5% for all three allergic conditions (59). They reported the clinician diagnosed prevalence and incidence of asthma, eczema and rhinitis, and co-prevalence in a retrospective cohort study (n=43,477, birth - 18 yrs.), using validated coding measures from the UK General Practice Research Database.

Worldwide ISAAC percentages of children suffering from two allergic conditions ranged from 1% to 3.5% in both age groups (7). Again, these were lower than the Sturley finding that 1.5% to 6.7% of young Irish children suffer the co-morbidity of two allergic conditions (11).

2.8 ASSOCIATIONS WITH CHILDHOOD ALLERGIC DISEASE

Many putative associations have been interrogated over recent years. Cross-sectional studies have been useful in highlighting possible associations. Several birth cohort studies have emerged which target the examination of these associations. Causation, associations and hypotheses emerging from cross-sectional studies, systematic reviews and birth cohort studies are discussed in the following section.

2.8.1 Breastfeeding

One of the first factors placed under scrutiny in relation to childhood allergy was breastfeeding. The protective effect of breastfeeding in relation to allergy was first proposed in 1936 in relation to eczema (167). However, empirical evidence suggests that its role in the prevention of allergic diseases is uncertain. Biologically it is very plausible that breastfeeding would have a protective effect, as it has many immunomodulatory components such as antigens, cytokines, immunoglobulins, chemokines (168) and lactoferrin (a protein which has microbicidal, immunostimulatory, and anti-inflammatory actions, which inhibit the cascade of activation of proinflammatory cytokines (169)). In 2010, a systematic review of the link between transforming growth factor-beta (TGF-β) in human milk and immunological outcomes in infancy and early childhood, concluded that high levels of TGF-β in human milk appear to protect against the development of allergic disease. However, they recommended more investigation, as they found large inconsistencies between studies (170).

A recent meta-analysis on the effect of breastfeeding on asthma found that current evidence supports a beneficial effect of breastfeeding on wheeze in early childhood until approximately 7-8 years old, but thereafter it becomes a risk factor in the development of asthma (167). They found that it was mainly earlier reviews (2000 – 2001) that reported a protective effect of breastfeeding on asthma, and that definitions of asthma in many studies were not robust (171, 172). The evidence of protection against wheeze in early childhood may be confounded by the protective effect of breastfeeding on respiratory infections (173). The rationale behind the positive association thereafter is uncertain, but is supported by many prospective cohort studies, such as *The Tucson Children's Respiratory Study*, which found breastfeeding was positively associated with asthma after the age of 6 years (174). Evidence of this risk extending into later life also exists, as *the Tasmanian Longitudinal Health Study* found that exclusive breastfeeding for the first 3 months of life was positively associated with asthma between 14 and 44 years (175). Similar findings were reported from the *Dunedin Multidisciplinary Health and Development Research Study*, which found that breastfeeding was associated with an increased risk of asthma between 9 and 26 years (176). A recent meta-analysis of the association between breastfeeding and childhood asthma, recommended further investigation with attention to study design, as all studies pertaining to asthma had several limitations with regard to defining asthma, breastfeeding and eliminating reverse causation (167).

With regard to allergic rhinitis (AR), a meta-analysis of the effect of breastfeeding found that overall, it had a non-significant protective effect on the risk of AR (177). No association between AR and breastfeeding was found in children with a family history of atopy, but a significant protective effect was found in children without a family history of allergy. However, all studies pertained to prior to 4 years of age, so many cases of AR may have been missed (167).

The examination of the effect of breastfeeding on the development of eczema has also yielded conflicting results and methodological issues. In 2001 a systematic review and meta-analysis found that breastfeeding for the first 3 months protected against developing eczema, especially in children predisposed to atopy (178). Conversely, a systematic review and meta-analysis in 2009 found no association between eczema and exclusive breastfeeding for the first 3 months for children with or without a family history of allergy (179). Diversity of assessment and definition existed in studies and furthermore, there does not appear to be any study which examines the association into adulthood (167).

A recent meta-analysis of the effect of breastfeeding on childhood allergy development also found overall that the current evidence was inconclusive. The authors reported that studies had many methodological limitations which included reverse causation, recall bias, and various differing definitions of breastfeeding and allergic disorders. These issues need to be addressed in future studies (167).

2.8.2 Environmental tobacco smoke exposure

The negative effects of passive smoking on children's lung function have long been investigated, with positive associations (180, 181). The evidence from systematic reviews initially supported the view that the effect of exposure to tobacco smoke was confined to younger children, which was explained by the negative impact of exposure to tobacco smoke on the immature narrow bronchial airways producing transient wheezers, which resolved upon maturation (181, 182). Also, positive associations were found to only pertain to children born to high-risk parents (183). However, a recent meta-analysis of 38 cohort studies examining the association of second-hand tobacco smoke on asthma induction, found a consistent pattern of positive association between exposure to tobacco smoke in the home and the risk of developing asthma in childhood, regardless of age group or population risk (184).

The effect of tobacco smoke exposure on the development of childhood eczema has also been measured. Wang et al. investigated the effect of smoking in pregnancy by obtaining maternal and cord blood for cotinine levels at birth and examining the development of eczema using the ISAAC questionnaire at the age of 2 years (n=150 mother and child pairs). They reported a dose-response increase in the risk of developing eczema and cord blood cotinine levels (p for trend =0.01) (185). The effect of exposure to tobacco in early childhood has been examined, but the results are inconsistent. Studies have reported no association (186, 187), positive associations (185, 188) and even protective effects (189). A possible explanation offered for the finding of an inverse association is that parents who perhaps ceased smoking when their child presented with an allergy, may have incorrectly reported their child as being unexposed in early life (recall bias), thereby pushing the relative risk downwards (184). Furthermore, parental smoking behaviour in relation to their child's health is a sensitive subject and findings may be prone to under-reporting (183).

2.8.3 The hygiene hypothesis

The *Hygiene Hypothesis* was first proposed by Strachan in 1989 (17). He hypothesised a direct relationship between increased standards of home hygiene combined with decreasing family sizes and the increasing prevalence of atopic conditions. Noting the increasing prevalence of childhood asthma and atopy in the more affluent populations within developed countries, Strachan asserted that as society developed and became wealthier, family size reduced and hygienic practices became norm. The consequential decrease in microbial burden (antenatally and in early childhood) both from the surrounding environment and from reduced sibling contact, delay the development of the immune system rendering it vulnerable to atopic immune responses (17, 18). The theory gained plausibility as epidemiological studies demonstrated that farmers' children exposed to endotoxin (gram-negative bacteria) in early life suffered less allergy and asthma (190). Support for the hypothesis gained further credence, as murine studies provided evidence of the role of Th1 and Th2 cells in the immune system (191) and clinical immunological evidence emerged demonstrating Th cell imbalance in the immune system of asthmatics (117, 191, 192). These findings supported the contention that the protective mechanism was mediated by microbial exposure activating the innate immune pathways through expression of toll-like receptors (TLRs) and *CD14*. The move to immune system maturity by expansion of Th2 helper cells over Th1 helper cells prevents the development of asthma and allergy (117). Previous approaches to understanding the hygiene hypothesis centred on immunological mechanisms of allergy, with an emphasis on the Th1-Th2 paradigm. However, the theory has evolved to a more evolutionistic understanding; that the increase in allergies is due to gene-environment interactions (22).

Subsequent to the theory, epidemiological research comparing the prevalence of allergic conditions between children exposed to high and low microbial environments (e.g. family size, birth order, antibiotic therapy; immunisations and infections) emerged.

2.8.3.1 *Family size and structure*

A fundamental component of the hygiene hypothesis is that decreased microbial exposure in early life, or prenatally, is associated with the development of allergy (17). Strachan noted that increases in childhood eczema and allergic rhinitis prevalence occurred concurrently with reductions in family size. Exposure to siblings was deemed a proxy measure for exposure to unhygienic microbial loaded environments and cross-infection. The decrease in family size resulted in decreased microbial exposure from sibling transmitted infections (especially from older siblings) and caused unbalanced development of the immune system and the development of atopy (17, 18). Since the inception of the hypothesis, many studies have been performed to examine the hypothesised *sibling effect*. In 2002, a systematic review of 53 studies examining the sibling effect, concluded that overall (n=48 studies) a protection is conferred from having a higher number of siblings against all or some of the outcome measures for asthma or allergy (more often for hayfever and atopic sensitisation, than for asthma or eczema) (193). The reviewers noted that the investigation into the sibling effect produced many studies of heterogenic methods (different outcome measures of sibling effect), rendering it difficult to compare. Since the review, the *Manchester Asthma and Allergy Study* (MAAS) a birth cohort study (n=1085 children, reviewed at 1, 3 and 5 years, parental report and skin-prick tests) found that the protective effect of having older siblings only existed in relation to rhino-conjunctivitis (OR, 0.72; 95% CI, 0.54 – 0.97) (194).

Conflicting evidence also exists. More recently, the *Prevention and Incidence of Asthma and Mite* (PIAMA) birth cohort study (n= 3963, 0 – 8 years old) reported that early day-care attendance was associated with increased respiratory symptoms until the age of 4, with fewer symptoms thereafter, only in children without older siblings. No protection was conferred by early day-care attendance against the development of asthma symptoms, hyperresponsiveness, or allergic sensitization at the age of 8 years (195). Wickens et al. statistically refute the sibling effect as the sole causal link for the increase in prevalences, having calculated summary weighted odds ratios for the associations between birth order, family size and prevalence of atopic disease from 1961 to 1991 census data (196). Similar conclusions were reached using identical analysis on US census data (197). Karmaus et al. propose an alternative hypothesis; that the sibling effect originates in utero, as maternal blood IgE levels reduce with each pregnancy (198, 199).

2.8.3.2 *Day-care attendance*

As expected, attendance at day-care centres exposes children to a diverse amount of microbes and infections. It is associated with increased risk of upper and lower respiratory tract infections (195, 200). A systematic review of studies examining the effects of day-care attendance performed by Nystad in 2000 concluded that the results were inconclusive and recommended birth cohort studies in the future (201). Subsequent to the review, the Tucson Children’s Respiratory Study (year 6 and 11, n=1035 children) reported that attending day-care before six months of age and having older siblings was found to increase frequent wheezing prior to 2 years of age (OR, 1.4, 95% CI, 1.1 – 1.8, p=0.001), but to reduce the risk of wheezing by the age of 6 years (OR, 0.8; 95% CI, 0.6 – 1.0, p=0.03) until 13 years (OR, 0.3; 95% CI, 0.2 – 0.5, p<0.001) (202).

In 2008, the MAAS birth cohort study found the risk of current asthma was significantly reduced in children who commenced day-care between 6 and 12 months (OR, 0.25; 95% CI, 0.11-0.60) and after 12 months of age (OR, 0.65; 95% CI, 0.44-0.98), however, positive associations were found between entering day-care in the first 6 months of life and atopy (OR, 2.47, 95% CI, 1.23-4.95) (194).

In 2011, the *influence of Life-style factors on the development of the Immune System and Allergies in East and West Germany Plus the influence of traffic emissions and genetics study* (LISAplus) birth cohort study (n=3097 children aged 0-6 years) found that early day-care attendance was associated with increased incidence and prevalence of childhood eczema (203). The authors suggest that the higher eczema incidence may be due to increased levels of stress from day-care attendance. A systematic review of nine studies concluded that day-care attendance is associated with higher cortisol levels than home care (204). The *Assessment of Lifestyle and Allergic Diseases During Infancy* (ALADDIN, n=203) birth cohort study demonstrated an association between high cortisol levels and atopic sensitisation and eczema (205). Results measuring cortisol levels need to be taken with caution as reverse causation may exist; sensitisation and allergic symptoms in themselves may induce production of higher levels of cortisol (205). However, studies are emerging which further demonstrate the importance of psycho-neuroimmunological dynamics in the development of eczema, particularly from disruption of the family unit. The LISAplus cohort study reported increased risk for developing eczema (206) and Th2 bias of cytokine secretion (207) from exposure to the stressful early life event of separation/divorce.

It is apparent that inconsistencies in findings persist. Most studies appeared to make no allowance for variance in time spent in day-care and the size of the day-care centres attended. Therefore, as surrogate markers of microbial exposure, yes/no responses may not be truly indicative, or comparable measures (208).

2.8.3.3 *Immunisations*

The link between immunisations and asthma and allergy and direction of the proposed association has been investigated for many years (209-214). A positive association has been suggested, as the rise in asthma and allergy has coincided with the development of comprehensive vaccination programmes in the western world (214). The underlying hypothesis is that immunisation causes asthma or allergy directly by some unknown immune potentiating effect or indirectly by reducing childhood exposure to infections and thus priming the immune system towards a Th2 predominant immune response (215).

At ecological study level, ISAAC found no association between childhood immunisation and the prevalence of symptoms of atopic disease (216), although, ecological level studies are prone to a multitude of confounding factors. However, overall, the evidence is very contradictory. Some studies have found beneficial effects (217), some increased risk (29), some found no association (211, 215, 218, 219), even in children with a predisposition to atopy (220), while others found different results for different vaccinations (221).

Pertussis and Bacille Calmette-Guérin (BCG) vaccines are of particular interest as they have immune-modulatory potential (IgE production in animal (222, 223) and human models (224, 225)). A meta-analysis of all available comparative studies (receipt *vs*. non-receipt of vaccine, validated by medical records) investigating the association between asthma and whole-cell pertussis (within diphtheria-tetanus-pertussis vaccine) and BCG vaccinations (1996 – 2006) found the evidence could not support any association (positive or negative) with the development of childhood or adolescent asthma (226). They noted issues around the heterogeneity of the studies with many being of poor methodological quality.

A nationwide Danish study examined the association of the Measles-Mumps-Rubella (MMR) vaccine and asthma in early childhood (n=871,234) by using the outcomes of hospital admissions with an asthma diagnosis and asthma medication (227). All data was attained from a civil registration system which is in place for all Danish citizens. They reported that MMR-vaccinated children were less often hospitalised with an asthma diagnosis (OR, 0.75, 95% CI, 0.73-0.78) and used less asthma medication (OR, 0.92; 95% CI, 0.91-0.92) than children who were unvaccinated. Beneficial effects of MMR were also found in children who were hospitalised with status asthmaticus (OR, 0.63; 95% CI, 0.49-0.82) and taking long-acting β2 antagonist inhalant asthma medication (OR, 0.68; 95% CI: 0.63-0.73), but not for taking systemic b2-agonist anti-wheeze medication OR, 1.02; 95% CI, 1.01-1.02) (227). A large Swiss cross-sectional study, The *Swiss Surveillance Program of Childhood Asthma and Allergies with respect to Air Pollution and Climate* (SCARPOL, n=1537 children aged 13-15years) also reported an inverse relationship between the risk of asthma and MMR vaccination (OR, 0.45; 95% CI, 0.21-0.98).(216). Using parentally completed questionnaires and serum tests for atopic sensitisation, they also found no increase in the risk of sensitisation to common allergens from receiving the MMR vaccine (216). Therefore, the evidence points towards a protective effect against asthma from the MMR vaccine, although more evidence is required.

Atopic predisposition has also been implicated as potentially increasing the immunomodulatory effect of immunisation, however, in a population of high atopic risk, the *Tasmanian Longitudinal Health Study* (n=5729, age 7 to 44 years) found no association between childhood immunisations and the development of asthma and allergy by age 7, or the prevalence of asthma and allergy at 44 years (215).

A recent meta-analysis of the effect of childhood vaccinations concluded that as childhood vaccination programmes have been continually evolving to include newly developed vaccines, it was difficult to extricate individual components and differentiate the individual effects of each vaccine (226). Also, the heterogeneity of studies and conflicting findings in research compound the lack of clarity. Yet, clarity regarding the issue of childhood immunisation is imperative, as parental uncertainty may have a catastrophic effect upon national immunisation programmes and ultimately public health (228).

2.8.3.4 *Childhood infections*

According to the hygiene hypothesis, early childhood infections confer protection against the development of asthma and allergy (17), however, the evidence regarding the effect of different infections is contradictory (39). A recent review of the role of infections in the development of asthma and allergy concluded that the role of infections is more complex than the hygiene hypothesis first presumed (229). Infections may promote or protect against allergic diseases depending upon time of exposure, type/severity of the infection and the predisposition of the host.

A cross-sectional study involving parentally completed ISAAC questionnaires (n=1584 children with serious notified infectious diseases 0-4 years and 2539 children from general population) found no significant difference in the prevalence of current asthma symptoms between the children in the infectious diseases group *vs.* children from the general population, irrespective of type or location of infection (230). A pilot study of 89 children post hospitalisation with confirmed pertussis infection in the first six months of life, compared with 172 children without pertussis, found children who had infantile pertussis were more likely to suffer "asthma symptoms" (OR, 2.8; 95% CI, 1.1-7.0) at toddler age (13-45 months) (231).

Gastrointestinal infections

The hygiene hypothesis supports the notion that enteric infections would enhance maturation by stimulation of the gut and protect against atopy, especially given the fact that the gut-associated lymphoid tissue (GALT) is the largest lymphoid organ in the body. GALT contains a large number of T_{reg} cells, including Foxp3$^+$ T_{reg} cells which are essential for immune homeostasis (25). However, the literature with regard to the effect of gastrointestinal infections on allergy development is inconsistent. Exposures to foodborne infections and Hepatitis A virus (HAV) (markers of unhygienic exposure to orofaecal and foodborne microbes) have been found to protect against the development of allergy. A landmark study in Italy (n=1659 male military cadets, aged 17-24), reported that cadets with HAV antibodies, had significantly lower prevalence of atopy than those who were seronegative for HAV, irrespective of sibling status (26). A retrospective case-control study of the same cohort of Italian military cadets (n=240 atopic cases and

240 controls), demonstrated that the prevalence of atopy reduced in a dose response fashion with previous exposure to Helicobacter Pylori (H pylori), Toxoplasma gondii (T gondii) and HAV (p=0.000045 for trend). They also reported very low incidence of allergic asthma and allergic rhinitis in the cadets who were exposed to at least two of the infections (28). An inverse association between HAV seropositivity and atopic prevalence, was also reported in men and women living an anthroposophic lifestyle (n= 1527, aged ≥20 years, serum obtained from the *Enzyme Linked ImmunoSorbent Assay* (ELISA) study) (27).

H pylori was found protective against the childhood (≤15 years old) development of asthma (OR; 0.63, 95% CI, 0.43-0.93) and allergic rhinitis (OR, 0.55; 95% CI, 0.37-0.82) in the US *Third National Health and Nutrition Study* (n=7663, age >17 years) (232). In 2012, a meta-analysis (n=19 studies) examining the effect of H pylori on asthma prevalence concluded that although the evidence is weak, it demonstrates a protective effect of H pylori exposure on asthma development (233).

A Sardinian study comparing pre-school children (0- 4years) hospitalised for Salmonella (n=148) and non-bacterial enteritis (n=167), reported lower prevalences of asthma and allergic rhinoconjunctivitis by school age, in children with Salmonella (asthma: 3.4% vs. 12.6%, p=0.006, allergic rhinoconjunctivitis: 5.4% vs. 13.8%, p=0.019) (234).

Conversely, recurrent gastroenteritis (>3 episodes) in the first two years of life was found to be associated with the development of asthma by age 6 (OR, 2.0; 95% CI, 1.5 – 2.75) in the Melbourne Atopy Cohort Study (MACS) (29). No association has also been reported. A retrospective UK study using a GP database (n=29,238 children, range of follow-up=birth to 11 years and median follow-up = birth to 2.9 years) of personal medical history, reported no effect of early gastrointestinal childhood infections in the development of childhood allergy (30).

Respiratory infections

A German longitudinal *Multicentre Allergy Study* (MAS, n=499 children of high atopic risk and 815 children of low atopic risk, 0 – 7 years) found infectious diseases other than lower respiratory tract infections in the first three years of life were inversely related to a diagnosis of asthma by 7 years of age (OR, 0.31; 95% CI, 0.11 - 0.85 >4 infections *vs.* <3 infections), current wheeze at age 7 (OR, 0.55; 95% CI, 0.20 - 1.48), and bronchial hyperreactivity at age 7 (OR 0.40; 95% CI, 0.16 - 1.01) (235). On further dissection of results, only viral infections showed a significant negative association with asthma; bacterial, fungal, gastrointestinal or urinary tract infections had no significant effect. In contrast, lower respiratory tract infections with wheezing showed a strong positive association with asthma at the age of 7 (OR, 6.19 95% CI, 2.17 - 17.63) for >2 wheezing infections *vs.* no infection. Some infections appear to convey protection, while others, (especially severe lower respiratory tract infections) in early childhood are positively associated with the development of asthma.

Respiratory viral illness

Moderate to severe febrile and wheeze inducing viral lower respiratory-tract infections appear to play a key role in the development of asthma (38, 236), especially in children pre-disposed to atopy (40, 41, 237).

Bronchiolitis is a respiratory illness commonly occurring in young babies under 6 months of age which is usually viral in origin and presents with wheezing, tachypnoea, airway inflammation and respiratory distress. Characterised clinically by pyrexia, tachypnoea, wheeze and respiratory distress, the usual causal pathogens are Human Rhinovirus (HRV) and Respiratory Syncytial Virus (RSV) (238-240). *The Childhood Origins of Asthma birth cohort STudy* (COAST, n=259/289 high risk children from 0 – 6 years, 90% follow-up) assessed the aetiology of childhood wheeze as it arose, using nasal lavage, culture, and multiplex reverse transcriptase–polymerase chain reaction (241). They reported that overall, 90% of wheezing illnesses were of viral origin and 86.6% (26/30) of the children who had rhinovirus (RV) at age 3, had asthma by the age of 6. The risk of developing asthma increased each year with having had rhinovirus and by year 6 the risk was extremely high (OR, 31.7; 95% CI, 10.6 - 94.9) in this at risk group of children.

The negative implications of viral exposure and asthma continue after asthma diagnosis. RSV infections are the also the most common cause of childhood asthma exacerbations (240, 242). In a population-based retrospective birth cohort study, Carroll et al. investigated healthy term infants from 1995-2000 (n=90, 341 children) and demonstrated a dose-response relationship between the severity of bronchiolitis symptoms and both the development of early childhood asthma and asthma morbidity (243). Furthermore, the negative implications of viral respiratory infections persist into adulthood. When exposed to rhinovirus, adults with asthma were reported to suffer lower respiratory infections twice more frequently with more severe symptoms of longer duration than non-asthmatics (244).

The reasons why asthmatics are more susceptible to lower respiratory tract infections from viral exposure remain under investigation. In-vitro studies have revealed that asthmatic bronchial epithelial cells have a deficient innate immune response to rhinovirus infection (245-247). Asthmatic epithelial cells have deficient interferon (IFN) production, which results in impaired viral elimination (245, 247). IFN-β and IFN-λ are critical in the initiation of apoptosis and viral elimination and are vital triggers in a cascade of protective anti-viral pathways (248, 249).

The relationship between early viral respiratory infection and asthma is complex; in a recent review, Gern suggests that there are three main theories of association (42). The first theory proposes that early viral respiratory illness directly causes the development of asthma, rationalised by early childhood (immature immune and respiratory system) presenting a critical window of vulnerability to asthma from viral infection (250). The second, questions viral illness as being causal and instead asserts that viral illness reveals children with pre-existing tendency to asthma. The third, combining the former two theories, suggests that viral-induced respiratory infections increase the risk of the development of asthma in children who are already atopically predisposed (40-42).

Recent evidence strongly supports the latter theory. Maternal atopy was found to be significantly associated with more severe human RV bronchiolitis in a prospective cohort study of healthy term infants (n=630) (251). Severe febrile viral lower respiratory tract infections in infancy and early atopy were found to be risk factors for persistent wheeze and asthma in a prospective birth-cohort study of 147 children (0 – 10 years) with high atopic risk (41). Infantile respiratory infections were monitored and virology tests performed. Skin prick tests for atopy were attained at 6 months, 2 years and 5 years. Information regarding occurrences of wheeze and physician diagnosed asthma and eczema was sought at regular intervals. At the end of the 10 years, they reported that 60% of the children were atopic, 25.9% had current eczema, 18.4% current asthma, 20.4% persistent wheeze and 35.8% experienced ≥1 lower respiratory infection associated with fever and/or wheeze in their first year of life. Children who suffered a lower tract respiratory infection with a fever in infancy and were atopic by 2 years, were significantly more likely to report persistent wheeze (OR, 3.51; 95% CI 1.83-6.70; $p<0.001$) and current asthma (OR, 4.92; 95%CI 2.59-9.36; $p<0.001$) at 10years. The key risk factor for developing asthma was the presence of a fever during the respiratory illness, indicating severity (41).

2.8.3.5 *Antibiotics*

The positive association between antibiotics and allergy has been found in many studies, however, as antibiotics are prescribed for respiratory tract infections (bacterial and viral), uncertainty exists as to whether the association has merit or is due to reverse causation (32). Nevertheless, increasingly animal and human evidence demonstrate that the risk is biologically plausible (252-254). Antibiotics reduce commensal gut flora biodiversity which is necessary to maintain human-microbial symbiosis, in order to provide optimum conditions (for TLR signalling and cytokine pathways) to ensure T_{reg} activation and thereby promote normal immunoregulation (31). A recent systematic review found a positive association between prenatal and early life exposure to antibiotics and the risk of developing childhood asthma (OR, 1.52; 95% CI, 1.30 – 1.77, n=20 studies) (255). They found that retrospective self-reported studies demonstrated the highest risk estimate for asthma (OR, 2.04; 95% CI, 1.83–2.27, n=8) by comparison with database and prospective studies (OR, 1.25; 95% CI, 1.08–1.45, n=12). However, they note that in the latter group, it was the prospective studies of relatively small sample size which showed nonsignificant asthma risk. Database and retrospective studies are prone to recall bias and lack the ability to establish temporal occurrence of events, consequently, caution remains regarding their validity to determine causal inference, rather than reverse causality. In 2009, a prospective cohort study in Poland of 310 children born to non-smoking mothers aged 18 – 35 without chronic illness adjusted for the severity of respiratory infections and found a significant association between the consumption of broad spectrum antibiotics (macrolide (OR, 2.14; 95% CI, 1.16 – 3.95) and cephalosporin (OR, 1.98; 95% CI, 1.14 – 3.37) and the development of asthma by the age of 5 years having adjusted for respiratory infections (256).

In Canada, a 6 year follow-up study using population-based data (n=128,872 children, data from 1997 – 2005) (257) reported that prior to diagnosis, children with asthma had a higher consumption of antibiotics than those without (adjusted rate ratio 1.66 – 2.32). Furthermore, predominantly with diagnoses of upper and lower respiratory tract infections, over half of the children with asthma had antibiotics in the 6 months prior to diagnosis and antibiotic prescriptions were at their highest in the month prior to diagnosis compared to the previous 5 months (OR, 1.66; 95%, CI, 1.60 – 1.71) therefore demonstrating that children with asthma were more likely to be misdiagnosed as having a respiratory infection and be prescribed unnecessary antibiotics (257). Murk et al. describe the phenomenon of misdiagnosis of early asthma symptoms as respiratory infection, as a form of reverse causality and label it *protopathic bias* (255).

In a large US birth-cohort study (from 1997 – 2000, n=1401 children born to mothers with diagnosed asthma, with asthma symptoms and a random sample control group without asthma or symptoms), Risnes et al. aiming to reduce the risk of protopathic bias, investigated very early antibiotic use (prior to 6 months of age), years prior to the onset of symptoms of asthma and excluded children with asthma diagnosis prior to 6 months of age (258). They also examined indications for antibiotic use, adjusting for and examining separately, children who were prescribed antibiotics for respiratory infections from those who had a diagnosis unrelated to asthma symptoms (258). They reported that antibiotic consumption was associated with: developing asthma (OR, 1.52; 95% CI, 1.07 – 2.16), children having their first diagnosis of asthma after 3 years of age (OR, 1.66; 95% CI, 0.99 – 2.79), asthma diagnosis in children with no history of lower respiratory infection in the first year of life (OR, 1.66; 95% CI, 1.12 – 3.46) and allergic asthma confirmed by serum IgE or skin prick test (OR, 1.59; 95% CI,1.10 – 2.28). The association was particularly evident in children with no family history of asthma (OR, 1.89; 95% CI, 1.00 – 3.58). This study demonstrated a clear association between early antibiotic consumption and asthma and allergy at 6 years of age (258). However, additional prospective studies are required to build the body of empirical evidence required to establish if a definite causal relationship exists (255, 258).

2.8.3.6 *Anthroposophic lifestyle*

Leading an anthroposophic lifestyle involves limited use of antibiotics, antipyretics and immunisation and promotes an organic diet in its purest, simplest form. A cross-sectional study involving parentally completed questionnaires and skin-prick tests were performed to compare the lifestyle factors and prevalence of atopy in children (age 5-13) from Steiner schools (n=295, born to families who lead anthroposophic lifestyles) and children from neighbouring schools (n=380) (259). Steiner school children had lower levels of atopy (OR, 0.62; 95% CI, 0.43 – 0.91), consumed less antibiotics (52% vs. 90%), received less MMR immunisations (18% vs. 93%) and consumed a diet containing fermented vegetables and live lactobacilli (63% vs. 4.5%) compared with children from the control schools. An inverse relationship was found between the number of characteristic features of an anthroposophic lifestyle and risk of atopy (p for trend=0.01).

To study the phenomenon further, a large multi-centre cross-sectional study of 6630 children aged 5-13 years (n=4606 from Steiner school and n=2024 from control schools) was performed (PARSIFAL Study) (260). Parentally completed questionnaires and blood samples for atopic sensitisation were obtained from consenting participants. Confirming the findings of the previous study (259), Floistrup et al. found lower prevalence of current and doctor diagnosed eczema and rhino-conjunctivitis, doctor diagnosed asthma and atopic sensitisation in Steiner school children than in the control children. MMR vaccination and early consumption of antipyretics and antibiotics were positively associated with doctor diagnosis and reported symptoms of allergic disease (260), providing supporting epidemiological evidence for the hygiene hypothesis.

2.8.3.7 *Farm effect*

Several studies examined the prevalence of allergic conditions in children from rural environments and/or comparing children living the anthroposophic lifestyle with controls from neighbouring rural areas. The *Swiss Surveillance Program of Childhood Asthma and Allergies with respect to Air Pollution* (SCARPOL) study investigated children from three rural communities (age 6–15 years, n=1620 parentally completed questionnaires and IgE serum testing for six common aeroallergens n=404 age 13–15 years) and found farming to be protective against allergic rhinitis symptoms (OR 0.34; 95% CI, 0.12–0.89) and sensitisation (OR, 0.31; 95% CI, 0.13–0.73) (261). Similar protective farm effects against asthma and allergy have been noted in Australia (262), Finland (263), Canada (264) and England (265).

Ege et al. combined the results of two multicentre studies conducted in Germany, Austria and Switzerland (PARSIFAL - *Prevention of Allergy-Risk Factors for Sensitisation in Children Related to Farming and Anthroposophic Lifestyle* and GABRIELA – Multidisciplinary Study to Identify the *Genetic and Environmental Causes of Asthma in the European Community* [GABRIEL] *Advanced* Study). Both studies had compared children living on farms with a control group and found that the children exposed to a rural lifestyle had lower prevalences of asthma and atopy (266). Measuring asthma and atopy prevalence against microbial exposure (from mattresses and bedrooms) revealed that a wider diversity of microbial exposure was inversely related to the risk of asthma (PARSIFAL: OR, 0.62; 95% CI, 0.44 – 0.89; GABRIELA: OR, 0.86; 95% CI, 0.75 – 0.99).

In England, Perkin and Strachan, (employing the methodology of the ISAAC questionnaire, a food frequency questionnaire and objective allergy tests of skin prick testing, visible eczema examination, height and weight, venipuncture and dust sample collection from the children’s home) found that farmers’ children had less current asthma and seasonal allergic rhinitis. However, they did not have significantly less eczema or atopy than their rural non-farming counterparts (265). Unpasteurised milk consumption was determined to be the exposure mediating the protective effect on the sample children irrespective of farming association. Previously, the *Allergy and Endotoxin* (ALEX) Study (performed in Austria, Germany and Switzerland, n=812 children), found that exposure to farm milk in the first year of life reduced the prevalence of atopy and continual long-term exposure to stables until age 5 years was associated with the lowest frequencies of asthma, hay fever and atopic sensitisation (validated by random samples of serum for specific IgE antibodies) (267). They also found a significant protective element to asthma and atopy from the combined exposures of mothers being active on the farm antenatally and of infants who were exposed to stables in their first year of life.

Majkowska-Wojciechowska et al. (n=404 children, age 10-16 years, parentally completed questionnaire on diet and exposure to animals/crops, skin prick testing, serum IgE) compared the prevalence of allergy and atopy in children living in both rural and industrialised urban environments in central Poland, (268). They also found a lower prevalence of allergic sensitisation and symptoms of asthma and allergic rhinitis in school children living rurally. Farm milk consumption and antenatal contact with pigs were the protective exposures.

The PARISFAL study team investigated the role of prenatal maternal farm related exposures and alterations in the innate immune system of their children (parentally completed ISAAC and ALEX questionnaires: n=8263, serum IgE: n=2086) (126). In a subsample (n=322), they assessed the gene expression of Toll-like receptors (*TLR2* and *TLR4*) and *CD14*. Prenatal maternal exposures to stables were found to result in atopic sensitisation and the gene expression of receptors of innate immunity (adjusted odds ratio, 0.58; 95% CI, 0.39-0.86). The genes upregulated in a dose-response fashion according to the number of different farm animals encountered antenatally. Each additional farm animal species encountered, increased the expression of *TLR2*, *TLR4* and *CD14* by a factor of 1.16 (95% CI, 1.07-1.26), 1.12 (95% CI, 1.04-1.2), and 1.10 (95% CI, 1.03-1.23), respectively.

The effect of prenatal farming exposures has been further investigated by the *Protection Against Allergy Study in Rural Environments Study* (PASTURE). They recruited women during pregnancy and examined the effects of rural exposures on 922 mother and child pairs. They measured cord blood IgE levels for common inhalant allergens and reported a protective effect from prenatal contact with animal sheds and cord blood IgE levels against seasonal allergens and prenatal contact with hay in the sheds enhanced the protective effect to grass pollen (269). However, on investigation of the genetic make-up of farming-exposed populations, Ege et al. were unsuccessful in detecting interactions between farming related exposures and

500,000 genotyped SNPs, although lack of statistical power in their study may have been a possible reason for this failure (270).

However, contradictory findings to the protective effect of farming also exist. In New Zealand, Wickens et al. reported that current farm abode increased the risk of having symptoms associated with allergy, but not skin prick test positivity (271). They found that levels of endotoxin were lower in farming homes, attributable to the practice of removing all farming attire and washing before entering the home (271). Also, a Canadian cross-sectional study (n=553 children aged 6–13 years, parentally completed questionnaires) found that certain farming activities involving exposure to dust increased the odds of children developing respiratory symptoms (272). The exposures of risk included emptying and filling grain bins (OR, 2.18; 95% CI, 1.03-4.62), playing on or near hay bales (OR, 1.89; 95% CI, 1.19-3.01), (OR, 2.08; 95% CI, 1.07-4.06), and cleaning pens (OR = 2.70, 95% CI, 1.05-6.97). However, the amount and intensity of exposures were not ascertained and may be a critical component to establish if associations exist. Diaries recording the extent of exposure are recommended in future studies (272).

While overall, children reared on farms demonstrate a lower prevalence of asthma and atopy than their non-farming peers, findings vary in different studies despite using similar methodology (19). The ALEX study team reported that interactions between exposures and antibody responses were specific to the allergens found in each environment (57). Protective farm effects were confined to Th2-dependant IgG1, IgG4 and IgE expression, which is suggestive that distinct mechanisms regulate individual steps. Different allergen exposures cause varying sensitisation effects in different environments, therefore more investigation is required (265). Efforts are currently underway to combine international birth-cohort data by the *Global Allergy and Asthma European Network* (GA^{2}LEN). GA^{2}LEN aims to increase understanding of the complex interaction between timing of exposures, environment and genetics (273).

2.8.3.8 *Drinking water*

Another factor which may be protective against the development of atopic conditions in childhood is a high microbial content in drinking water. There has been little investigation in this area. In Karelia, two samples of school children (Russian and Finnish) were examined (n=563) (274). The inhabitants of Russian Karelia obtain their water from Lake Ladoga, while those from Finnish Karelia acquire theirs from Municipal water plants. Samples of drinking water were obtained from schools and examined for microbial content. Skin prick positivity tests for 14 common airborne and food allergens were measured. They found that high content of micro-organisms in drinking water was dose-dependently inversely associated with atopy in schoolchildren, following adjustment for other determinants. These findings were concordant with those from two earlier studies in the Tropics (275, 276). Rural water is greatly affected by the microbial content of the surrounding soil (277) provided it is not heavily treated. The hypothesis is that, with minimal water treatment, micro-organisms present in the lake from surrounding soil, will gain access to the gut via drinking water and may have significant immunomodulatory potential. Private supply may be less chemically treated than that of the public water supply. As the investigation into the protective element of farming continues, it seems reasonable to explore the possibility that there may be an inverse relationship between drinking water in farms and the development of asthma and atopic conditions.

2.8.3.9 *Indoor exposures*

Many studies have examined the effects of indoor exposures on the development of childhood asthma and allergy. Some of the factors investigated include, household furry pets and increased household heating causing exposure to humidity and mould (278).

Pet dander

The association between childhood allergic disorders and home exposure to furry pets (cats and dogs dander) has been examined repeatedly over the years. Traditionally, high risk families were advised to avoid exposing their children to cats and dogs as empirical evidence, at the time, suggested that pet exposure was a risk factor for allergy development (279). However, more recent systematic reviews and meta-analyses demonstrate that the evidence regarding whether pet exposure is a risk factor or if it conveys protection against allergy development is inconclusive. In 2008 a meta-analysis of 30 birth cohort studies revealed that most studies found no effect of early dog/cat exposure on asthma development (280). They also performed a meta-analysis of 47 cross-sectional studies and found inconsistent results.

A 2012 systematic review of 8 birth cohort studies also found contradictory evidence (281). One study found no association. Six studies found perinatal exposure to dogs or cats conveyed protection. Two studies found that perinatal exposure increased the risk of allergy in predisposed children. This positive association may be confounded by pet-keeping choices in high risk families (281). Furthermore, the reviewers noted that different studies examined children at different age groups and used varying levels of analysis, impeding the ability to draw conclusions. Pet exposure can cause increased symptoms in sensitised children (282). However, allergen avoidance studies have not focussed on assessing the effect of pet avoidance on allergy development, therefore its beneficial effect cannot be assured (278). Overall, recommendations of animal avoidance are not supported by current evidence (281).

Mould and dampness

Cross-sectional studies over recent years, have repeatedly found a positive association between parentally reported mould and dampness in children's homes and childhood allergy (283). A recent meta-analysis of eight birth cohort studies (0-10 years) by *The Environmental Health Risks in European Birth Cohorts* (ENRIECO) collaboration also revealed that early exposure to visible mould and/or dampness was associated with an increased risk of developing asthma by early childhood and allergic rhinitis by school age (284).

Although a consistent positive association has been found, the causal agents have not been identified. Some fungi have been implicated in immune system activation (285) and sensitisation (286). For example, some studies have reported a positive association between exposure to *Penicillium* spores and respiratory infections/wheeze in the first year of life (287, 288). The ENRIECO birth cohorts did not assess the fungal components in the air of children's homes. The authors suggest that future studies might employ highly sensitive and specific molecular methods and measurements of airborne enzyme activity in order to assist in the identification of causal agents (284).

Endotoxin/microbial exposures

The protective association against allergic disease from early exposure to a high microbial environment is the central tenet of the hygiene hypothesis (17). A recent meta-analysis of 19 cross-sectional studies/reviews demonstrated that endotoxin exposure was positively associated with early childhood wheeze (infants and toddlers) and protective against asthma development in older children (289). A review of the PARSIFAL and GABRIELA studies also found a protective effect against the development of childhood asthma from early exposure to a wide diversity of microbes in mattresses and bedrooms of children from rural environments (266).

2.8.3.1 *Where does the hygiene hypothesis currently stand*

Since first proposed in 1989, the hygiene hypothesis has been responsible for initiating a huge amount of associated experimental, epidemiological and clinical research. As a consequence of this research, the world has gained an enormous body of evidence which has led to increased understanding of the pathophysiology of asthma and allergy (21). Previous approaches to understanding of the hygiene hypothesis centred on immunological mechanisms of allergy, with an emphasis on the Th1-Th2 paradigm. Current evidence promotes a newly developed version of the hygiene hypothesis, one which embraces the notion that allergy development is not only mediated by microbial stimuli, but also by gene-environment interactions, gene-gene interactions and predisposition to atopy (21, 22).

Socio-economic influence

The hygiene hypothesis is supported by a large body of evidence (22). On the other hand, the high prevalence of asthma and allergy in inner city children from African American and Hispanic communities in America, living in conditions of extreme poverty, with high microbial content, is contradictory to the hypothesis (21). The exposures of risk in these populations include cockroach, rodent urine/faeces, tobacco smoke, damp, mould and living in conditions of dirt and poverty (290, 291). However, the poverty and deprivation, combined with high smoking prevalence and other exposures of risk in inner city populations do not compare with the relatively mild on-going oro-faecal and food borne infection exposures which have been demonstrated to convey protection, and support the hygiene hypothesis (21). Matricardi asserts that it is the concomitant chronic exposure to secondary risk factors such as overcrowding, dampness, smoking and poor access to health care, that are the most likely contributors to the high prevalence of allergic disease in this inner city population (21).

2.9 CONTRIBUTIONS OF THIS THESIS TO THE LITERATURE

This thesis aims to provide the trends of prevalence of childhood asthma, allergic rhinitis and eczema for the first time in young children (from Cork city and suburbs, aged 6-9 years), using the validated ISAAC methodology and protocol (Study 1). This Thesis will also provide comparisons of environmental exposures in both rural and urban environments for the first time in the Irish context and examine the effects of exposures in both environments (study 2). This is particularly relevant, as prevalence of childhood allergic conditions and associated exposures vary between populations and environments (7, 130), and farming remains a significant exposure in the Cork region (51). The Sturley study contained a sample of primarily urban and suburban children. By extending the study to include rural children; this study aims to be more reflective of children from both milieus. It also aims to perform a follow-on study; examining children aged 6-9 during the 2002 study who had reached early adolescence (age 11-13) in the 2007 study (Study 3). This aspect of the thesis aims to portray the natural history of allergic disease in this population.

Finally it will provide a continuation of prevalence trends in Irish adolescents (Study 4).

Chapter 3

Materials and Methods

3.1 INTRODUCTION

This chapter outlines the materials and methods used in *The Study of Asthma and Allergy in Cork*. It contains an overview of the study design and methodology of the 4 individual study components in the thesis. As the ISAAC protocol is used, the background to ISAAC is described. The use of a cross-sectional study design is critiqued. The data analysis specific to each component of the thesis is individually outlined.

3.2 STUDY DESIGN AND PARTICIPANTS

The *Study of Asthma and Allergy in Cork* is an epidemiological quantitative study examining the trends of prevalence of asthma, allergic rhinitis and eczema and associated risk or protective factors in Cork schoolchildren, using the ISAAC questionnaire and standardised study protocol. The ISAAC questionnaire used, was the parentally completed version for 6-7 year old children.

The *Study of Asthma and Allergy in Cork* comprises of four individual studies (studies 1 - 4), of which two examine children aged 6-9 years, and two which examine adolescents aged 11-13 years. The overall study design is cross-sectional; however, a quasi-retrospective cohort study design is employed for Study 3. The population and studies are presented in the study schematic in Figure 3.1.

Study 1 is a repeat cross-sectional study of the Sturley (2002) study of children (aged 6-9), from the same 24 urban/suburban schools. It aims to examine the trends of prevalence of childhood allergic diseases in this population from 2002 to 2007. Sturley examined 1474 children aged 6-9 years from 24 randomly selected schools, using the ISAAC core questionnaire and methodology. This study examined children aged 6-9, from the same 24 schools, 5 years later. The time trend analysis cross-sectional studies were carried out in the same season and used identical methodologies, thus allowing for direct comparison. In trends studies, for reliability and comparability, it is imperative that identical tools and methodology are used. In ISAAC high methodological standards with standardised protocols were maintained in each Phase (8, 292, 293). This trends study used the ISAAC protocol, maintained the same high standards, and used identical methodology to ensure comparability.

The inclusion criteria for the 2007 study were:

- Children aged 6-9 from 1st and 2nd class (years 3 and 4 in primary school)
- Children from the same 24 urban/suburban schools as Sturley (2002)

Study 2 is a cross-sectional study which aims to examine the factors associated with the development of childhood allergic disease in 3464 schoolchildren aged 6-9 years from Cork city and county. Parents were asked to complete questionnaires containing the core ISAAC questions with additional questions enquiring about putative risk and protective factors associated with the development of childhood allergic disease. The specific focus of enquiry was to examine the effect of rural versus urban exposures on allergy development in this population. The study population included 1416 students from urban schools and 2048 students from rural schools to allow for environmental comparisons**.**

Inclusion criteria

- Children aged 6-9
- Children from rural and urban schools in Cork City and county

Study 3 aims to examine the natural history of childhood allergic diseases in a cohort of children from the ages of 6-9 until 11-13 years. In 2002, Sturley performed a cross-sectional study in Cork schoolchildren aged 6-9 years from 24 randomly selected state-funded schools in Cork city and suburbs. This study was repeated five years later (Duggan, 2007), in the same season and within the same population of children. The 2007 study re-examined children from the 3rd year of primary school, (aged 6-9 during the 2002 study), again when they were in the final (8th) year of primary school (aged 11-13). As the 2002 study (n=1474) surveyed children from both years 3 and 4, the 2007 study-eligible population consisted of approximately half the population (n=706) from the original study. Parents were asked to complete identical ISAAC-based questionnaires at ages 6-9 and 11-13. This study availed of the unique opportunity to re-examine children from within the same cohort. The data was not individually-linked, as the dataset from 2002 was unavailable (due to circumstances outside the researcher’s control). However, according to school management, there is only a 5% variance in the drop-in/out rate of children in this period of school life.

Inclusion criteria for the 2007 study:

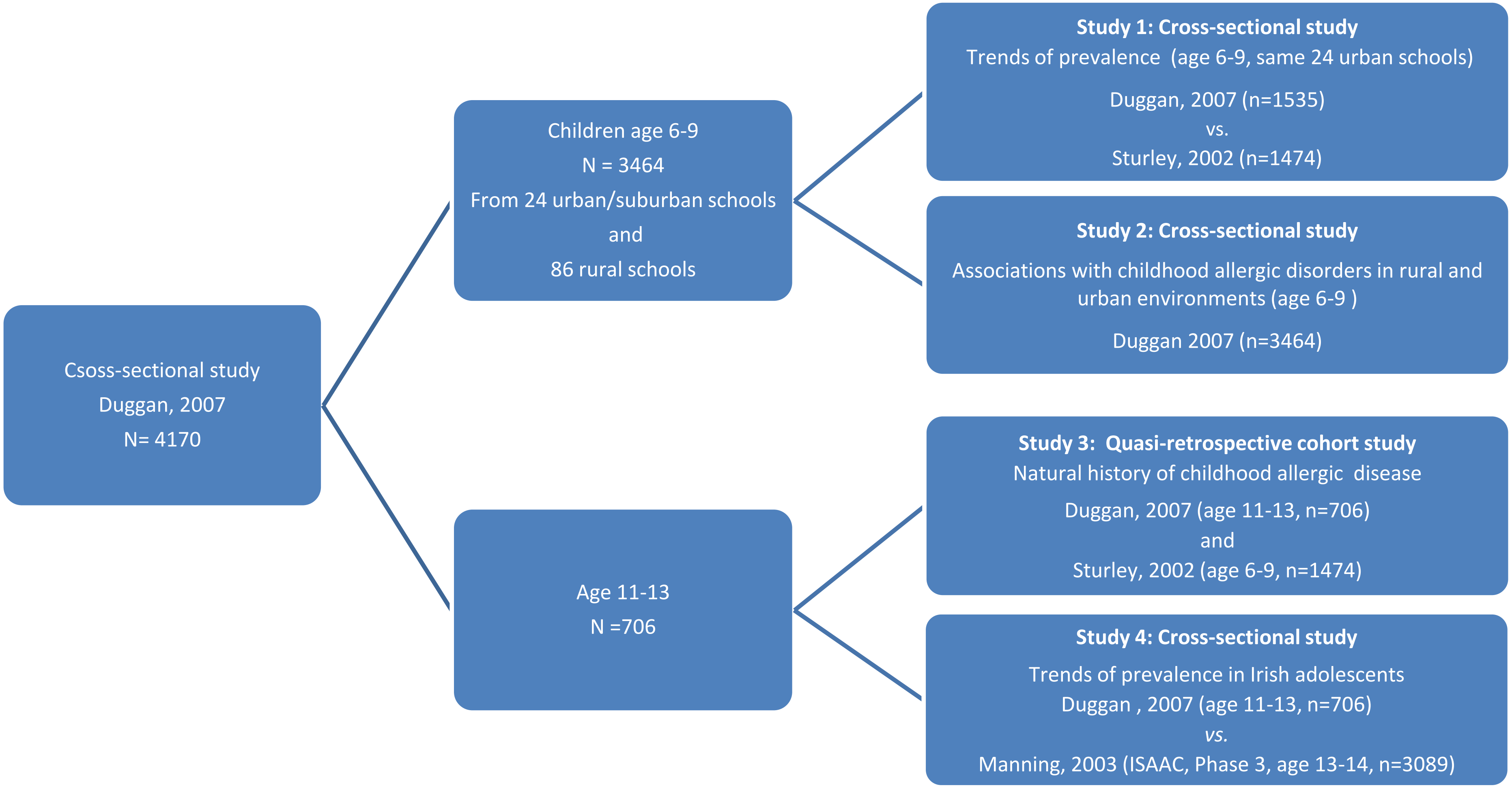
- Children aged 11-13 (year 8 of primary school) who were aged 6-9 when examined by Sturley (year 3-4 of primary school) in 2002

Study 4 is a cross-sectional study which compares the prevalence of parentally-reported childhood allergic diseases in cork adolescents (n=706, aged 11-13) with the published self-reported prevalence data from the Irish Phase 3 ISAAC study population (Manning et al., 2003, age 13-14, n=3089). It aims to examine the trends of prevalence of childhood allergic diseases in Irish adolescents.

Inclusion criteria for the 2007 study

- Children aged 11-13 (year 8 of primary school)

Components of the Study of Asthma and Allergy in Cork



Csoss-sectional study
Duggan, 2007
N= 4170

Children age 6-9
N = 3464
From 24 urban/suburban schools
and
86 rural schools

Age 11-13
N =706

Study 1: Cross-sectional study
Trends of prevalence (age 6-9, same 24 urban schools)
Duggan, 2007 (n=1535)
vs.
Sturley, 2002 (n=1474)

Study 2: Cross-sectional study
Associations with childhood allergic disorders in rural and urban environments (age 6-9)
Duggan 2007 (n=3464)

Study 3: Quasi-retrospective cohort study
Natural history of childhood allergic disease
Duggan, 2007 (age 11-13, n=706)
and
Sturley, 2002 (age 6-9, n=1474)

Study 4: Cross-sectional study
Trends of prevalence in Irish adolescents
Duggan , 2007 (age 11-13, n=706)
vs.
Manning, 2003 (ISAAC, Phase 3, age 13-14, n=3089)

Figure 3.1 *Schematic of the study components in the study*

3.2.1 Research protocol

As mentioned previously, the questionnaire and protocol developed and validated by the ISAAC collaboration were used in the *Study of Asthma and Allergy in Cork* (10). This study used the ISAAC standardised methodology and documentation and employed a cross-sectional study design using the protocol from ISAAC Phase I and III.

3.2.1.1 *The International Study of Asthma and Allergies in Children (ISAAC)*

The ISAAC initiative stemmed from two multinational collaborative projects from New Zealand and Germany in 1990 (8). In the 1980s and 1990s many studies, using different methodologies, highlighted a rising prevalence in childhood asthma and allergic disorders (294). The apparently rising problem of asthma and allergy combined with the deficit of a standardised tool and methodology to measure their prevalence, raised concern regarding the inability to examine the true scale of the problem and compare results. To investigate worldwide prevalence results of childhood asthma and atopy in a standardised fashion, the International Study of Asthma and Allergies in Childhood (ISAAC) was set up and a standardised questionnaire developed and validated (8). Strict standardised protocols were devised and adhered to in all study centres in order to ensure comparability.

ISAAC Phase 1

The worldwide ISAAC Phase 1 involved 700 000 children, aged 6-7 and 13-14 years, from 156 centres in 56 countries (7). The aims of ISAAC Phase 1 were to examine the prevalence and severity of asthma in children in order to obtain a global map and make international comparisons, to obtain baseline measurements for future trend analysis and to provide a framework for aetiological research into lifestyle, environmental, genetic and medical contributing or modifying factors.

ISAAC phase 2

ISAAC Phase 2 examined 30,000 children aged 9-11 years and involved 36 centres in 22 countries (292). It aimed to assess differences of prevalence, severity and bio-markers of asthma and allergy in different centres in the world, to examine assumed determinants in relation to prevalence and severity and make worldwide comparisons. They also aimed to look at genotypes in relation to phenotypes, focusing on gene interactions with environmental exposures (292). This comprehensive study looked at children from "informative" geographical areas, they were areas of previously low or high prevalence in ISAAC Phase 1 or interesting exposure or living conditions such as Ecuador, Iceland and West Bank. They used the ISAAC Phase 1 questionnaire for parents of 6-7 year olds. They also used skin prick tests and measured serum IgE and DNA for genotyping. Standardised bronchial challenges and physical examinations for flexural eczema were carried out. Homes were examined for levels of dust mite for endotoxins and aeroallergens (292).

ISAAC Phase 3

ISAAC Phase 3 examined data obtained from 498,083 children. In the 13- to 14-yr age group 106 centres in 56 countries participated, and in the 6- to 7-yr age group 66 centres in 37 countries participated. It was a repeat of ISAAC Phase 1 and used identical methodology, but added an optional new environmental element questionnaire. It aimed to examine the direction and magnitude of trends of prevalence of asthma and allergy, to extend the analysis to previously unexamined geographical areas and to further examine hypotheses raised from ISAAC Phase 1 and any new hypothesis generated in the interim between the two studies, both at an individual and ecological level (293, 295). The protocol recommended that data collection was to take place in the same time of year as the Phase 1. The time period between Phases 1 and 3 was specified to be a minimum of 5 years. This was deemed an appropriate interval to detect any alterations in prevalence that may have occurred (295).

ISAAC Phase 4

ISAAC Phase 4 is currently underway and will remain on-going. Its focus is towards the development and expansion of the ISAAC website in which it aims to create an in-depth database of resources such as manuals for diagnosis of asthma and allergy, links to current related research and symposiums (9). It is hoped that the resource section will be of great benefit to ISAAC collaborators, especially those from low and middle income countries.

Potential sources of bias in ISAAC

The use of a standardised questionnaire and protocol in ISAAC aims to ensure comparability between studies and to minimise the introduction of bias. The protocols address in detail, the selection of participants, the measurement of variables, and management of several eventualities in data collection, in order to prevent potential selection or measurement bias and confounding (10, 295). Overall good rates of compliance to the protocol guidelines were apparent in centres throughout the world (296).

Although standardised protocols and questionnaires were developed, they do not guarantee precision or the absence of bias in results. Non-response is a potential point of entry for bias. This was investigated for asthma (as asthma is a major cause of school absenteeism), in Phase 3 and found not to be a source of bias to the results (297). To reduce the risk of symptom related bias, ISAAC enquired about symptoms suffered in the previous year. There is however, a strong possibility of recall bias in the ISAAC questionnaire, as parents are requested to provide information with regard to exposures which occurred several years earlier. Another potential source of entry for bias occurs in the translation of the ISAAC questionnaire into different languages and its use in different cultures. Disease labels differ between languages and don't even exist in some languages (298). ISAAC found that the translation caused a negative or positive influence for one or more questions in 7 out of 49 translations (298). They removed the results of these questions from the worldwide comparisons.

3.2.2 Cross-sectional studies

This thesis employs a cross-sectional study design. Cross-sectional studies are valuable epidemiological research tools. Being descriptive in nature, they offer a “snapshot” in time, where disease and exposure are measured concurrently. They are an efficient, economical means to examine disease prevalence and fixed characteristics of individuals, such as socio-demographic data, and compare them against exposures and health-related habits, thereby facilitating health care needs assessments (299). Cross-sectional studies also are beneficial for the measurement of prevalence trends, which health care providers depend upon for management and planning resources (300).

Cross-sectional studies also have their limitations. They are also prone to recall error. As with ISAAC, this study aimed to combat this by confining the period prevalence of asthma and allergy symptoms to one year, however, it may be said that some of the questions regarding early childhood experiences may be subject to this limitation, as they enquire about exposures from several years prior to the study.

Cross-sectional studies do not have the ability to determine cause and effect relationships. As they examine only one moment in time, it is not be possible to distinguish the temporal relationship of exposure and disease, i.e. whether the exposure preceded or followed the disease. Therefore we can only assume an association between factors of interest and disease (301). However, criteria which were described in 1965 by Sir Austin Bradford-Hill, are still used today to assist researchers in assessing whether a finding is likely to be causal or a chance association (302). Taken in isolation, none of the criteria have the ability to indisputably determine cause and effect, but together they can assist the researcher in their judgement.

1. Strength of association – is there a high relative risk or odds ratio for the association?
2. Consistency – has the result been repeatedly found in other studies?
3. Specificity – is the association specific to individual populations who are exposed to particular environments?
4. Temporal relationship – does the cause precede the disease?
5. Biological gradient – does a dose-response relationship exist?
6. Plausibility – is the association biologically plausible?
7. Coherence – Is the association in line with previous knowledge of the natural history and biology of the disease?
8. Experiment – is the condition or disease ameliorated/prevented by removing the cause in experimental studies?
9. Analogy – have alternative explanations been taken into consideration?

Cross-sectional studies are invaluable tools for large epidemiological studies which are vital to investigate the complex interaction between genes and environmental exposures in the development of asthma and allergy. It is from epidemiological studies that hypotheses are raised regarding pathogenesis and causality from which further research findings may increase our understanding of these heterogonous diseases (300, 303, 304).

3.2.3 Research instrument

Although the studies were not part of ISAAC, the core questions from ISAAC and its methodology were used. ISAAC support the use of their research tool as long as it is acknowledged (305). As with ISAAC, the main outcome measures used to assess prevalence of asthma, rhinitis and eczema, were the 12 month prevalence of symptoms of asthma (wheeze), allergic rhinitis (rhinitis - nasal problems in the absence of a cold or flu and rhino-conjunctivitis - associated with itchy eye) and eczema (persistent rash in flexural areas). The questionnaire comprised of the validated core questions from the ISAAC questionnaire as well as additional questions developed by the research team to examine other possible environmental influences/modifying factors related to childhood allergy disease development (Appendix 6). The integrity of the core questions was maintained and, as ISAAC recommended, the core questions preceded the questions pertaining to environmental exposures (295). Timelines of exposures to potential determinants of asthma and allergy were prenatal, perinatal, postnatal, 1st year of life and current. Data obtained, related to age, sex, birth weight, mode of delivery, breastfeeding, parental and child nationality and education, family size, birth order, immunisation, childcare, antibiotic use in the first 2 years of life, infections in the first 3 years of life, exercise, exposures to indoor swimming pools, pre natal, first year of life and current exposures to urban or rural living, unpasteurised milk consumption, pets, farm animals, environmental tobacco smoke, source of drinking water (Table 3.1).

3.2.4 Pilot study

A pilot study was performed and any necessary amendments were made to the questionnaire. Questionnaires were given to work colleagues (including 2 experts in the field of Immunology and Epidemiology) and friends who reflected the target population (parents of young children n=15). Some formatting issues were highlighted and corrected, for example, making the sections more defined by introducing clear headings and correcting aesthetic elements. Naturally, the core ISAAC questions remained in situ. Any questions investigating exposures, or socio-demographic data which were deemed to be ambiguous were more clearly defined. Subsequently, the questionnaire was redistributed to the group in the original pilot study and reviewed again to ensure clarifications were efficacious.

3.3 STUDY LOGISTICS

To facilitate expediency, as the study was large, the questionnaire was uploaded on to a computer containing the scanning software, *Teleform*® (306) at design stage. The questionnaire was designed to a suitable format on an optical scanning field and uploaded to the computer. Each questionnaire required printing (with clear instructions regarding the importance of due care and attention), as photocopying does not preserve the exact integrity required for electronic reading when inputting the data.

3.3.1 School selection

As with ISAAC, the children were sampled through schools. State schools are the predominant providers of primary school education in Ireland, therefore, are representative of all socio-economic groups nationally. A list of schools and all information regarding each school was attained from the Department of Education and Science website (307). In total, *The Study of Asthma and Allergy in Cork* examined children from 110 schools, 24 of which were urban/suburban and 86 of which were in rural locations. Figure 3.2 depicts the geographical location of the Cork City and County schools, in which the study was performed.

School selection was achieved in two ways:

a) In 2002, the Sturley study had randomly selected 24 schools out of a possible 62 schools in Cork city and suburbs. In 2007, the schools from the Sturley prevalence study (2002) were again approached to repeat the 2002 study, to enable comparisons to be drawn.

b) As the Sturley study examined children from urban and suburban environments, the 2007 study extended the number of schools examined to include a rural component. From the 18 main towns in Cork, 7 were randomly selected, by pulling the names of towns to be included in the study, from a hat. All schools from the selected towns and throughout the town hinterlands were invited to participate in the study. In total 89 rural schools were approached, 3 of which declined involvement (reason cited was because of preparation for Communion), leaving 86 who took part in the study.

Cluster randomisation of schools is considered the most feasible manner of recruitment of children for epidemiological studies (308) and was also employed by ISAAC. Simple randomisation of schools for inclusion in this study, from the county list would have been the optimum selection method, as it reduces the risk of selection bias (308). However, the random selection of towns and inviting participation from all schools within the towns and hinterlands was considered to be the most feasible because, due to limited financial resources, the researcher performed all the data collection and funded the travel costs. Furthermore, it was envisaged that this method would minimise the risk of selection bias, as researchers were not individually involved in selecting or eliminating any particular school.

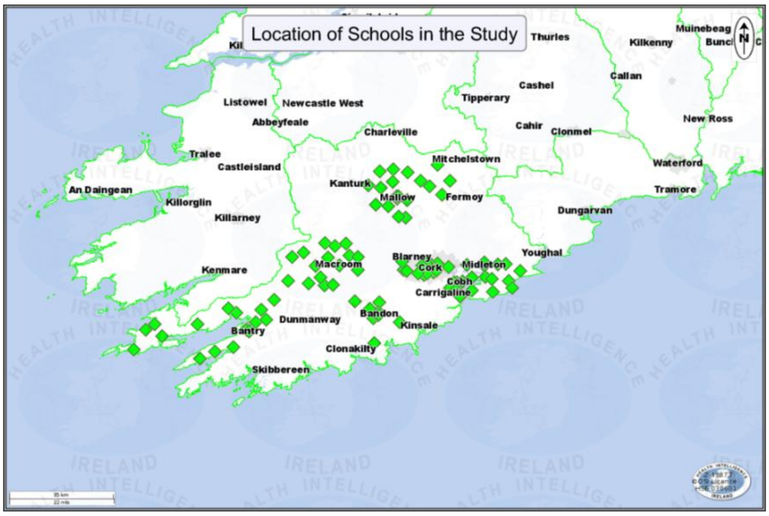

Location of Schools in the Study
N
Thurles
Kilkenny
Muinebeag
Callan
Cashel
Tipperary
Listowel
Newcastle West
Abbeyfeale
Charleville
Cahir
Clonmel
New Ross
Tralee
Castleisland
Mitchelstown
Waterford
Kanturk
Mallow
Fermoy
Tramore
An Daingean
Killorglin
Killarney
Dungarvan
Youghal
Kenmare
Macroom
Blarney
Cork
Midleton
Cobh
Carrigaline
Dunmanway
Bandon
Kinsale
Bantry
Clonakilty
Skibbereen

Figure 3.2 *Location of schools in the study*

3.3.2 Sample size

In total, *The Study of Asthma and Allergy in Cork* examined data from parents of 4170 school children (6-9 years, n=3464 and 11-13 years, n=706) who were recruited from 110 randomly selected state primary schools from urban, suburban and rural environments throughout Cork City and County. A large sample size is necessary in order to provide study power, reduce standard error of an estimate and guarantee precision (301). As severe symptoms are less common, a larger sample size is necessary to detect relative differences in severity (10). ISAAC chose a sample size of 3000 children in each centre, as it gave 99% power to detect differences between different centres, at 1% level of significance (where prevalence of wheezing is 25% in one centre and 30% in another) and 90% power at the 1% level of significance for the severity of wheezing (where prevalence is 3% in one centre and 5% in another) (10). The core element of this study examined 3464 children aged 6-9 years; therefore it had sufficient power to obtain precise estimates of both mild and severe prevalence and to identify associations.

3.3.3 Data collection

The groundwork for the study was set in place in March 2007. Data collection closely followed the ISAAC protocol in most ways, except that the names of children were not requested. As recommended by ISAAC, regular research team meetings were held throughout the process of planning and data collection. The data was collected during the final primary school term from Easter to summer (April to June inclusive). This is in accordance with the recommendations of ISAAC, that at least half of the study population be investigated prior to the commencement of the main pollen season (8). For manageability, the contact with the schools was made in a relay fashion of approximately 10 schools per week. The step by step procedure for data collection was standardised and closely aligned to the ISAAC protocol. The steps were as follows:

1. Each school principal was contacted initially by letter and then by telephone within the following week, their participation was discussed, and a suitable date for a visit was made.

2. To promote optimal response rates, teachers/principals and children were spoken with personally, wherever possible. Some requested an information session prior to commencement of the study, which was facilitated.
3. Questionnaires and personally hand-signed cover letters were placed in a sealable envelope (sticker on the outside of envelope with the researcher's details and date for return).
4. Teachers were requested to hand out the questionnaires and cover letters as the children were leaving the school, so that they would be fresh in the minds of the children, and increase the chances of their parents receiving them.
5. Questionnaires for any absent children were left with the class teacher.
6. A date was agreed (usually one week from distribution) for return of the questionnaires.
7. A reminder phone call was made to the school the day before collection.
8. Any questionnaires returned to the school after the collection date were forwarded to the University by the principals/teachers, as stamped addressed envelopes were left in the school to cover this eventuality (ISAAC recommendation).
9. Detailed documentation in the form of field book records was maintained throughout the data collection process.
10. A thank you letter was sent to all schools at the beginning of the next term.
11. A preliminary report of study findings was sent to each school after 1 year.

3.3.4 Data management

As in ISAAC, sealable envelopes were provided for the return of completed questionnaires to the class teachers, which were collected one week after distribution. Questionnaires were processed, i.e. removed from envelopes, counted and stored in boxes denoting only the names of the schools. The questionnaires were stored securely, with access only available to the research team. Computer records were maintained on password protected computer files in a locked office. No individual pupil is identifiable in any way.

3.3.5 Data entry

All questionnaires were visually checked, prior to being scanned using the *Bowe Bell & Howell SideKick 1200* scanner, which imported the data into an Excel CMV file. The scanner is an invaluable tool which allows large quantities of data to be scanned and entered electronically onto a database. On the other hand, scanners are also known to have very high error rates (309), therefore extreme accuracy in the preparation and handling of questionnaires is required. The questionnaire was prepared in a precise digital format on the computer using *TeleForm* ® (306). As the questionnaires were scanned, each scanned entry was contemporaneously visible on the computer monitor using the *Teleform*® verifier and any necessary corrections from scanning errors were made. Each entry was manually checked for export errors against the original questionnaire and any necessary corrections were made.

Each electronic entry in Excel was rechecked for export integrity. There were many technical issues with the export of data. Initially, data for participants was entered as that of others. A consultant company for *Teleform*® called "Inpute" were contacted. Following 2-3 days of consultation on the telephone with "Inpute" (the software company licensed for *Teleform*® in Ireland (306)), alterations were made to the design format to correct the fault. Scanning progressed, although the excel files required vigilant checking as there were many entries that did not export correctly and were not picked up by the *Teleform*® verifier. This took on average 5 minutes per questionnaire. After satisfactory review for export integrity, the database was exported to SPSS and data cleaning began.

3.3.6 Data inspection and cleaning

As the questionnaire was uploaded onto the *Teleform*® in a comma delimited format, it scanned and exported also in this format which resulted in many variables being joined together in one field. Therefore it was necessary to separate out many variables into binary format for analysis. Syntax were developed for each variable to achieve this task. The variables in question included height, weight, duration of breastfeeding, exclusive breastfeeding, date of birth, age at crèche, age at preschool, distance to factory, paternal atopic disorders, maternal atopic disorders, exposures to farm animals during different time points and continuous data on nasal problems during each month of the year and antibiotic consumption. The data was visually inspected for any inconsistency errors such as the age not matching the date of birth and females in male schools. Range checks for ages, heights, weights were performed using descriptive analysis. "Skip question" checks were performed and syntax were developed to counteract the issue of respondents who answered "No" to the questions relating to ever having suffered wheezing, nasal problem or rash and subsequently ignoring the "skip instructions" by responding to current symptoms and symptom severity.

3.3.6.1 *Coding and condensing variables*

The data was coded and labelled in SPSS. Variables were condensed into meaningful codes numerically, dogs and cats into furry animals, in water supply, well and spring were combined, and carpets/rugs were combined. Maternal Education was condensed to Junior Certificate, Leaving Certificate and Third Level. In large families, if the child had more than 5 siblings they were recoded as >5. Regarding swimming, numerically very few parents reported that their child swam every day, or 4-6 days a week, therefore, they were recoded into weekly and monthly. To build models for logistic regression and adjust for child atopy, the other two atopic disorders not being examined as the dependant variable were grouped together by developing and running an appropriate syntax.

3.4 ETHICS AND CONFIDENTIALITY

Ethical approval was sought and granted from the *Clinical Research Ethics Committee of the Cork Teaching Hospitals*. Cover letters were attached to the questionnaires to inform parents regarding the details of the study. Consent was implied by return of the questionnaire. To promote confidentiality, sealable envelopes were provided for the return of completed questionnaires to the class teachers. Data was collected anonymously. No pupil is identifiable.

3.5 DATA ANALYSIS

3.5.1 Study 1 – Trends of prevalence in 6-9 year old children

The main outcome measures to assess the prevalence of asthma, allergic rhinitis and eczema were identical in both studies (ISAAC outcome measures). Prevalence rates of childhood allergic disease in 2002 and 2007 were compared based on the 95% Confidence Intervals for the difference, calculated using Normal approximation to the Binomial distribution (310, 311). Alterations in the male:female ratio of allergic symptoms from 2002 to 2007 were assessed using logistic regression models containing the main effects of sex and study and the interaction between the sex and study.

3.5.2 Study 2 – Associations with childhood allergic disorders

Associations between the putative risk/protective factors and the prevalence of childhood allergic disorders were examined univariately using chi-square tests and multivariately, using multiple logistic regression analysis. To explore the effect of age, prevalence tables were developed symptoms of each condition, as no effect was apparent between age groups, age was not adjusted for in the logistic regression analysis.

3.5.2.1 *Univariate analysis*

The enquiry commenced with classification of linked putative factors into groups.
The classifications defined were Genetic, Parental childhood/Prenatal/Perinatal, Socio-economic, Medical and Environmental exposures (Table 3.1). Cross-tabulations and chi-square tests were performed to look for associations between all variables under investigation and the dependant variables. The dependent variables under examination in this study were the ISAAC outcome measures of the symptoms associated with asthma (*wheeze ever, wheeze in the past 12 months and asthma ever)*, allergic rhinitis, (*nasal problems ever, nasal problems in the past 12 months, nasal problems with associated ocular involvement and hayfever ever)* and eczema

(persistent rash ever, persistent rash in the past 12 months, eczema ever). Significant variables ($p \leq 0.25$) were assessed for progression to multivariate analysis.

Table 3.1 *Categorised putative protective or risk factors*

	Genetic	Socio-economic	Parental Childhood & Pre/perinatal	Medical	Child Environment (Year 1/Current)
Maternal/Paternal atopy	●				
Gender	●				
Birth weight			●		
Gestation			●		
Mode of birth			●		
Twin			●		
Infections <3 years				●	
Antibiotics <2 years				●	
Immunisations				●	
Place in Family		●			
Breastfeeding			●		
Day-care attendance					●
Tobacco smoke			●		●
Damp bedroom					●
Location of child's home					●
Carpet					●
Furry animals			●		●
Farm animals			●		●
Drinking water					●
Rural/urban environment			●		●
Stable			●		
Barn			●		
Unpasteurised milk			●		●
Swimming pools					●
Child Atopy	●				
Maternal education		●			
School					●

3.5.2.2 *Multivariate analysis – Logistic regression analysis*

To further explore significant associations found in univariate analysis ($p \leq 0.25$) and to adjust for confounding variables, multivariate logistic regression analysis was performed. Multiple regression models are recommended when an outcome is predicted by several variables (301). The logistic regression analysis was divided into several steps. Analysis at each stage of the process was performed using manual stepwise. The genetic variables of parental atopy, child atopy and gender and the socio-economic variables of maternal education and place in the family are well established potentially confounding variables and were therefore adjusted for, in multivariate analysis. Any potential cluster effect was addressed by also adjusting for "school" in multivariate analysis. The schematic for the logistic regression pathway is presented in Figure 3.3. The management of the three categories of variables under investigation are as follows:

For the *Medical* category, we considered three multiple logistic regressions involving, infections prior to 3 years old, immunisations and antibiotics consumed prior to 2 years old respectively. Factors emerging as significant ($p \leq 0.25$) were entered into a final multiple logistic regression model for this category.

To examine associations in the *Parental childhood, pre/perinatal* category, we considered three logistic regressions, involving exposures during parental childhood, during pregnancy with the child in the study and perinatal period respectively. As in the medical category, factors emerging as significant ($p \leq 0.25$) were entered into a final multiple logistic regression model for this category. The results of the final multiple logistic regression models are presented as p-values, odds ratios (OR) and 95% Confidence Intervals (CI). Nagelkerke R^2 is presented as a measure of model fit, where $R^2 = 1$ is the optimum model fit (312).

According to Field, it is critical to test for multicolinearity following a logistic regression analysis (313). Multicolinearity pertains to a situation where there is strong correlation between two or more predictor variables, in which case it is difficult to distinguish which predictor variable which is driving the association. Based on the variance inflation factor (VIF), colinearity diagnostics for the terms included in the final model, revealed that multi-colinearity between predictor variables was not a problem (VIF <10).

3.5.2.3 *Missing values*

Missing data can be a major problem in multivariate models, as all subjects with missing data in any of the variables in a given model are excluded. Crosstabs between variables under examination and the main outcome measures revealed the amount of missing data for the dependent variables. For the most part, the variables in the questionnaire had minimal (0.2% - 0.5%) missing data. For the variables pertaining to early childhood infections and immunisations 6-9% of data was missing. Crosstabs revealed no significant difference in the presence or absence of allergic symptom prevalence between those with and without missing data. For the results, the subjects with missing values are excluded. The use of a separate variable to model missing data is not recommended, as it fails to fully adjust for relevant variables and also it frequently results in biased estimates of the regression coefficients (314).

Missing values were an issue for the variable “exclusive breastfeeding”. Of those who reported breastfeeding, 33% (n=513 cases) did not indicate whether or not they had exclusively breastfed. Therefore, exclusive breastfeeding was excluded from progression to the final model.

STAGES OF LOGISTIC REGRESSION MODEL DEVELOPMENT

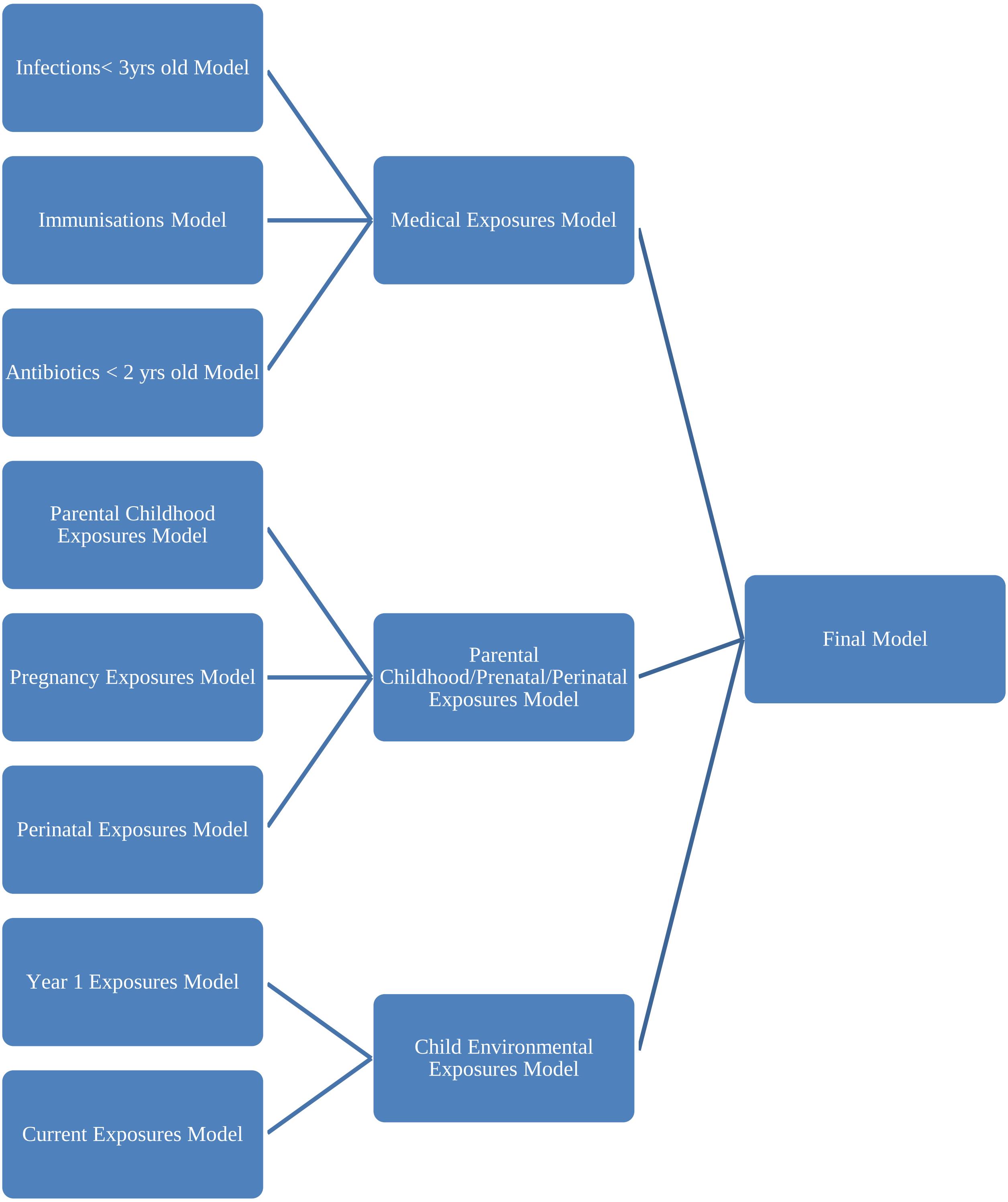

Infections< 3yrs old Model
Immunisations Model
Antibiotics < 2 yrs old Model
Medical Exposures Model
Parental Childhood Exposures Model
Pregnancy Exposures Model
Perinatal Exposures Model
Parental Childhood/Prenatal/Perinatal Exposures Model
Final Model
Year 1 Exposures Model
Current Exposures Model
Child Environmental Exposures Model

Figure 3.3 *Schematic of logistic regression pathway*

3.5.3 Study 3 – The natural history of childhood allergic diseases

Prevalence of childhood allergic diseases used ISAAC main outcome measures. Regarding analysis of the quasi-cohort study, two problems emerged. Firstly, the data were not individually linked. Therefore it was not possible to consider a repeated measures analysis which would allow for the correlation between repeated measurements on the same child. Secondly, there was little overlap between ages in the two time periods making it difficult to separate age and period effects. As a result, p-values are not reported; instead, estimates and 95% CI for the prevalence of allergic symptoms in the two time periods are presented. Differences in prevalence of allergic symptoms are described and not analysed. However, if confidence intervals do not overlap, the difference in prevalence in both timeframes is statistically significant (315).

3.5.4 Study 4 – Trends of prevalence in Irish adolescents

When comparing symptom prevalence between the older children in this study and ISAAC Phase Three, there is a problem because the age groups differ (11-13 in this study versus 13-14 in ISAAC). Therefore, to report p-values would be inappropriate and trend results are presented as estimated prevalence and 95% confidence intervals. Furthermore, in the 2007 study, the data was attained by parentally completed questionnaires, whereas, the ISAAC population of 13-14 year old adolescents completed their own questionnaires. Comparison of parentally versus adolescent completed questionnaires has, on the whole, found that adolescents report higher prevalence of current and lifetime allergy than their parents (316, 317). This fact was taken into consideration when interpreting the difference in prevalence between the two groups of adolescents in this study.

Chapter 4

Results

4.1 INTRODUCTION

Chapter 4 presents the research results of the thesis. It will commence with the socio-demographic and descriptive data for all the children and parents who participated in the research studies. Subsequently, the results of the four studies will be presented individually.

4.2 SOCIO-DEMOGRAPHIC AND DESCRIPTIVE DATA

To present the socio-demographic and descriptive data, the study participants are divided into two groups, Group 1 pertains to all children aged 6-9 in Cork City and County, examined in the 2007 component of studies 1 and 2. Group 2 comprises of the children who were examined by Sturley in 2002, when they were aged 6-9 in year 3-4 of primary school and again in 2007, when they were aged 11-13 years old (relates to the children in the 2007 component of studies 3 and 4).

Group 1 comprised of 50.1% boys, only 0.9% of the children were adopted. The average age of the participants was 7.7 years (S.D. = 0.7), the mode was 8. Ages ranged from 6 to 9 years old. Group 2 comprised of 49.6% boys and only 1.1% of children were adopted. The average age of the participants was 12.11 years (S.D. = 0.44), the mode was 12. Ages ranged from 11 to 13 years old.

4.2.1.1 *Birth*

In Group 1, 91.8% (n=3242) were born at term. Vaginal deliveries were the most common mode of birth (77.9%) and 2.9% (n=99) of the children were twin deliveries. Mean birth weight was 3507gms. In Group 2, also the majority of children (90.4%, n=630) were born at term. Vaginal deliveries were the most common mode of birth (82.3%) and 2.4% (n=17) of children were twins. Mean birth weight was 3498gms.

4.2.1.2 *Country/Continent of origin*

The continent of origin of the parents and children in the study are summarised in Table 4.1. In Group 1, most of the participants were born in Ireland (89.5%) to Irish mothers (88.2%) and fathers (87.5%). Similarly, in Group 2, most of the participants were born in Ireland, to Irish mothers (93.9%) and fathers (94.4%).

Table 4.1 *Country/Continent of birth of children and parents*

	Group 1 (n=3464, age 6-9)			**Group 2 (n=706, age 11-13)**		
Country	**Child N (%)**	**Father N (%)**	**Mother N (%)**	**Child N (%)**	**Father N (%)**	**Mother N (%)**
Ireland	3060 (89.5)	2830 (87.5)	2876 (88.2)	652 (93.0)	614 (94.5)	622 (94.0)
Britain	139 (4.1)	176 (5.4)	159 (4.9)	24 (3.4)	10 (1.5)	19 (2.9)
EU	22 (0.6)	28 (0.9)	42 (1.3)	4 (0.6)	3 (0.5)	2 (0.3)
Ac. EU	71(2.1)	69 (2.1)	68 (2.1)	7 (1.0)	6 (0.9)	6 (0.9)
Africa	22 (0.6)	38 (1.1)	32 (1.0)	3 (0.4)	2 (0.3)	1 (0.2)
Asia	53 (1.6)	71 (2.2)	55 (1.7)	5 (0.7)	7 (1.1)	5 (0.8)
Oceania	8 (0.2)	8 (0.2)	6 (0.2)	0 (0.0)	1 (0.1)	1 (0.2)
Russia	5 (0.1)	1 (0.01)	2 (0.1)	1 (0.1)	2 (0.3)	2 (0.3)
America	38 (1.1)	14 (0.4)	22 (0.7)	5 (0.7)	5 (0.8)	4 (0.6)

4.2.1.3 *Breastfeeding*

In Group 1, 43.5% (n=1498) were breast fed ever, of which, 27.7% (n=415) were breastfed for ≥16 weeks. Of the children who were breastfed ever, 20.2% (n=699) were exclusively breastfed, of which 26.0% (n=182) were breastfed exclusively for ≥ 16 weeks. In the older children in Group 2, over a third (34.8%, n=245) were breastfed ever, of which, 27.4% (n=67) were breastfed for ≥16 weeks. Of the children who were breastfed ever, 45.7% (n=112) were exclusively breastfed, of which 25.0% (n=28) were breastfed exclusively for ≥ 16 weeks. For both groups, the average duration of breastfeeding ever was 14 weeks and the mode was 4 weeks. The reported details of breastfeeding are summarised in Table 4.2.

Table 4.2 *Breastfeeding history of children in the study*

	Group 1 (n=3464, age 6-9)	**Group 2 (n=706, age 11-13)**
	N (%)	**N (%)**
Ever Breastfed	1498 (43.5)	245 (34.8)
Breastfed ≥16 weeks	415 (12.0)	67 (9.5)
Breastfed exclusively	699 (20.2)	112 (15.9)
Breastfed exclusively ≥ 16 weeks	182 (5.3)	28 (4.0)

4.2.1.4 *Birth order*

In both age groups of the study, two-thirds of the participants were born first or second in the family (Figure 4.1).

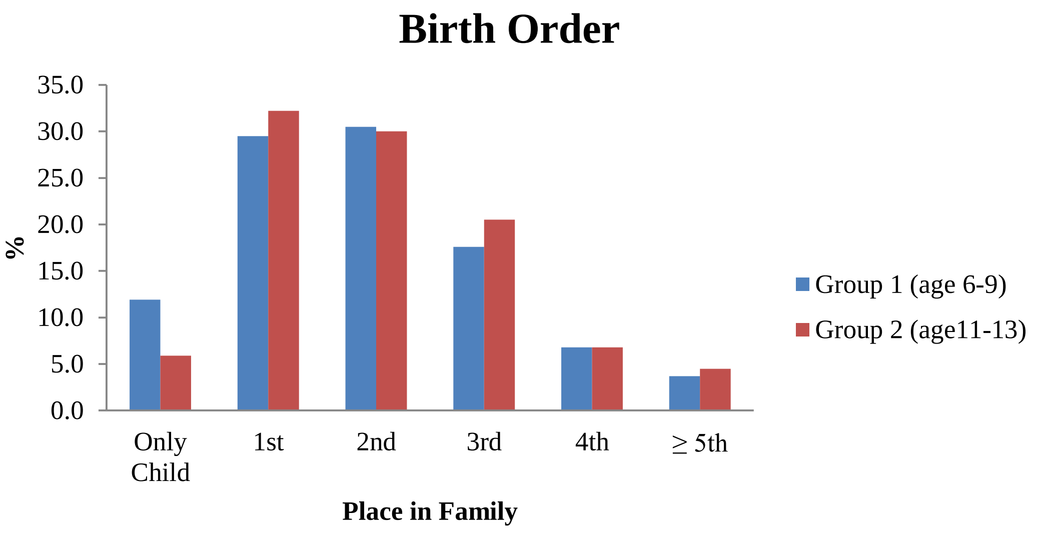


Figure 4.1 *Birth order of children in the study*

4.2.1.5 *Crèche/preschool attendance*

In total, 16.1% (n=559) of children had attended a full-time crèche and 90.3% (n=3098) had attended preschool. Figure 4.2 depicts the age (in months) that the children attended a day-care facility for the first time. Fewer children from this older study group 12% (n=85) had attended a full-time crèche than in the younger study group (16.1%), but similar percentage (89%, n=620) had attended preschool.

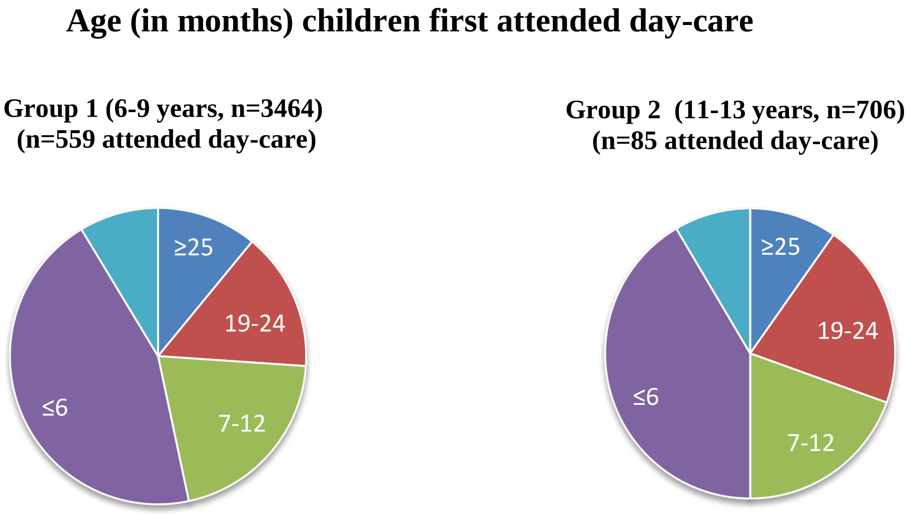


Figure 4.2 *Age in months, when children first attended day-care*

4.2.1.6 *Immunisations*

Table 4.3 shows the uptake of the sample population of the National Immunisation Programme. In Group 1, the mean percentage of uptake of immunisations is 89.7%, excluding BCG, as universal BCG immunisation was not offered in the Cork region from 1972 to 2008 (318). Marginally less than the younger study group, the mean percentage of uptake of immunisations is 88.2% in the older children in Group 2 (excluding BCG).

Table 4.3 *Immunisations received*

	Group 1 (n=3464, age 6-9)	Group 2 (n=706, age 11-13)
Immunisation	**N (%)**	**N (%)**
3/5-in-one	3354 (96.8)	672 (95.2)
MMR	3305 (95.4)	682 (96.6)
HiB	3002 (86.7)	577 81.7)
Men C	2768 (79.9)	560 (79.3)
BCG	1281 (37.0)	249 (35.3)

4.2.1.7 *Infections in early childhood*

Table 4.4 demonstrates the reported occurrence of disease of the participants before they were three years of age.

Table 4.4 *Infections prior to 3 years of age*

	Group 1 (n=3464, age 6-9)	Group 2 (n=706, age 11-13)
Infection	**N (%)**	**N (%)**
Measles	206 (6.0)	65 (9.2)
Mumps	37 (1.1)	11 (1.6)
German Measles	62 (1.8)	18 (2.5)
Chickenpox	1744 (50.3)	363 (51.4)
Meningitis	31 (0.9)	6 (0.8)
Ear infection	130 (3.8)	29 (4.0)
Gastroenteritis	836 (24.1)	181 (25.6)
Pneumonia	122 (3.5)	33 (4.7)
Whooping Cough	135 (3.9)	25(3.5)
Bronchitis	390 (11.3)	80 (11.3)
Croup	511 (14.8)	95 (14.5)
Bronchiolitis	437 (12.6)	108 (15.3)

4.2.1.8 *Antibiotics prior to 2 years of age*

Parents reported that 70.5% (n=2443) of children had taken antibiotics in the first two years of age. In both age groups, of the majority of children who had taken antibiotics in the first two years of life, received 1-2 courses (Table 4.5).

Table 4.5 *Antibiotics received prior to 2 years of age*

Antibiotic courses < 2yrs of age	Group 1 (n=3464, age 6-9) N (%)	Group 2 (n=706, age 11-13) N (%)
None	968 (28.4)	219 (31.0)
Had antibiotics, amount not specified	362 (10.5)	67 (9.5)
1-2 courses	982 (28.3)	186 (26.3)
3-4 courses	566 (16.3)	117 (16.6)
5-6 courses	280 (8.1)	50 (7.1)
≥7 courses	253 (7.3)	58 (8.2)

4.2.1.9 *Home location*

Parents were asked the current location of their home and the location of their home during the first year of their child's life (Table 4.6). In Group 1, 44.3% - 36.9% of children lived in the city/city suburbs during Year 1 and currently, respectively. Group 2 children mostly resided in the city and suburbs during both timeframes.

Table 4.6 *Home location, currently and during the first year of life*

	Group 1 (n=3464, age 6-9)		Group 2 (n=706, age 11-13)	
Home Location	**Year 1 N (%)**	**Currently N (%)**	**Year 1 N (%)**	**Currently N (%)**
City	618 (18.1)	449 (13.0)	216 (30.8)	197 (27.9)
City Suburbs	898 (26.2)	827 (23.9)	367 (52.1)	370 (52.4)
Town	762(22.0)	749 (21.6)	56 (7.9)	57 (8.1)
Village	302 (8.8)	369 (10.7)	20 (2.8)	30 (4.2)
Countryside – not farm	597 (17.4)	812 (23.5)	41 (5.8)	50 (7.1)
Farm	246 (7.2)	252 (7.3)	3 (0.4)	2 (0.3)

4.2.1.10 *Environmental exposures*

Table 4.7 highlights the environmental exposures at two time scales, namely during the first year of life and current (during the study).

Table 4.7 *First year of life and current exposures*

	Group 1 (n=3464, age 6-9)		Group 2 (n=706, age 11-13)	
Exposures	**Year 1** **N (%)**	**Currently** **N (%)**	**Year 1** **N (%)**	**Currently** **N (%)**
Damp spots in bedroom	431 (12.5)	281 (8.1)	85 (12.0)	50 (7.1)
Carpets (vs. bare floor)	2025 (58.5)	1250 (36.1)	515 (72.9)	255 (36.1)
Dog	1439 (41.5)	2095 (60.5)	245 (34.7)	418 (59.2)
Cat	578 (16.7)	928 (26.8)	82 (11.6)	119 (16.9)
Farm Animals	353 (10.2)	480 (13.9)	22 (3.1)	25 (3.5)
Other Animals	115 (3.3)	306 (8.8)	24 (3.4)	48 (6.8)
Barn	134 (3.9)	229 (6.6)	9 (1.3)	16 (2.3)
Stable	31 (0.9)	217 (6.3)	1 (0.1)	22 (3.1)
Unpasteurised Milk	116 (3.4)	178 (5.2)	18 (2.5)	19 (2.7)

4.2.1.11 *Water Supply*

Table 4.8 shows that the majority of the participants receive their water supply from a municipal main water source. In both groups, there was an increase in the use of water filters from the year 1 to currently.

Table 4.8 *Sources of water supply*

	Group 1 (n=3464, age 6-9)		Group 2 (n=706, age 11-13)	
Water Supply	**Year 1** **N (%)**	**Currently** **N (%)**	**Year 1** **N (%)**	**Currently** **N (%)**
Municipal Water	2794 (81.4)	2664 (77.0)	677 (95.9)	675 (95.8)
Home well	536 (15.6)	679 (19.6)	23 (3.3)	25 (3.5)
Group Scheme	101(2.9)	117 (3.4)	4 (0.6)	5 (0.7)
Water Filter	500 (14.6)	901 (26.0)	61 (8.6)	173 (24.5)

4.2.1.12 *Smoking*

The children’s smoking exposures are summarised in Figure 4.3. In Group 1, over a quarter (28.9%, n=1002) of mothers reported smoking in the first year of their child’s life, and 26.3% (n=907) reported smoking currently. Maternal smoking during pregnancy was 19.8% (n=686) and 20.5% (n=709) of parents reported that cigarettes are smoked in their homes. Higher than in the younger age group, over a third (34.7%, n=245) of mothers in Group 2 reported smoking during the first year of their child's life and 29.6% (n=209) reported currently smoking. Maternal smoking during pregnancy was 23.8% (n=168). However, 24.4% of parents reported that cigarettes are smoked in their homes, which is 4% higher than the parents in the younger age group.

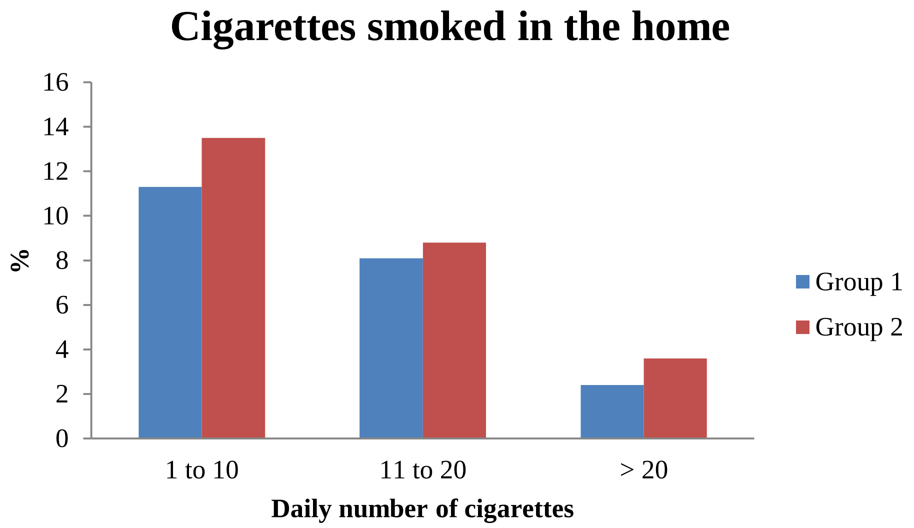


Figure 4.3 *Current amount of cigarettes smoked in the children's homes*

4.2.1.1 *Paternal exposures*

Parents were asked about paternal current and childhood farm related exposures. In Group 1, 19.2% (n=624) of fathers were reared on a farm, of which 74.4% (n=464) were actively involved with farming activities. Only 2.2% were currently working as farmers during this study time period. In Group 2, 9.1% (n=64) were reared on a farm and were actively involved with farming activities as children; 0.2% (n=1) reported working as farmers during this study period.

4.2.1.2 *Maternal exposures*

Maternal exposures are summarised in Table 4.9. In Group 1, 18.1% (n=591) of mothers were reared on a farm and 3.5% (n=120) reported regular exposure to the farm whilst pregnant with the child involved in this study. In Group 2, 8.2% (n=58) of mothers were reared on a farm and no mother reported farm exposure during pregnancy.

Table 4.9 *Maternal exposures during childhood and pregnancy*

	Group 1 (n=3464, age 6-9)		Group 2 (n=706, age 11-13)	
Exposures	**During Childhood N (%)**	**During Pregnancy N (%)**	**During Childhood N (%)**	**During Pregnancy N (%)**
Unpasteurised Milk	664 (19.2)	153 (4.4)	88 (12.5)	20 (2.8)
Dog	2129 (61.5)	1312 (37.9)	391 (55.4)	199 (28.2)
Cat	1183 (34.2)	510 (14.7)	155 (22.0)	55 (7.8)
Farm Animals	760 (21.9)	267 (7.7)	89 (12.6)	15 (2.1)
Other Animals	346 (10.0)	146 (4.2)	70 (9.9)	16 (2.3)
Barn	796 (23.0)	168 (4.8)	60 (8.5)	13 (1.8)
Stable	316 (9.1)	106 (3.1)	48 (6.7)	9 (1.3)

Figure 4.4 shows that the percentage of parents completing third level education increased from the older children in Group 2 to the younger children in Group 1.

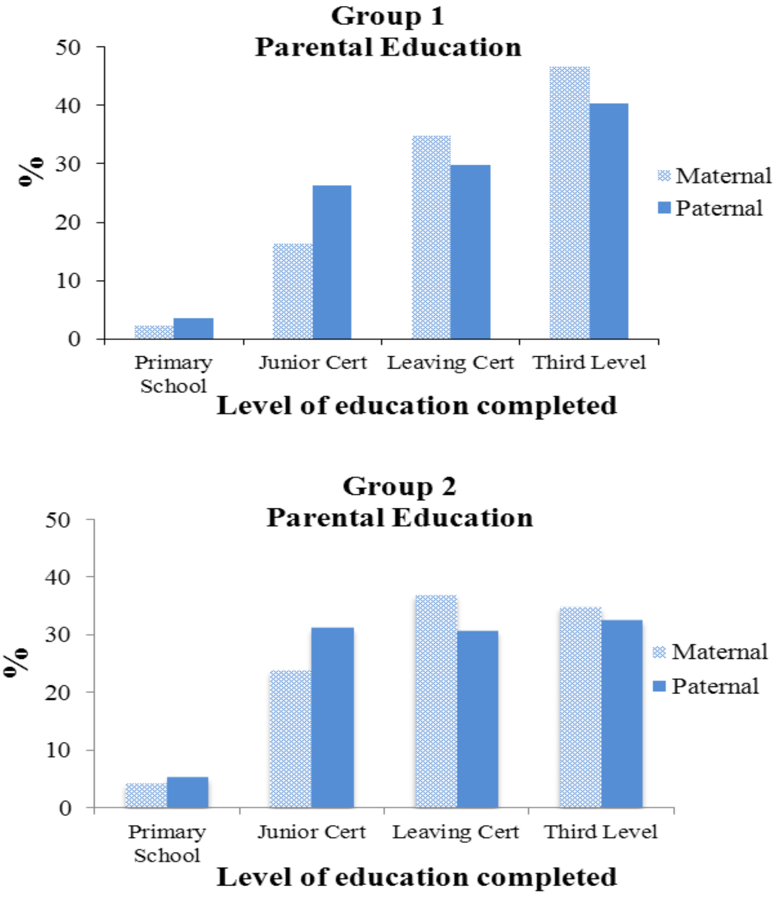


Figure 4.4 *Highest level of education attained by parents*

4.3 STUDY 1 TRENDS OF PREVALENCE OF ATOPIC DISORDERS

4.3.1 Study and population characteristics of study 1

The 2002 Sturley study involved 1474 children aged 6-9 years, of which 47.3% were males (mean age = 8.0 years). The 2007 Duggan study involved 1535 children aged 6-9 years, of which 52.1% were males (mean age = 7.6 years). The response rates were 74.8% in 2002 and 76.2% in 2007. Study and population characteristics are presented in Table 4.10.

Table 4.10 *Characteristics of the 2002 and 2007 prevalence studies*

	Sturley, 2002	**Duggan, 2007**
Participants		
Male	47.3%	52.1%
Age		
6 years	26 (1.8%)	36 (2.3%)
7 years	357 (24.3%)	627 (40.8%)
8 years	702 (47.8%)	722 (47.0%)
9 years	368 (25.1%)	150 (9.8%)
Mean age	8 years	7.6 years
Studies		
Total Sample	1474	1535
Response Rate	74.8%	76.2%

4.3.2 The prevalence of childhood allergic conditions in 2002 and 2007

Table 4.11 demonstrates the trends of prevalence of asthma, allergic rhinitis and eczema in 6-9 year old children, over the 5 year period from 2002 to 2007. There was no significant alteration in the prevalence of current asthma, asthma ever or severe asthma; however, the symptom of night cough had significantly decreased from 31.1% to 21.8% (p<0.001) from 2002 to 2007. In 2007, 14% (n=215) of children suffered from a dry night cough, current and lifetime asthma, while 14.8% (n=228) were being treated for asthma. Of the children with asthma ever, 10.7% (n=41) suffered from a dry night cough in the absence of current wheeze, of which 90.2% (n=37) received treatment for asthma.

Most symptoms of allergic rhinitis remained unchanged from 2002 to 2007, except for the prevalence of rhino-conjunctivitis, which had increased significantly from 7.6% to 10.6% ($p<0.005$). In 2002, the prevalence of rhinitic symptoms peaked (approx.12%) during winter and spring, sharply declined (6-7%) over summer and sharply increased again over autumn (Figure 4.5). In 2007, symptoms peaked (12%) in late spring/early summer, decreased and levelled off to approximately 6% during late summer and autumn months and rose again to 7- 9% in winter.

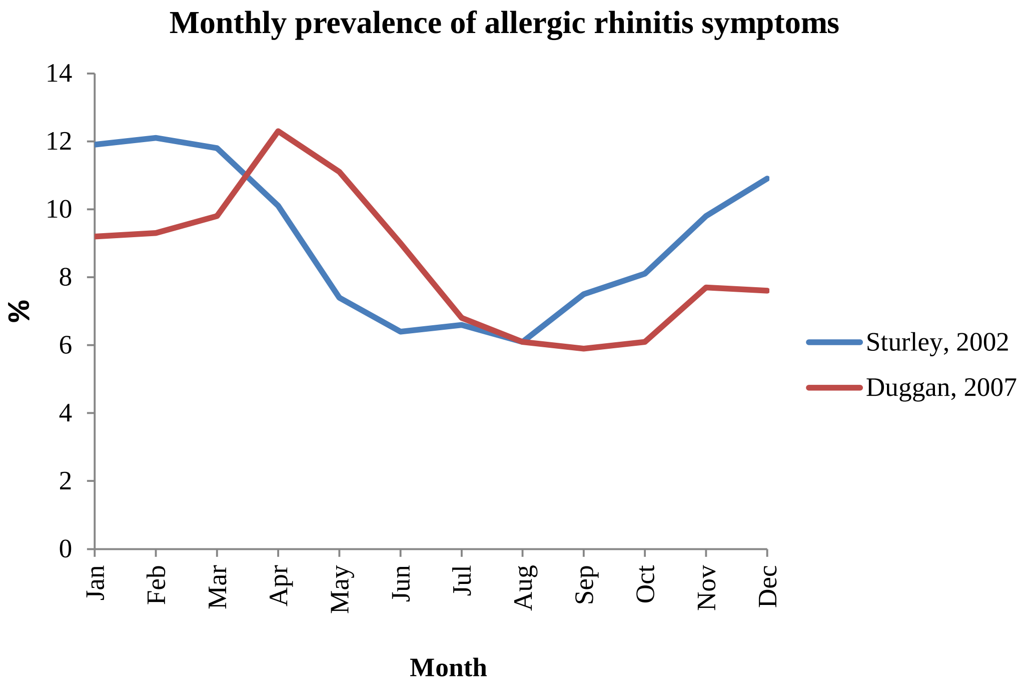


Figure 4.5 *Monthly prevalence of symptoms of allergic rhinitis in children aged 6-9*

There were significant increases (all to $p<0.001$) in the symptoms of rash ever (14.2% to 20.7%), current rash (11.8% to 16.2%), current eczema (8.9% to 13.5%) and occurrence of rash <2 years of age (4.5% to 7.8%). Lifetime diagnosis eczema had significantly reduced from 21.6% to 15.0% ($p<0.001$) and the severity of eczema symptoms suffered, remained unaltered.

Table 4.11 *Prevalence of allergic disease symptoms in children aged 6-9 years in 2002 and 2007**

	Sturley, 2002 (n=1474) N (%)	**Duggan, 2007 (n=1535) N (%)**	**Difference (95% CI)**	***p*- value**
Asthma				
Ever wheezed	610 (41.3%)	620 (40.4%)	0.9% (-3.0%, 5.0%)	0.580
Current wheeze	321 (21.7%)	360 (23.5%)	1.8% (-1.0%, 5.0%)	0.272
Exercise-induced wheeze	228 (15.5%)	236 (15.4%)	0.1% (-3.0%, 3.0%)	0.943
Night cough	458 (31.1%)	335 (21.8%)	9.3% (6.0%, 12.0%)	< 0.001
Ever had asthma	375 (25.4%)	382 (24.9%)	0.5% (-3.0%, 4.0%)	0.726
Speech limitation	54 (3.7%)	57 (3.7%)	0.1% (-1.0%, 1.0%)	0.942
≥4 wheeze attacks/past year	96 (6.5%)	104 (6.8%)	0.3% (-2.0%, 2.0%)	0.773
Woken by wheeze ≥1night/wk	58 (3.9%)	78 (5.1%)	1.2% (-0.4%, 3.0%)	0.130
Allergic Rhinitis				
Nasal problems ever	433 (29.4%)	470 (30.6%)	1.2% (-2.0%, 5.0%)	0.450
Current allergic rhinitis	385 (26.1%)	418 (27.2%)	1.1% (-2.0%, 4.0%)	0.491
Associated itchy eye	112 (7.6%)	162 (10.6%)	3.0% (1.0%, 5.0%)	0.005
Ever had hayfever	133 (9.0%)	159 (10.4%)	1.4% (-1.0%, 4.0%)	0.216
Mod/Severe interference with ADL	56 (3.8%)	78 (5.1%)	1.3% (-0.2%, 3.0%)	0.088
Eczema				
Ever had persistent rash	209 (14.2%)	318 (20.7%)	6.5% (4.0%, 9.0%)	< 0.001
Current persistent rash	174 (11.8%)	248 (16.2%)	4.4% (2.0%, 7.0%)	< 0.001
Affecting flexural areas	131 (8.9%)	207 (13.5%)	4.6% (2.0%, 7.0%)	< 0.001
Ever had eczema	319 (21.6%)	230 (15.0%)	6.6% (4.0%, 9.0%)	< 0.001
1st occurrence <2yrs	66 (4.5%)	120 (7.8%)	3.3% (2.0%, 5.0%)	<0.001
Not cleared in past year	49 (3.3%)	58 (3.8%)	0.5% (-1.0%, 2.0%)	0.501
Kept awake ≥1night/wk	17 (1.2%)	27 (1.8%)	0.6% (-0.3%, 2.0%)	0.167

**Parental Report* *CI (Confidence Interval)* Interval)* *ADL (Activities of daily living)*

4.3.3 Sex-specific prevalence

Stratification by sex demonstrated no significant alterations in the distribution of asthma symptoms from 2002-2007 (Table 4.12). In 2007, a male preponderance for current asthma was still apparent (M:F 1.2:1), although it had lost its significance since 2002 (M:F 1.5:1, $p<0.001$). The move towards equalisation was due to a significant increase in current wheeze in girls (17.4% -21.4%, $p=0.05$) and the alteration was close to statistical significance. Both timeframes revealed a male predominance in most asthma symptoms, except for severe symptoms, which were equally distributed between both sexes. Although statistically non-significant, the M:F ratio for most of the allergic rhinitis symptoms had moved away from equal sex distribution to male predominance. Most apparent, was the lifetime diagnosis of hayfever in which the M:F ratio moved from 1:1 to 1.5:1, due to a significant increase in male diagnosis (9.1% to 12.3%, $p=0.05$). The prevalence of all the reported symptoms of eczema were equally distributed between the sexes during both timeframes, except for the lifetime diagnosis of eczema which had moved from male predominance to equal sex distribution ($p<0.001$, sex/study interaction).

Table 4.12 *Sex distribution of allergic symptoms in children aged 6-9 years in 2002 and 2007**

	Male/Female				*Male : Female Ratio*				*Ratio Alteration*
	2002		*2007*		*2002*		*2007*		*2002 - 2007*
	Boys (n=699)	Girls (n=775)	Boys (n=795)	Girls (n=740)	M:F Ratio	*p*-value**	M:F Ratio	*p*-value**	*p*-value†
Asthma									
Ever wheezed	317 (45.4%)	295 (38.1%)	355 (44.6%)	262 (35.4%)	1.2 : 1	0.005	1.3 : 1	< 0.001	0.563
Current wheeze	187 (26.8%)	135 (17.4%)	200 (25.2%)	158 (21.4%)	1.5 : 1	< 0.001	1.2 : 1	0.075	0.057
Ever had asthma	205 (29.4%)	172 (22.2%)	221 (27.8%)	158 (21.4%)	1.3 : 1	0.002	1.3 : 1	0.005	0.880
Exercise-induced wheeze	134 (19.2%)	98 (12.7%)	139 (17.5%)	96 (13.0%)	1.5 : 1	0.001	1.3 : 1	0.018	0.486
Night cough	239 (34.3%)	228 (29.4%)	193 (24.3%)	139 (18.8%)	1.2 : 1	0.049	1.3 : 1	0.012	0.528
Speech limitation	29 (4.2%)	25 (3.2%)	31 (3.9%)	26 (3.5%)	1.3 : 1	0.346	1.1 : 1	0.813	0.694
≥4 Wheeze attacks/past year	54 (7.7%)	42 (5.4%)	58 (7.3%)	46 (6.2%)	1.4 : 1	0.073	1.2 : 1	0.962	0.482
Woken ≥1night/wk	29 (4.2%)	29 (3.7%)	42 (5.3%)	36 (4.9%)	1.0 : 1	0.688	1.1 : 1	0.559	0.954
Allergic Rhinitis									
Nasal problems ever	220 (31.5%)	215 (27.7%)	264 (33.2%)	201 (27.2%)	1.1 : 1	0.117	1.2 : 1	0.012	0.498
Current allergic rhinitis	197 (28.2%)	189 (24.4%)	237 (29.8%)	176 (23.9%)	1.2 : 1	0.098	1.3 : 1	0.009	0.499
Associated itchy eye	56 (8.0%)	56 (7.2%	88 (11.1%)	73 (9.9%)	1.1 : 1	0.570	1.1 : 1	0.459	0.948
Ever had hayfever	64 (9.1%)	69 (8.9%)	98 (12.3%)	60 (8.1%)	1.0 : 1	0.866	1.5 : 1	0.007	0.083
Mod/Severe interfere ADL	33 (4.7%)	23 (3.0%)	51 (6.4%)	27 (3.6%)	1.6 : 1	0.079	1.8 : 1	0.118	0.763
Eczema									
Ever had persistent rash	98 (14.0%)	112 (14.5%)	158 (19.9%)	157 (21.2%)	1.0 : 1	0.813	0.9 : 1	0.486	0.811
Current persistent rash	79 (11.3%)	95 (12.3%)	117 (14.7%)	128 (17.3%)	1.0 : 1	0.570	0.8 : 1	0.075	0.639
Affecting flexural areas	62 (8.9%)	69 (8.9%)	98 (12.3%)	107 (14.5%)	1.0 : 1	0.982	0.8 : 1	0.762	0.477
Ever had eczema	172 (24.6%)	50 (19.4%)	121(15.2%)	108 (14.6%)	1.3 : 1	< 0.001	1.0 : 1	0.802	< 0.001
Not cleared in past year	23(3.3%)	21 (2.7%)	28 (3.5%)	30 (4.1%)	1.2 : 1	0.513	0.9 : 1	0.901	0.395
Woken by rash ≥1night/wk	6 (0.9%)	10 (1.4%)	15 (1.9%)	12 ((1.6%)	0.6 : 1	0.424	1.2 : 1	0.365	0.384

*Parental report

ADL (Activities of daily living)

** *P*-value for difference between sex distribution of symptoms within each study

†*P*-value for sex/study interaction

4.3.4 Co-morbidity of allergic disease

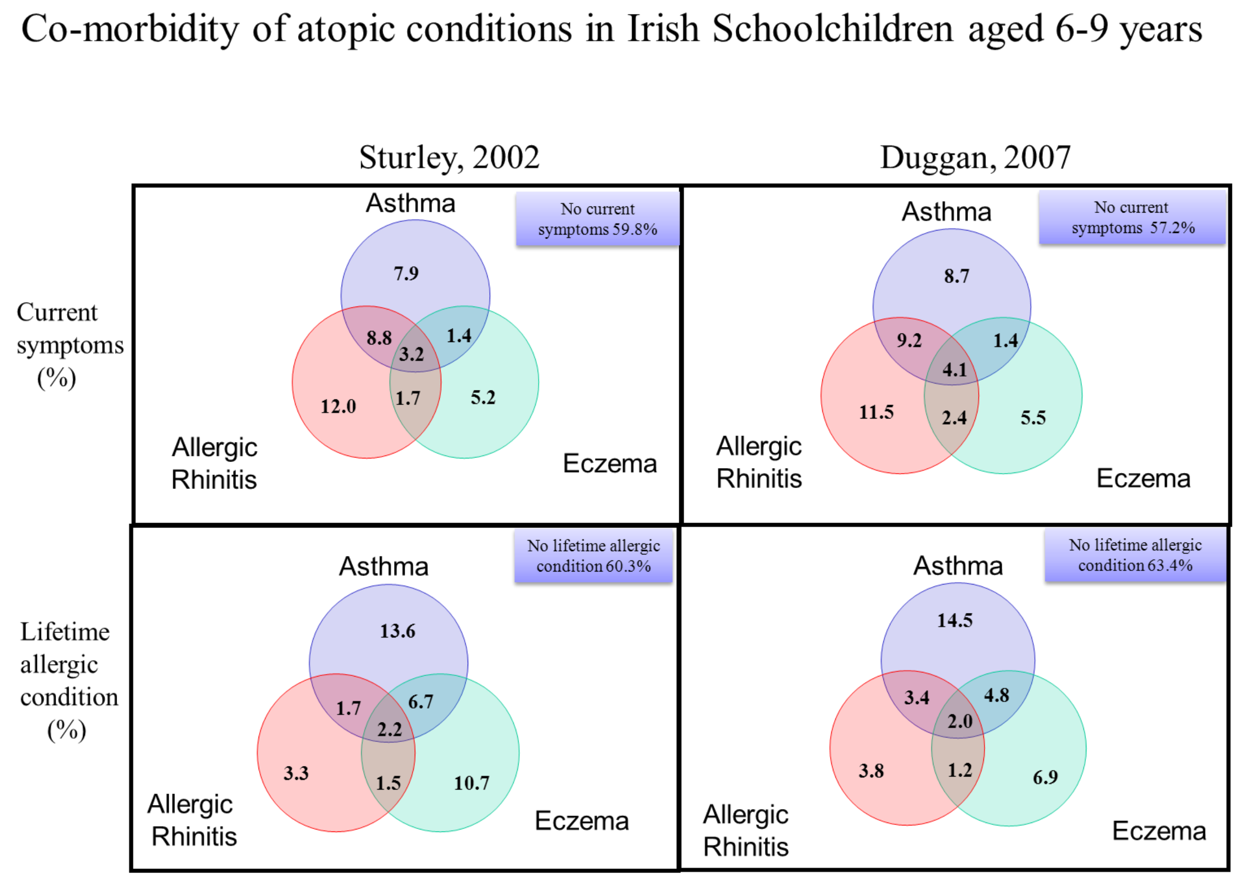
A high level of co-prevalence of current symptoms and lifetime diagnosis of asthma, allergic rhinitis and eczema persists (Figure 4.6). From 2002 to 2007, all levels of co-morbidity of current asthma, allergic rhinitis and eczema symptoms had increased (≥ 1 condition – 40% to 42.8%, ≥ 2 conditions – 15.1 to 17.1% and symptoms of all three conditions – 3.2% to 4.1%). The only statistically significant increase was in the percentage of children suffering from current symptoms of all three conditions (p<0.001). All indices of co-prevalence of lifetime diagnosis had decreased non-significantly between 2002 and 2007 (diagnosed with at least one condition - 39.7% to 36.6%, at least two - 12.1% to 11.4% and diagnosed with all three conditions – 2.2% to 2%).

4.3.5 Tobacco smoking

There was a significant reduction in the prevalence of maternal smoking during pregnancy (33.3% to 21.0%, p<0.001), in the first year of life (38.1% to 31.1%, p<0.001) and currently (35.4% to 28.9%, p<0.001) during the study interval (Table 4.13). Secondary tobacco smoke exposure in the home also decreased significantly (39.7% to 22.3%, p<0.001).

Table 4.13 *Reported prevalence and exposure to tobacco smoking in 2002 and 2007*

	Sturley, 2002 (n=1474) N (%)	**Duggan, 2007 (n=1535) N (%)**	**Difference (95% CI)**	***p*-value**
Mother smoked during pregnancy	491 (33.3)	323 (21.0)	12.3% (9.0%, 15.0%)	< 0.001
Mother smoked in Year 1	562 (38.1)	477 (31.1)	7.0% (3.7%, 10.0%)	< 0.001
Mother currently smoking	522 (35.4)	443 (28.9)	6.5% (3.2%, 9.9%)	< 0.001
Home exposure to tobacco smoke	586 (39.7)	342 (22.3)	17.4% (14.2%, 20.7%)	< 0.001



Co-morbidity of atopic conditions in Irish Schoolchildren aged 6-9 years

Figure 4.6 *Co-morbidity of atopic disorders in 2002 and 2007study populations (age 6-9)*

4.4 STUDY 2 – ASSOCIATIONS WITH ASTHMA AND ALLERGY

Study 2 examines the associations with childhood allergic diseases in 3464 children, aged 6-9 years, living in rural and urban locations. The response rate was 75.8%.

4.4.1 Study and population characteristics of study 2

Of the 3,464 children, 2048 (59.1%) attended a rural school. The age distribution, sex and nationality of the children and parents from both the rural and urban schools are similar (Table 4.14). There is also strong agreement between the school and home location in our study. Of the children who are living the county, 96.1% (n=1966) attend rural schools and 84.7% (n=1196) of the children living in the city attend city schools.

Table 4.14 *Characteristics of rural and urban schoolchildren*

	Rural schools (n=2048) N (%)	*Urban schools (n=1416) N (%)*
Male	995 (48.9)	728 (51.8)
Age		
6 years	52 (2.5)	35 (2.5)
7 years	774 (37.9)	579 (40.9)
8 years	973 (47.6)	667 (47.1)
9 years	244 (11.9)	134 (9.5)
Mean age	7.7 yrs.	7.6 yrs.
Born in Ireland	1799 (89.0)	1261 (90.3)
Born to Irish mother	1673 (86.4)	1203 (90.7)
Born to Irish father	1665 (86.7)	1165 (88.7)
Self-reported home location	2182 (63.1)	1276 (36.9)
Response rate	77.2%	74.4%

The stratification of symptom prevalence by age demonstrated no significant differences in prevalence rates across the age groups (Table 4.15).

Table 4.15 *Prevalence of childhood allergic diseases stratified by age**

	Combined ages (n=3458) N (%)	Age 6 (n=87) N (%)	Age 7 (n=1353) N (%)	Age 8 (n=1640) N (%)	Age 9 (n=378) N (%)	*p*-value
Asthma						
Ever wheezed	1272 (36.7)	31 (35.6)	504 (37.3)	594 (36.2)	143 (37.8)	0.905
Current wheeze	699 (20.2)	16 (18.4)	279 (20.6)	324 (19.8)	80 (21.2)	0.863
Exercise-induced wheeze	445 (12.8)	10 (11.6)	178 (13.3)	197 (12.1)	60 (16.0)	0.233
Night cough	648 (18.7)	16 (18.6)	252 (18.8)	304 (18.7)	76 (20.4)	0.903
Ever had asthma	757 (21.9)	18 (20.7)	292 (21.7)	352 (21.7)	95 (25.2)	0.472
Speech limitation	100 (2.9)	3 (3.5)	34 (2.5)	50 (3.0)	13 (3.4)	0.552
≥4 wheeze attacks/past year	211 (6.1)	3 (3.5)	76 (5.6)	103 (6.2)	29 (7.7)	0.271
Woken by wheeze ≥1night/week	129 (3.7)	2 (2.3)	58 (4.3)	58 (3.5)	11 (2.9)	0.548
Allergic Rhinitis						
Nasal problems ever	959 (27.7)	24 (27.6)	374 (27.7)	453 (27.7)	107 (28.4)	0.994
Current allergic rhinitis	858 (24.8)	22 (25.3)	330 (24.4)	403 (24.6)	102 (27.0)	0.766
Associated itchy eye	360 (10.4)	8 (9.2)	126 (9.3)	179 (10.9)	47 (12.4)	0.262
Ever had hayfever	360 (10.4)	9 (10.3)	124 (9.2)	181 (11.2)	46 (12.2)	0.237
Mod/Severe interference with ADL	151 (4.4)	5 (5.7)	61 (4.5)	61 (3.7)	24 (6.4)	0.158
Eczema						
Ever had persistent rash	675 (19.5)	15 (17.4)	260 (19.2)	326 (19.9)	72 (19.1)	0.920
Current persistent rash	520 (15.0)	12 (13.8)	202 (14.9)	253 (15.4)	53 (14.0)	0.786
Affecting flexural areas	439 (12.7)	9 (10.3)	167 (12.3)	216 (13.2)	47 (12.4)	0.815
Ever had eczema	477 (13.8)	10 (11.5)	189 (14.1)	223 (13.7)	54 (14.3)	0.908
1st occurrence <2yrs	156 (4.5)	2 (2.3)	54 (4.0)	80 (4.9)	20 (5.3)	0.235
Not cleared in past year	137 (4.0)	2 (2.3)	58 (4.3)	70 (4.3)	7 (1.9)	0.129
Kept awake ≥1night/wk	49 (1.4)	1 (1.2)	17 (1.3)	26 (1.6)	5 (1.3)	0.901

**Parental Report* *ADL (Activities of daily living)*

4.4.2 Univariate analysis

The association between the 6 divisions of home location (ranging from city to farm) currently and during the first year of life and the 12 month prevalence of asthma, allergic rhinitis and eczema were examined by univariately by chi-square test and logistic regression analysis for trend across the categories. An overall association between home location during both timeframes and the 12 month prevalence of asthma (year 1: $p=0.005$, current: $p<0.001$, $p<0.001$ for trend across categories) and allergic rhinitis (year 1 and current: $p<0.001$, $p<0.001$ for trend in year 1 location and $p<0.001$ for trend in current location) was found (Figure 4.7). No association was evident between home location and the prevalence of childhood eczema. It is apparent that the prevalence of current asthma appears to decrease as the home location becomes more rural. The reduction of prevalence between city and farm habitation is also apparent in current allergic rhinitis; however, the dose-response effect as home location moves towards that of a rural abode is not graphically evident.

The univariate analysis results from categorised putative factors associated with the three outcome measures of: current asthma, current allergic rhinitis and current eczema are presented in tables 4.16-4.19. It is apparent that there were many associations with current atopic disorders at univariate level, which progressed to multivariate analysis. Tables for the other main outcome measures are not presented.

Current asthma and current allergic rhinitis prevalence according to home location

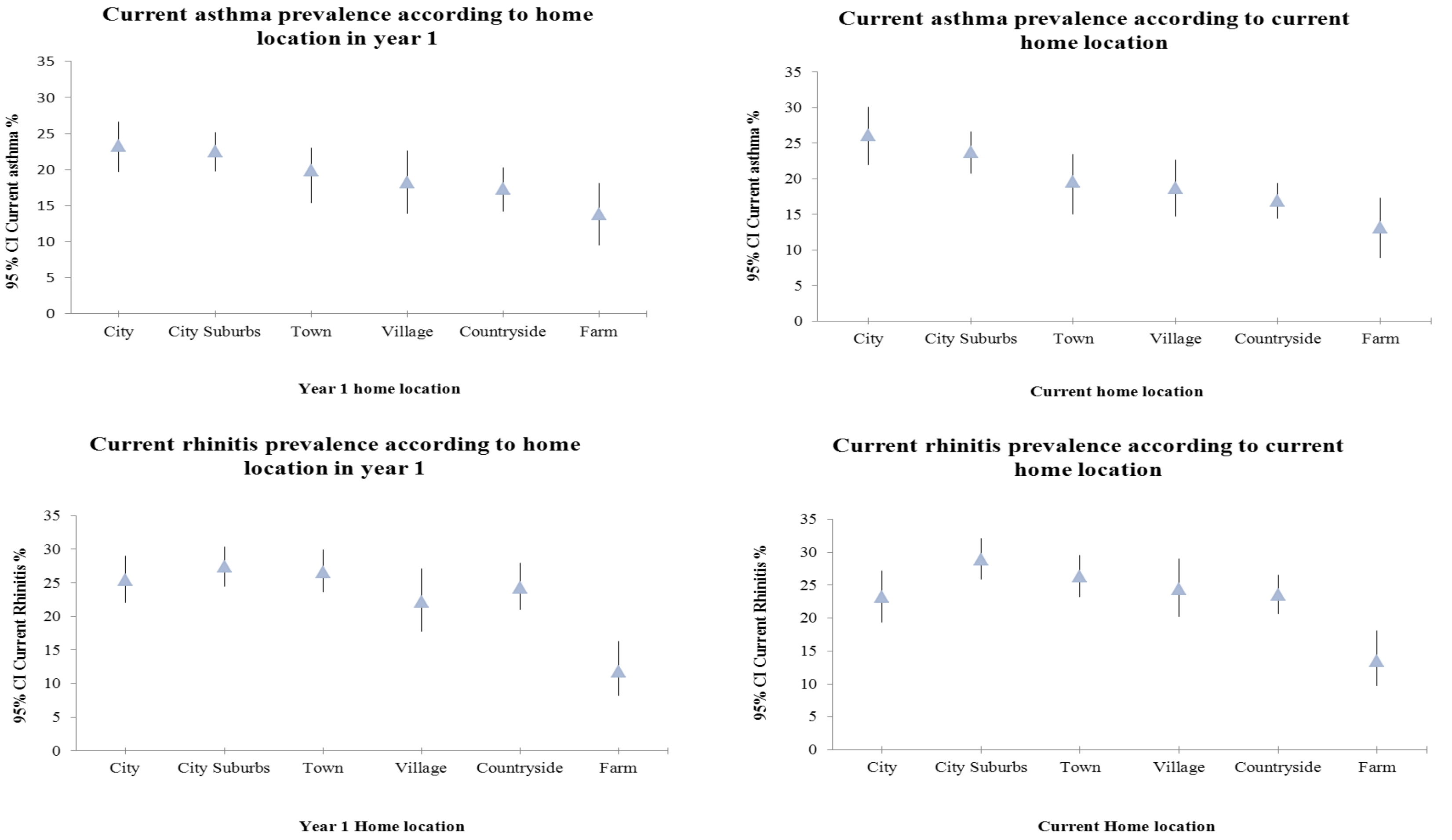


Figure 4.7 *Current asthma and current allergic rhinitis prevalence according to home location*

Table 4.16 *Associations between home location and current asthma, rhinitis and eczema from univariate analysis*

	N (%) Current Asthma (n=699)	*N (%) No Current Asthma (n=2765)*	*p-value*	*N (%) Current AR (n=858)*	*N (%) No current AR (n=2606)*	*p-value*	*N (%) Current Eczema (n=439)*	*N (%) No Current Eczema (n=3025)*	*p-value**
Year 1 Home Location									
City	144 (20.6)	474 (17.2)		157 (18.3)	461 (17.7)		82 (18.7)	536 (17.7)	
City suburbs	202 (28.9)	696 (25.2)	0.713	246 (28.7)	652 (25.0)	0.389	126 (28.7)	772 (25.5)	0.672
Town	152 (21.8)	610 (22.1)	0.132	203 (23.7)	559 (21.5)	0.603	98 (22.3)	664 (22.0)	0.823
Village	55 (7.9)	247 (8.9)	0.079	67 (7.8)	235 (9.0)	0.286	28 (6.4)	274 (9.1)	0.081
Countryside – not farm	103 (14.7)	494 (17.9)	0.009	145 (16.9)	452 (17.3)	0.653	78 (17.8)	519 (17.2)	0.917
Farm	34 (4.9)	212 (7.7)	0.002	29 (3.4)	217 (8.3)	< 0.001	26 (5.9)	220 (7.3)	0.280
Current Home Location									
City	117 (16.7)	332 (12.0)		104 (12.1)	345 (13.2)		60 (13.7)	389 (12.9)	
City suburbs	196 (28.0)	631 (22.8)	0.350	239 (27.9)	588 (22.6)	0.028	112 (25.5)	715 (23.6)	0.928
Town	147 (21.0)	602 (21.8)	0.010	197 (23.0)	552 (21.2)	0.226	89 (20.3)	660 (21.8)	0.452
Village	69 (9.9)	300 (10.9)	0.013	90 (10.5)	279 (10.7)	0.681	46 (10.5)	323 (10.7)	0.704
Countryside – not farm	137 (19.6)	675 (24.4)	< 0.001	191 (22.3)	621 (22.8)	0.885	104 (23.7)	708 (23.4)	0.779
Farm	33 (4.7)	219 (7.9)	< 0.001	34 (4.0)	218 (8.4)	0.002	28 (6.4)	224 (7.4)	0.388

**P-value based on univariate logistic regression analysis, where city is the reference category*

Table 4.17 *Associations with current asthma, rhinitis and eczema from univariate analysis in the medical category*

MEDICAL VARIABLES	***N (%) Current Asthma (n=699)***	***N (%) No Current Asthma (n=2765)***	***p-value****	***N (%) Current AR (n=858)***	***N (%) No Current AR (n=2606)***	***p-value ****	***N (%) Current Eczema (n=439)***	***N (%) No Current Eczema (n=3025)***	***p-value****
INFECTIONS <3yrs									
German Measles	7 (1.0)	55 (2.0)	0.009	12 (1.4)	50 (1.9)	0.012	4 (0.9)	58 (1.9)	0.330
Measles	42 (6.0)	164 (5.9)	0.243	49 (5.7)	157 (6.0)	0.147	30 (6.8)	176 (5.8)	0.522
Mumps	10 (1.4)	27 (1.0)	0.128	9 (1.0)	28 (1.1)	0.125	10 (2.3)	27 (0.9)	0.021
Croup	164 (23.5)	347 (12.5)	< 0.001	182 (21.2)	329 (12.6)	< 0.001	88 (20.0)	423 (14.0)	0.001
Pertussis	46 (6.6)	89 (3.2)	< 0.001	55 (6.4)	80 (3.1)	< 0.001	33 (7.5)	102 (3.4)	< 0.001
Bronchiolitis	282 (40.3)	397 (14.4)	< 0.001	261 (30.4)	418 (16.0)	< 0.001	115 (26.2)	564 (18.6)	< 0.001
Pneumonia	47 (6.7)	75 (2.7)	< 0.001	46 (5.4)	76 (2.9)	< 0.001	17 (3.9)	105 (3.5)	0.907
Gastroenteritis	255 (36.5)	581 (21.0)	< 0.001	304 (35.4)	532 (20.4)	< 0.001	130 (29.6)	706 (23.3)	0.016
Ear Infections	43 (6.2)	87 (3.3)	< 0.001	53 (6.2)	77 (3.0)	< 0.001	24 (5.5)	106 (3.5)	0.123
Meningitis	12 (1.7)	19 (0.7)	0.014	14 (1.6)	17 (0.7)	0.002	8 (1.8)	23 (0.8)	0.078
Chickenpox	377 (53.9)	1367 (49.4)	0.063	458 (53.4)	1286 (49.3)	0.090	238 (54.2)	1506 (49.8)	0.209
IMMUNISATIONS									
Three in 1	682 (97.6)	2672 (96.6)	0.154	836 (97.4)	2158 (96.6)	0.334	425 (96.8)	2929 (96.8)	0.162
Hib	609 (87.1)	2393 (86.5)	0.274	750 (87.4)	2252 (86.4)	0.447	383 (87.2)	2619 (86.6)	0.904
Meningitis C	568 (81.3)	2200 (79.6)	0.550	712 (83.0)	2056 (78.9)	0.034	350 (79.7)	2418 (79.9)	0.759
BCG	249 (35.6)	1032 (37.3)	0.616	318 (37.1)	963 (37.0)	0.869	176 (40.1)	1105 (36.5)	0.338
MMR	671 (96.0)	2634 (95.3)	0.673	818 (95.3)	2487 (95.4)	0.922	421 (95.9)	2884 (95.3)	0.489
ANTIBIOTICS<2yrs									
Yes/No	595 (85.1)	1848 (66.8)	< 0.001	711 (82.9)	1732 (66.4)	< 0.001	343 (78.1)	2100 (69.4)	< 0.001
None	94 (13.4)	867 (31.4)	< 0.001	137 (16.0)	824 (31.6)	< 0.001	88 (20.0)	873 (28.9)	< 0.001
At least 1-amt. not specified	104 (14.9)	265 (9.6)	< 0.001	116 (13.5)	253 (9.7)	< 0.001	64 (14.6)	305 (10.1)	< 0.001
1-2 courses	142 (20.3)	840 (30.4)	0.002	189 (22.0)	793 (30.4)	0.003	102 (23.2)	880 (29.1)	0.362
3-4 courses	157 (22.5)	409 (14.8)	< 0.001	199 (23.2)	367 (14.0)	< 0.001	84 (19.1)	482 (15.9)	0.001
5-6 courses	83 (11.9)	197 (7.1)	< 0.001	102 (11.9)	178 (6.8)	< 0.001	50 (11.4)	230 (7.6)	< 0.001
≥7 courses	110 (15.7)	143 (5.2)	< 0.001	106 (12.4)	147 (5.6)	< 0.001	43 (9.8)	210 (6.9)	< 0.001

P-value based on chi-square test

***Table 4.18** Associations with current asthma, rhinitis and eczema (univariate analysis in parental childhood, pregnancy and perinatal category)*

PARENTAL CHILDHOOD, PREGNANCY AND PERINATAL VARIABLES	***N (%) Current Asthma (n=699)***	***N (%) No Current Asthma (n=2765)***	***p-value***	***N (%) Current AR (n=858)***	***N (%) No Current AR (n=2606)***	***p-value***	***N (%) Current Eczema (n=439)***	***N (%) No Current Eczema (n=3025)***	***p-value***
PARENTAL CHILDHOOD									
Mother: Reared on Farm	109 (15.6)	482 (17.4)	0.211	119 (13.9)	472 (18.1)	0.002	81 (18.5)	510 (16.9)	0.408
Barn	110 (15.7)	457 (16.5)	0.613	137 (16.0)	430 (16.5)	0.714	79 (18.0)	488 (16.1)	0.324
Stable	64 (9.2)	252 (9.1)	0.973	83 (9.7)	233 (8.9)	0.518	46 (10.5)	270 (8.9)	0.291
Furry Pets	448 (64.1)	1785 (64.6)	0.818	563 (65.6)	1670 (64.1)	0.415	284 (64.7)	1949 (64.4)	0.914
Farm Animals	134 (19.2)	626 (22.6)	0.048	166 (19.3)	594 (22.8)	0.034	103 (23.5)	657 (21.7)	0.409
Unpast. Milk	127 (18.2)	537 (19.4)	0.392	150 (17.5)	514 (19.8)	0.121	94 (21.4)	570 (18.8)	0.193
Father: Reared on Farm	104 (14.8)	519 (18.8)	0.014	128 (14.9)	495 (18.9)	0.003	81 (18.5)	542 (17.9)	0.827
PREGNANCY									
Farm	20 (2.9)	100 (3.6)	0.329	17 (2.0)	103 (4.0)	0.006	15 (3.4)	105 (3.5)	0.954
Barn	23 (3.3)	145 (5.2)	0.032	25 (2.9)	143 (5.5)	0.002	29 (6.6)	139 (4.6)	0.068
Stable	16 (2.3)	90 (3.3)	0.185	23 (2.7)	83 (3.2)	0.457	21 (4.8)	85 (2.8)	0.025
Furry Pets	279 (39.9)	1145 (41.4)	0.473	368 (42.9)	1056 (40.5)	0.221	171 (39.0)	1253 (41.4)	0.326
Farm Animals	37 (5.3)	230 (8.3)	0.007	47 (5.5)	220 (8.4)	0.005	34 (7.7)	233 (7.7)	0.975
Unpasteurised Milk	23 (3.3)	130 (4.7)	0.101	28 (3.3)	125 (4.8)	0.052	21 (4.8)	132 (4.4)	0.684
Tobacco Smoke	172 (24.6)	514 (18.6)	0.002	180 (21.0)	506 (19.4)	0.317	81 (18.5)	605 (20.0)	0.539
PERINATAL									
Born at Term	640 (91.6)	2602 (94.1)	0.014	794 (92.5)	2448 (93.9)	0.147	417 (95.0)	2825(93.4)	0.201
Caesarean Section	158 (22.6)	590 (21.3)	0.545	204 (23.8)	544 (20.9)	0.092	100 (22.8)	648 (21.4)	0.617
Twin	19 (2.7)	80 (2.9)	0.818	30 (3.5)	69 (2.7)	0.192	11 (2.5)	88 (2.9)	0.637
Breastfed Ever	251 (35.9)	1247 (45.1)	< 0.001	349 (40.7)	1149 (44.1)	0.064	202 (46.0)	1296 (42.8)	0.447
Breastfed $\geq$16 wks. (vs. $\leq$15)	75 (10.7)	340 (12.3)	0.402	110 (12.8)	305 (11.7)	0.069	62 (14.1)	353 (11.7)	0.236
Birth Weight (continuous)	-	-	0.359	-	-	0.622	-	-	0.922
Low Birth Weight $\leq$ 2.5KG	23 (3.3)	102 (3.7)	0.147	31 (3.6)	94 (3.6)	0.885	10 (2.3)	115 (3.8)	0.123

P-value based on chi-square test

Table 4.19 *Associations with current asthma, rhinitis and eczema from univariate analysis in environmental category*

ENVIRONMENTAL VARIABLES	*N (%) Current Asthma (n=699)*	*N (%) No Current Asthma (n=2765)*	*p-value*	*N (%) Current AR (n=858)*	*N (%) No Current AR (n=2606)*	*p-value*	*N (%) Current Eczema (n=439)*	*N (%) No Current Eczema (n=3025)*	*p-value*
EXPOSURES YEAR 1									
Full-time Crèche	97 (13.9)	462 (16.7)	0.081	145 (16.9)	414 (15.9)	0.499	80 (18.2)	479 (15.8)	0.210
Tobacco Smoke	231 (33.0)	771 (27.9)	0.008	245 (28.6)	757 (29.0)	0.797	109 (24.8)	893 (29.5)	0.034
Damp Bedroom	113 (16.2)	318 (11.5)	0.001	124 (14.5)	307 (11.8)	0.038	62 (14.1)	369 (12.2)	0.259
Carpet flooring	424 (60.7)	1601 (57.9)	0.389	489 (57.0)	1536 (58.9)	0.304	248 (56.5)	1777 (58.7)	0.509
Furry Pets	302 (43.2)	1272 (46.0)	0.184	409 (47.7)	1165 (44.7)	0.130	190 (43.3)	1384 (45.8)	0.331
Farm Animals	46 (6.6)	307 (11.1)	< 0.001	66 (7.7)	287 (11.0)	0.005	44 (10.0)	309 (10.2)	0.901
Barn	19 (2.7)	115 (4.2)	0.078	23 (2.7)	111 (4.3)	0.038	21 (4.8)	113 (3.7)	0.287
Stable	4 (0.6)	27 (1.0)	0.311	7 (0.8)	24 (0.9)	0.777	8 (1.8)	23 (0.8)	0.027
Unpasteurised Milk	12 (1.7)	104 (3.8)	0.008	15 (1.7)	101 (3.9)	0.003	13 (3.0)	103 (3.4)	0.633
Mains Drinking Water	595 (85.1)	2199 (79.5)	0.001	728 (84.8)	2066 (79.3)	< 0.001	361 (82.2)	2433 (80.4)	0.516
CURRENT EXPOSURES									
Maternal Tobacco Smoke	220 (31.5)	687 (24.8)	< 0.001	219 (25.5)	688 (26.4)	0.569	111 (25.3)	796 (26.3)	0.617
Damp Bedroom	70 (10.0)	211 (7.7)	0.039	77 (9.0)	204 (7.8)	0.278	37 (8.4)	244 (8.1)	0.798
Carpet flooring	228 (32.7)	1022 (37.0)	0.092	271 (31.6)	979 (37.6)	0.005	134 (30.5)	1116 (37.0)	0.019
Furry Pets	459 (65.7)	1842 (66.6)	0.634	574 (66.9)	1727 (66.3)	0.735	289 (65.8)	2012 (66.5)	0.778
Farm Animals	65 (9.3)	415 (15.0)	< 0.001	85 (9.9)	395 (15.2)	< 0.001	54 (12.3)	426 (14.1)	0.313
Stable	37 (5.3)	180 (6.5)	0.236	48 (5.6)	169 (6.5)	0.350	33 (7.5)	184 (6.1)	0.246
Barn	33 (4.7)	196 (7.1)	0.024	34 (4.0)	195 (7.5)	< 0.001	28 (6.4)	201 (6.6)	0.834
Unpasteurised Milk	28 (4.0)	150 (5.4)	0.129	33 (3.8)	145 (5.6)	0.048	21 (4.8)	157 (5.2)	0.720
Mains Drinking Water	576 (82.4)	2088 (75.5)	< 0.001	696 (81.1)	1968 (75.5)	0.001	344 (78.4)	2320 (76.7)	0.481

P-value based on chi-square test

4.4.3 Asthma

The final models for the three main outcome measures for asthma, namely: Wheeze Ever, Current Asthma and Asthma Ever are presented in Tables 4.20-4.22. The final logistic regression model for Wheeze Ever (Table 4.20) revealed positive associations for year 1 exposure to a damp bedroom (OR 1.6; 95% CI 1.25, 2.10), respiratory infections (OR 3.2; 95% CI 2.68, 3.87, p<0.001) and gastroenteritis (OR 1.3; 95% CI 1.10, 1.63, p=0.003) in the first 3 years of life and antibiotics consumed in the first 2 years of life (p<0.001). A protective effect was found with exposure to farm animals (OR 0.6; 95% CI 0.46, 0.85).

In the final model for Current Asthma (Table 4.21), positive associations were found for having consumed antibiotics prior to 2 years of age (p< 0.001), respiratory infections (OR 1.9; 95% CI 1.55, 2.40, p=<0.001), gastrointestinal infections (OR 1.3; 95% CI 1.07, 1.67, p=0.011) prior to 3 years of age and current maternal tobacco smoking (OR, 1.4; 95% CI 1.07, 1.73, p=0.011). Inverse associations were found with current farm animal exposure (OR 0.6; 95% CI 0.40, 0.98, p=0.038) and having attended a crèche full-time in the first year of life (OR 0.7; 95% CI 0.53, 0.94, p=0.018). The protective effect of living outside the city was evident at univariate analysis and when partially adjusted for the main potential confounders. However, home location lost significance when fully adjusted in the final model.

In the ***Asthma Ever*** final model (Table 4.22), as with the current asthma model, the risk factors of respiratory infections (OR 2.1; 95% CI 1.74, 2.64, p<0.001) and gastrointestinal infections (OR 1.3; 95% CI 1.07, 1.63, p=0.011) < 3years of age, having consumed antibiotics in the first two years of life (p<0.001) and exposure to a damp bedroom in the first year of life (OR 1.4; 95% CI 1.07, 1.89, p=0.015) emerged as significant. The only protective factor found for lifetime asthma was current farm animal exposure (OR 0.6; 95% CI 0.43, 0.90, p=0.012). The associations for the three outcome measures for asthma found in this study are presented graphically in Figure 4.8.

Figure 4.9 depicts the crude and percentage of antibiotic courses prescribed in children with asthma and without (graphs a-c) and the adjusted odds ratios for current asthma and antibiotic courses (graph d). It is clear that asthmatic children were prescribed significantly more antibiotics than non-asthmatic children.

Factors associated with symptoms of Asthma in children aged 6-9, in multivariate analysis

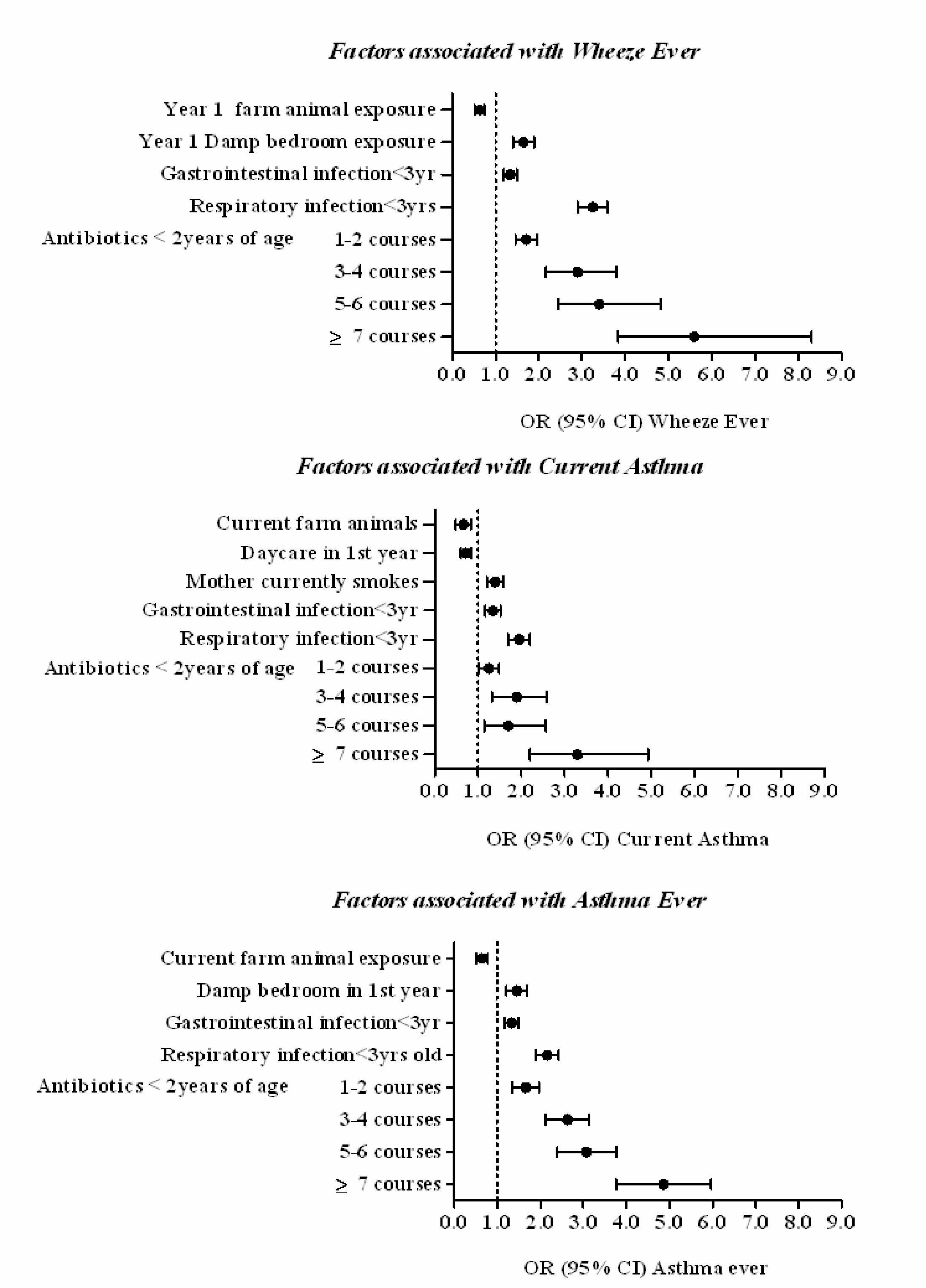


Figure 4.8 *Risk and protective factors associated with the symptoms of Asthma in children aged 6-9 years (n=3464)*

The relationship between antibiotic courses consumed ≤ 2 years of age and symptoms of Asthma in children aged 6-9 years (n=3464)

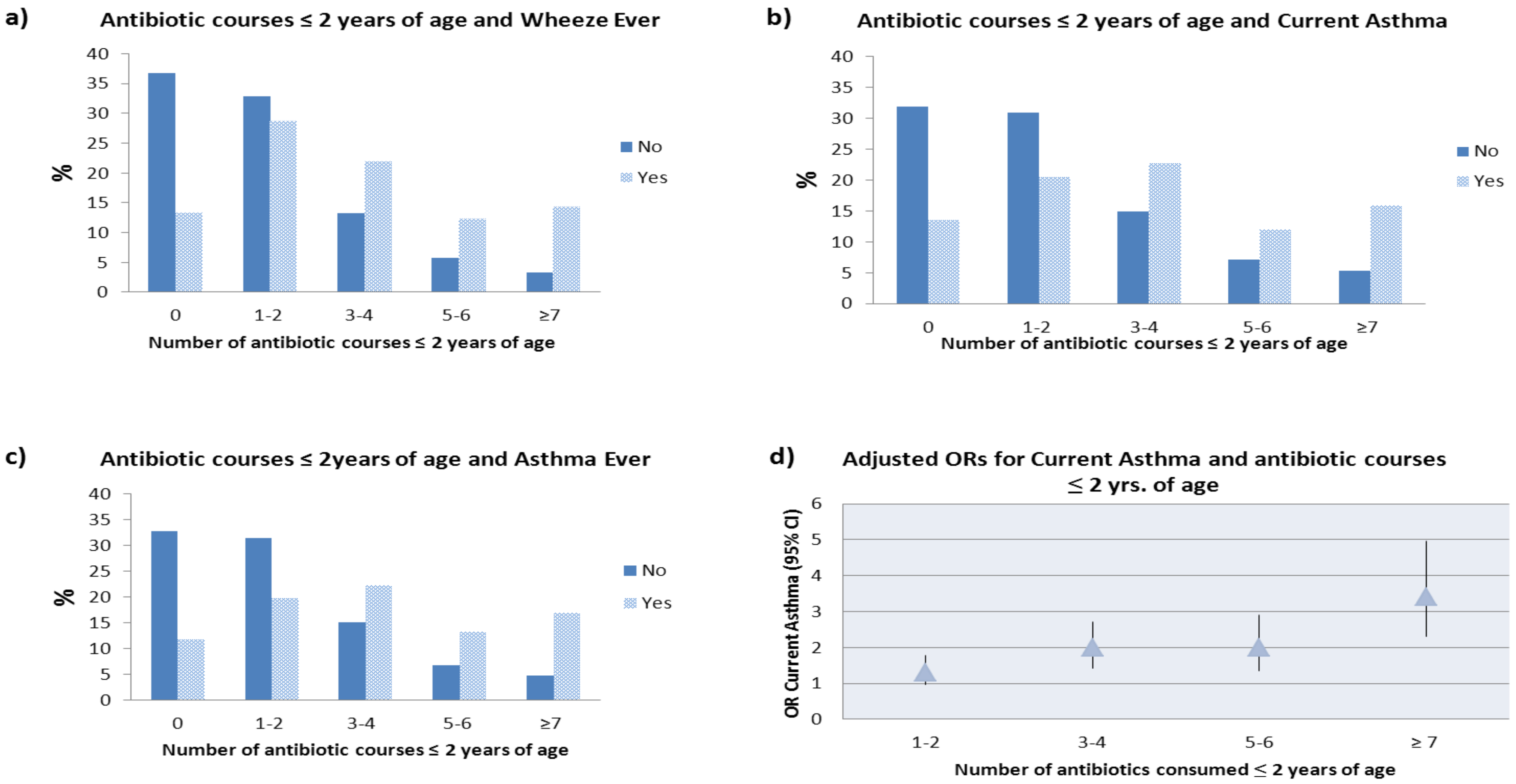


Figure 4.9 *The relationship between antibiotic courses consumed <2 years and symptoms of asthma in children aged 6-9 years*

Graphs a - c : Crude percentages of antibiotic courses consumed ≤ 2 yrs. and prevalence of asthma symptoms
Graph d : Adjusted odds ratios for current asthma and number of antibiotic courses ≤ 2 years of age

Table 4.20 *Final model for factors associated with Wheeze Ever in children aged 6-9 years (n=3464)**

	N (%) Among Wheeze Ever (n=1272)	***N (%) Among No Wheeze Ever (n=2192)***	***Univariate OR***	***p-value***	***Partially Adjusted OR*****	***p-value***	***Fully Adjusted OR†***	***p-value***
MEDICAL								
Infections <3yrs old								
No Respiratory	558 (43.9)	1741 (79.5)	1.0					
Yes Respiratory	714 (56.1)	450 (20.5)	5.0 (4.25, 5.76)	< 0.001	4.4 (3.69, 5.14)	< 0.001	3.2 (2.68, 3.87)	< 0.001
No Gastrointestinal	717 (56.4)	1616 (73.8)	1.0					
Yes Gastrointestinal	444 (38.2)	392 (19.5)	2.6 (2.17, 3.00)	< 0.001	2.1 (1.76, 2.50)	< 0.001	1.3 (1.10, 1.63)	0.003
Antibiotics <2yrs old								
Overall				< 0.001		< 0.001		< 0.001
None	167 (13.3)	794 (36.8)	1.0					
1-2 courses	276 (22.0)	706 (32.8)	1.9 (1.50, 2.31)	< 0.001	1.8 (1.44, 2.30)	< 0.001	1.7 (1.29, 2.15)	< 0.001
3-4 courses	279 (22.2)	287 (13.3)	4.6 (3.66, 5.84)	< 0.001	3.8 (2.92, 4.87)	< 0.001	2.9 (2.17, 3.80)	< 0.001
5-6 courses	156 (12.4)	124 (5.8)	6.0 (4.48, 7.99)	< 0.001	4.7 (3.43, 6.42)	< 0.001	3.4 (2.44, 4.83)	< 0.001
≥7 courses	181 (14.4)	72 (3.3)	12.0 (8.68 , 16.46)	< 0.001	10.0 (7.04, 14.09)	< 0.001	5.6 (3.83, 8.31)	< 0.001
ENVIRONMENTAL								
Year 1 Exposures								
No Damp bedroom	1061 (83.4)	1943 (88.7)	1.0					
Yes Damp bedroom	202 (16.0)	229 (10.5)	1.6 (1.32, 1.98)	< 0.001	1.5 (1.21, 1.91)	< 0.001	1.6 (1.25, 2.10)	< 0.001
No Farm animals	1180 (92.8)	1930 (88.1)	1.0					
Yes Farm animals	92 (7.2)	261 (11.9)	0.6 (0.45, 0.74)	< 0.001	0.6 (0.44, 0.76)	< 0.001	0.6 (0.46, 0.85)	0.002

**Parental report*

***Partially adjusted odds ratios when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted)*

†Fully adjusted odds ratios when adjusted for sex, maternal education, parental and child atopy and birth order, maternal childhood exposure to farm animals, year 1 and current home location, born at term, pregnancy, year 1 tobacco smoke, current flooring and all other variables in the final model

Nagelkerke R^2=0.334

Table 4.21 *Final model for factors associated with Current Asthma in children aged 6-9 years (n=3464)**

	N (%) Current Asthma (n=699)	***N (%) No Current Asthma (n=2765)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections <3yrs old								
No Respiratory	306 (43.6)	1994 (72.1)	1.0					
Yes Respiratory	393 (56.2)	771 (27.9)	3.3 (2.80, 3.94)	< 0.001	2.6 (2.15, 3.15)	< 0.001	1.9 (1.55, 2.40)	< 0.001
No Gastroenteritis	379 (59.8)	1954 (77.1)						
Yes Gastroenteritis	255 (40.2)	581 (22.9)	2.3 (1.88, 2.72)	< 0.001	1.8 (1.45, 2.19)	< 0.001	1.3 (1.07, 1.67)	0.011
Antibiotics <2yrs old								
Overall				< 0.001		< 0.001		< 0.001
None	94 (13.6)	867 (31.9)	1.0					
1-2 courses	142 (20.6)	840 (30.9)	1.6 (1.18, 2.06)	0.002	1.4 (1.07, 1.95)	0.017	1.2 (0.88, 1.68)	0.230
3-4 courses	157 (22.8)	409 (15.0)	3.5 (2.67, 4.69)	< 0.001	2.5 (1.83, 3.40)	< 0.001	1.9 (1.32, 2.59)	< 0.001
5-6 courses	83 (12.0)	197 (7.2)	3.9 (2.79, 5.42)	0.001	2.6 (1.77, 3.70)	< 0.001	1.7 (1.15, 2.57)	0.008
≥7 courses	110 (15.9)	143 (5.3)	7.1 (5.12, 9.84)	< 0.001	4.9 (3.39, 7.05)	< 0.001	3.3 (2.20, 4.93)	< 0.001
ENVIRONMENTAL								
Exposures Year 1								
No Full-time crèche	590 (85.9)	2277 (83.1)	1.0					
Yes Full-time crèche	97 (14.1)	462 (16.9)	0.8 (0.64, 1.03)	0.081	0.7 (0.57, 0.96)	0.026	0.7 (0.53, 0.94)	0.018
Current Exposures								
Mother not smoking tobacco	478 (68.5)	2068 (75.1)	1.0					
Mother smoking tobacco	220 (31.5)	687 (24.9)	1.4 (1.16, 1.66)	< 0.001	1.4 (1.10, 1.70)	0.005	1.4 (1.07, 1.73)	0.011
No Farm animals	634 (90.7)	2350 (85.0)	1.0					
Yes Farm animals	65 (9.3)	415 (15.0)	0.6 (0.44, 0.77)	< 0.001	0.6 (0.43, 0.80)	0.011	0.6 (0.40, 0.98)	0.038

**Parental report*

***Partially adjusted odds ratios when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted)*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy and birth order, pregnancy farm animal exposure, born at term, year1 and current home location and the other variables in the model.

Nagelkerke $R^2=0.302$

Table 4.22 *Final model for factors associated with Asthma Ever in children aged 6-9 years (n=3464)**

	N (%) Asthma Ever (n=757)	***N (%) No Asthma Ever (n=2707)***	***Univariate OR***	***p-value***	***Partially Adjusted OR****	***p-value***	***Fully Adjusted OR†***	***p-value***
MEDICAL								
Infections<3yrs old								
No Respiratory	325 (42.9)	1956 (72.8)	1.0					
Yes Respiratory	432 (57.1)	729 (27.2)	1.7 (1.56, 1.85)	< 0.001	2.8 (2.32, 3.35)	< 0.001	2.1 (1.74, 2.64)	< 0.001
No Gastrointestinal	401 (53.0)	1917 (71.4)	1.0					
Yes Gastrointestinal	280 (41.1)	556 (22.4)	2.4 (2.02, 2.89)	< 0.001	1.9 (1.55, 2.31)	< 0.001	1.3 (1.07, 1.63)	0.011
Antibiotics<2yrs old								
Overall				< 0.001		< 0.001		< 0.001
None	87 (11.6)	866 (32.8)	1.0					
1-2 courses	148 (19.7)	829 (31.4)	1.8 (1.34, 2.36)	< 0.001	1.7 (1.23, 2.25)	0.001	1.6 (1.16, 2.21)	0.005
3-4 courses	167 (22.2)	397 (15.0)	4.2 (3.15, 5.57)	< 0.001	3.1 (2.29, 4.26)	< 0.001	2.5 (1.82, 3.56)	< 0.001
5-6 courses	99 (13.2)	179 (6.8)	5.5 (3.96, 7.66)	< 0.001	3.9 (2.75, 5.63)	< 0.001	2.9 (1.99, 4.34)	< 0.001
≥7 courses	126 (16.8)	127 (4.8)	9.9 (7.10, 13.75)	< 0.001	7.3 (5.10, 10.48)	< 0.001	4.6 (3.09, 6.89)	< 0.001
ENVIRONMENTAL								
Exposures Year 1								
No Damp bedroom	626 (83.4)	2359 (88.6)	1.0					
Yes Damp bedroom	126 (16.6)	305 (11.4)	1.5 (1.23, 1.94)	< 0.001	1.4 (1.08, 1.80)	0.011	1.4 (1.07, 1.89)	0.015
Current Exposures								
No Farm animals	691 (91.3)	2276 (84.8)	1.0					
Yes Farm animals	66 (8.7)	414 (15.2)	0.5 (0.40, 0.70)	< 0.001	0.6 (0.40, 0.75)	0.001	0.6 (0.43, 0.90)	0.012

**Parental report*

***Partially adjusted odds ratios when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted).*

†Fully adjusted odds ratios when adjusted for sex, maternal education, parental and child atopy and birth order, pregnancy exposure to farm animals, german measles infection <3 years of age, year 1 source of drinking water, year 1 and current home location, current flooring and all other variables in the model.

Nagelkerke R^2=0.273

4.4.4 Allergic rhinitis

The final models for the four main outcome measures for allergic rhinitis, namely, nasal problems ever, current allergic rhinitis, current rhinoconjunctivitis and hayfever ever are presented in Tables 4.23-4.26. Figure 4.10 depicts the factors which are associated with the four main outcome measures for allergic rhinitis.

In the final Nasal Problems Ever model (Table 4.23), positive associations were found with having consumed antibiotics < 2years of age (p=0.007), respiratory infections (OR 1.4; 95% CI 1.10, 1.87, p=0.009), gastrointestinal infections (OR 1.4; 95% CI 1.05, 1.82, p=0.021) < 3years of age and exposure to furry pets in the first year of life (OR 1.4; 95% CI 1.05, 1.75, p=0.02).

In the final model for Current Allergic Rhinitis (Table 4.24), positive associations were found for having consumed antibiotics in the first two years of life (p<0.001), respiratory infections (OR 1.3; 95% CI 1.04, 1.55, p=0.019) and gastroenteritis (OR 1.4; 95% CI 1.15, 1.73, p=0.001) ≤ 3 years of age. Inverse associations were found with current exposure to a barn (OR 0.6; 95% CI 0.35, 0.95, p=0.031). Home location was not significant in the final model.

The final model for Current Rhinoconjunctivitis (Table 4.25) demonstrated positive associations gastrointestinal infection < 3 years of age (OR 1.5; 95% CI 1.12, 1.91, p=0.005), current exposure to furry pets (OR, 1.3; 95% CI 1.02, 1.75, p=0.037) and antibiotic treatment prior to 2 years of age (p=0.008). Respiratory infections and having ever been breastfed were significantly associated at univariate and partial adjustment, but lost significance when fully adjusted.

In the Hayfever Ever model (Table 4.26), positive associations were found with having a respiratory infection < 3 years of age (OR 1.4; 95% CI 1.03, 1.76, p=0.027) and having consumed antibiotics prior to 2 years of age (p=0.021). Gastrointestinal infections were significantly associated at univariate and partial adjustment, but lost significance when fully adjusted for all putatively associated covariates.

Figure 4.12 demonstrates the relationship between antibiotic courses consumed ≤ 2 years of age and symptoms of allergic rhinitis, from which it is apparent that children with symptoms of allergic rhinitis received more antibiotics than those children without.

Factors associated with symptoms of Allergic Rhinitis in children aged 6-9, in multivariate analysis (n=3464)

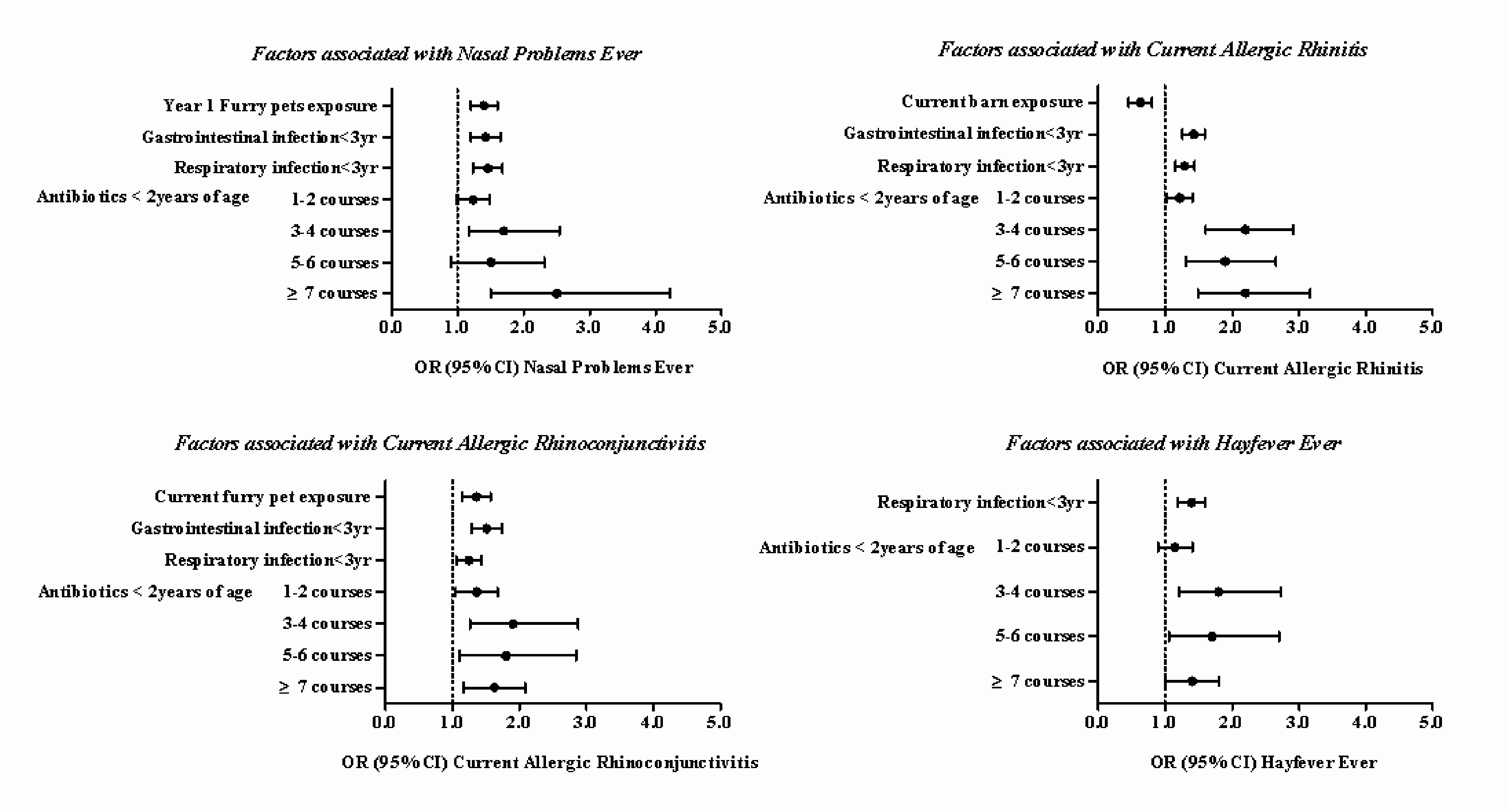


Figure 4.10 *Risk and protective factors associated with the symptoms of Allergic Rhinitis in children aged 6-9 years (n=3464)*

The relationship between antibiotic courses consumed ≤ 2 years of age and symptoms of Allergic Rhinitis in children aged 6-9 years (n=3464)

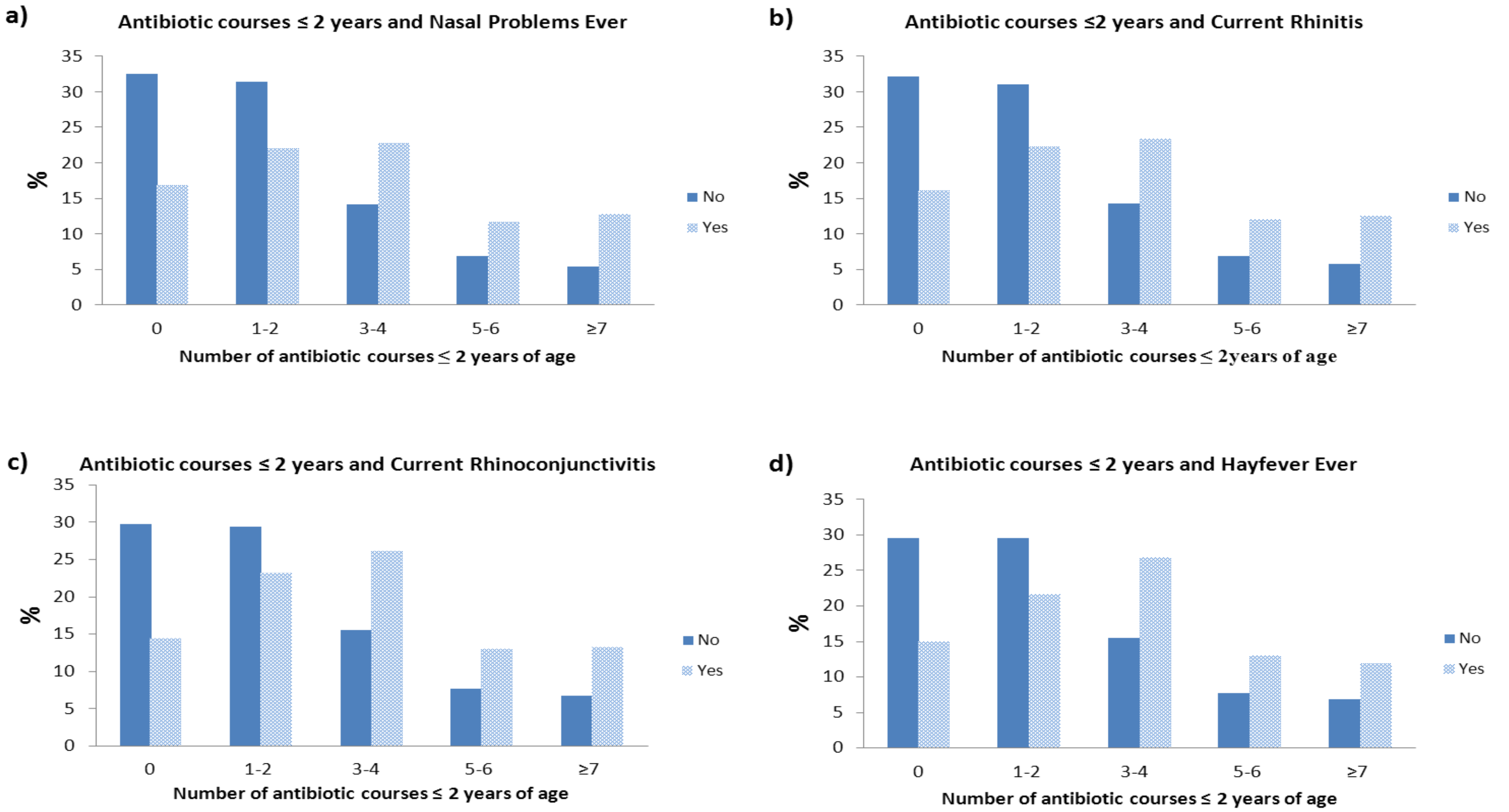


Figure 4.11 *Crude percentages of antibiotics consumed < 2years and the prevalence of Allergic Rhinitis symptoms in children aged 6-9*

Table 4.23 *Final model for factors associated with Nasal Problems Ever in children aged 6-9 years (n=3464)**

	N (%) Nasal Problems Ever (n=959)	***N (%) No Nasal Problems Ever (n=2505)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections < 3yrs old								
No Respiratory	491 (51.2)	1804 (72.2)	1.0					
Yes Respiratory	468 (48.8)	695 (27.8)	2.5 (2.12, 2.89)	< 0.001	1.7 (1.40, 1.98)	< 0.001	1.4 (1.10, 1.87)	0.009
No Gastrointestinal	537 (61.7)	1793 (78.1)	1.0					
Yes Gastrointestinal	334 (38.3)	502 (21.9)	2.2 (1.88, 2.63)	< 0.001	1.8 (1.38, 2.02)	< 0.001	1.4 (1.05, 1.82)	0.021
Antibiotics < 2 yrs. old								
Overall				< 0.001		< 0.001		0.007
None	160 (16.9)	798 (32.5)	1.0					
1-2 courses	210 (22.1)	772 (31.4)	1.4 (1.08, 1.71)	0.009	1.3 (1.00, 1.64)	0.053	1.2 (0.82, 1.69)	0.364
3-4 courses	216 (22.8)	350 (14.2)	3.1 (2.42, 3.91)	< 0.001	2.3 (1.75, 2.97)	< 0.001	1.7 (1.17, 2.54)	0.006
5-6 courses	111(11.7)	168 (6.8)	3.3 (2.46, 4.42)	< 0.001	2.1 (1.48, 2.84)	< 0.001	1.5 (0.90, 2.32)	0.127
≥7 courses	121 (12.8)	132 (5.4)	4.6 (3.39, 6.17)	< 0.001	2.6 (1.82, 3.56)	< 0.001	2.5 (1.50, 4.22)	< 0.001
ENVIRONMENTAL								
Exposures Year 1								
No Furry pets	502 (52.3)	1385 (55.4)	1.0					
Yes Furry pets	458 (47.7)	1116 (44.6)	1.1 (0.98, 1.31)	0.104	1.2 (1.03, 1.44)	0.022	1.4 (1.05, 1.75)	0.020

**Parental report*

***Partially adjusted odds ratios when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted).*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy, birth order, year 1 and current home location and other variables in the model

Nagelkerke R^2=0.652

Table 4.24 *Final model for factors associated with Current Allergic Rhinitis in children aged 6-9 years (n=3464)**

	N (%) Current AR (n=858)	***N (%) No Among No Current AR (n=2606)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections < 3yrs old								
No Respiratory	455 (51.9)	1855 (71.2)	1.0					
Yes Respiratory	413 (48.1)	751 (28.8)	2.2 (1.58, 3.20)	< 0.001	1.5 (1.25, 1.79)	< 0.001	1.3 (1.04, 1.55)	0.019
No Gastrointestinal	481 (61.3)	1852 (77.7)	1.0					
Yes Gastrointestinal	304 (38.7)	532 (22.3)	2.2 (1.85, 2.62)	< 0.001	1.7 (1.38, 2.03)	< 0.001	1.4 (1.15, 1.73)	0.001
Antibiotics < 2 yrs. old								
Overall				< 0.001		< 0.001		< 0.001
None	137 (16.1)	824 (32.2)	1.0					
1-2 courses	189 (22.3)	793 (31.0)	1.4 (1.13, 1.82)	0.003	1.3 (1.02, 1.71)	0.037	1.2 (0.89, 1.56)	0.250
3-4 courses	199 (23.4)	367 (14.3)	3.3 (2.54, 4.19)	< 0.001	2.3 (1.77, 3.07)	< 0.001	2.2 (1.61, 2.92)	< 0.001
5-6 courses	102 (12.0)	178 (6.9)	3.5 (2.55, 4.67)	< 0.001	2.1 (1.50, 2.91)	< 0.001	1.9 (1.31, 2.66)	< 0.001
≥7 courses	106 (12.5)	147 (5.7)	4.3 (3.19, 5.90)	< 0.001	2.3 (1.62, 3.22)	< 0.001	2.2 (1.49, 3.17)	< 0.001
ENVIRONMENTAL								
Current exposures								
No barn	824 (96.0)	2411 (92.5)	1.0					
Yes Barn	34 (4.0)	195 (7.5)	0.5 (0.35, 0.74)	< 0.001	0.6 (0.37, 0.82)	0.004	0.6 (0.35, 0.95)	0.031

**Parental report*

***Partially adjusted odds ratios when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted).*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy, birth order, year1 and current home location and other variables in the model

Nagelkerke $R^2 = 0.220$

Table 4.25 *Final model for factors associated with Current Rhino-conjunctivitis in children aged 6-9 years (n=3464)**

	N (%) Current Rhino-conj. (n=360)	***N (%) No Current Rhino-conj.(n=3104)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections < 3yrs. old								
No Respiratory	172 (47.8)	2128 (68.6)	1.0					
Yes Respiratory	188 (52.2)	976 (31.4)	2.4 (1.84, 3.11)	< 0.001	1.4 (1.11, 1.80)	0.005	1.2 (0.94, 1.60)	0.140
No Gastrointestinal	190 (57.8)	2143 (75.5)	1.0					
Yes Gastrointestinal	139 (38.6)	697 (22.5)	2.3 (1.78, 2.85)	< 0.001	1.6 (1.25, 2.08)	< 0.001	1.5 (1.12, 1.91)	0.005
Antibiotics < 2 yrs. old								
Overall				< 0.001		< 0.001		0.008
None	51 (14.3)	910 (29.8)	1.0					
1-2 courses	83 (23.2)	899 (29.4)	1.7 (1.15, 2.36)	0.007	1.4 (0.95, 2.02)	0.094	1.3 (0.86, 1.92)	0.220
3-4 courses	93 (26.1)	473 (15.5)	3.5 (2.45, 5.02)	< 0.001	2.2 (1.48, 3.20)	< 0.001	1.9 (1.26, 2.87)	0.002
5-6 courses	46 (12.9)	234 (7.7)	3.5 (2.30, 5.36)	< 0.001	2.0 (1.28, 3.16)	0.002	1.8 (1.10, 2.85)	0.019
≥7 courses	47 (13.2)	206 (6.7)	4.0 (2.66, 6.22)	< 0.001	1.8 (1.12, 2.81)	0.015	1.5 (0.90, 2.48)	0.118
ENVIRONMENTAL								
Current Exposures								
No Furry pets	104 (28.9)	1059 (34.1)	1.0					
Yes Furry pets	256 (71.1)	2045 (65.9)	1.3 (1.00 – 1.62)	0.047	1.4 (1.05 – 1.76)	0.020	1.3 (1.02, 1.75)	0.037

**Parental report*

***Partially adjusted odds ratios when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted).*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy, birth order, home location and other variables in the model.

Nagelkerke R^2=0.176

Table 4.26 *Final model for factors associated with Hayfever Ever in children aged 6-9 years (n=3464)**

	N (%) Hayfever Ever (n=360)	***N (%) No Hayfever Ever (n=3104)***	***Univariate OR***	***p-value***	***Partially Adjusted OR*****	***p-value***	***Fully Adjusted OR†***	***p-value***
MEDICAL								
Infections < 3yrs. old								
No Respiratory	171 (47.5)	2108 (68.5)	1.0					
Yes Respiratory	189 (52.5)	969 (31.5)	2.4 (1.93, 3.00)	< 0.001	1.5 (1.20, 1.94)	0.001	1.4 (1.03, 1.76)	0.027
No Gastrointestinal	201 (60.2)	2115 (75.2)	1.0					
Yes Gastrointestinal	136 (39.8)	700 (24.8)	2.0 (1.59, 2.54)	< 0.001	1.4 (1.09, 1.81)	0.009	1.3 (0.97, 1.64)	0.089
Antibiotics < 2 yrs. old								
Overall				< 0.001		0.001		0.021
None	53 (14.9)	898 (29.6)	1.0					
1-2 courses	77 (21.6)	898 (29.6)	2.3 (1.48, 3.45)	< 0.001	1.2 (0.80, 1.71)	0.433	1.1 (0.73, 1.62)	0.698
3-4 courses	95 (26.7)	469 (15.5)	3.4 (2.41, 4.89)	< 0.001	2.2 (1.47, 3.15)	< 0.001	1.8 (1.21, 2.73)	0.004
5-6 courses	46 (12.9)	234 (7.7)	3.3 (2.19, 5.07)	< 0.001	1.9 (1.21, 2.96)	0.005	1.7 (1.06, 2.70)	0.029
≥ 7 courses	42 (11.8)	209 (6.9)	3.4 (2.21, 5.25)	< 0.001	1.5 (1.00, 2.45)	0.069	1.3 (0.78, 2.14)	0.317

**Parental report*

***Partially adjusted odds ratios for variables when adjusted for sex, maternal education, parental atopy, child atopy (each variable individually adjusted).*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy, birth order, home location and other variables in the model.

Nagelkerke $R^2=0.170$

4.4.5 Eczema

The final models for the three main outcome measures for childhood eczema (*Rash Ever, Current Eczema* and *Eczema Ever)* are presented in Tables 4.27-4.29. Figure 4.12 depicts the factors which are inversely and positively associated with the four main outcome measures for childhood eczema.

In the final Rash Ever model (Table 4.28), positive associations were found with maternal consumption of unpasteurised milk in childhood (OR 1.4; 95% CI 1.10, 1.73, p=0.005) respiratory infections < 3years of age (OR 1.5; 95% CI 1.25, 1.84, p<0.001). Protective factors were pregnancy exposures to furry pets (OR 0.8; 95% CI 0.66, 0.97, p=0.021) and year 1 maternal smoking (OR, 0.8; 95% CI 0.62, 0.95, p=0.017).

In the final model for Current Eczema (Table 4.29), positive associations were found for pregnancy exposure to barn (OR 2.0; 95% CI 1.27, 3.04, p=0.002), stable exposure in the 1st year of life (OR 3.7; 95% CI 1.55, 8.93, p=0.003). Maternal smoking in the 1st year of life was found to be protective against current eczema (OR 0.7; 95% CI 0.57, 0.94, p=0.017). Respiratory infections were significantly associated at univariate analysis and following partial adjustment, but lost significance when adjusted.

The final model for Eczema Ever (Table 4.30) demonstrated positive associations with respiratory infection < 3 years of age (OR 1.3; 95% CI 1.02, 1.58, p=0.035), mother being reared on a farm (OR 1.4; 95% CI 1.06, 1.83, p=0.017). Inverse associations with pregnancy exposures to furry pets (OR 0.8; 95% CI 0.61, 0.95, p=0.015) and year 1 maternal tobacco smoking (OR 0.8; 95% CI 0.58, 0.97, p=0.026) were found.

Factors associated with symptoms of Eczema in children aged 6-9, in multivariate analysis (n=3464)

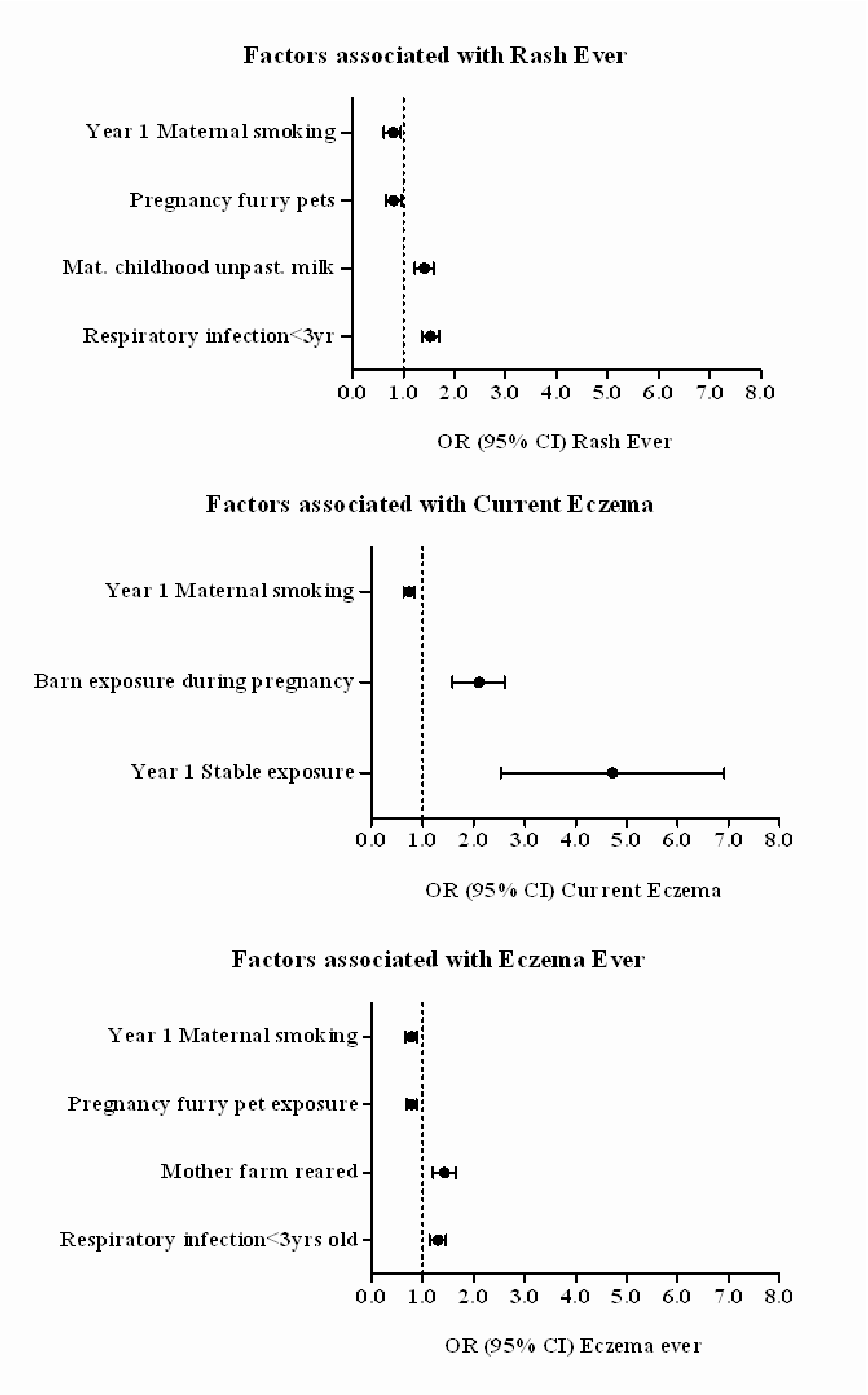


Figure 4.12 *Risk and protective factors associated with the symptoms of Eczema in children (6-9yrs)*

Table 4.27 *Final model for factors associated with Rash Ever in children aged 6-9 years (n=3464)**

	N (%) Rash Ever (n=675)	***N (%) No Rash Ever (n=2789)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections < 3yrs old								
No Respiratory	368 (54.5)	1929 (69.3)	1.0					
Yes Respiratory	307 (45.5)	854 (30.7)	1.9 (1.59, 2.24)	< 0.001	1.5 (1.22, 1.78)	< 0.001	1.5 (1.25, 1.84)	< 0.001
PARENTAL CHILDHOOD, PRENATAL								
Maternal Childhood								
No Unpasteurised Milk	488 (77.0)	2108 (80.3)	1.0					
Yes Unpasteurised Milk	147 (23.0)	517 (19.7)	1.2 (0.99, 1.51)	0.059	1.4 (1.07, 1.67)	0.010	1.4 (1.10, 1.73)	0.005
Pregnancy								
No Furry pets	418 (61.9)	1618 (58.1)	1.0					
Yes Furry pets	258 (38.1)	1166 (41.9)	0.9 (0.72, 1.02)	0.073	0.8 (0.68, 1.00)	0.035	0.8 (0.66, 0.97)	0.021
ENVIRONMENTAL								
Year 1 Exposures								
No Tobacco Smoke	502 (74.4)	1932 (70.0)	1.0					
Yes Tobacco Smoke	173 (25.6)	829 (30.0)	0.8 (0.66, 0.97)	0.025	0.8 (0.62, 0.95)	0.013	0.8 (0.62, 0.95)	0.017

**Parental report*

***Partially adjusted odds ratios for variables when adjusted for sex, maternal education, parental atopy, child atopy, birth order (each variable individually adjusted)*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy, birth order, mumps infection prior to 3 years of age, year 1 farm animal exposure, current flooring, year 1 stable and other variables in the model.

Nagelkerke R^2 =0.091

Table 4.28 *Final model for factors associated with Current Eczema in children aged 6-9 years (n=3464)**

	N (%) Current Eczema (n=439)	***N (%) No Current Eczema (n=3025)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections < 3yrs old								
No Respiratory	246 (56.0)	2054 (67.9)	1.0					
Yes Respiratory	193 (44.0)	971 (32.1)	1.7 (1.35, 2.03)	< 0.001	1.2 (1.00, 1.55)	0.054	1.3 (1.00, 1.56)	0.055
PRENATAL								
Pregnancy								
No Barn	410 (93.4)	2886 (95.4)	1.0					
Yes Barn	29 (6.6)	139 (4.6)	1.5 (0.97, 2.22)	0.068	2.0 (1.30, 3.08)	0.002	2.0 (1.27, 3.04)	0.002
ENVIRONMENTAL								
Year 1 Exposures								
No Tobacco smoke	330 (75.2)	2107 (70.2)	1.0					
Yes Tobacco smoke	109 (24.8)	893 (29.8)	0.8 (0.62, 0.98)	0.034	0.7 (0.57, 0.94)	0.016	0.7 (0.57, 0.94)	0.017
No Stable	431 (98.2)	3002 (99.2)	1.0					
Yes Stable	8 (1.8)	23 (0.8)	2.4 (1.08, 5.45)	0.032	3.6 (1.52, 8.64)	0.004	3.7 (1.55, 8.93)	0.003

**Parental report*

***Partially adjusted odds ratios for variables when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted)*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy, birth order, antibiotic consumption, pregnancy exposure to stable, year 1 barn exposure, current flooring and other variables in the model.

Nagelkerke R^2=0.085

Table 4.29 *Final model for factors associated with Eczema Ever in children aged 6-9 years (n=3464)**

	N (%) Eczema Ever (n=477)	***N (%) No Eczema Ever (n=3104)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections < 3yrs old								
No Respiratory	262 (54.9)	2021 (68.2)	1.0					
Yes Respiratory	215 (45.1)	942 (31.8	1.8 (1.45, 2.14)	< 0.001	1.3 (1.01, 1.55)	0.041	1.3 (1.02, 1.58)	0.035
PARENTAL CHILDHOOD, PRE/PERINATAL								
Maternal Childhood								
Not reared on farm	359 (80.0)	2308 (82.3)	1.0					
Reared on farm	94 (20.0)	497 (17.7)	1.2 (0.91, 1.50)	0.228	1.4 (1.05, 1.79)	0.022	1.4 (1.06, 1.83)	0.017
Pregnancy								
No Furry pets	301 (63.1)	1722 (58.1)	1.0					
Yes Furry pets	179 (36.9)	1245 (41.9)	0.8 (0.66, 0.99)	0.040	0.8 (0.62, 0.95)	0.016	0.8 (0.61, 0.95)	0.015
ENVIRONMENTAL								
Year 1 Exposures								
No Tobacco smoke	359 (75.4)	2066 (70.2)	1.0					
Yes Tobacco smoke	117 (24.6)	885 (29.8)	0.8 (0.62, 0.96)	0.021	0.7 (0.57, 0.93)	0.012	0.8 (0.58, 0.97)	0.026

**Parental report*

***Partially adjusted odds ratios for variables when adjusted for sex, maternal education, parental atopy, child atopy and birth order (each variable individually adjusted)*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental and child atopy and birth order, chickenpox prior to 3 years old, current flooring, year 1 damp bedroom and other variables in the model.

Nagelkerke R^2=0.109

4.4.6 Co-morbidity with all three atopic conditions

In the final model for co-morbidity with all three atopic conditions (Table 4.30), positive associations were found for having consumed antibiotic in the first two years of life (p=0.006), respiratory infections <3 years of age (OR 2.1; 95% CI 1.42, 3.14, p<0.001). Year 1 exposure to farm animals (OR 0.3; 95% CI, 0.11, 0.85, p=0.023) and having ever breastfed (OR 0.7; 95% CI 0.45, 1.10, p=0.052) were found to be protective. Figure 4.13 depicts the factors which are associated with childhood co-morbidity of asthma, rhinitis and eczema.

Factors associated with symptoms of co-morbidity of childhood asthma, allergic rhinitis and eczema in children aged 6-9, in multivariate analysis (n=3464)

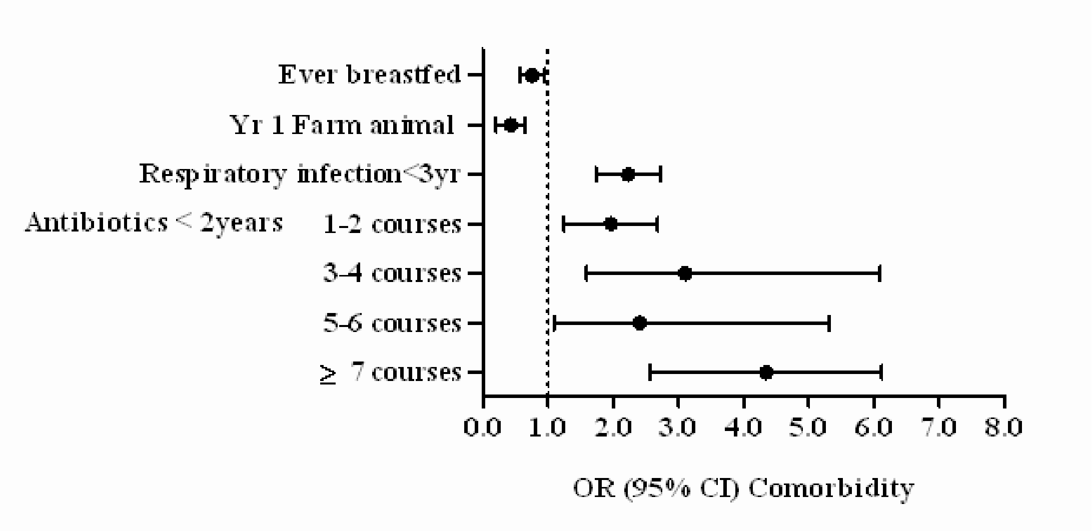


Figure 4.13 *Factors associated with the co-morbidity of symptoms of asthma, allergic rhinitis and eczema in children aged 6-9 years (n=3464)*

Table 4.30 *Final model for factors associated with co-morbidity with all three conditions in children aged 6-9 years (n=3464)*

	N (%) Co-morbid with all 3 conditions (n=135)	***N (%) Not co-morbid with all 3 conditions (n=3329)***	***Univariate OR***	***P-Value***	***Partially Adjusted OR*****	***P-Value***	***Fully Adjusted OR†***	***P-Value***
MEDICAL								
Infections < 3yrs old								
No Respiratory	54 (40.0)	2246 (67.5)	1.0					
Yes Respiratory	81 (60.0)	1083 (32.5)	3.1 (2.19, 4.42)	< 0.001	2.7 (1.86, 3.88)	< 0..001	2.1 (1.43, 3.14)	< 0.001
Antibiotics < 2 yrs old								
Overall				< 0.001		< 0.001		0.006
None	13 (9.8)	948 (28.9)	1.0					
1-2 courses	26 (19.5)	956 (29.2)	2.0 (1.01, 3.88)	< 0.001	1.9 (0.96, 3.71)	0.067	1.7 (0.85, 3.32)	0.138
3-4 courses	35 (26.3)	531 (16.2)	4.8 (2.52, 9.17)	< 0.001	4.1 (2.12, 7.90)	< 0.001	3.1 (1.59, 6.09)	0.001
5-6 courses	16 (12.0)	264 (8.1)	4.4 (2.10, 9.30)	< 0.001	3.3 (1.53, 7.25)	0.002	2.4 (1.09, 5.31)	0.030
≥7 courses	22 (16.5)	231 (7.0)	7.0 (3.45, 13.99)	< 0.001	5.6 (2.72, 11.61)	< 0.001	3.6 (1.70, 7.73)	0.001
PARENTAL CHILDHOOD, PRE/PERINATAL								
Perinatal								
Never Breastfed	92 (61.8)	1855 (55.7)	1.0					
Breastfed Ever	43 (31.9)	1455 (44.0)	0.6 (0.41, 0.86)	0.005	0.6 (0.41, 0.86)	0.006	0.7 (0.45, 1.10)	0.052
ENVIRONMENTAL								
Year 1 Exposures								
No Farm animals	128 (94.8)	2983 (89.6)	1.0					
Yes Farm animals	7 (5.2)	346 (10.4)	0.5 (0.22, 1.02)	0.050	0.4 (0.15, 0.92)	0.032	0.3 (0.11, 0.85)	0.023

**Parental report*

***Partially adjusted odds ratios for variables when adjusted for sex, maternal education, parental atopy and birth order (each variable individually adjusted).*

†Fully adjusted odds ratios for variables when adjusted for sex, maternal education, parental atopy, birth order, current flooring and other variables in the model..

Nagelkerke $R^2 = 0.102$

4.5 STUDY 3 – QUASI RETROSPECTIVE COHORT STUDY

Table 4.31 summarises the characteristics of the studies and participants in both elements of the quasi-cohort study; namely, the 2002 study population, half of which were surveyed again in their final year of primary school, in the 2007 study (the other half had moved onto second level education and were therefore lost to follow-up).

Table 4.31 *Characteristics of children in the quasi-retrospective cohort study*

	Sturley 2002	Duggan, 2007
Population		
Male	699 (47.3%)	357 (49.4%)
Mean age	8.0 years	12.1 years
Study		
Sample size	1474	706
Response rate	74.8%	70.8%

Table 4.32 demonstrates the results of the quasi-retrospective cohort study, which consisted of two identical cross-sectional studies in the same cohort of children, in 2002 (school years 3 and 4, age 6-9) and 2007 (school year 8, age 11-13). The prevalence of current asthma had reduced in this cohort of children from 21.7% in 2002, to 17.1% in 2007. The symptom of night cough had also diminished (31.0% to 16.0%). Exercise-induced wheeze and the severity of asthma symptoms suffered remained unaltered.

In terms of allergic rhinitis, having nasal problems ever and current allergic rhinitis remained unchanged, however there were increases in rhino-conjunctivitis and the interference with daily living as a result of the symptoms of allergic rhinitis. The prevalence of lifetime hayfever also increased from 9.0% to 14.9%. Examination of seasonal variations in the prevalence of rhinitis symptoms revealed higher winter/springtime prevalence in both studies (Figure 4.14). The prevalence of symptoms indicative of eczema remained unchanged over time, but the prevalence of lifetime eczema decreased from 21.6% to 12.0% in this cohort of children.

There was a shift in the male:female ratio of asthma symptom prevalence, from male dominance to equalisation in current wheeze (1.5:1 to 1.2:1) and night cough (1.5:1 to 1.3:1), while severe symptoms were more prevalent in females (Table 4.33). Exercise induced wheeze remained more prevalent in boys (1.3:1 to 1.5:1). The sex distribution of symptoms of allergic rhinitis remained at equal dispersion over the intervening years. All eczema symptoms moved to female dominance from childhood to early adolescence.

Figure 4.15 demonstrates the co-morbidity of atopic conditions in 2002 and 2007 (age 6-9 to 11-13 years). Decreases were found in current symptom co-morbidity of asthma with rhinitis (8.8% to 7.2%) and asthma with eczema (1.4% to 1.1%). Current symptom co-morbidity of asthma with eczema increased from 1.7% to 2.8%. Co-morbidity increased with age in lifetime comorbid asthma with hayfever (1.7% to 5.0%) and hayfever with eczema (1.5% to 4.5%). Co-morbid lifetime asthma with eczema, decreased with age (6.7% to 3.1%). However, co-morbidity remains high, as 11.1% of children suffered from current symptoms of two conditions, 12.6% were diagnosed with two co-morbid conditions and 3.0% suffered current symptoms and were diagnosed with all three conditions.

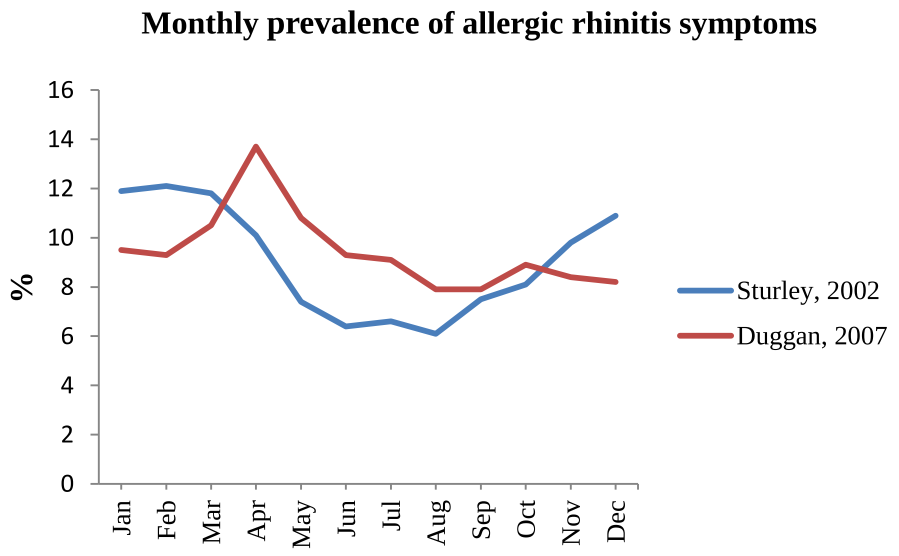


Figure 4.14 *Monthly allergic rhinitis symptoms prevalence in children aged 6-9 and 11-13*

Table 4.32 *Prevalence of allergic disease symptoms in the 2002-2007 retrospective cohort study (from 6-9 years to 11-13 years)**

	Sturley, 2002 (n=1474, age 6-9)		***Duggan, 2007 (n=706, age 11-13)***		
	N (%)	**95% CI**	**N (%)**	**95% CI**	**Direction****
Asthma					
Ever wheezed	610 (41.4)	38.8, 43.8	265 (37.5)	34.0, 41.2	↔
Current wheeze	321 (21.7)	19.6, 23.8	121 (17.1)	14.5, 20.1	↓
Exercise induced wheeze	228 (15.5)	13.5, 17.3	97 (13.7)	11.4, 16.4	↔
Night cough	458 (31.1)	28.6, 33.4	113 (16.0)	13.4, 18.9	↓
Ever had asthma	375 (25.4)	23.2, 27.6	174 (24.7)	21.6, 27.9	↔
Speech limitation	54 (3.7)	2.7, 4.7	18 (2.5)	1.6, 3.9	↔
≥4 wheeze attacks/past year	96 (6.5)	5.3, 7.9	36 (5.1)	3.7, 6.9	↔
Woken by wheeze ≥1 night/week	58 (3.9)	2.9, 4.9	17 (2.4)	1.5, 3.9	↔
Allergic Rhinitis					
Nasal problems ever	433 (29.4)	26.9, 31.5	209 (29.6)	26.3, 33.1	↔
Current allergic rhinitis	385 (26.1)	23.9, 28.3	184 (26.1)	22.9, 29.4	↔
Associated itchy eye	112 (7.6)	6.2, 8.0	97 (13.7)	11.4, 16.4	↑
Hayfever ever	133 (9.0)	7.5, 10.5	105 (14.9)	12.4, 17.6	↑
Mod/severe interference/daily living	56 (3.8)	2.9, 4.9	52 (7.4)	5.6, 9.5	↑
Eczema					
Persistent rash ever	209 (14.2)	12.4, 16.0	111 (15.7)	13.8, 18.6	↔
Current persistent rash	174 (11.8)	10.2, 13.4	83 (11.8)	9.5, 14.3	↔
Affecting flexural areas	131 (8.9)	7.4, 10.4	74 (10.5)	8.4, 12.9	↔
Eczema ever	319 (21.6)	19.5, 23.7	85 (12.1)	9.8, 14.6	↓
Not cleared in past year	49 (3.3)	2.5, 4.3	24 (3.4)	2.3, 4.9	↔
Kept awake ≥ 1 night/week	17 (1.2)	0.7, 1.8	6 (0.8)	0.4, 1.7	↔

Parental Report* *95% CI (Confidence Interval)* * Based upon degree of overlap of confidence intervals*

Table 4.33 *Sex-distribution of allergic symptoms in children aged 6-9 to 11-13 years**

	Male/Female				*Male : Female Ratio*			
	2002		*2007*		*2002*		*2007*	
	Boys (n=699)	Girls (n=775)	Boys (n=349)	Girls (n=357)	M:F Ratio	*p*-value**	M:F Ratio	*p*-value**
Asthma								
Ever wheezed	317 (45.4%)	295 (38.1%)	144 (41.3)	121(33.9)	1.2 : 1	0.005	1.2 : 1	0.043
Current wheeze	187 (26.8%)	135 (17.4%)	65 (18.6)	56 (15.7)	1.5 : 1	< 0.001	1.2 : 1	0.844
Ever had asthma	205 (29.4%)	172 (22.2%)	95 (27.2)	79 (22.1)	1.3 : 1	0.002	1.2 : 1	0.116
Exercise-induced wheeze	134 (19.2%)	98 (12.7%)	57 (16.3)	40 (11.2)	1.5 : 1	0.001	1.4 : 1	0.049
Night cough	239 (34.3%)	228 (29.4%)	63 (18.1)	50 (14.0)	1.2 : 1	0.049	1.3 : 1	0.142
Speech limitation	29 (4.2%)	25 (3.2%)	7 (2.0)	11 (3.1)	1.3 : 1	0.346	0.7 : 1	0.365
≥4 Wheeze attacks/past year	54 (7.7%)	42 (5.4%)	15 (4.3)	21 (5.9)	1.4 : 1	0.073	0.7 : 1	0.086
Woken by wheeze ≥1night/wk	29 (4.2%)	29 (3.7%)	8 (2.3)	9 (2.5)	1.0 : 1	0.688	0.9 : 1	0.548
Allergic Rhinitis								
Nasal problems ever	220 (31.5%)	215 (7.8%)	112 (32.1)	97 (27.2)	1.1 : 1	0.117	1.2 : 1	0.152
Current allergic rhinitis	197 (28.2%)	189 (24.4%)	100 (28.7)	84 (23.5)	1.2 : 1	0.098	1.2 : 1	0.121
Associated itchy eye	56 (8.0%)	56 (7.2%	53 (15.2)	44 (12.3)	1.1 : 1	0.570	1.2 : 1	0.270
Ever had hayfever	64 (9.1%)	69 (8.9%)	52 (14.9)	53 (14.9)	1.0 : 1	0.866	1.0 : 1	0.996
Mod/Severe interference with daily living	33 (4.7%)	23 (3.0%)	26 (7.5)	26 (7.3)	1.6 : 1	0.079	1.0 : 1	0.483
Eczema								
Ever had persistent rash	98 (14.0%)	112 (14.5%)	47 (13.5)	64 (19.7)	1.0 : 1	0.813	0.7 : 1	0.097
Current persistent rash	79 (11.3%)	95 (12.3%)	29 (8.3)	54 (15.1)	1.0 : 1	0.570	0.6 : 1	0.005
Affecting flexural areas	62 (8.9%)	69 (8.9%)	26 (7.5)	48 (13.4)	1.0 : 1	0.982	0.6 : 1	0.009
Ever had eczema	172 (24.6%)	50 (19.4%)	36 (10.3)	49 (13.7)	1.3 : 1	< 0.001	0.8 : 1	0.156
Not cleared in past year	23(3.3%)	21 (2.7%)	7 (2.0)	17 (4.8)	1.2 : 1	0.513	0.4 : 1	0.458
Woken by rash ≥1night/wk	6 (0.9%)	10 (1.4%)	1 (0.3)	5 (1.4)	0.6 : 1	0.424	0.2 : 1	0.312

**Parental report*

*** P-value for difference between sex distribution of symptoms within each study using a chi-square test*

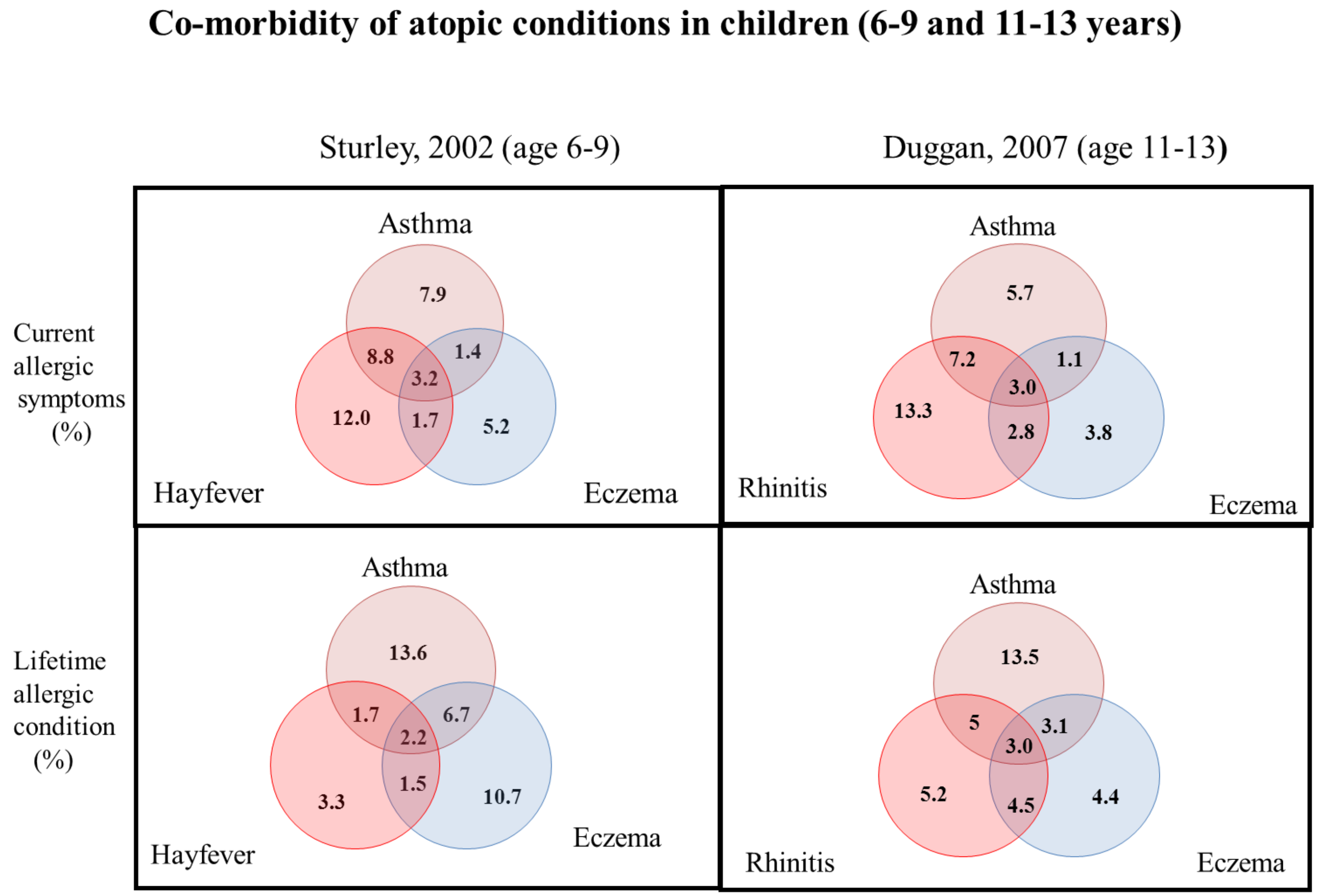

Co-morbidity of atopic conditions in children (6-9 and 11-13 years)
Sturley, 2002 (age 6-9)
Duggan, 2007 (age 11-13)
Current allergic symptoms (%)
Asthma
7.9
8.8
1.4
3.2
12.0
1.7
5.2
Hayfever
Eczema
Asthma
5.7
7.2
1.1
3.0
13.3
2.8
3.8
Rhinitis
Eczema
Lifetime allergic condition (%)
Asthma
13.6
1.7
6.7
2.2
3.3
1.5
10.7
Hayfever
Eczema
Asthma
13.5
5
3.1
3.0
5.2
4.5
4.4
Rhinitis
Eczema

Figure 4.15 *Comorbidity (%) of atopic conditions in a cohort of Irish schoolchildren aged 6-9 and 11-13 years*

4.6 STUDY 4 – TRENDS OF ASTHMA AND ALLERGY IN OLDER CHILDREN

Comparing the prevalence of allergic conditions between our population of 11-13 year old children and the Irish element of ISAAC (age 13-14), we found the 2007 prevalence of asthma and lifetime hayfever were lower than the Irish adolescent ISAAC study with no overlap of confidence intervals. Other reported symptoms remained largely unchanged (Table 4.34).

Table 4.34 *Prevalence of allergic disease in Irish adolescents 2002-2007*

	Manning, 2002/3 (13-14 years)† (n=3089)		***Duggan, 2007 (11-13years)* (n=706)***		
	N (%)	**95% CI**	**N (%)**	**95% CI**	**Trend****
Current asthma	825 (26.7)	25.2, 28.3	121 (17.1)	14.5, 20.1	↓
Asthma ever	667 (21.6)	20.2, 23.1	174 (24.6)	21.6, 27.9	↔
Current rhinoconjunctivitis	478 (15.5)	14.2, 16.8	97 (13.7)	11.4, 16.4	↔
Hayfever ever	973 (31.5)	29.9, 33.2	105 (14.9)	12.4, 17.6	↓
Current Eczema	226 (8.6)	6.4, 8.3	74 (10.5)	8.4, 12.9	↑
Eczema ever	442 (14.3)	13.1, 15.6	85 (12.0)	9.8, 14.6	↔

**Parental Report* *† Self Report* *95% CI (95% Confidence Interval)*
***Based upon degree of overlap of confidence intervals*

Figure 4.16 depicts the overall trends of prevalence of current symptoms of asthma, rhinoconjunctivitis and eczema in Irish adolescents since 1995. The prevalence of asthma and rhinoconjunctivitis are on a declining trend, while eczema decreased between Irish ISAAC Phases 1 and 3, but has increased in the older children in 2007.

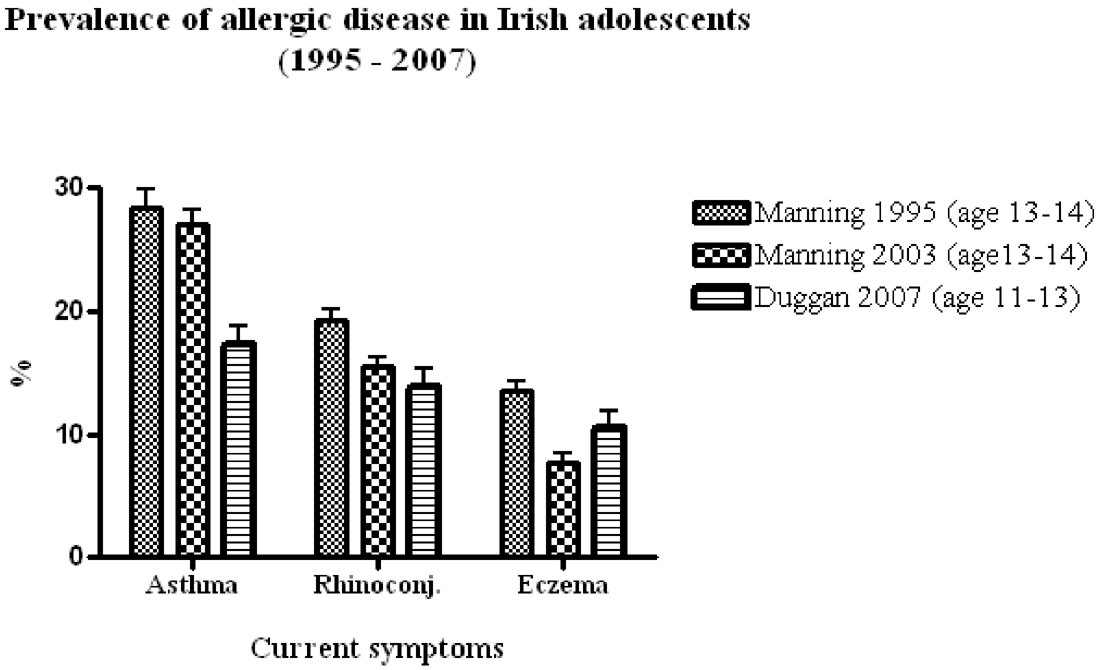


Figure 4.16 *Trends of prevalence of current allergic conditions in Irish adolescents*

Chapter 5

Discussion

5.1 INTRODUCTION

This thesis is the first Irish study to examine trends of asthma, allergic rhinitis and eczema in young children aged 6-9 years. It is also the first Irish study to attain data pertaining to the same cohort of children over two time periods (age 6-9 until 11-13), providing some insight into the natural history of allergy in this population. By extending the prevalence study to examine a rural population, this study has enabled comparisons of the effects of exposures from different environments. This extension also provides a baseline prevalence which is reflective of populations from different environments, from which to compare the findings of future studies.

In this final chapter, I intend to discuss the main findings of this thesis in the context of intra-study factors and in relation to current international literature. Strengths and limitations of each individual study will be highlighted. I also propose to discuss the implications of the findings of this body of research and make recommendations for future research.

5.2 STUDY 1 – TRENDS OF PREVALENCE IN 6-9 YEAR OLD CHILDREN

Study 1, which examined the trends of prevalence in 6-9 year old children from Cork city and suburbs, found that the previously high prevalence of asthma has plateaued. The prevalence of rhino-conjunctivitis and eczema has increased and a large percentage of young children continue to suffer the burden of co-morbidity of two or all three conditions. Sex-specific trends revealed an increase in the current prevalence of asthma in females causing the distribution to move towards sex equalisation, and the increase in the prevalence of lifetime hayfever in males resulting in equal sex-distribution.

5.2.1 Asthma prevalence

In this young population (6-9 years), the prevalence of current asthma and lifetime diagnosed asthma had remained constant, but high in relation to many other countries (7). The finding of a broadly static prevalence of current asthma is in agreement with ISAAC Phase Three findings in Hong Kong and in Belgium and Austria in a similar age group (age 6-7) (7). Conversely, in Western Europe nine out of eleven centres found increases in the prevalence of current asthma in 6-7 year old children, albeit the increases were small in many instances (7). Many variations exist worldwide; Irish ISAAC data were not gathered for this age group.

The prevalence of the symptom of night cough significantly decreased over the five year period. The lower prevalence of dry night cough in our 2007 study compares favourably with others worldwide (137, 162). Night cough is a recognised associated symptom of asthma and shares many of the long-term effects of classic wheezing asthma e.g. airway remodelling (70). However, while cough variant asthma is well recognised in adults, there is a paucity of related empirical data in children (72). In the 2007 study, 9.5% of children who suffered from a dry night cough without wheeze had lifetime asthma compared with only 1% of children in 2002. Recognition and treatment of cough variant asthma is included in the GINA guidelines (5). Increased ascertainment of cough variant asthma, following the implementation of the GINA guidelines, is a possible explanation for our findings. Reduced exposure to tobacco smoke may also have been a contributory factor. In this study the prevalence of maternal smoking during pregnancy, the first year of the child's life and currently, combined with smoking in the home had decreased significantly over the study periods; this reduction is in agreement with national figures (319) and is most likely as a result of anti-smoking legislation and governmental educational campaigns during the intervening years.

5.2.2 Allergic rhinitis prevalence

We found a significant increase in the prevalence of rhino-conjunctivitis in the study interval. This finding is in agreement with the worldwide trend of an overall (although slight) increase in the prevalence of rhino-conjunctivitis in 6-7 year olds (320). There is increasing evidence that exposure to busy roads has negative respiratory and sensitisation implications for children (321, 322). ISAAC Phase 3 found an exposure-response relationship between self-reported truck traffic exposure (validated by objective measures of traffic density) and rhino conjunctivitis prevalence (323). Between 2002 and 2007, the Irish population moved from public transport to private car ownership (22% greater), whilst car dependence, even for short journeys and commute times increased significantly (46). It is possible that the consequent higher traffic-related air pollution may have been a significant factor in the increasing prevalence of rhino-conjunctivitis. Examination of seasonal prevalence of rhinitis symptom demonstrated different patterns in both studies. In 2002, there was high winter/spring prevalence, which alleviated during the summer months and increased again for winter, indicating that symptoms were possibly of infectious rather than allergic origin (320). In 2007, the prevalence of symptoms of rhinitis peaked in late spring early summer, which is more suggestive of allergic aetiology.

In both time periods, the reported prevalence of current allergic rhinitis and eczema symptoms was significantly higher than the reported lifetime prevalence of hayfever and eczema respectively. Over-estimation of symptom prevalence is a recognised limitation of epidemiological questionnaires, and misclassification of symptoms has also been found to often lead to physician underdiagnosis (102, 324). Alterations in disease labelling and diagnostic practice greatly challenge epidemiological findings. Our study found good agreement between the prevalence of reported current asthma symptoms and lifetime asthma in both 2002 and 2007.

The finding that asthma prevalence had stabilised while rhino-conjunctivitis had increased in this study is paradoxical, considering that both diseases are so related in pathogenesis (325). However, it was the increase in prevalence of allergic rhinitis and eczema, as found in the current study, which supported the original proposal of the “hygiene hypothesis”. Much debate and speculation exists about the differing impacts of environment on the development of childhood allergy in different populations and ages. Asher et al. (7) suggest that environmental changes may have a greater impact on the prevalence of eczema and rhinitis, rather than asthma, in young children. The complex interactions of environmental factors and the diversity of any subsequent changes that occur within these factors, vary between exposure, location and population, often resulting in contradictory findings (7, 102, 320). Nevertheless, some environmental factors authentically operate at population level, and the assessment of determinants and/or modifiers in the prediction of health effects can be of critical importance in highlighting interventions (7).

5.2.3 Eczema prevalence

We found the prevalence of current eczema had significantly increased in our young population (age 6-9 years). Raised symptom awareness from media and internet sources, may have resulted in reporting mild, non-persistent symptoms, however, our finding concurs with ISAAC worldwide trends in 6-7 year old children (102). The increasing prevalence is most likely due to strong environmental influences, rather than simply being of genetic origin (102). It is plausible that the increasing eczema prevalence in the young children in our study is associated with elevated hygiene practices around young children and their activities, influenced by increased affluence and standard of living linked to Ireland's economic success in the 1990s and early 2000s (46, 96, 326, 327). In contrast to the rising prevalence of current eczema symptoms, the prevalence of lifetime eczema decreased over the study period. This may be due to recall bias; however, alterations are more like to be multifactorial. Improved diagnostic practice from the implementation of new criteria may have reduced physician misclassification of contact dermatitis as eczema. Also, parents may self-treat mild symptoms rather than present to their doctor.

5.2.4 Sex-specific prevalence of allergic disease

We stratified our prevalence results by sex and in so doing, were able to demonstrate the direction of sex-specific alterations attributing to distributional changes. The most striking changes were firstly, the increase of reported current wheeze in girls (23%), decreasing the ratio of male:female dominance, towards sex equalisation and secondly, the increase of lifetime prevalence of hayfever in boys (6%), resulting in equal sex-distribution.

Male preponderance to asthma in young children had traditionally been the accepted norm, however, this male:female gap appeared to diminish in many studies, as substantial increases in asthma prevalence in young female children were reported (137, 143, 144, 162, 166). Increased awareness and reporting of mild symptoms is a possible cause for the increase in female current asthma symptoms (143), although it is unlikely to be the only factor, as it would have affected both sexes. Another hypothesis, is that current increasing levels of female precocious puberty (328) may be decreasing the age of disadvantage for young males and in turn have contributed to the relatively higher increases in asthma prevalence in girls than in boys (166). However, further examination of sex-specific trends and risk factors are required to assess this hypothesis (143).

The sex-specific prevalence of rhinitis and eczema are not reported to the same extent as asthma and to date, no clear pattern has emerged (137, 162, 166). In the current study, the only sex-specific alteration in the prevalence of eczema related symptoms was the equalisation in the distribution of lifetime eczema, as a result of a significant reduction in the prevalence of lifetime eczema in boys.

5.2.5 Co-morbidity of allergic disease

We demonstrated that a high percentage of young Irish children continue to suffer symptoms of more than one allergic disease. Our 2007 study showed a significant increase (3.2 - 4.1%, $p<0.001$) since 2002, in the current symptom prevalence of all three conditions. Both study findings are significantly higher than ISAAC Phase Three, in which only 1% of 6-7 year old children suffered symptoms of all three conditions (7). From 2002 to 2007, we also found increases (non-significant) in children suffering comorbidity of two conditions. Internationally, ISAAC Phase Three also reported overall increases in co-prevalence at all levels, however the increases were very small, ranging from 0.1% to 0.4%. Lifetime prevalence of all three allergic disorders in our 2007 study was 2%, minimally lower than in 2002 (2.2%). Our results compare favourably with those of Punekar and Sheikh, who found a clinician diagnosed co-prevalence of 2.5% for all three conditions (59). Although a cohort study (0–18 years), a significant portion of children in their study who suffered co-morbidity of allergic disorders were diagnosed with all three conditions in early childhood allowing comparisons to be made with our study population.

5.2.6 Strengths and limitations of Study 1

The use of the validated ISAAC core questionnaire and methodology aim to ensure the comparability of results. Our sample size of circa 1500 during both timeframes may have limited our statistical power to detect severity of symptoms and our study interval of five years may have contributed to many of our unchanged indices. On the other hand, although ISAAC recommended a sample size of 3000, they accepted trend data from centres with >1000 participants and also deemed five years as being an acceptable time interval for trend studies (7). Our study population were marginally younger in 2007 than in 2002, and the children in both our studies are slightly older than ISAAC (6-7 *versus* 6-9). However overall, the trends found in our studies correlate well with worldwide ISAAC trends.

We investigated the possibility of demographic alterations between 2002 and 2007 threatening the comparability of our results. From 2002, Ireland was experiencing an economic boom, which attracted migrant workers and their families to work and settle in Ireland. According to National statistics, a large immigration from Eastern Europe occurred in 2004, after the Sturley study of 2002 (46). The 2002 study did not collect data on nationalities; however, immigration was not evident in the 2007 study, as it contained 88.2% Irish parents (the remaining 11.8% were divided evenly over several different nationalities). Therefore, it is fair to say that demographically, both populations examined in each timeframe are comparable.

As with many ISAAC centres, both studies were performed in the same mixed urban and suburban settings, different patterns may be apparent in rural populations which were not reported in this phase of our project. We did not perform clinical reviews of every respondent or diagnostic testing for the allergic phenotypes being studied.

5.3 STUDY 2 – ASSOCIATIONS WITH ASTHMA AND ALLERGY

Study 2, which examined the associations with asthma and allergy in 6-9 year old children (n=3464) from urban and rural locations in Cork, observed many positive and negative associations with parental and child exposures (exposures ranging from during parental childhood to currently in the child’s life). Early childhood antibiotic consumption was positively associated with the development of asthma and allergic rhinitis (both current and lifetime). Having had an early childhood respiratory infection was a risk factor for current and lifetime asthma, current and lifetime allergic rhinitis and lifetime eczema. Positive associations between early gastrointestinal infection and current asthma and current allergic rhinitis were also found. Passive smoking was a risk factor for current asthma, while maternal smoking in the child's first year of life was found to protect against lifetime and current eczema prevalence. An inverse association was observed between current exposure to farm animals and both current and lifetime asthma. Current barn exposure was protective against the development of current allergic rhinitis, while positive associations between lifetime eczema and the mother being farm reared were observed. Pregnancy barn exposure and year 1 stable exposure were risk factors for current eczema. An inverse association was found between exposure to furry pets during pregnancy and lifetime eczema and current furry pet exposure was positively associated with current rhinoconjunctivitis. Damp bedroom exposure during the first year of life was positively associated with lifetime asthma and full time crèche attendance in the first year of life was inversely associated with current asthma.

5.3.1 Antibiotics and allergic airway disorders

This study demonstrates that children with asthma and/or allergic rhinitis are more likely to have been prescribed antibiotics in the first two years of life. Asthma and allergic rhinitis are intrinsically linked, often concomitant allergic airway disorders, which have been described as "one airway one disease"(85). The mechanism of association between allergic disease and antibiotic consumption is biologically plausible, as GALT is a prime site for potential immunomodulatory effects. GALT is not only the largest lymphoid organ in the body, it also houses a large amount of T_{reg} cells and transcription factor Foxp3 T_{reg} cells, which are critical for immune regulation (25). Antibiotics destroy naturally occurring gut bacteria, thereby causing a reduction in flora diversity which may have a negative impact on immunoregulation (31). Another factor supporting the causal role of antibiotics in this study is dose response relationship which is evident for asthma. This dose-response relationship for antibiotics was not evident for allergic rhinitis and the strength of association between antibiotic exposure and allergic rhinitis is weak with odds ratios ranging from 1.2 – 2.2 for all levels of antibiotics consumed. This is a slight anomaly considering that the two conditions are closely related, in terms of pathophysiology (325).

5.3.2 Respiratory infections and allergy development

The strength of the positive associations between having had a respiratory infection prior to 3 years of age and the prevalence of current and lifetime asthma, allergic rhinitis and lifetime eczema in this study are weak. However, supporting evidence of a causative role of severe respiratory infections is strong for asthma (the investigated allergy is most commonly asthma), if the infection is viral in nature (41, 241, 243). A US population-based retrospective birth cohort study observed a dose-response relationship between the severity of bronchiolitis symptoms and both the development of and severity of early childhood asthma (243). Our study does not have data relating to the type of respiratory infection each child suffered, however, bronchiolitis is a very commonly reported childhood respiratory infection, and is usually of viral aetiology (241).

Initial understanding of the hygiene hypothesis supported the notion that infections promoted Th2 cell maturation and therefore protected against allergy development. However, early childhood viral respiratory infections, which are severe in nature, have been found to be positively associated with slow Th1 development and allergic disease (40). The proposed causative link is complex, but three main theories exist (42). Firstly, it is suggested that early exposure may cause asthma in a period when the respiratory and immune system are immature and vulnerable (250). Secondly, it is hypothesised that respiratory viral infections may be more evident in children who are pre-disposed to allergy. Thirdly, combining the two former theories, it is postulated that respiratory infections increase the risk of the development of asthma in children who already have a pre-existing risk of developing an atopic condition (40-42). This is thought to be caused by a synergistic interaction between the inflammatory response and pre-existing sensitisation in rapidly developing immature lungs (229, 329). Evidence is increasingly emerging to support the latter theory. A recent birth cohort study reported that severe viral lower respiratory tract infections in infancy and early atopy were found to be risk factors for persistent wheeze and asthma in a cohort of children with high atopic risk (41) and COAST found that having suffered from RV by the age of 3, hugely increased the risk of developing asthma by the age of 6 (OR, 31.7; 95% CI, 10.6 - 94.9) in a high risk population (241).

The literature naturally focusses upon the allergic disease of asthma, as opposed to eczema and allergic rhinitis and therefore, the current study does not have supporting evidence towards the associations found between early respiratory infections and the development of these allergic diseases. However, the causal link found for eczema and allergic rhinitis is biologically plausible, considering that asthma development is often preceded by eczema in pre-disposed children, and the close aetiological link between asthma and allergic rhinitis, compounded by the fact that many children suffer concomitant allergic disorders (61, 88).

5.3.3 Respiratory infections, antibiotics and allergic airway disorders

The joint association with current allergic airway disease, early exposure to antibiotics and early respiratory infections in this study highlights the possibility that children may have been incorrectly diagnosed and treated with antibiotics for what may have been viral infections. While it may be due to reverse causation, the association is biologically plausible and merits exploration.

Respiratory infections are common in early childhood, often causing parents in developed countries to consult their General Practitioner (GP). Despite the majority of respiratory symptoms being of viral aetiology, and therefore self-limiting, with no proven benefit from antibiotic therapy (330), GPs often prescribe antibiotics for their treatment (331). It is accepted that it can be very difficult to make a diagnosis of asthma rather than of viral respiratory infection in children, as the symptoms may be similar and children without asthma can present with the classic symptoms of wheeze or cough (146). In recognition of this, the *Global Strategy for the Diagnosis and Management of Asthma in Children 5 Years and Younger* was developed as a resource of evidence based information which provides step-by-step guidance regarding diagnosis and care of children with asthma (146).

There is widespread recognition that the overuse of antibiotics has negative implications in terms of population resistance (332-334), nevertheless, GPs often prescribe antibiotics because they have diagnostic uncertainty and fear potential complications associated with respiratory tract infections(331) (331). The *National Institute for Health and Clinical Excellence* (NICE) recently published evidence-based guidelines regarding the management of patients with respiratory tract infections, presentations of respiratory infections which are likely to develop complications and antibiotic management strategies (no antibiotic prescribing, delayed antibiotic prescribing and immediate antibiotic prescribing) (335). Advising to delay "filling the antibiotic script" and only to fill the prescription if the symptoms persist is already employed by many GP's (336, 337). However, GPs need to be convinced with regard to the available evidence; antibiotic prescriptions are on the increase and have shifted towards antibiotic prescription for non-specific upper respiratory symptoms (256). Scepticism exists amongst GPs regarding the balance of prescribing to prevent complications and the risk of antibiotic resistance (338). The fear is that they may be side-stepping the guidelines by avoiding using the formal diagnoses for which NICE have recommended delayed or no antibiotic therapy (256).

Perceived parental pressure has also been demonstrated to affect antibiotic prescribing practices (331, 339) although, communication of information and negotiation regarding management between parents and their GP has been demonstrated to be effective in relieving this pressure (340-343). Effective communication negotiating antibiotic strategies, combined with setting realistic expectations about the duration of the signs and symptoms, may reduce parental fear and anxiety (341, 342, 344). Time is not a relevant argument, as no difference has been found between the time spent by GPs with children who receive antibiotics and those who do not (345). Nonetheless, it is accepted that parental expectation can be a powerful persuasive factor in the prescribing of antibiotics. Many studies have shown that parents expect that their child will be prescribed antibiotics when they go to their GP for a consultation (339, 346, 347).

An Irish study examining the practices and attitudes of GPs revealed that most felt under pressure to prescribe and over half had prescribed antibiotics inappropriately.

Practitioners with heavy workloads and younger GPs (under 40 years) were more likely to inappropriately prescribe antibiotics (339). Antibiotic resistance is a cause for concern in Ireland as there has been a dramatic increase in antibiotic consumption (especially broad spectrum penicillin) in the recent years (mid-to-high range use in Europe), raising concern about developing resistant bacteria (348-350). A programme of GP education has been put in place to address the rising antibiotic prescriptions (348) and public awareness campaigns are reducing public expectation of antibiotic therapy (256), however in order for campaigns to be successful they need to employ modern marketing strategies and technical expertise to attract attention and effect change (351). Continuing Medical Education programmes provide an ideal forum for educating GPs regarding treatment of viral respiratory illness without antibiotics. Qualitative assessment of a blended-learning initiative for GPs called *Stemming the Tide of Antibiotic Resistance* (STAR) *Educational Program* increased GP awareness of the dangers of antibiotic resistance and built confidence in diagnosing viral illness while improving their communication skills (352).

The information in our study in relation to antibiotics during the first two years of life was attained retrospectively when the children were aged 6-9 years, and therefore recall bias has to be considered. Furthermore, it has been suggested that parents of asthmatic children may remember more about treatment of their children than those of non-asthmatic children, however no empirical evidence exists to support this bias (37). Associations with allergy development are mainly found with broad-spectrum antibiotic consumption (32, 353, 354). We did not acquire information regarding the type of antibiotics consumed (narrow or broad spectrum).

5.3.4 Gastrointestinal infections and allergic disease

This study found a positive association between gastrointestinal infections and the prevalence of asthma and current allergic rhinitis symptoms. We do not know the temporality of the gastrointestinal infection and allergy development in this study and the strength of association is weak (current asthma: OR 1.3; 95% CI 1.07, 1.67, lifetime asthma: OR 1.3; 95% CI 1.07, 1.63) and current allergic rhinitis: OR 1.4 95% CI 1.15, 1.73). However, this finding is biologically plausible because of the potential immunomodulatory effect of alterations, caused by infectious allergens, to the gut microflora in GALT (25). The hygiene hypothesis would support a protective effect from gastrointestinal infections, that being said, the literature to-date is inconsistent. Exposures to foodborne infections, HAV, H pylori, T gondii have been found to protect against the development of allergy (26, 27, 233). The outcome of no association between gastroenteritis in early childhood and allergy development has also been reported (30). On the other hand, the findings in this study are supported by those of the MAC study, which reported that ≥ 3 episodes of gastroenteritis in the first two years of life was associated with an increased risk of developing asthma by 6 years of age (29). The authors suggest that an exposure/response relationship may exist. We do not have data on the number of infections suffered by each child.

The immunomodulatory capacity of GALT remains an enigma, primarily due to the complexity of gut microflora. Probiotics may hold the key to allergy prevention. Initial studies examining the effect of probiotics such as lactobacilli or bifidobacteria on allergy development appeared promising, although methodological issues were evident (355). However, in 2010, a review of 7 randomised controlled trials which examined the association of pro, pre and synbiotics concluded that the results were conflicting and therefore no conclusions could be drawn nor recommendations made (356). It is apparent that further examination is merited, as current knowledge of the properties and functionality of probiotics, as well as the inherent complexity of gut flora remains limited. Genome-wide association studies (GWASs) may assist in unravelling some of the complex interactions between gut flora and allergy development (229).

5.3.5 Maternal smoking and allergic disease

This study demonstrated a positive association with current maternal tobacco smoking and current asthma symptoms. The risk of developing childhood asthma from exposure to environmental tobacco smoke has been repeatedly investigated with positive associations (180, 181, 357), although the evidence from systematic reviews initially supported that its effect was confined to younger children (358) (rationalised by its effect resulting in transient wheezers due to immature narrow bronchial structures) and children born to high-risk parents (183). Nevertheless, a recent meta-analysis of cohort studies examining the association of home tobacco smoke exposure on asthma development, found a positive association, irrespective of age or risk (184). Environmental tobacco smoke contains approximately 4000 toxic chemicals (182). The biological mechanism through which exposure to tobacco smoke might lead to asthma has also been explored and although the evidence is inconclusive, some theories exist. Suggested mechanisms include exposure to smoking as being a direct irritant to the lungs, causing inflammation, or resulting in immunological hypersensitivity to allergens and exposure resulting in genetic mutations (180, 182). Endotoxin exposure (high levels found in tobacco smoke) from exposure to tobacco smoke in the home has also been implicated. The suggested mechanism is that endotoxin exposure causes high IgE levels, thereby predisposing exposed children to atopy (184).

Smoking is a modifiable behavioural risk factor and therefore merits on-going focus in legislation and public health campaigns. Ireland has been a world leader in anti-smoking initiatives through prohibiting smoking in the workplace (359) and the overall prevalence of tobacco smoking in Ireland is steadily declining (23.6% in 2010) (360). Public health campaigns to highlight the dangers of passive smoking to children and legislation to ban smoking in the presence of children in cars are currently being debated (361).

In contrast, a protective association between maternal smoking during the child's first year of life and the prevalence of current and lifetime eczema was also found in this study. Inverse associations have been previously reported (362). However, the findings in the literature are inconsistent, as no association (187, 188, 363) and positive associations (186, 189, 364) have also been found. It may be beneficial to employ Bradford-Hill's criteria (302), when evaluating the likelihood of the finding being true or as a result of chance (Table 5.1).

Table 5.1 *Application of the Bradford Hill Criteria to examine the inverse association between maternal tobacco smoking and childhood eczema*

Bradford Hill Criteria	**Study findings**
Strength of association	OR is small (current eczema: OR 0.7; 95% CI 0.57, 0.94 and lifetime eczema: OR 0.8; 95% CI 0.58, 0.97).
Consistency	The finding has been previously reported (362).
Specificity	The association is not specific to children exposed to tobacco smoke, as eczema also occurs in unexposed children.
Temporal relationship	The temporal relationship cannot be ascertained, but it is likely that maternal smoking preceded childhood eczema.
Biological gradient	A dose-response relationship does not exist.
Plausibility	Bacterial endotoxin is an active component of cigarette smoke (365). Endotoxin exposure has been found to protect against eczema development (366). Therefore The association is biologically plausible.
Coherence	The finding is supported by the predominant theory of the microbial (hygiene) hypothesis.
Experiment	It is unethical to experiment with childhood exposure to tobacco smoke.
Analogy	Parents who may have ceased to smoke when their child presented with an allergy may have incorrectly reported their child as being unexposed in early life, thereby not reflecting the reality and pushing the relative risk downwards (184). Also, parental smoking behaviour in relation to their child's health is a sensitive subject and results may be skewed by under-reporting (183).

Taking all these considerations into account demonstrates that maternal smoking may be protective against the development of childhood eczema. However, irrespective of whether or not protection is conveyed, smoking has such deleterious effects on human health; it will not be posited as a preventative measure against childhood eczema development.

5.3.6 Rural exposures and allergic disease

This study found that the prevalence of current and lifetime asthma decreased steadily as home location became more rural. In logistic regression analysis, farm home location was significantly associated with current asthma and current allergic rhinitis at univariate level; however, the association lost significance when adjusted. Following full adjustment, current farm animal exposure remained inversely associated with both current and lifetime asthma and current barn exposure remained protective against the development of current allergic rhinitis. These inverse associations between the environmental exposures of barns and livestock and childhood allergic diseases are have been demonstrated by many studies throughout the world since the nineties (262, 263, 265, 267, 268, 367-369). Despite this, the mechanism of the protective effect is not fully understood. This is most probably due to the complexity and timing of a multitude of gene-environment interactions with different stages of innate and adaptive immunity (20). The diversity of microbes to which farming children are exposed appears to be a key factor in promoting modulation of the immune system (266).

While most protective effects were associated with current exposures to farming interactions in this study, we also observed that exposure to farm animals in the first year of life protected against co-morbidity with the three allergic diseases of asthma, allergic rhinitis and eczema. Epidemiological data highlights early exposure (prenatal, perinatal and the first three years of life) as being a critical period of importance for the beneficial epigenic and immunomodulatory effects from exposure to a farming environment (20, 126). For example, cord blood analyses from neonates of farming mothers have demonstrated higher T_{reg} cell counts and more efficient T_{reg} cell functioning in comparison to cord blood from neonates of non-farming mothers (329).

Much evidence exists demonstrating the consumption of unpasteurised milk as being protective against the development of childhood allergic disease (267, 268, 369), however, this was not apparent in the current study. This is unusual, considering that raw milk consumption is a commonplace practice in Irish farming families (54). The vague wording of the question relating to unpasteurised milk may have contributed to the lack of association found in this study. Parents were asked if they or their child regularly consumed unpasteurised milk, but “regularly” was not defined. Furthermore, there are many types of milk available on the market, it is possible that parents may have been confused by what was meant by the term “unpasteurised milk”.

Paradoxically, this study found a positive association between pregnancy barn exposure and year 1 stable exposure and the development of current eczema and also between the mother being farm reared and lifetime eczema. Perkin and Strachan also found that the protection of farming environments did not extend to protection against eczema although they did not find them as a risk factor either (265). The relationship between eczema and farming has not been extensively reported in the literature. The PARSIFAL study examined the effect of the farming environment on the development of eczema symptoms and reported that the only apparent significant association was a protective effect from the child’s involvement in haymaking (370). This was associated with elevated TLR levels in children, indicating the innate immune system’s recognition of microbes. Alternatively, this finding may be due to reverse causation, as children with eczema may be unable to participate in haymaking (370). That being said, perhaps another confounding exposure exists to explain the causation of childhood eczema in the rural setting.

Results worldwide are variable, most likely reflecting the different farming practices and microbial exposures. Further studies which assess the multitude of microbial exposures associated with different types of farming and in different populations are merited. For example, arable farming has different environmental exposures to livestock farming. Arable farming exposure demonstrated no protective effects against childhood allergy in an Australia, however, farming methods are perhaps different in Australia to those in Europe (262). Modern technological advances such as GWAS may be useful in classifying the various interactions and presentations.

As the prevalence of current asthma decreased from urban to rural habitation in this study, the impact of air quality must be addressed. A recent review of prospective cohort studies which examined the effect of traffic exhaust on allergic sensitisation and asthma development concluded that exposure to traffic exhaust fumes increases the risk of respiratory symptoms in children (371). This study did not enquire about distance from busy roads or traffic exposure; instead, it used the proxy of self-reported location of home to assess air quality exposure and therefore cannot make any causal inferences.

5.3.7 Furry pets and allergic disease

This study found a protective association between exposure to furry pets during pregnancy and lifetime eczema. Paradoxically, current furry pet exposure was positively associated with current rhinoconjunctivitis. The strength of the inverse and positive associations are weak (OR 0.8; CI 0.61, 0.95 and OR 1.3; 95% CI 1.02, 1.75 respectively), nonetheless, they are supported by findings in other studies. A recent systematic review of birth cohort studies reported that that perinatal exposure to dogs or cats conveyed protection against eczema by 3 years of age (281). Furthermore, as mentioned earlier, the prenatal period appears to be a “critical window” for immune system modulation towards protection against allergic diseases from animal and microorganism exposures (126, 266, 270, 281, 329). As with the effects from rural exposures, potential mechanisms of the protective immunomodulatory effects of pet exposure also remain elusive, although, cat allergen exposure in the home has been demonstrated to effect chemokine receptor expression on $CD8^+$ cells (372).

Current evidence suggests that pet allergen exposure exacerbates the symptoms of allergy once sensitisation has occurred (282), which might explain the positive association of current pet exposure in relation to rhino-conjunctivitis in our study. A factor to consider is the possible variation in levels of contact that people have with their pets both within each household and throughout the world. For example, it is suggested that protective associations may be confounded by avoidance behaviour in families who are at high risk (281). Cultural norms may also be influential. Traditionally, in Ireland, dogs and cats were reared for their functionality on farms for animal and vermin control, as opposed to being family pets. This cultural attitude still prevails (373) and while many Irish families have a pet, it is often the case that the pets live outdoors, especially in the countryside. In other cultures, pets are generally accepted as indoor co-inhabitants. Future studies need to elucidate further information regarding the pet environment, by enquiring whether the pet is kept indoors or outside and establish the amount and intensity of pet contact to which the child is regularly exposed.

5.3.8 Damp bedroom and allergic disease

Our finding that damp bedroom exposure in the first year of life was a risk factor for lifetime asthma (OR 1.4; 95% CI 1.07, 1.89) is in line with international evidence (283, 374). Despite the fact that this exposure has been implicated in the development of asthma for several years, the mechanisms of the effects and all of the causal agents have not yet been identified. Some fungi have been associated with immune system activation (285) and sensitisation (286). Positive associations have been found between exposure to *Penicillium* spores and the prevalence of wheeze and respiratory infections in the first year of life (287, 288). However, studies to date have not collected fungal components from children's homes for analysis or identification (284). With current technological advancements, this may be an area which would merit further investigation. Identification of causal agents may reveal further knowledge regarding the mechanisms of causality.

5.3.9 Early daycare attendance and allergic disease

This study found that having attended a crèche full-time in the first year of life was protective against the development of current asthma at 6-9 years. Although the association is weak (OR, 0.7; 95% CI, 0.53, 0.94), this finding correlates with the Tucson Children's Respiratory Study and MAAS birth cohort study, both of whom reported inverse associations between early daycare attendance and wheezing by the ages of 13 and 5 years respectively (194, 202). In accordance with the hygiene hypothesis, the assumed mechanism of protection is that early daycare attendance provides a microbial rich environment which promotes immune system development (194). This is plausible as attendance at day-care centres exposes children to many infections and is associated with increased risk of upper and lower respiratory tract infections (195, 200).

We did not find any significant associations between allergic rhinitis and eczema. Perhaps a more comprehensive questionnaire would elucidate the size of the day-care centre attended, as well as the frequency and duration of attendance.

5.3.10 Strengths and limitations of study 2

This is a cross sectional study and therefore is unable to definitively ascertain causality, as the temporality of exposure and disease cannot be determined. However, international cross-sectional studies, such as ISAAC, have provided valuable associations for further investigation. Many exposures may genuinely operate at population level, and the identification of modifying factors in disease development can be of huge benefit in highlighting areas for further research (7). Furthermore, to assess causal links, associations were evaluated using the Bradford-Hill criteria.

Recall bias most likely exists, as many of the questions pertain to events from several years prior to the study. This may have been particularly evident in the relatively large number of positive responses to questions relating to children having suffered the notifiable childhood infections of meningitis and measles. That being said, this study demonstrated many significant associations which are in accordance with current literature.

5.4 STUDY 3 – QUASI-RETROSPECTIVE COHORT STUDY

Study 4, which examined the natural history of allergic disease in children aged 6-9 until they were aged 11-13 (2002-2007) found a decrease in current asthma prevalence, while lifetime asthma prevalence remained stable. There was an increase in current rhino-conjunctivitis and lifetime hayfever, whereas the prevalence of current allergic rhinitis remained stable. It also found a stabilisation of current eczema prevalence, but an increase in lifetime eczema. Most asthma symptoms moved from male dominance to sex equalisation or female dominance, eczema symptoms had shifted to female preponderance and there were no differences in the sex-distribution of the symptoms of allergic rhinitis.

5.4.1 Asthma prevalence (age 6-9 to 11-13 years)

In this cohort of children, we found that the prevalence of current asthma had decreased since they were surveyed in 2002. Most asthma symptoms moved from male dominance to sex equalisation or female dominance. The trajectory found in this study for asthma of reducing prevalence during middle childhood and early adolescence is in agreement with long term studies of the natural history of the disease (81). Furthermore, we can presume that the reduction is most likely to be due to an age effect rather than a period effect, as the simultaneous study of young children in the same schools (Study 1) revealed a 23.5% asthma prevalence, which is much higher than the older children in this study when they were concurrently examined.

5.4.2 Allergic rhinitis prevalence (age 6-9 to 11-13 years)

We found that the prevalence of current rhino-conjunctivitis and the severity of allergic rhinitis symptoms became higher as our children grew older and that the prevalence of lifetime hayfever also increased. Similar findings were reported by a German multi-centre cohort study (0-13years), which found that the prevalence of allergic rhinitis symptoms increased steadily each year from the age 4 to 13 years, with over half of the children affected being classified as having severe/persistent allergic rhinitis by 13 years of age (89). Paradoxically, the prevalence of current allergic rhinitis symptoms remained stable over time.

The prevalence of allergic rhinitis symptoms in the 2002 study were higher in spring than in the peak pollination season of summer, indicating that symptoms may have been associated with infection rather than allergy (320), although the possible effects of tree pollination cannot be ruled out. The 2007 study demonstrated a peak in reported allergic rhinitis symptoms in late spring/early summer, which coincided with the data collection period. However, of note, the question pertaining to seasonal symptom prevalence is prone to recall bias in cross-sectional studies. We found no differences in the sex-distribution of the symptoms of allergic rhinitis. Different gender effects have been noted between atopic and non-atopic rhinitis (89, 375), however, we did not perform sensitisation diagnostics on our study population.

5.4.3 Eczema prevalence (age 6-9 to 11-13 years)

We found a sizable decrease in the prevalence of lifetime diagnosed eczema (21.6% to 12.0%), which may be partly due alterations in disease labelling and diagnostics over the study interval, which are recognised issues with longitudinal studies (102). On the other hand, we found no alteration the prevalence of current eczema symptoms from 2002 to 2007 in our cohort of children. The natural history of eczema is unclear, as examination has uncovered several phenotypes with varying patterns of remission and relapse (376). However, the general consensus from birth cohort studies is that eczema symptoms present prior to 2 years of age with approximately 50% remission into adolescence and adulthood (376, 377). Our finding of a shift to female preponderance of eczema symptoms in adolescence is in line with other studies (376, 378). Puberty is considered a critical period for the transition of sex-distribution of eczema and is thought to be attributable to hormonal triggered alterations in skin surface pH and/or stimulation of pro-inflammatory cytokines (376).

5.4.4 Co-morbidity of allergic disease (age 6-9 to 11-13 years)

The prevalence of co-morbidity with current allergic symptoms remained largely unchanged. However, lifetime diagnosed co-morbidity of asthma with hayfever and hayfever with eczema increased, while co-morbid asthma and eczema decreased with age. Co-morbidity remains an issue of concern for our population of children aged 11-13. Further in-depth, matched longitudinal studies are required to assess the temporality of symptom incidence in this population.

The decrease in the prevalence of asthma, combined with the stabilisation of eczema prevalence and the increase in the prevalence of rhino-conjunctivitis from young children to adolescents, is in agreement with the findings of other studies throughout the years (81, 89, 375, 376). To examine the prevalence of asthma and allergy into adulthood is problematic, as no adult version of ISAAC exists. The *National Asthma Campaign Manchester Asthma and Allergy Study* (n=5687) found that 9.7% of adults were diagnosed with asthma, 20.6% with hayfever and 13% with eczema (379). The prevalence for adult asthma and eczema was predominantly female and allergic rhinitis prevalence was equally distributed between the sexes. These findings further support the trajectory we found in our cohort study.

5.4.5 Strengths and limitations of study 3

A limitation to this quasi-retrospective cohort study is the fact that the data was not individually linked; however, we know that only a 5% variance of class drop-in/out existed, which is unlikely to be associated with the prevalence of asthma and allergy. Also, the 2007 study only included half of the 2002 study population. We cannot account for prevalence in the other half of the population, as they had progressed to secondary school; however, there is no reason to suggest that their inclusion would have altered the prevalence in any direction.

However, these facts considered, the findings in this study are well supported by the reports of other longitudinal studies. There is a strong possibility of recall bias in questions relating to early childhood exposures from 8-10 years earlier. Parents of children with allergic conditions may remember more about treatment of their children than those without, however no empirical evidence exists to support this bias (37).

5.5 STUDY 4 – TRENDS OF PREVALENCE IN IRISH ADOLESCENTS

Study 4, which examined the trends of prevalence in adolescents, aged 11-13 in this 2007 study and adolescents aged 13-14 years in the Irish ISAAC study of 2002/3, revealed a decrease in the prevalence of current asthma and a stabilisation in the prevalence of lifetime asthma. Lifetime hayfever had decreased, while rhino-conjunctivitis prevalence remained stable. The prevalence of current eczema had increased, while lifetime eczema prevalence had stabilised.

When interpreting these data it is important to consider the slight age variation between study populations and that the data in the ISAAC study was attained by self-report, whereas in the 2007 study, the data was achieved by parental report.

The finding of a large decrease in the prevalence of current asthma (26.7% to 17.1%) is in agreement with the ISAAC Phase Three finding of decreases in current asthma prevalence in centres with previously high prevalence (7), as Ireland was previously found to have the 2nd highest asthma prevalence in Europe (380). The research comparing parental and adolescent responses have found that adolescents report higher prevalence of asthma than their parents (316, 317, 381), therefore perhaps the actual decrease may not be as large as found in this study.

We found that the prevalence of rhino-conjunctivitis remained unaltered since 2002/3. Phase Three ISAAC found a slight overall increase in adolescent rhino-conjunctivitis prevalence since Phase One, however, the Irish ISAAC data revealed a significant decrease in lifetime prevalence in the study interval (320). In contrast, we found that the prevalence of lifetime hayfever had plummeted from 31.5% to 14.9%. Perhaps part of the reduction in lifetime hayfever could be explained by the fact that adolescents tend to report higher prevalences of allergic rhinitis than their parents (316, 317). That being said, it is also fair to say that as the decrease in prevalence is so large, a true reduction in prevalence is also a likely conclusion.

We also found rising current eczema prevalence while lifetime eczema prevalence had stabilised. This is in concordance with the international findings of stabilising or decreasing rates in many centres (from developed countries) with previously high rates (102). In this age group, Irish ISAAC data revealed a significant decrease from Phase One to Phase Three having previously had a high prevalence in the former (102). Comparisons show higher current eczema prevalences when reported by adolescents, whereas higher lifetime eczema prevalences are evident when questionnaires are parentally reported. These factors give further credence to the findings in this study.

5.5.1 Strengths and limitations of Study 4

This study has two major limitations. Firstly, the age of the two study populations is slightly different (ISAAC age 13-14, Duggan, age 11-13), however, it is unlikely that a marked variance in prevalence would exist between the age groups; bar the possible deleterious effect should the children have commenced smoking in the interim (382).

Secondly, the data in the ISAAC study was attained by self-report, whereas, in the 2007 study, parentally reported data was used, as the adolescents were younger. Except for lifetime eczema prevalence, in ISAAC, adolescents have been demonstrated to report higher prevalences of allergic disease than parental report. The potential variation in results have been taken into consideration when examining the prevalence results in this study, however it does impede our ability to estimate prevalence trends.

5.6 IMPLICATIONS OF THIS THESIS

This thesis contributes to the published work in a number of ways. Providing baseline prevalence rates and on-going trends of prevalence of childhood allergic disease are critical components of healthcare planning and management, as they assist in formulating policy to source and allocate funding and resources towards the care of those who are in most need. Furthermore, they ensure that the burden of childhood allergies remain high on the public health agenda, thereby promoting targeted national and international research funding for investigation into causative, preventative and treatment measures. Moreover, the prevalence estimates in this thesis are likely to be generalisable to the Irish population. Cork is reflective socio-demographically to the rest of Ireland, as each county has a city or large town and a rural component.

This study provides an insight into the natural history of allergic disease in Irish school children. It increases the body of knowledge regarding the impact of age and gender on expression of these allergic diseases from childhood to adolescence in this population. Longitudinal studies are important as they assist with clinical recognition, prognosis assessment and ultimately improve management.

The finding of early childhood respiratory infection and antibiotic therapy as risk factors for developing asthma and allergic rhinitis, raises the possibility that children with allergic airway disease may have been incorrectly diagnosed and treated for viral infections, prior to diagnosis. The time is right for antibiotic stewardship, as antimicrobial resistance is an issue of worldwide concern. This study finding may increase the impetus for antibiotic stewardship and provide a focus for educational campaigns for both GPs and the public. Educational programmes which encourage the use of effective communication during consultations, to ensure realistic parental expectations about the duration of the signs and symptoms, may reduce fear and anxiety in parents and reduce the pressure brought to bear on physicians to prescribe antibiotics unnecessarily.

The finding that passive smoking was a risk factor for current childhood asthma supports the continuation of public health campaigns to highlight the dangers of passive smoking to children. This positive association also gives credence to future legislative action in order to protect children from exposure to tobacco smoke, such as the one planned in Ireland of banning smoking in cars when children are present.

The study finding of lower prevalence of allergic airways disorders in rural schoolchildren and the protective association between early childhood farm animal exposure and current asthma, adds to previous calls regarding the potential benefits of early exposure to an environment with a wide diversity of microbes. This adds to the burgeoning evidence which is moving the world towards a new understanding of the hygiene hypothesis; perhaps in the future the “microbial hypothesis” will be the conversant descriptive expression.

5.7 RECOMMENDATIONS FOR FUTURE RESEARCH

Trend analyses of asthma and allergy needs to continue in this population and can now examine trends in young children from both urban and rural environments. A longitudinal study to examine the course of allergic disease is now also possible as this study included data to enable matching. This thesis highlighted some very interesting associated risk and protective factors with childhood asthma and allergy, some of which merit further interrogation.

The urban/rural gradient in asthma and allergic rhinitis prevalence, found in this study, requires further enquiry. Questionnaires need to be more specific in their examination, for example, to quantify how much farm animal exposure and to which animals are children exposed. Also, when enquiring about regular unpasteurised milk consumption, questionnaires need to ensure clarity of what is meant by unpasteurised milk, as well as defining the term “regularly”. Additional exploration of microbial exposures and determination of dietary components (for example, raw milk) may unravel more knowledge regarding the protective elements in a rural environment.

Birth cohort studies to examine allergic diseases in Ireland are warranted as they are the ideal study design to determine causality. Ireland is one of the few countries where farming remains a viable occupation for many families and where children still partake in farming activities. It is an ideal location to examine diverse farming exposures in children as there are 117, 900 agricultural holdings, of which 94% are family owned and run (53). The Irish farming exposures are predominantly associated with livestock. In 2007, 93% of farms specialised in livestock of which, 16% focussed on dairy farming, 23% in breeding sheep, goats and other grazing livestock and 54% mainly reared cattle. Further identification of protective farm related exposures may advance our understanding of the protective mechanism and may potentially lead to the development of preventative measures to alleviate the global burden of these complex childhood allergic diseases.

It is possible that other unidentified protective exposures exist in the rural environment. For example, new evidence is emerging that Vitamin D plays a significant role in immune development (374); and considering that farming involves a large outdoor component, this may be another mediating factor conveying protection. Future studies might include measurement of Vitamin D serum levels, diet and sunlight exposure in rural and urban environments.

This study included questions about the source of drinking water in the first year of life and currently, but found no association with childhood allergy. Rural water has been demonstrated to be greatly affected by the microbial content of the surrounding soil (277) provided it is not too heavily chemically treated. This study did not enquire into the presence or absence of chemical treatments of home wells/group scheme water sources. Future studies may be more specific in their questions and/or obtain samples from wells in an effort to examine this hypothesis further. Another factor to consider is to extend the enquiry to elucidate if the household regularly uses bottled water for consumption.

We used self-reported location of home to assess air quality exposure. Future work in this area might obtain home addresses and employ GIS-based measures, to examine location characteristics, such as proximity to roads, traffic speeds, traffic jams, truck lanes, bus stops, intersections, industry and population density and trends in air quality (weather/seasonal patterns). The development of statistical models to assess associations with allergy using this data have been found to be of particular benefit in other studies, but remains at developmental stage (383).

In view of the associations found in this study in relation to gastrointestinal infections, future studies might include detailed assessments of hygiene practices in early childhood as well as qualitative information regarding the type and frequency of gastrointestinal infections to which each child is exposed. Furthermore, taking into consideration the immunomodulatory capability of microbiota on GALT, continued interrogation of probiotics is warranted. Research needs to investigate the possible as-yet-unknown probiotic interactions between probiotics and gut microflora, the complex functions of different probiotics, as well as the impact of a wide diversity of probiotics on allergy development.

Respiratory infections are implicated as causative for childhood allergic airways disease. Therefore the type, frequency and treatment of those infections require more detailed inspection. Considering the powerful negative association between asthma and RSV-induced bronchiolitis, another avenue which may deserve further investigation is prophylaxis through the administration of anti-viral agents. This is not a new concept; anti-viral agents are available, but very expensive and their long-term benefits have not been proven (384, 385).

The issue of the putative role of antibiotics in the development of allergic disease deserves further attention, as it may have implications for practice. Future studies might investigate the type of antibiotics consumed, narrow or broad spectrum, as associations with asthma development are mainly found with broad-spectrum antibiotic consumption and atopic sensitisation (32, 353, 354). Qualitative assessment of practices might be effective in highlighting consultation process issues. It would be particularly advantageous to examine the experiences of parents and children regarding the process of symptom development, prescriptions, diagnosis of allergic disease, their experiences with associated health services and the effect upon quality of life.

On-going dynamic research into different populations and environments is critical to unravel protective exposures so that we may increase our understanding of the complex mechanism through which these exposures convey their effect. This may guide future interventions to alleviate the burden of childhood allergic disease.

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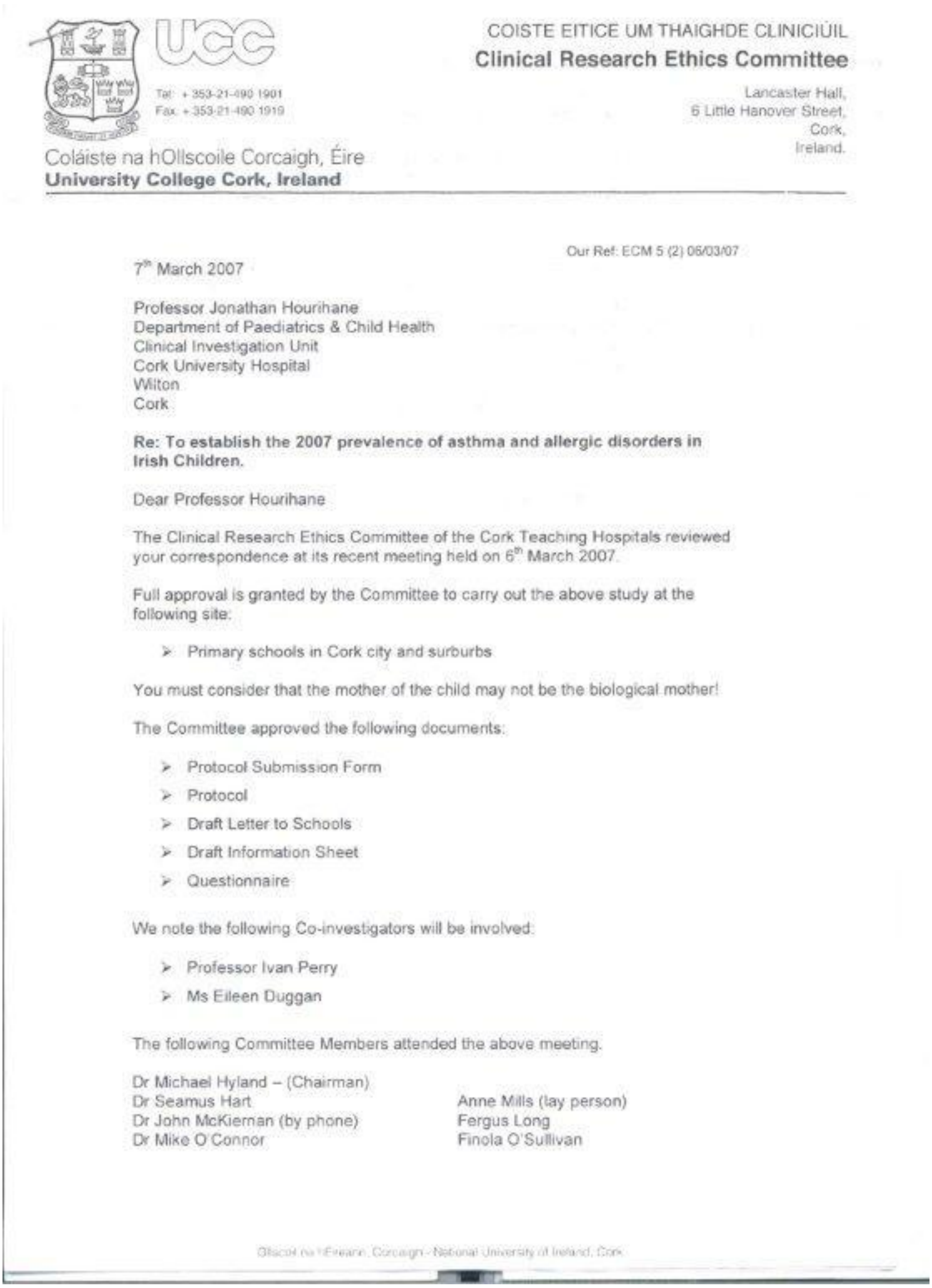
Appendices

Appendix 1 Ethical Approval Form



UCC

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Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

COISTE EITICE UM THAIGHDE CLINICIÚIL
Clinical Research Ethics Committee

Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Our Ref: ECM 5 (2) 06/03/07

7th March 2007

Professor Jonathan Hourihane
Department of Paediatrics & Child Health
Clinical Investigation Unit
Cork University Hospital
Wilton
Cork

Re: To establish the 2007 prevalence of asthma and allergic disorders in Irish Children.

Dear Professor Hourihane

The Clinical Research Ethics Committee of the Cork Teaching Hospitals reviewed your correspondence at its recent meeting held on 6th March 2007.

Full approval is granted by the Committee to carry out the above study at the following site:

- Primary schools in Cork city and surburbs

You must consider that the mother of the child may not be the biological mother!

The Committee approved the following documents:

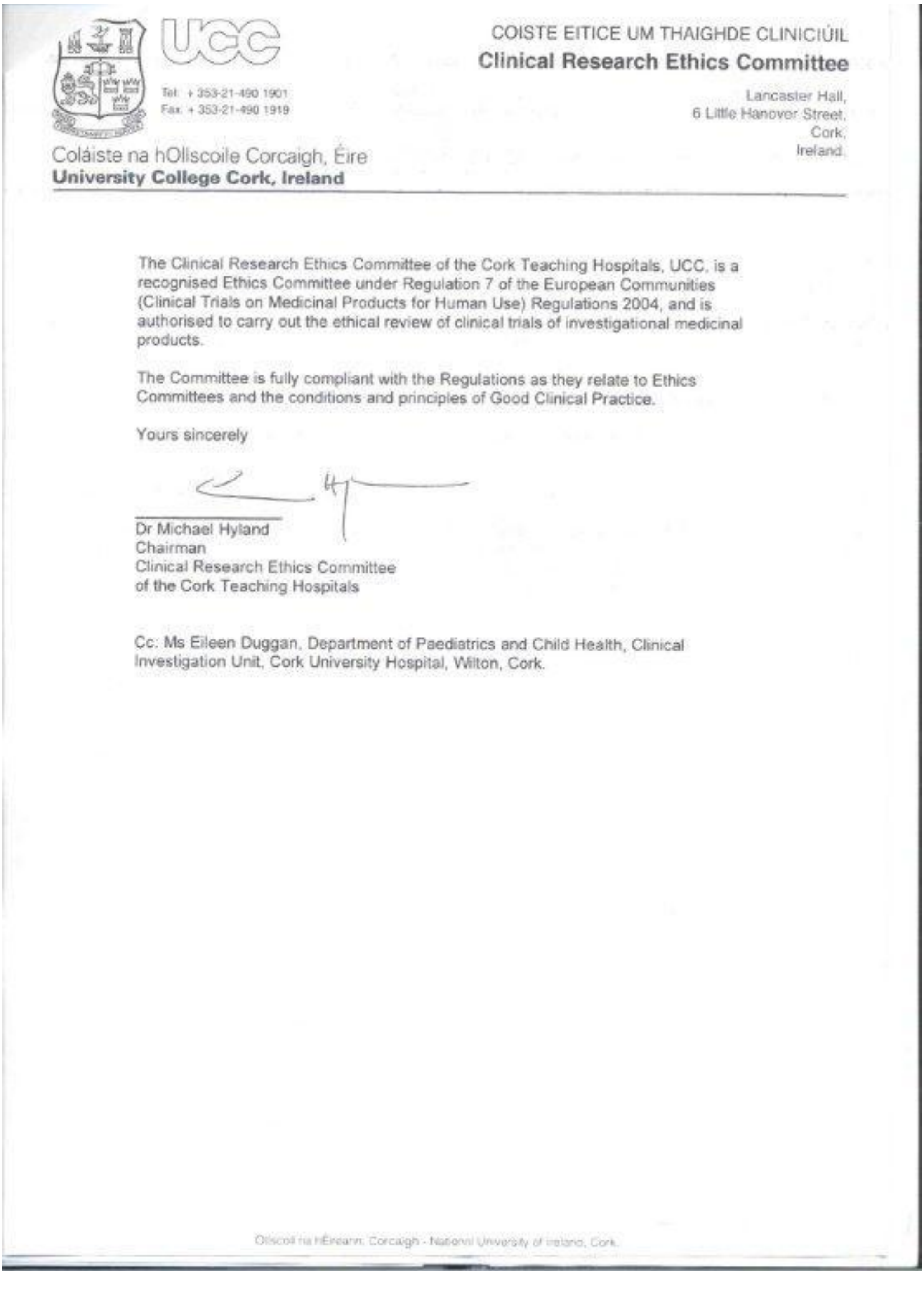
- Protocol Submission Form
- Protocol
- Draft Letter to Schools
- Draft Information Sheet
- Questionnaire

We note the following Co-investigators will be involved:

- Professor Ivan Perry
- Ms Eileen Duggan

The following Committee Members attended the above meeting.

Dr Michael Hyland – (Chairman)	
Dr Seamus Hart	Anne Mills (lay person)
Dr John McKiernan (by phone)	Fergus Long
Dr Mike O'Connor	Finola O'Sullivan



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Lancaster Hall,
6 Little Hanover Street,
Cork,
Ireland.

Coláiste na hOllscoile Corcaigh, Éire
University College Cork, Ireland

The Clinical Research Ethics Committee of the Cork Teaching Hospitals, UCC, is a recognised Ethics Committee under Regulation 7 of the European Communities (Clinical Trials on Medicinal Products for Human Use) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to Ethics Committees and the conditions and principles of Good Clinical Practice.

Yours sincerely

Dr Michael Hyland
Chairman
Clinical Research Ethics Committee
of the Cork Teaching Hospitals

Cc: Ms Eileen Duggan, Department of Paediatrics and Child Health, Clinical Investigation Unit, Cork University Hospital, Wilton, Cork.

Ollscoil na hÉireann, Corcaigh - National University of Ireland, Cork.

Appendix 2 Letter to previously studied schools

Headed Notepaper

Date

Dear XXXX,

We are writing to ask if your school would be willing to participate in a follow-up study investigating the recent increase in allergies and asthma in children. You may remember assisting us with such a study a few years ago. That study found very high rates of allergy in children in Cork and we have been given funding by the Irish Lung Foundation to repeat the study this year. This study will pertain to first and second class students, however, we also wish to re-examine the sixth class students involved in the 2002 study, as performed by Ms. Jennifer Sturley, who was awarded a PhD for this project, last year.

As with the previous study, this study does not involve the children directly, but is based on information provided by the parents of children in first, second and sixth class, on questionnaires relating to the health of their child. Your assistance would be appreciated (through the class teachers) to facilitate the distribution and collection of the questionnaires provided by us.

We will contact you by phone within a week to offer you further information and discuss possible participation in the study. We would be very happy to visit your school to discuss any concerns or questions you or your staff might have.

By participating in this study, which is approved by the Cork Clinical Research Ethics Committee, you can contribute to improving the health of children in Ireland. Your participation would be greatly valued.

Yours faithfully,

____

Eileen Duggan, MA in Health Promotion
Researcher, UCC

Principal Investigators:
Professor Jonathan Hourihane,
Head of Department of Paediatrics and Child Health, UCC
Professor Ivan Perry,
Head of Department of Epidemiology and Public Health, UCC

Appendix 3 Letter to previously unstudied schools

Headed Notepaper

Date

Dear XXXX,

We are writing to ask if your school would be willing to participate in a follow-up study investigating the recent increase in allergies and asthma in children. In 2002, a study of children, in 25 Cork city and suburban Primary Schools found very high rates of asthma and allergy. We have been given funding by the Irish Lung Foundation to repeat the study in Cork city and to extend it to include Primary Schools in Cork county.

The study will pertain to first and second class students. It does not involve the children directly, but is based on information provided by the parents, on questionnaires relating to the health of their child. Your assistance would be appreciated (through the class teachers) to facilitate the distribution and collection of the questionnaires provided by us.

We will contact you by phone within a week to offer you further information and discuss possible participation in the study. We would be very happy to visit your school to discuss any concerns or questions you or your staff might have.

By participating in this study, which is approved by the Cork Clinical Research Ethics Committee, you can contribute to improving the health of children in Ireland. Your participation would be greatly valued.

Yours faithfully,

____
Eileen Duggan, MA in Health Promotion
Researcher, UCC

Principal Investigators:
Professor Jonathan Hourihane,
Head of Department of Paediatrics and Child Health, UCC
Professor Ivan Perry,
Head of Department of Epidemiology and Public Health, UCC

Appendix 4 Information to parents previously in 2002 study

Headed Notepaper

Dear Parent/Guardian,

The number of children with allergic breathing and skin problems is increasing. The Department of Paediatrics and Child Health in UCC is carrying out a large study to investigate these conditions in children in first, second and sixth classes in Primary schools in the Cork area. If your child is in sixth class you may remember filling in a similar form a few years ago. That study found very high rates of allergy in Cork and we have been given funding by the Irish Lung Foundation to repeat the study this year. The study does not involve the children directly and is based on information provided by you, the parents, in the enclosed questionnaire. Most of the questions only require you to fill in the circle beside the correct answer, and it does not take long to fill in.

If your child is adopted or fostered you may not know the answers to all the questions relating to your child, but please answer as many as you know. However, please do not answer the questions relating to the child's biological father and mother if your child is adopted or fostered.

We would greatly appreciate it if you would fill in and return the questionnaire to the school, sealed in the envelope provided, even if your child doesn't have any breathing or skin problems. We need information from as many parents as possible in order to assess the size of the problem and to increase our understanding of why these conditions are becoming more common.

The information that you give is confidential. Once the questionnaire has been returned you will not be contacted again, however, if you would like further information, please do not hesitate to contact the department at 021/4205015.

This study is approved by the Cork Clinical Research Ethics Committee. By participating, you may help to improve the health of children in Ireland. Your contribution is greatly appreciated.

Yours faithfully,

____

Eileen Duggan, MA in Health Promotion
Researcher, UCC

Principal Investigators:
Professor Jonathan Hourihane,
Head of Department of Paediatrics and Child Health UCC
Professor Ivan Perry,
Head of Department of Epidemiology and Public Health UCC

Appendix 5 Information to newly recruited parents

Headed Notepaper

Dear Parent/Guardian,

The number of children with allergic breathing and skin problems is increasing, and the Department of Paediatrics and Child Health in UCC is carrying out a large study to investigate these conditions in children in first and second classes in Primary schools in the Cork area. A study in 2002 found very high rates of allergy in Cork and we have been given funding by the Irish Lung Foundation to repeat the study this year. The study does not involve the children directly and is based on information provided by you, the parents, in the enclosed questionnaire. Most of the questions only require you to put a tick in a box, and it does not take long to fill in.

If your child is adopted or fostered you may not know the answers to all the questions relating to your child, but please answer as many as you know. However, please do not answer the questions relating to the child's biological father and mother if your child is adopted or fostered.

We would greatly appreciate if you would fill in and return the questionnaire to the school, sealed in the envelope provided, even if your child doesn't have any breathing or skin problems. We need information from as many parents as possible in order to assess the size of the problem and to increase our understanding of why these conditions are becoming more common.

The information that you give is confidential. Once the questionnaire has been returned you will not be contacted again, however, if you would like further information, do not hesitate to contact the department at 021/4205015.

By participating in this study, which is approved by the Cork Clinical Research Ethics Committee, you can contribute to improving the health of children in Ireland. Your participation is greatly appreciated.

Yours faithfully,

____

Eileen Duggan, MA in Health Promotion
Researcher, UCC

Principal Investigators:
Professor Jonathan Hourihane,
Head of Department of Paediatrics and Child Health, UCC
Professor Ivan Perry,
Head of Department of Epidemiology and Public Health, UCC

Appendix 6 Questionnaire

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YOUR CHILD'S BIRTH AND FIRST FEW WEEKS OF LIFE

1. What is your child's date of birth?	Date of Birth ☐☐ / ☐☐ / ☐☐☐☐	
2. What sex is your child?	○ Male	○ Female
3. How much did your child weigh at birth?	Grams ☐☐☐☐ **OR**	lbs ozs ☐☐ / ☐☐
4. In what country was your child born?	☐☐☐☐☐☐☐☐☐☐☐	
5. Was your child adopted?	○ Yes	○ No

If "YES", please continue to answer as many questions as possible

6. Was your child born by:	○ Normal vaginal delivery ○ Forceps delivery	○ Vacuum delivery ○ Caesarean section
7. Was your child born within 3 weeks of the expected delivery date?	○ Yes	○ No
If "No", was s/he born?	○ More than 3 weeks early ○ More than 3 weeks late	
8. Is your child a twin?	○ Yes	○ No
If "YES" was s/he born?	○ First	○ Second
9. Was your child ever breastfed?	○ Yes	○ No
If "YES", for how many weeks/months was s/he breastfed?	Weeks ☐☐	Months ☐☐
Was s/he breastfed exclusively (Fed without topping up with artificial bottle milk/other foods/fruit juices)?	○ Yes	○ No
If "YES" for how many weeks/months was s/he exclusively breastfed?	Weeks ☐☐	Months ☐☐
Even if s/he was breastfed exclusively, did your baby ever get **EVEN ONE** bottle of artificial milk in the first few weeks of his/her life?	○ Yes	○ No

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YOUR CHILD'S BROTHERS AND SISTERS

10. Does your child have any older brothers and sisters? ○ Yes ○ No

If "YES", how many older brothers? ☐☐

how many older sisters? ☐☐

11. Does your child have any younger brothers and sisters? ○ Yes ○ No

If "YES", how many younger brothers? ☐☐

how many younger sisters? ☐☐

CHILDCARE

12. Did your child ever go to a full-time day care facility (e.g. creche)? ○ Yes ○ No

	Weeks	Months	Years
If"YES", at what age did your child go to a full-time day care facility?	☐☐	☐☐	☐☐

13. Did your child ever go to pre-school (e.g. Playgroup, Montessori etc.)? ○ Yes ○ No

	Weeks	Months	Years
If"YES", at what age did your child go to preschool?	☐☐	☐☐	☐☐

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YOUR CHILD'S CHEST

14. Has your child ever had wheezing or whistling in the chest at any time in the past?
○ Yes ○ No

IF YOU HAVE ANSWERED "NO PLEASE SKIP TO QUESTION 19

15. Has your child had wheezing or whistling in the chest in the past 12 months?
○ Yes ○ No

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 19

16. How many attacks of wheezing has your child had in the past 12 months?
○ None
○ 1 to 3
○ 4 to 12
○ More than 12

17. In the past 12 months, how often, on average, has your child's sleep been disturbed due to wheezing?
○ Never woken with wheezing
○ Less than one night per week
○ One or more nights per week

18. In the past 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 ○ No

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19. Has your child ever had asthma?
○ Yes ○ No

20. In the past 12 months, has your child's chest sounded wheezy during or after exercise?
○ Yes ○ No

21. In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?
○ Yes ○ No

22. In the past 12 months, has a Doctor or Medical Specialist prescribed medication for your child to treat wheezing or asthma?
○ Yes ○ No

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YOUR CHILD'S NOSE

23. Has your child ever had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or the flu? ○ Yes ○ No

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 28

24. In the past 12 months, has your child had a problem with sneezing, or a runny, or blocked nose when he/she DID NOT have a cold or a flu? ○ Yes ○ No

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 28

25. In the past 12 months, has this nose problem been accompanied by itchy-watery eyes? ○ Yes ○ No

26. In which of the past 12 months did this nose problem occur? (Please fill in any circles that apply).

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

27. In the past 12 months, how much did this nose problem interfere with your child's daily activities?

○ Not at all
○ A Little
○ A Moderate Amount
○ A Lot

---

28. Has your child ever had hayfever? ○ Yes ○ No

29. In the past 12 months, has a Doctor or Medical Specialist prescribed medication for your child to treat nose problems? ○ Yes ○ No

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YOUR CHILD'S SKIN

30. Has your child ever had an itchy rash which was coming and going for at least six months?
○ Yes ○ No

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 36

31. Has your child had this itchy rash at any time in the past 12 months?
○ Yes ○ No

IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 36

32. 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 ○ No

33. At what age did this itchy rash first occur?
○ Under 2 years
○ Age 2 - 4 years
○ Age 5 or more

34. Has this rash cleared completely at any time during the past 12 months?
○ Yes ○ No

35. In the past 12 months, how often, on average, has your child been kept awake at night by this itchy rash?
○ Never in the past 12 months
○ Less than one night per week
○ One or more nights per week

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36. Has your child ever had eczema?
○ Yes ○ No

37. In the past 12 months, has a Doctor or Medical Specialist prescribed medication for your child to treat skin problems?
○ Yes ○ No

38. In the past 12 months, have you bought unprescribed cream for your child from the pharmacist to treat skin problems?
○ Yes ○ No

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YOUR CHILD'S GENERAL HEALTH

39. Do you think that your child received his/her vaccinations? You may wish to check his/her vaccination card. If unavailable, please answer as many as you can from memory.

The 3 in 1 (now the 5 in 1) (Whooping cough, Diphtheria and Tetanus)	○ Yes	○ No	○ Don't know
Measles, Mumps, Rubella (MMR)	○ Yes	○ No	○ Don't know
Hib (Haemophylus influenzae type b)	○ Yes	○ No	○ Don't know
Meningitis C (Men C)	○ Yes	○ No	○ Don't know
BCG (Tuberculosis/TB)	○ Yes	○ No	○ Don't know

40. Has your child had any of the following diseases **Before he/she was 3 years old?** (Fill in as many circles as apply)

Measles	○ Yes	○ No	○ Don't know
Mumps	○ Yes	○ No	○ Don't know
German measles (Rubella)	○ Yes	○ No	○ Don't know
Chickenpox	○ Yes	○ No	○ Don't know
Meningitis	○ Yes	○ No	○ Don't know
Glue Ear	○ Yes	○ No	○ Don't know
Gastroenteritis	○ Yes	○ No	○ Don't know
Pneumonia	○ Yes	○ No	○ Don't know
Whooping Cough	○ Yes	○ No	○ Don't know
Bronchitis	○ Yes	○ No	○ Don't know
Croup	○ Yes	○ No	○ Don't know
Bronchiolitis	○ Yes	○ No	○ Don't know
Constant runny nose	○ Yes	○ No	○ Don't know

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41. Did your child require antibiotics in the first TWO years of life? ○ Yes ○ No

If "YES", how often did your child require antibiotics in the first TWO years of life? ☐☐

42. Does your child take a reliever inhaler (usually blue)? ○ Yes ○ No

If "YES" how often does s/he take the reliever inhaler?
○ Daily
○ Only with symptoms

43. Does your child take a preventer inhaler (usually brown)? ○ Yes ○ No

If "YES" how often does s/he take the preventer inhaler?
○ Daily
○ Only with symptoms

44. Does your child take any other inhaler? ○ Yes ○ No

If "YES" please name the inhaler. ☐☐☐☐☐☐☐☐☐☐

How often does s/he take this inhaler?
○ Daily
○ Only with symptoms

WASP OR BEE STINGS

45. Has your child ever been stung by a bee or wasp? ○ Yes ○ No

If "NO" please go directly to Question 51.

46. How many times, in your child's lifetime have they been stung by a bee or a wasp? (Please write the number of times). ☐☐

47. Has your child ever had a swelling next to the sting site that was larger than 5cm and lasted for more than 2 days? ○ Yes ○ No

48. Has your child ever had any skin reactions,such as a rash (hives?) or swelling in other body parts (except for the sting site), within 1 hour following the sting? ○ Yes ○ No

49. Has your child ever experienced difficulties in breathing, asthma attack, abdominal pain or loss of consciousness within 1 hour following the sting?
○ Yes ○ No

50. Has your child ever been taken to hospital because of the sting?
○ Yes ○ No

YOUR CHILD TODAY

51. If a measure is available to you, what height is your child now?
Centimetres ☐☐☐ **OR** Feet ☐☐ / inches ☐☐

How was this measured? (Please write in block capitals).
☐☐☐☐☐☐☐☐☐☐

52. If scales are available to you, what does your child weigh today?
Kgs ☐☐ / gms ☐☐☐ **OR** Stone ☐☐ / Pounds ☐☐

53. Would you consider your child to be:
○ Underweight
○ Normal weight
○ Overweight
○ Obese

54. Does your child walk to school most days (i.e. 4 or 5 days)?
○ Yes ○ No

If "YES", what distance does s/he walk to school?
Miles ☐☐ / yards ☐☐☐ **OR** Kms ☐☐ / metres ☐☐☐

55. Outside school hours, how often does your child usually exercise so much that s/he gets out of breath or sweats? (Please fill in one circle only).
○ Everyday
○ 4-6 times a week
○ 2-3 times a week
○ Once a week
○ Once a month
○ Less than once a month

56. How often does your child swim in a heated indoor swimming pool? (Please fill in one circle only).
○ Everyday
○ 4-6 times a week
○ 2-3 times a week
○ Once a week
○ Once a month
○ Less than once a month

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YOUR CHILD'S HOME ENVIRONMENT

In this section we ask a number of questions on your child's home and home surroundings. For each question, please provide answers for the home in which your child lives at present and for the home in which your child lived during the first year of his/her life, (in case you have moved, please choose the home in which your child spent most of his or her time during their first year of life). Please make sure you answer for both times in your child's life.

57. Which of the following best describes the surrounding of your child's home? (Please fill in one circle for the surroundings of your child's home at both times in his/her life).

At present	**During your child's first year of life**
○ In a city	○ In a city
○ In the suburbs (outskirts) of a city	○ In the suburbs (outskirts) of a city
○ In a village	○ In a village
○ In a town	○ In a town
○ In the suburbs (outskirts) of a town	○ In the suburbs (outskirts) of a town
○ On a farm	○ On a farm
○ In the countryside, but not on a farm	○ In the countryside, but not on a farm

58. Does or did your child have contact at least once a week with any of the following animals? (Please fill in the circles regarding each type of animal for both times in your childs life, **OR** under the heading "no" if your child is or was not regularly exposed to the animals).

No	**Yes, at present**	**Yes, during the child's first year of life**
○ Dog	○ Dog	○ Dog
○ Cat	○ Cat	○ Cat
○ Farm animals	○ Farm animals	○ Farm animals
○ Other animals	○ Other animals	○ Other animals

59. Does or did your child play or work at least once a week in the following places? (Please fill in the circles for each place and for both times in your child's life **OR** under the "no" heading if your child does or did not play or work in a barn or stable).

No	**Yes, at present**	**Yes, during the child's first year of life**
○ Barn	○ Barn	○ Barn
○ Stable	○ Stable	○ Stable

60. Does or did your child regularly drink unpasteurised milk?

At present	**During the child's first year of life**
○ Yes	○ Yes
○ No	○ No

61. During your child's first year of life did s/he live close to a factory? ○ Yes ○ No

If "YES", what type of factory? (Please write in block capitals). ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

What distance was your child's home from the factory?

Miles ☐☐ / yards ☐☐☐ **OR** Kms ☐☐ / metres ☐☐☐

62. Does your child at present live close to a factory? ○ Yes ○ No

If "Yes", what type of factory? (Please write in block capitals). ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

What distance is your child's home from the factory?

Miles ☐☐ / yards ☐☐☐ Kms ☐☐ / metres ☐☐☐

63. What kind of floor covering is or was in your child's bedroom?

At present	**During the child's first year of life**
○ Fitted carpets	○ Fitted carpets
○ Loose carpets/rug	○ Loose carpets/rug
○ Bare floor (wood or tiles)	○ Bare floor (wood or tiles)

64. Does or did your child's home have damp spots on the walls or ceilings?

At present	**During the child's first year of life**
○ Yes	○ Yes
○ No	○ No

65. Does or did your child's mother smoke?

At present	**During the child's first year of life**
○ Yes	○ Yes
○ No	○ No

66. Does anybody, at present smoke inside your child's home? ○ Yes ○ No

If "YES", how many cigarettes in total are smoked per day in your child's home? (For example, mother smokes 4 + father smokes 5 + other person smokes 3 = 12)

○ 1 - 10 cigarettes
○ 11 -20 cigarettes
○ More than 20 cigarettes

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WATER SUPPLY

67. What is and was the water supply to your house? (Please fill in one circle for the water supply for each time in your child's life).

At present	**During the child's first year of life**
○ Mains water	○ Mains water
○ Your own well	○ Your own well
○ Your own spring water	○ Your own spring water
○ Group scheme water	○ Group scheme water

68. Do you or did you use a water filter in your home?

At present	**During the child's first year of life**
○ Yes	○ Yes
○ No	○ No

If "YES", why did you decide to use a filter?(Please write in block capitals). ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Is the water filter:
○ Fitted directly to sink in kitchen
○ A manual filter, e.g. "Brita"?
○ Other (Please specify) ☐☐☐☐☐☐☐☐

THE NEXT TWO SECTIONS ARE ABOUT YOUR CHILD'S BIOLOGICAL PARENTS; IF YOUR CHILD IS ADOPTED PLEASE SKIP TO QUESTION 81

ABOUT YOUR CHILD'S BIOLOGICAL FATHER

69. What is the nationality of your child's father? (Please write in block capitals). ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

70. Was your child's father reared on a farm? ○ Yes ○ No ○ Don't know

71. Does or did your child's father regularly work on a farm? (Please fill in any circles that apply)
○ Yes, during childhood
○ Yes, at present
○ No

72. Has your child's father ever had any of the following diseases? (Please fill in any circles that apply).
○ Asthma
○ Hay fever
○ Eczema
○ None of the above diseases

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ABOUT YOUR CHILD'S BIOLOGICAL MOTHER

73. What is the nationality of your child's mother? (Please write in block capitals) ☐☐☐☐☐☐☐☐☐☐☐☐☐☐

74. Was your child's mother reared on a farm? ○ Yes ○ No

75. While pregnant with this child did your child's mother work on a farm? ○ Yes ○ No

76. Does or did your child's mother have contact at least once a week with the following places? (Please fill in the circles for each place and for both times in your child's mother's life, **OR** under the heading "No" if your child's mother was not exposed to a barn or stable during these times).

No	**Yes, during her childhood**	**Yes, during pregnancy with this child**
○ Barn	○ Barn	○ Barn
○ Stable	○ Stable	○ Stable

77. Does or did your child's mother have contact at least once a week with the following animals? (Please fill in the circles regarding each type of animal and for both times in your child's mother's life, **OR** under the heading "No" if your child's mother was not exposed to the animals during these times).

No	**Yes, during her childhood**	**Yes, during pregnancy with this child**
○ Dog	○ Dog	○ Dog
○ Cat	○ Cat	○ Cat
○ Farm animals	○ Farm animals	○ Farm animals
○ Other animals	○ Other animals	○ Other animals

78. Does or did your child's mother regularly drink unpasteurised milk?

During her childhood	**During pregnancy with this child**
○ Yes	○ Yes
○ No	○ No

79. During her pregnancy with this child, did your child's mother smoke? ○ Yes ○ No

80. Has this child's mother ever had any of the following diseases? (Please fill in any circles that apply).

○ Asthma
○ Hay fever
○ Eczema
○ None of the above diseases

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81. What level of education did your child's mother receive?

○ Primary School
○ Second level up to Inter/Junior-Cert
○ Second level up to Leaving Cert
○ Third level Education, College, University

82. What level of education did your child's father receive?

○ Primary School
○ Second level up to Inter/Junior-Cert
○ Second level up to Leaving Cert
○ Third level Education, College, University

83. Who answered this questionnaire?

○ Father
○ Mother
○ Other person

Thank you very much for giving us your time to complete this questionnaire. Please return it to the class teacher in the sealed envelope provided, as soon as possible.

Appendix 7 Instructions for questionnaire completion

INSTRUCTIONS FOR COMPLETION

- PLEASE FILL IN THE QUESTIONNAIRE AND RETURN IN THE ENVELOPE TO THE CLASS TEACHER AS SOON AS POSSIBLE.

- MOST QUESTIONS REQUIRE YOU TO ANSWER BY FILLING IN THE CORRECT CIRCLE, FOR EXAMPLE IF YOUR CHILD WAS BORN BY NORMAL DELIVERY, ANSWER AS FOLLOWS:

● Normal vaginal delivery	○ Vacuum delivery
○ Forceps delivery	○ Caesarean section

- PLEASE WRITE ANY ANSWERS IN BLOCK CAPITALS INTO THE BOXES PROVIDED, FOR EXAMPLE IF YOUR CHILD WAS BORN IN IRELAND, ENTER AS FOLLOWS:

I	R	E	L	A	N	D

- PLEASE FILL IN ANY NUMBERS INTO THE BOXES PROVIDED, FOR EXAMPLE IF YOUR CHILD WEIGHED 6 POUNDS 5 OUNCES, AT BIRTH, ENTER AS FOLLOWS:

0	6	POUNDS	0	5	OUNCES

OR, IF YOUR CHILD WEIGHED 3650 GRAMS AT BIRTH, ENTER AS:

3	6	5	0

- PLEASE FILL IN THE DATE OF BIRTH OF THE CHILD AS FOLLOWS:

- FOR EXAMPLE IF YOUR CHILD WAS BORN ON THE 19TH OF MAY 1995 ENTER AS:

1	9	0	5	1	9	9	5

Appendix 8 List of participating schools

Ballyhass Mixed National School, Cecilstown, Mallow, Co. Cork

Ballygown Mixed National School, Mallow, Co. Cork

Scoil Ghobnatain Mixed National School, Mallow, Co. Cork

Mercy Convent, Mixed National School, Buttevant, Mallow, Co. Cork

Glantane Mixed National School, Glantane, Mallow, Co. Cork

Saint Patrick’s Boys National School, Mallow, Co. Cork

Rathan Mixed National School, Rathan, Mallow, Co. Cork

Lisgriffin Mixed National School, Lisgriffin, Buttevant, Mallow, Co. Cork

Dromahane Mixed National School, Dromahane Mallow, Co. Cork

Castletownroche Mixed National School, Castletownroche, Mallow, Co. Cork

Burnfort Mixed National School, Burnfort, Mallow, Co. Cork

Mallow No. 1 Mixed National School, Shortcastle, Mallow, Co. Cork

Ath Na Lionta Mixed National School, Mourneabbey, Mallow, Co. Cork

Baltydaniel Mixed National School, Newtwopothouse, Mallow, Co. Cork

Ballyclough Mixed National School, Ballyclough, Mallow, Co. Cork

Mercy Convent Girls National School, Doneraile, Mallow, Co. Cork

Little Island Mixed National School, Little Island, Co. Cork

Ringaskiddy Lower Harbour Mixed National School, Ringaskiddy, Co. Cork

Shanbally Mixed National School, Shanbally, Ringaskiddy, Co. Cork

Crosshaven Girls National School, Crosshaven, Co.Cork

Walterstown Mixed National School, Walterstown, Cobh, Co. Cork

Bellevue Mixed National School, Bellevue, Cobh, Co. Cork

Templebrady Mixed National School, Crosshaven, Co. Cork

Rushbrook Mixed National School, Cobh, Co. Cork

Monkstown Mixed National School, Monkstown, Co. Cork

Crosshaven Boys National School, Crosshaven, Co. Cork

Kilcredan Mixed National School, Ladysbridge, Castlemartyr, Co. Cork

Baile Ui Chroinín Mixed National School, Cloyne, Midleton, Co. Cork

Scoil Naisiúnta Na Scarta Leithe, Saleen, Cloyne, Midleton, Co. Cork

Shanagarry Mixed National School, Shanagarry, Midleton, Co. Cork

Castlemartyr Mixed National School, Castlemartyr, Midleton, Co. Cork

Whitegate Mixed National School, Whitegate, Midleton, Co. Cork

St. John the Baptist Mixed National School, Midleton, Co. Cork
Scoil Mhuire Naofa Boys National School, Carrigtwohill, Midleton, Co. Cork
Ballintotas Mixed National School, Castlemartyr, Midleton, Co. Cork
Scoil Realt Na Mara Mixed National School, Ballycotton, Midleton, Co. Cork
Gaelscoil Mhainastir na Corann, Midleton, Co. Cork
Midleton Convent Girls National School, Midleton, Co. Cork
Cloyne Mixed National School, Cloyne,Midleton, Co. Cork
Kildorrery Mixed National School, Kildorrery,Mitchelstown, Co. Cork
Scoil Mhuire Mixed National School, Ballyhooley, Fermoy, Co. Cork
Glanworth Mixed National School, Glanworth, Fermoy, Co. Cork
Cahermore New Central Mixed National School, Cahermore, Eyeries, Bantry, Co. Cork
Scoil Chaitigheirn na hAoirí Mixed National School, Eyries, Bantry, Co. Cork
St James' Mixed National School, Durrus, Bantry, Co. Cork
Kealkill Mixed National School, Bantry, Co. Cork
Drumclough Mixed National School, Drumclough, Bantry, Co. Cork
Derrycreha Mixed National School, Derrycreha, Bantry, Co. Cork
St Brendan’s Mixed National School, Bantry, Co. Cork
Óir Cheann Mixed National School, Eyries, Bantry, Co. Cork
Inchiclough Mixed National School, Inchiclough, Bantry, Co. Cork
Scoill Fhiachna Mixed National School, Glengarriff Co. Cork
Adrigole Mixed National School, Adrigole, Bantry, Co. Cork
Scoil An Chroí Ró Naofa Mixed National School, Castletownbere, Bantry, Co. Cork
Bantry Boys National School, Bantry, Co. Cork
Gaelscoil Bheanntraí Mixed National School, Warner House Bantry, Co. Cork
Our Lady of Mercy Girls National School, Bantry, Co. Cork
Kilcrohane Mixed national School, Durrus, Bantry, Co. Cork
Carrigboy Mixed National School, Durrus, Bantry, Co. Cork
Rushnacarra Mixed National School, Rushnacarra, Durrus, Bantry, Co. Cork
Mochomhog Mixed National School, Cappaboy, Kealkil, Bantry, Co. Cork
Ballyvognane Mixed National School, Aghina, Macroom, Co. Cork
Chúil Aodha Barr d’Inse Mixed National School, Cúil Aodha, Macroom, Co. Cork
Canovee Mixed National School, Carrigadrohid, Macroom, Co. Cork
Scoil na Mona Fliche Mixed National School, Macroom, Co. Cork
Carraig An Ime Mixed National School, Macroom, Co. Cork

Tarelton Mixed National School, Tarelton, Macroom, Co. Cork

Rusheen Mixed National School, Coachford, Macroom, Co. Cork

Kilbarry Mixed National School, Kilbarry Macroom, Co. Cork

Dromleigh Mixed National School, Dromleigh, Macroom, Co. Cork

Ballinagree Mixed National School, Ballinagree, Macroom, Co. Cork

Ballyvourney Mixed National School, Carraig and Adhmaid, Macroom, Co. Cork

Macroom Convent Mixed National School, Macroom, Co. Cork

Scoil Lachtán Naofa Mixed National School, Cill na Martra, Macroom, Co. Cork

Inchigeela Mixed National School, Inchigeela, Macroom, Co. Cork

Clondrohid Mixed National School, Clondrohid, Macroom, Co. Cork

Scoil Bhríde Mixed National School, Crossmahon, Bandon, Co. Cork

Timoleague Mixed National School, Timoleague, Bandon, Co. Cork

Presentation Convent Mixed National School, Bandon, Co. Cork

Laragh Mixed National School, Laragh, Bandon, Co. Cork

Ballinadee Mixed National School, Ballinadee, Bandon, Co. Cork

Castlealack Mixed National School, Castlealack, Bandon, Co. Cork

Bandonbridge Mixed National School, Bandon, Co. Cork

Newcestown Mixed National School, Newcestown, Bandon, Co. Cork

Gaelscoil Droichead na Bandán, Charley Hurley Park, Bandon, Co. Cork

St Catherine’s Girls National School, Model Farm Road, Cork

Scoil and Spiorad Naoimh Girls National School, Curraheen Road, Bishopstown, Cork

STt Patrick’s Boys National School, Gardiners Hill, Ballyhooley Road, Cork

Our Lady of Lourdes Girls National School, Ballinlough, Cork

Scoil Muire na nGrás Greenmount, Cork

Togher Boys National School, Togher, Cork

Scoil Maoimh Bríd Girls National school, Eglantine House, Ballinlough, Cork

Scoil Athair Maitiu Girls National School, Togher, Cork

Scoil Mhuire Banríon Girls National School, Mayfield, Cork

Realt na Maidine Mixed National School, Ballyphehane, Cork

Scoil Iosagáin Boys National School, Faranree, Cork

Scoil Barra Naofa Boys National School, Beaumount, Cork

Scoil Barra Naofa Girls National School, Beaumount, Cork

St Joseph’s Boys National School, Mardyke, Cork

Scoil Aiseiri Chriost Girls National School, Faranree, Cork

Mhuire ar Chnoc hAoine Mixed National School, Knocknaheeney, Cork
Maria Assumpta Girls National School, Ballyphehane, Co. Cork
Scoil Mhuire Gan Smal Girls National School, Glasheen Road, Glasheen, Cork
Scoil Mhuire Gan Smal Boys National School, Glasheen Road, Glasheen, Cork
Scoil Naoimh Eoin Easpal, Mayfield, Cork
Naoimh Antaine Boys National School, Ballinlough Cork
Cloghroe Mixed National School, Blarney, Co. Cork
Scoil Barra, Innishmore, Ballincollig, Co. Cork
Scoil Naoimh Eoin Boys National School Ballincollig, Co. Cork

Appendix 9 Outputs associated with this thesis

Journal Publications

Published papers

Duggan, E.M., Sturley, J., Fitzgerald, A.P., Perry, I,J., Hourihane, J. O'B. The 2002- 2007 Trends of Prevalence of Asthma, Allergic Rhinitis and Eczema in Irish Schoolchildren. *Pediatric Allergy and Immunology.* 2012 Aug;23(5):464-71. (386).

Papers in preparation

Duggan, E.M., Sturley, J., Fitzgerald, A.P., Perry, I,J., Hourihane, J. O'B. The Prevalence of Childhood Asthma, Allergic Rhinitis and Eczema in Irish Rural and Urban Environments.

Duggan, E.M., Sturley, J., Fitzgerald, A.P., Perry, I,J., Hourihane, J. O'B. Antibiotics and Childhood Allergy Development in Ireland.

Conference Outputs

CONFERENCE	ABSTRACT TITLE	DATE
Poster presentation at the American Academy of Allergy, Asthma & Immunology Conference in Washington	Examining longitudinal trends in the prevalence of allergic diseases in Ireland 2002-2007, using the ISAAC methodology. Published Abstract (387).	March 2009
Electronic presentation at the European Respiratory Society Conference in Vienna	Irish prevalence of childhood asthma, 2002-2007. Is there a sex equalisation in the prevalence of asthma?	Sept. 2009
Oral presentation at the European Association of Asthma and Allergy Conference in Venice	The Impact of Exclusive Breast Feeding on Asthma In Irish School Children Aged 6-9 Years. E Duggan, J. Lutomski, AP Fitzgerald, I Perry, JO'B Hourihane Published Abstract No. 32 (388).	Nov. 2009