The Behaviour of Three Year Olds in Relation to Allergy and Exposure to Artificial Additives

Volume One of Two

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ABSTRACT

FACULTY OF MEDICINE, HEALTH AND BIOLOGICAL SCIENCES
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THE BEHAVIOUR OF THREE YEAR OLDS IN RELATION TO ALLERGY AND EXPOSURE TO ARTIFICAL ADDITIVES

by Belinda J Bateman

Behaviour problems are common in young children. Problems associated with Attention Deficit Hyperactivity Disorder have been the main focus of study, partly because of the consequences for achievements in education and subsequent social integration. However other factors implicated as affecting childhood behaviour include physical illness such as allergic disease and environmental factors. There is also literature suggesting that artificial food additives may have an adverse effect on behaviour.

This study had two components. The first was a population survey to ascertain the prevalence of behaviour problems and/or allergy and their associated risk factors. The second part of the study was a randomised placebo controlled cross-over trial. The study population consisted of 2731 3-year-olds resident on the Isle of Wight. There was a 70% response rate to the behavioural assessment which consisted of 3 parent completed, validated questionnaires. 50% of the population were also assessed for atopic status (at least one positive skin prick test of $\geq$ 2mm mean wheal diameter) and allergic symptoms (questions from the International Study Asthma Allergies in Childhood). There was no difference between those who consented to assessment and those who did not. 277 of these children (10%) completed a 4 week randomised placebo controlled cross-over trial. Children defined as both atopic and hyperactive were selected and matched for sibship position, maternal education and month of birth with 3 other children, who were atopic only, hyperactive only or neither. The challenge was 20mg of artificial food colourings (sunset yellow, tartrazine, carmoisine, and ponceau 4R) and 45mg of sodium benzoate, within a daily mixed fruit juice vehicle. The challenge and placebo were shown to be indistinguishable in taste and appearance. The child's attention, impulsivity and activity was assessed with weekly clinic-based tests, and a daily parental questionnaire.

Using validated cut off scores from the parental questionnaires 11.6% of the 3-year-olds had a general behaviour problem, 10.4% had problems with impulsivity, activity and attention, referred to as hyperactive behaviour. Parental rating of their child's behaviour as hyperactive or not was confirmed by clinic tests (t 3.87, df 275, $p<0.001$). Atopy and allergic symptoms within the preceding 12 months were common; 19% were atopic, 33% reported wheeze, 27% symptoms of rhinitis, 19% symptoms of eczema. 0.6% reported life-threatening symptoms associated with food. All four conditions were associated with atopy. Although wheeze and rhinitis were more prevalent in children in deprived circumstances, atopy was associated with affluence. Atopy per se was not significantly associated with an increased risk of behaviour problems but children with symptoms of eczema and/or rhinitis had an increased risk of behaviour problems reported by parents, not substantiated by clinic testing. In the randomised placebo controlled cross-over trial there was a improvement in behaviour when artificial food additives were withdrawn, and significant elevations in hyperactive behaviour during the active period based on parental reports, but not confirmed by clinic tests. These effects were observed across the whole group of children, not specifically in those with prior behaviour problems, and independent of their atopic status.

This study confirms the multifactoral nature of allergic symptoms in the pre-school child, with physical environment exerting a complex effect. Atopy was important in the aetiology of allergic symptoms and was linked to affluence. However, respiratory and nasal symptoms were persistently more common in deprived children. Any direct link between atopy and behaviour was refuted, although symptoms of allergic disease adversely affected these children's behaviour. There was a general adverse behavioural effect of artificial food colouring and benzoate preservatives, with an effect size from parental ratings of half a standard deviation increase in hyperactive behaviour from baseline.

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Preface

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Declaration

This work was carried out by a team that worked from the David Hide Asthma and Allergy Research Centre, St. Mary's Hospital, Newport, Isle of Wight, UK.

I managed this team, with the support of a steering committee, and operationalised the whole study.

I designed the initial contact letters and consent forms. I transferred the behaviour questionnaires into the format that was used. I designed the medical questionnaires. The research psychologist and myself put together the behavioural clinic tests (that had been chosen by the steering committee) to measure behavioural change during the randomised controlled trial.

I administered a small proportion of the behaviour questionnaires, all the medical questionnaires and some of the clinic tests.

I designed the statistical data base to manage all the data, made a significant contribution to the input and cleaning of the data. I undertook all the analysis, with the help of the research psychologist, and support of the steering committee.

Acknowledgements

I would like to thank my supervisors Professors Jim Stevenson and John Warner for their help and support throughout the undertaking of this research, and writing of the thesis. I would also like to thank the FAB Steering Committee, and staff of The David Hide Asthma and Allergy Centre, without whom this research would not have succeeded. I would also like to thank my partner Tim Carpenter, and my friends for their infinite patience and finally the families of the Isle of Wight deserve my biggest thanks.

Definitions

1. Behavioural Variables

General Behaviour Problems (GBP)

An index of the number of general behavioural problems shown by the children was obtained using a Behaviour Checklist (BCL)[1], a 12 item behaviour check list rated on a 0-2 scale of problem severity. Children who score 10 or more were designated as having an extreme behaviour problem

Behaviour Problems associated with Hyperactivity (HB)

The child was defined as hyperactive:
I) <u>for the epidemiological data</u> if
they scored 20 or more on the Weiss-Werry-Peters (WWP) activity questionnaire[2] and a mean of 4.2 or more on the activity component of the Emotionality, Activity and Sociability Temperament questionnaire (EAS)[3].
<u>II) for the randomised controlled trial</u> if they scored 20 or more on WWP[2], and a mean of 4.0 or more on the EAS Temperament questionnaire[3]

2. Atopy and Allergic symptoms

Atopic

Atopic subjects were defined as those who produce IgE antibody to environmental allergens with or without the clinical manifestations of asthma, eczema and rhinoconjunctivitis (hayfever). The atopic immunological status was assessed by reactions to prick tests with a panel of common allergens relevant to the subject's environment.[4] A mean wheal diameter of any reaction ≥ 2mm following skin prick testing to a panel of allergens; D.pteronyssinus, grass pollen, cat, egg, milk and peanut (ALK, Hørsholm, Denmark) in the presence of a negative (normal saline) and positive (histamine 10mg in 1ml) control on the volar aspect of the child's forearm using Pepy's method[5]

Allergic Symptoms - ISAAC questions [6]

Respiratory symptoms	
lifetime wheeze	ever had wheezing or whistling in the chest at any time in the past?
current wheeze	had wheezing or whistling in the chest in the last 12 months?
current nocturnal cough only	in the last 12 months had a dry cough at night apart from a cough associated with a cold or a chest infection, in the absence of wheeze?
lifetime asthma	ever had asthma?
Nose and eye symptoms	
lifetime rhinitis	in the last 12 months had a problem with sneezing or a runny or a blocked nose when he or she did not have a cold or the flu?
current rhinitis	in the last 12 months had a problem with sneezing or a runny or a blocked nose when he or she did not have a cold or the flu?
current rhinoconjunctivitis	in the last 12 months has this nose problem been accompanied by itchy-watery eyes?
lifetime hayfever	ever had hayfever?
Skin symptoms	
lifetime itchy rash	ever had itchy rash coming and going for 6 months?
current itchy rash	itchy rash at any time in the last 12 months?
current flexural itchy rash	itchy rash last 12 months at any time affected any of the following places folds of elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?
lifetime eczema	ever had eczema?

Allergic Symptoms - FAB questions

Gastrointestinal symptoms	
lifetime gastrointestinal symptoms	ever diarrhoea or vomiting which you think was related to an intolerance or allergy to a food or drink?
current gastrointestinal symptoms	diarrhoea or vomiting which you think was related to an intolerance or allergy to a food or drink in the last 12 months?
Anaphylactic type symptoms	
lifetime urticaria (only)	ever had an episode of urticaria (only urticaria (described as a skin rash that comes and goes and looks as if the skin has been wiped with a nettle) – children with other acutely associated skin or mucous membrane symptoms excluded)
lifetime any allergic (probable IgE mediated) symptoms	ever had an episode of urticaria or/and lip swelling or/and face swelling or/and swelling of back of mouth and throat or/and collapse secondary to *any* cause (not trauma)
lifetime significant allergic symptoms	ever had an episode of face swelling or/and swelling of back of mouth and throat or/and collapse secondary to *any* cause (not trauma)
lifetime serious allergic symptoms (including anaphylaxis)	ever had an episode of swelling of back of mouth or throat or/and collapse secondary to *any* cause (not trauma)

3. Environmental factors

Physical environment	
Annual household income	1. less than £12,000 2. £12,000 - £17,999 3. £18,000 - £29,999 4. £30,000 - £41,999 5. greater than £42,000

Housing tenure	housing – defined as either owner occupied or rented/other (eg tied housing)
Vehicle ownership	household ownership of a car or van
Family social environment	
Maternal education	maternal age at leaving full-time education 1. *'less than or at age 16 years'* mothers who left school with either no qualifications or with GCSEs or their equivalent 2. *'17-20 years'* mothers who went on to further education, including those with more 'trade' type qualifications, A-levels and some professional qualifications 3. *'greater than or equal to 21 years'* mothers most likely to have attained degree level qualification - also includes mothers who had achieved professional qualifications such as nursing qualifications
Lone parent family	one adult living with child
Two parent family	two adults living with child (not necessarily child's biological parents)
Maternal/paternal age	age of biological mother/father
Birth order	child number of her/his mother (pregnancies carried beyond 24 wks) 1. 1st 2. 2nd 3. 3rd 4. >3rd
Maternal employment	1. full time employment/student 2. part time employment/student 4. full time at home
Current exposure to smoke	any adults living in child's household who smoke (indoors or outdoors)

4. Social measures

Birth weight (kgs)	
Gestation (weeks)	
Antenatal smoke exposure	any maternal smoking during pregnancy
Admission to special care baby unit (SCBU)	any reason for admission to special care baby unit
Height	(at phase II centimetres)
Breast feeding	breast feeding (not exclusive) (weeks)
Introduction of solids	introduction of solids (age in weeks)

Chapter 1

Introduction

1.1 General introduction

Behaviour problems in childhood are common, persistent and important. They are associated with distress in child or parents and have short and long term educational and social sequelae. Approximately 20% of al ages of children at any one time have psychological problems and in half of these children these problems are classified as moderate to severe. There are often varying combinations of difficult behaviour, anger, irritability, nervousness, eating and sleep problems and poor family and peer relations.[7]

The search for possible risk factors associated with behaviour problems have included wider societal influences such as social deprivation and urban living and more family-based problems including parental mental health problems, marital discord and parenting style.

Comorbidity of childhood behavioural problems with impaired physical health has also been examined. The allergic conditions, asthma, eczema and hayfever have been implicated with complex and confounded inter-relationships. As well as physical ill health, other influences on children's behaviour including food and drinks are widely blamed for over overactive behaviour with particular emphasis upon the behavioural effect of artificial additives.

1.2 Behaviour problems

Estimates from the general population of the point prevalence of problem behaviours in 3-year-olds lie between 10 and 15%. This is remarkably consistent across studies and different populations.[8] In the pre-school age group problems seem to cluster into two types; the first characterised by timidity and fearfulness and termed internalising behaviours, the second typified by aggressive behaviour and termed externalising behaviours. The group of externalising behaviours include the triad of overactivity, inattention and impulsivity, which have loosely been termed

'hyperactivity'. Epidemiological definitions of hyperactivity produce a much larger group than the clinical group meeting the diagnostic criteria for attention deficit hyperactivity disorder (ADHD).[9]

A reasonable supposition has been that some of these problems; overactivity, inattention, peer and sibling relationships, and eating, toileting and sleep problems are so common they may be age-related manifestations of developmental transitions. However evidence points clearly to the continuity of externalising behaviour problems from pre-school into school years. At least half of children identified with problems at the age of 3 years are likely to have problems at 8 years.[1;11] About half of children identified as hyperactive between the ages of 7-11 have persisting problems aged 15 years.[12] There is also evidence of persistence of problems into adulthood. School age children with both ADHD and antisocial behaviour problems appear to be particularly at risk of antisocial behaviour through adolescence and serious criminal offending as adults.[13]

Attempts have been made to identify factors associated with the emergence of behaviour problems, and those that affect the long-term trajectory of problems. Although family, adoptee and twin studies indicate a strong role for genetic factors in the aetiology of hyperactivity[14] there is also much evidence that environmental factors are associated with more general behaviour problems in childhood.[15] The association of socio-economic adversity with behaviour problems appears to be mediated through parenting styles, with some effect of the wider community. Poverty appears to negatively affect children's behaviour by increasing the risk of family adversity and frustrating good parenting.[7] Other parental risk factors include parental mental health problems, particularly maternal depression,[16] but less is known about the effects of parental personality disorder and low parental IQ.[15] Adolescent and lone parenthood also appear to increase the risk of childhood behaviour problems, but there is only limited understanding of the mechanisms involved.[7;17] Family risk factors are characterised by facets of disorganised parenting and family dysfunction that include lack of committed, positive parent-child relationships, unresolved conflict, discordant, negative and coercive parenting,[18;19] parental deficiencies in social problem solving, models of violence and lack of impulse control and inadequacies in parental supervision.[15] How socio-economic adversity impinges upon these family styles is less clear.

Interactions between multiple genetic risks and multiple environmental risks account for the variation in psychopathology in childhood.[15] A New Zealand longitudinal study showed that young adults with serious criminal offending were more likely to have had antisocial behaviour that had emerged early, between the ages of 5-7 years. They were a distinct subgroup within the group of children with ADHD, identified by both family adversity and evidence of early neuropsychological deficits such as motor problems and later reading problems. Family adversity was a composite variable within this study that included aspects of parental mental health as well as socio-economic position, which was likely to have biological and social facets. The heritable traits shared between parents and child such as poor verbal intelligence or physiological vulnerability to substance dependence may have contributed to the coexistence of behaviour disorder and adverse conditions in a family.[13]

Rutter suggests that in older children symptoms of conduct disorder are more clearly a function of childrearing practices and overall family climate, whereas activity levels and inattention show clearer evidence of heritability.[20] Various estimates of the extent that heritability can explain variations in behaviour associated with attention deficit disorder lie between 0.5 and 0.9.[21]

1.3 Socio-economic adversity

Many other indicators of ill health are also associated with adverse socio-economic circumstances.[22] Socio-economic deprivation is associated with an increased risk of mortality and morbidity from infancy throughout childhood. Babies of more socio-economically deprived families are more likely to be preterm or low birth weight[23], more likely to die from sudden infant death syndrome[24], to fail to thrive as babies[25], to have more symptoms of ill health through childhood,[26] to have more accidental injury and death as children[27] and to be abused and neglected[28].

'Absolute' poverty, with insufficient resources to sustain life, clearly has an effect upon health. Severe poverty is all but eliminated in developed countries. How we define, measure and understand the mechanisms whereby living in 'relative' poverty affects health is more difficult, but important when comparing research findings. The European Union's (EU) poverty measure includes income below 50% of the national average. Other countries use a poverty measure that is based upon purchasing

power and, in real terms, is kept constant over time. The US poverty line varies by family size (in 2000 $11 250 for two persons, per year, with $2900 added for each additional person)[29] Classifications of families by head of the household occupation such as The Registrar General's Social Class are widely used but have some limitations. These including misclassification of families, and underestimation of the effect of environmental measures.[31] In response to such concerns socio-demographic indicators have been used to make up deprivation indices,[32;22] These also can result in misclassification of familes, as geographical units can carry pockets of deprivation. A measure of child poverty in Somerset UK, was based upon 6 weighted census variables; no adult in employment, rented accommodation, overcrowding (>1 person per room), lone parent family, no car and no central heating,[33] more precisely describing rural and child poverty.[30] The more direct measures of household income is commonly used in the USA, and proxy measures of income including car ownership, housing tenure and level of parental education have been shown to better discriminate than social class for health outcomes.[34]

Environmental factors have been conceptualised by their presumed level of action and divided into distal factors (acting at societal or international level), intermediate factors (mediating between the macroenvironment and the immediate environment) and proximal factors (directly causing disease).[35] Proximal factors include access to adequate levels of nutrition and to safe indoor and outdoor environments. Intermediate factors include structural factors that limit a poorer family's access to health and educational resources. The effect does not only lie at the material (physical) level, families with risk factors for socioeconomic deprivation have been shown to have a less extensive and less confiding social network.[36] Neighbourhoods with high concentrations of families with risk factors for socioeconomic deprivation have lower levels of social capital, a feature of social organisation that facilitates co-operation for mutual benefit.[37] Sheehan demonstrated that the effect of economic stress upon the variation in the birth weight of babies was largely mediated by lack of social support and family stress impinging upon parental behaviour.[38]

Further dimensions that increase the risk of adverse outcomes include the length of time that a child or family has spent exposed to deprivation.[40] At its most extreme this is illustrated by the intergenerational transfer of the effects of poverty on the birth weight of children.[41] The effect of debt may also directly affect a child's access to

adequate housing, food, heating and sanitation. Being in debt also affects the health and behaviour of parents through smoking and alcohol use. Furthermore women and children are additionally disadvantaged, receiving less of a family's resources.[29] Any attempt to examine causal associations between physical disease that may have socio-economic determinants and behaviour problems therefore needs careful control for these factors.

1.4 Atopy and allergic disease

I will refer to asthma, eczema and rhinoconjunctivitis and food allergy as 'allergic disease'. Any discussion of whether they increase the risk of behaviour problems needs first a more detailed look at the conditions themselves. Asthma, eczema and rhinoconjunctivitis are common diseases of childhood. Estimates vary according to diagnostic practices, and reference to lifetime or point prevalence. Studies dating from the 1990s identify one in five school age children with self-reported asthma[42-44], and between one in six[44] and one in ten[42] of children with eczema and hayfever. The prevalence of symptoms suggestive of asthma or eczema or rhinitis in pre-school children may be as high as one in six.[45]

Food intolerance describes any untoward reactions to foods, food allergy specifically identifies IgE mediated reactions. The prevalence of both these conditions is poorly documented. Bock estimated that 8% of a relatively unselected population of US children in the first 3 years of their life had challenge-confirmed food intolerance.[46] From the Isle of Wight 1989 birth cohort Tariq reported 0.5% point prevalence of peanut allergy in 4 year olds (from skin prick tests and a history of reaction).[47] Macdougall estimated the incidence of near fatal reactions as 0.02 and severe as 0.19 per 100 000 children aged 0-15 years per year.[48]

Although I have referred to asthma, eczema and rhinoconjunctivitis and food allergy as 'allergic disease', the pathogenesis is not actually as simple. Most clinical studies support the hypothesis that atopy plays a role in the pathogenesis of asthma[49], eczema[50], rhinoconjunctivitis[51] and food allergy[46]. Atopy is best described as an immunological state characterised by an exaggerated Th2 cell response to common proteins. All four diseases have proved difficult to define in the epidemiological setting, lacking an easily applied 'gold standard'.

1.4.1 Asthma

The term 'asthma' is used to describe a heterogeneous group of disorders characterised by reversible airway narrowing.[56] Some definitions also emphasise the importance of inflammation and bronchial hyperreactivity. Childhood population settings have increasingly used symptom-based definitions[57], previous reliance upon physician-diagnosis of asthma resulted in bias associated with differential health care access and diagnostic practices.[58] The prevalence of asthma has increased in the English-speaking world in the last 30 to 40 years.[43;52-54] Doctor-diagnosed asthma was 4.1% in the early 1960s in Aberdeen, and had increased to 10.2% in 1989[42] and 19.6% in 1994[55].

Defining asthma in the pre-school child is particularly complex. Respiratory symptoms in this age group result from several pathological processes.[59;60] Cohort studies have defined three clinical sub-groups, only the 2nd and 3rd have asthma; 1) transient early wheezers, 2) persistent wheezers and 3) late-onset wheezers.[61;62;63] It has been assumed that one factor explaining the increased prevalence of asthma was a rise in the prevalence of atopy. Geographical and temporal differences in the prevalence of atopy do not explain the differences in the prevalence of asthma. A higher prevalence of both asthma and atopy has been reported in Western as compared to Eastern Europe.[65] Similarly the prevalence of atopy increased from 19% to 27% between 1991 and 1996 in children in Eastern German but with no parallel increase in the prevalence of asthma;[66] with similar findings reported from Australia.[67] Pearce et al estimated the proportion of asthma cases attributable to atopy was less than 50% in childhood and adulthood.[68]

Wheeze is associated with the other allergic conditions. It is frequently reported in association with rhinoconjunctivitis or flexural eczema with more frequent, more severe[44] and more persistent respiratory symptoms.[64]

There is good evidence that exposure to tobacco smoke increases the risk of wheeze and bronchial hyperreactivity in childhood, and also that it increases morbidity in those who are already asthmatic.[69] Cook and Strachan estimate odds ratios for respiratory illnesses of 1.2 - 1.6 for either parent smoking, with higher ratios in pre-school children.[70] Such conclusions need to be treated with caution as

smoking parents have many characteristics apart from their smoking behaviour that may impact upon their child's respiratory symptoms (see discussion in Chapter Four). Smoking has not been shown to be associated with other non-respiratory allergic symptoms or atopy. Some studies have even reported a reduced incidence of eczema[71], hay fever [43;72] and atopy[73] in children exposed to tobacco smoke.

Studies from the UK[72] and USA[74] show a clear gradient by socio-economic status for childhood respiratory illness. Upper and lower respiratory tract infections in several UK cohorts are more common among children of lower socioeconomic status.[75] Bronchiolitis, has been associated with urban living, overcrowding and poor housing conditions.[76] Children of lower socioeconomic class have a higher prevalence of regular coughing, but not wheeze or asthma[75] and are more likely to be admitted to hospital with asthma.[77] Maternal factors associated with an increased risk of childhood wheezing and asthma include younger age[77-79], lack of prenatal care and longer duration of pregnancy[80]. Children with at least one sibling are more at risk of being admitted to hospital with a lower respiratory tract infection in infancy, but are less likely to have atopy.[81] Gender plays some part in the development of atopy and allergic symptoms. Boys are more likely to be atopic, more likely to have diagnosed asthma, and less likely to have undiagnosed recurrent wheeze.[82]

Examination of mechanisms to explain comorbidity between childhood respiratory symptoms and behaviour problems needs to control for environmental risk factors, including atopy, male gender and socio-economic adversity.

1.4.2 Rhinitis

Rhinitis results from inflammation of the lining of the nose accompanied by congestion, rhinorrhoea, sneezing or itching, and is less well described in childhood than adulthood.[83] Diagnosis is symptom based. The clinical consensus is that in the pre-school child atopy and infection plays an equal causal role with atopy becoming more important in later childhood. As with childhood wheeze the symptom-based diagnosis makes it difficult to distinguish between infection and allergy. Worldwide prevalence of rhinoconjunctivitis from ISAAC ranged from 0.8% to 14.9% in 6-7 year olds[84], and it appears that, as with asthma, in some countries the rates have doubled within the last 10-20 years[85].

There has been very little work examining environmental factors associated with an increased risk of rhinitis alone limiting conclusions explaining comorbidity with other allergic disease and behaviour problems.

1.4.3 Eczema

The diagnosis of eczema is made difficult by its diverse clinical patterns affected by its chronicity and the age of the individual.[86;87] ISAAC reports up to 60 fold differences in the worldwide prevalence of eczema in the 13-14 year age group[88], with the highest prevalence in areas as diverse as Scandinavia and Africa and the lowest prevalence in the former Soviet Union, Indonesia and China.[89] Between 15 and 28% of UK school age children report having had eczema,[44;90;91] making it 2 to 3 times more prevalent than 30 years ago.[42;43;92]

Atopy is the factor most strongly implicated in the development of eczema.[45] Infantile eczema is the harbinger of other later allergic disease.[47] Affluence is linked to an increased risk of eczema,[93;94] but whether this is independent of atopy is less clear. The inverse relationship reported between parental smoking and eczema may be attributed to the confounding affect of affluence.[91;95]

Children with one allergic disease are more at risk of other allergic diseases but the problem diagnosing them in childhood makes analysis more complex. Their different environmental associations need careful discrimination when examining and proposing mechanisms that may explain any associations with behaviour problems.

1.4.4 Food intolerance and food allergy

There are few estimates of the prevalence of food allergy and intolerance in either the general or the paediatric population. Epidemiological studies are complicated by the need to distinguish between parental beliefs that a particular food may have caused symptoms in their child, and proving the connection with the gold standard double-blind placebo-controlled challenge (DBPCC).[46] Bock's US cohort reported 28% of children with symptoms in their first three years attributed to a wide panel of ingested foods, but open challenges only confirmed this in 8% of all the children.[96] Most reactions occurred during the first year of life and only 0.8% of the children had

persistent problems at their third birthday. In this group of children virtually every food elicited a parental complaint, but there was a more restricted list of foods associated with positive challenges; cow's milk, soy, peanut, egg and more rarely wheat, corn and rice. The prevalence of reported food intolerance in Dutch 5-6 year olds was estimated at 3.8%. This study's inclusion criteria were over-inclusive.[97] Disentangling true causal links is clearly important.

Parents of older children also report associations between foods and symptoms in their child. Many food hypersensitivity symptoms have been confirmed in controlled trials in children, including systemic anaphylaxis, urticaria, angioedema, atopic dermatitis, rhinoconjunctivitis, laryngeal oedema, asthma, abdominal pain, nausea, vomiting and diarrhoea. Several other symptoms have been alleged but not confirmed, including migraines, enuresis, and tension fatigue syndrome, attention deficit hyperactivity disorder and sudden infant death syndrome.[96] There has been concern expressed from both sides of the Atlantic about the effects of parental beliefs about multiple food allergies on a child's psychology and growth.[98;99]

The prevalence of specific IgE to foods, either by skin prick testing, or radioimmunoassay has been estimated. There appears to be a progressive fall in the number of food specific IgE as a child gets older. The German Multicenter Allergy Study (MAS) estimates the rate of sensitisation to food allergens at the age of one year as 10%, and 3% at the age of 3 years.[100] The prevalence of children with allergic symptoms secondary to IgE mediated peanut allergy was estimated at 0.5% of a group of UK 4 year olds in a population cohort. Twice as many children had evidence of specific IgE (1.1%).[47]

One of the theories proposed to explain the increased prevalence of atopy-related diseases in the Western countries over the last 40 years is 'the hygiene hypothesis'.[65] It is postulated that early exposure to diverse infections is protective against the development of atopy by preventing the proliferation of Th2 helper cell clones by predominantly activating Th1-like helper cells.[101] There is evidence linking atopic disease with Western lifestyle;[102] the risk of atopic sensitisation is decreased with early day care, high family size, high birth order[103], and serological evidence of exposure to specific infections[104;105]. Whether increased exposure to infection is the mediator less unclear.

Other factors associated with an affluent lifestyle (eg increased birth weight and large head circumference) are associated with an increased risk of eczema[71] and raised serum IgE[106], although these associations are not confirmed by all.[107,108] The varying use of diagnostic outcomes goes some way to explaining conflicting associations; some have reported eczema[71], whereas others the presence of specific IgE[108].

1.5 Behaviour and allergic disease

1.5.1 General models explaining comorbidity

The environmental and family conditions associated with asthma throughout childhood include atopy and socio-economic adversity. Eczema is strongly associated with atopy and has environmental associations more typical of affluence. Childhood rhinitis has been less well studied. As well as these potential confounding environmental factors explaining any reported associations between allergic disease and behaviour the symptoms themselves may have behavioural effects.

In the 1950's it was suggested that allergic diseases could lead to certain psychological conditions or conversely certain psychological conditions could cause or exacerbate allergic disease.[119] Definitions of atopy and allergic disease are often imprecise, subjective, or rely upon physician diagnosis. The term atopy being used instead of eczema.[120] Many people have coexisting symptoms of allergic diseases, and there has been little, or confused attempts to control for this.

There are several possible mechanisms underlying any described comorbidity[122] 1) *Chance*: Allergic disease and childhood behaviour problems are common. Common disorders commonly coexist with the potential for wrongly assuming a causal relationship. 2) *Sampling Bias:* This may be particularly true for clinically ascertained samples, where features of treatment seeking may be greater in comorbid cases. 3) *Population stratification*: Allergic disease and behaviour problems may have different but associated risk factors. 4) *Symptom overlap*: If one uses measures such as sleep disturbance or school attendance to assess the severity of both allergic disease and behaviour problems the two will appear to be associated. 5) *Correlated error variance*: All measures of disorder have some

measurement error. When the measurement error for two disorders is correlated an association based upon only the measurement error can occur, and is more likely to happen when the same person is rating both disorders. 6) *A distinct group*: children with both sets of comorbid symptoms could represent a distinct group. 7) *Shared risk factors*: These risk factors could be environmental or genetic. 8) *Phenotypic causality*: One disorder confers a risk for the other, this may be in one direction or both.

Examining the 'phenotypic causality' model further psychological state of the child or family may affect allergic disease or its trajectory by: a) affecting the perception of allergic symptoms; b) affecting illness behaviour such as the taking of medication; c) affecting directly the symptoms or trajectory of disease, via neuroendocrine pathways. Allergic disease may affect psychological state in the child or family by; a) a direct neurological effect of neuroendocrine/cytokines or hypoxia; b) the effect of symptoms on intermediary factors like hearing or sleep; c) the behavioural effects of medication or c) the anxiety experienced by parents of the unpredictable disease.

One can postulate how the experience of feeling unwell, needing regular medical treatment and missing school would affect a child's behaviour. Some studies support this expectation[110-112], but other studies do not[113-115]. There is little evidence that specific conditions place a child at risk of particular psychological disorders,[111;116] other than conditions affecting the central nervous system.[117]

Many models of the psychological effect of childhood chronic illness upon the child and family emphasise the interaction between family functioning and the strain of the physical illness. A meta-analysis examining this identified; maternal maladjustment, decreased family cohesion, poor child self-concept, and decreased child IQ as the strongest predictors of psychological adjustment problems, with illness severity being a less strong predictor.[118]

1.5.2 Neuroendocrine models explaining comorbidity

There is evidence of a two-way interaction between the central nervous system and the immune system through multiple pathways involving neuroendocrine transmitters.[123] Cytokines are important in conditions that involve inflammatory

processes, including asthma, eczema and rhinoconjunctivitis, with associated systemic effects. Primate studies have demonstrated the psychoactive properties of the cytokine IL-1 that include loss of appetite, lethargy and somnogenesis. Stressors can affect the generation of cytokines; medical students undergoing exams have been shown to down regulate T-lymphocyte function with an altered interleukin response. The hypo-pituitary-adrenal axis and the central nervous system are operative in stress-induced suppression of anti-viral immunity and modulation of viral pathogenesis. Human studies have linked psychological stress index with increased risk of biologically verified common cold infection, feasibly affecting the frequency of viral induced exacerbations of asthma. There is also evidence of efferent pathways (autonomic and neuroendocrine) from the central nervous system to the airways, bone marrow, thymus and peripheral lymphoid tissue.[124].

'Common environment' may also affect the development of the central nervous system and the immune system. Geschwind, Galaburda and Behan hypothesised a common in utero environment (a high testosterone one) that influences both cerebral and immune system developments.[125] This hypothesis has gained further support from work demonstrating the individual and family associations between left handedness and autoimmune disease.[126]

1.5.3 Asthma and behaviour

Some studies report an increased risk of behaviour problems in children with asthma,[127-130] while others do not.[112;131-133] Some suggest that the increased risk of behaviour problems is limited to children with severe asthma symptoms.[112;129;132] Children hospitalised for difficult-to-control asthma have been found to have high rates of psychological disturbance.[134;135] Such children may be a distinct sub-group and the findings cannot necessarily be extrapolated to all children with asthma. Stein et al examined the records of children who died from asthma.[136] They identified 14 variables that distinguished the children who had died from the controls. Ten of these variables reflected the psychological adaptation of the child or family to the illness. Although they felt that the coping style of the child and family had somehow contributed to the severity of the child's asthma, they were not able to state categorically that the child's asthma symptoms had not driven the psychological mal-adaptation of the child and family. The behaviour of children severely affected by

asthma may be affected by their experience of worse symptoms or because they may be a different pathophysiological subtype.[112;132;137] Some types of asthma may be more associated with psychological problems. Two groups have reported children with non-atopic asthma having a higher rate of psychological problems but not children with atopic asthma.[138;139]

'Population stratification' may be responsible for the reported associations between asthma and psychological problems, common environmental conditions may predispose to their development. Adverse socio-economic circumstances are associated with infant wheeze, partly mediated by parental smoking[69] and low birth weight.[80] Upper and lower respiratory tract infections had been shown in several UK cohorts to be more common among children of lower socioeconomic status.[140] Children of lower socio-economic status are more likely to be admitted to hospital with asthma.[77] Deprivation at least partly explain behaviour problems in childhood.[15] Any examination of the associations between asthma and behaviour therefore needs careful control of environmental factors. Work examining the associations with smoking and cot death have illustrated how difficult it is to adequately control for social circumstances.[24]

Parents that describe asthma symptoms may also be more likely to describe psychological disturbance. Some studies that have depended upon parental (usually maternal) ratings of behaviour problems that have reported higher rates of behaviour disturbance in children with asthma but not confirmed by observer or child ratings.[141] Perrin additionally found no relationship between the child's asthma severity and parent ratings of their child's psychological disturbance.[142]

There may be a genetic basis for the association between some psychological traits and allergic disorders.[143] Hyperactivity[144] and atopy[145] have complex patterns of inheritance, neither allergic nor psychological phenotypes are due to a single gene pattern of inheritance. There are three plausible genetic mechanisms whereby common genetic influences may arise. 1) One or more of the genes coding for a vulnerability to atopic disease and a particular psychological phenotype may lie very close to each other on the same chromosome i.e. linked. 2) A gene may code for both the allergic and the psychological phenotypes i.e.phenotropy. This may be true for all or only a subgroup of people people. 3) The effect may be mediated

phenotypically; one condition with a strong genetic basis may predispose the child to develop the second condition.

The families of children and adults with allergic diseases have been examined for increased prevalence of psychological and behavioural problems. The first degree relatives of children severely affected by asthma have been shown to be at increased risk of affective disorders, post traumatic stress disorder, antisocial personality disorder and substance abuse.[135] Evidence from first degree relatives alone in such a clinical population is insufficient to support a substantial claim of genetic linkage, given the potential of confounding from common environment. Other studies have attempted to control for environmental factors by examining second degree relatives, and found an increased prevalence of eczema and rhinitis, but not asthma.[146]

Twin studies have examined the differential effect of genes and environment. Wamboldt examined 207 pairs of school-age twins.[143] They used Achenbach's CBCL/4-18 to identify problem behaviour that was summarised into three scores, externalising and internalising behaviours and total problem behaviours. They identified children with allergic symptoms using a 6-point questionnaire. A strong within-subject correlation was reported between the allergic-symptom score and all three subsets of behaviour. They also reported that a monozygotic twin of symptomatically allergic child was more likely to have behaviour problems than an dizygotic twin. With statistical modelling they estimated that 77% of the covariance between atopy and internalising symptoms was explainable by genetic factors. Simonoff reanalysed these data and cautioned against accepting the results, because of insufficient power to dismiss either unidirectional or bi-directional 'phenotypic causality', these data did not clarify whether behaviour was causing allergic symptoms or allergic symptoms were causing behaviour problems.[122] The study's conclusions are further weakened by the definition of atopy.

The evidence that the symptoms of asthma affect behaviour is weak. One may expect repeated symptoms of breathlessness to be associated with anxiety[147] but studies in children[148] and adults[149] with asthma have failed to confirm this relationship. Children with severe asthma, most notably those who have had

significant episodes of hypoxia, have been shown to have secondary deficits in memory and visuo-spatial skills.[150]

Psychological problems in child or family may directly affect allergic disease or the trajectory of allergic disease. A patient's psychological state affects how they report asthma symptoms. More anxious and more depressed people are likely to report worse symptoms of asthma. Importantly these reports are not corroborated by more objective measurements of bronchial hyperreactivity.[151-153] An child's psychological state may also affect the way they act upon the symptoms.[154;155] A small group of asthmatic children with a high level of anxiety and dependence were more likely to use excessive medication, independent of the severity of their asthma. The child's personality and excessive use of medication were both related to a highly cohesive family type. The authors remained unsure as to whether the family characteristics were intrinsic to the family or secondary to the stress of having an unwell child.[156] The issue is thus further complicated by the effect of the psychological and physical health of a parent on their reports of their child's allergic symptoms and behaviour.[157-159] Wamboldt was unable to show any relationship between child-reported anxiety and the severity of the child's asthma. Parental reports of their child's anxiety however were correlated with the severity of their child's asthma. Parental self-report of their own asthma symptoms was a stronger predictor of the child's anxiety than the severity of the child's asthma.[148] Perrin et al found no relationship between objective measurements of asthma severity and psychological problems, but did find that there was an association between parental ratings of asthma severity and higher ratings of child behaviour problems.[142] This is in contrast to the general underreporting by parents of children's internalising symptoms.[160] A child's asthma may indeed be more distressing to the asthmatic parent than to the child. Eksi and colleagues showed that behaviour problems were more common in children with mild and moderately severe asthma.[161] Behaviour problem scores for the asthmatic children however were also significantly correlated with parental friction and an unsatisfactory relationship with their siblings, suggesting that family environment exerts a moderating effect.

In a carefully controlled study parental stress has been shown to be correlated with subsequent wheeze in infants with a family history of allergic disease, although only

a small effect size was reported (RR 1.4 95%CI, 1.1-1.9). A direct mechanism is proposed operating from parental stress to infant wheeze.[162]

In summary although there appears to good evidence that children with asthma are at greater risk of externalising and internalising symptoms it is unclear whether this is confined to children with severe symptoms of asthma. Children with hard to control asthma, or who have died from asthma do appear to have greater rates of psychopathology, but the direction of causality remains unclear. Independent measures of behaviour and asthma appear to be important if a further source of bias is to be avoided. Some of the described comorbidity appears to be attributable to shared risk factors, the evidence from family studies points more strongly to shared environmental factors than shared genetic factors. As for other chronic illnesses family functioning appears to be playing a moderating effect between asthma symptoms and psychopathology. Parental stress appeared to be associated with subsequent infant wheeze, and behaviour problems in children with asthma were more related to family functioning than the severity of their asthma.

1.5.4 Rhinoconjunctivitis and behaviour

The signs and symptoms of allergic rhinitis include sneezing, nasal discharge, mouth breathing, snorting and throat clearing. Although there are associated nasal mucosa signs, the diagnosis is more dependent on child or family rated symptoms than asthma or eczema, making any reported associations with psychological problems susceptible to bias because of the dependence upon parental report.

There is no evidence that behaviour problems affect the development of rhinoconjunctivitis. Most work that has reported an association between rhinoconjunctivitis and psychological problems has hypothesised three mechanisms: 1) a direct effect of the nose and eye symptoms on cognitive functioning with an associated behavioural effect or a behavioural effect mediated by the effect on hearing or sleep. 2) a neurological effect of cytokines produced by the inflammatory process of rhinoconjunctivitis. 3) a common genetic basis of temperament, or psychological problems and rhinoconjunctivitis.

Allergic rhinitis is linked with an increased risk of intermittent hearing loss, secondary to Eustachian Tube dysfunction. There is good quality cohort evidence of behavioural and developmental sequelae of middle ear disease.[163;164] There is also indirect evidence of the effect of hearing loss upon behaviour from studies that focus upon short term improved behaviour after the early treatment of glue ear.[165] The potential effect of symptoms upon sleep will be discussed later.

The mechanisms explaining the reported link between introversion and hayfever (but not eczema or asthma) in unselected college students remains unclear.[166] Kagan and colleagues describe a family study that supports some common genetic basis for introversion, rhinitis and eczema.[146] They examined children in their second and third year of life and identified them as inhibited (shy) or uninhibited (sociable), using laboratory controlled encounters with strangers and novel situations. They then administered questionnaires to the first and second-degree relatives of the children. In the relatives of shy children there was no increased prevalence of asthma, but there was a greater prevalence of hayfever and eczema. This may provide evidence that the complex genetic factors mediating extreme degrees of shyness also may be responsible for influencing immunological vulnerability to eczema and hayfever.

In summary there is evidence of the association of rhinitis with Eustachian Tube dysfunction, subsequent hearing loss and behaviour problems. There is also evidence of a common genetic basis of inhibited temperament and rhinoconjunctivitis.

1.5.5 Eczema and behaviour

Genetic factors have been proposed as likely shared risk factors between eczema and temperament. Kagan's family study, described in the section on rhinoconjunctivitis, reported an increased risk of eczema in the first degree relatives of inhibited children.[146] The symptoms of eczema have been shown to affect children's behaviour. There have been reports of the increased prevalence of externalising symptoms in children with eczema. Roth administered behaviour tests to children in the remission phase of their eczema. The children with eczema were recruited from a dermatology clinic, with an inadequately matched control group. They reported an increase in attention problems within the group with eczema.[120]

Research from population and clinical studies have reported an increased prevalence of internalising symptoms (fearfulness) and sleep problems in children with eczema.[167-169] The extent of itching and scratching caused by the eczema has been strongly correlated with sleep disturbance.[169]

In a study looking at adults with a variety of itchy skin diseases including eczema patients were asked to assess the 'itchiness' of their condition. Their 'itch score' correlated well with their score on a depression scale.[170] The authors suggest that this is evidence in favour of depression affecting perception of physical symptoms. There again is the problem of assessing the direction of causality. Does depression affect one's perception of itchiness or does being itchy make one more likely to be depressed?

Finally, as eczema is a more prevalent condition in infancy there has been some work examining the effect of the child's symptoms upon the carer. Daud[168] showed no effect of severe atopic dermatitis on the security of the mother-child attachment, but did show an increase in minor behaviour problems in the child and distress in the mother. Pauli-Pott and colleagues[171] described mothers of infants with atopic dermatitis as more depressive, anxious and overprotective. The mothers were also more likely to describe their child's emotional behaviour negatively. This study illustrates the complexity of dissecting the causal relationships between the emotional state of both child and mother, and the atopic disposition and allergic symptoms of the child.

In summary there is some evidence of a common genetic basis of inhibited temperament and eczema and rhinoconjunctivitis. There are some studies showing that the symptoms of eczema may affect children's behaviour directly. Reports from work with adults indicate that perception of itching and psychopathology appear be closely interconnected. Given the apparent effect of infant eczema upon the mother's mental state, care should be taken when reliant upon only maternal reports for allergic and behavioural symptoms. Any further investigation of the increased prevalence of externalising behaviour in children with eczema needs better selection of cases and controls.

1.5.6 Sleep disturbance as a mediating effect of allergic symptoms upon behaviour

It is recognised that children with asthma, eczema and rhinitis may have symptoms that disturb their sleep, indeed the ISAAC questionnaire has 'frequency of sleep disturbance' as a measure of severity of two of these conditions.[89] The general literature on the relationship between childhood sleep problems and behaviour problems is complicated by a lack of clarity on what constitutes a sleep problem, and frequent reliance on parental definitions of problematic behaviour, only improved in some research with definitions based upon frequency of behaviours.[1] Most studies have concentrated upon waking and/or settling problems.[172] More specific problems such as teeth grinding, nightmares, night terrors, sleep walking and talking are not considered here, as their relationship with allergic symptoms seems less plausible.

The relationship between sleep disturbance and daytime behaviour problems is likely to vary between children and conditions. Many sleep problems co-occur making it difficult to tease apart any daytime effects of specific problems. It seems that sleep disturbance may occur as part of a wider profile of behaviour problems, but is also commonly reported as an isolated problem. Stevenson reviews four models of how sleep disturbance and daytime problems may be linked. Sleep disturbance may be caused by daytime problems; children with hyperactivity, depression and visual handicap may have sleep disturbance as a result of their wider problems. Sleep disturbance and daytime problems may have a common cause, children with Tourette's syndrome have been consistently reported with a wide range of sleep problems, probably as a result of disordered brain functioning. There was less evidence for the third model of sleep problems and daytime behaviour problems with different, but correlated causes. He postulated that the reported link between children with frequent temper tantrums and concurrent sleep disturbance may be due to family and social factors such as marital stress, maternal depression and poor child health. The fourth model best explains how allergic symptoms could lead to behaviour disturbance, mediated by sleep disturbance. He cites the obstructive sleep apnoea experienced by many children with Down's syndrome and its contribution to their behavioural disturbance.[172] Quine reported some indirect evidence that sleep problems may cause daytime problems. The successful management of sleep disorders in children with learning difficulties was

associated with a parallel improvement in daytime behaviour.[173] Similar findings were reported in a group of toddlers treated for sleep problems.[174]

It is difficult to separate the direct behavioural effects of allergic symptoms and those mediated by disturbed sleep.[164] Allergic rhinitis predisposes children to obstructive sleep apnoea.[175] The relationship between obstructive sleep apnoea, disturbed sleep and daytime poor cognitive functioning is well established, with good evidence of resolution with treatment.[177] Much of the work on eczema has concentrated on the effect on children's sleep, rather than the potential direct effect of itching and discomfort upon the child's behaviour. Dahl et al reported an association between sleep-related problems and difficulties in morning waking, daytime tiredness, irritability, and aggression in a cohort of school-age children with eczema.[178] A UK group found problems with 'night waking', but not with 'settling' in a younger group of children with eczema, compared with control children. Increased scratching was associated with more 'night waking'.[169]

Asthma has also been shown to affect behaviour via sleep disturbance. There is a detrimental effect of nocturnal asthma symptoms on sleep, and the subsequent psychological and learning ability of the child. As well as this indirect effect, there appears to be a direct effect of the symptoms on daytime functioning. When asthma symptoms were successfully treated objective measures of both the child's sleep and psychological functioning improved.[164] Israeli data from a community survey of children however showed no increased prevalence of sleep disturbance in children with physician-diagnosed asthma. The group were too young (aged 4-48 months, with mean age of the asthmatic children reported as 23.1 months), for many of them either to have a robust diagnosis of asthma or an established sleep pattern.[179]

1.5.7 Adverse drug effects as a mediating effect of allergic symptoms upon behaviour

There are few systematic studies of the effect on behaviour of medication used to treat allergic symptoms. The mainstay of treatment of acute exacerbations of asthma is inhaled or nebulised ß-agonists, usually salbutamol. Younger children are sometimes prescribed oral salbutamol, outside national guidelines, and product information states that '20% of these children may experience excitement'.[180] Adult

studies report adverse effects on the central nervous system leading to appetite suppression, headache, nausea, sleep disturbance and postural tremor.[181;182] Parents anecdotally report behavioural changes in their children akin to hyperactivity following inhaled salbutamol, but this finding was not confirmed by a recent short trial, although the authors acknowledged that frequent use of the drug could have different effects.[183]

Corticosteroids are administered either regularly in inhaled form, or orally or parenterally to manage asthma and rhinitis and topically for eczema. They have the systemic side effect of adrenal suppression.[184] Studies examining their adverse behavioural effects are limited to the oral route. A behavioural 'dose effect' has been demonstrated. Behavioural side effects (anxiety, aggressive behaviour and hyperactivity) were twice as common in a group of children treated blindly with Prednisolone 2mg/kg daily compared to the group treated with 1mg/kg, with comparable resolution of respiratory symptoms.[185] However there appear to be no long term effects on behaviour or cognitive function.[186;187] Theophyllines, now rarely used in the UK have largely reversible cognitive effects.[186]

Antihistamines are used in the treatment of rhinoconjunctivitis, urticaria, and eczema. There is evidence that first generation antihistamines (H-1 antagonists) (eg diphenhydramine) are sedating. H-1 antagonists are lipophilic and readily cross the blood brain barrier causing performance deficits in adults on tests of divided attention, working memory, vigilance and speed, that persist the next day.[188] Second and third generation H-1 antagonists are more lipophobic, and thus have less sedative effects. The sedative effects of the symptoms of rhinoconjunctivitis are likely to be worse than the effects of second and third generation antihistamines (such as loratidine, astemizole and fexofenadine). Adult studies reported improved vigilance, back into the upper level of the normal range.[189] This work has not been consistently confirmed in children.[190]

H-1 antagonists are used to treat the itch in eczema. Any specific antipruritic action is doubtful, and any effect is likely to be due to sedation. This makes a secondary behavioural effect very likely, although this has not been systematically assessed.[191]

In summary there is a biologically plausible mechanism for the behavioural effects of many of these drugs. Some studies in adults show central nervous system effects. There is anecdotal evidence from parents of adverse behavioural effects on children but there are few studies in childhood which only show no effect or a short-term behavioural effect.

1.5.8 Behaviour and allergic symptoms – summary

Common environments are a likely explanation for the co-occurrence of allergic symptoms and behaviour problems. The particular elements of environment increasing the risk of certain diseases have proved very difficult to separate.

There is some evidence for a genetic mechanism linking allergic symptoms and internalising and externalising behaviour problems within children. There is a small amount of evidence from families of a genetic linkage between shyness and eczema and hayfever. There has been some attempt to describe links at the neuroendocrine level. There is an increased risk of autoimmune disease in left handed people, the causal hypothesis proposed is a common high testosterone in utero environment. There is also biologically plausible evidence of autonomic and neuroendocrine pathways between the central nervous and immunological system.

There is conflicting evidence that chronic illness in childhood increases the risk of psychopathology in child and family, and probably family and child factors are more important than the illness itself. There may be some specific effects of symptoms such as hearing loss secondary to rhinitis and the direct effect of severe asthma symptoms particularly if associated with episodes of hypoxia with subsequent memory and cognitive defects. The effect on sleep of symptoms of eczema, asthma and rhinoconjunctivitis may be an exception, although the understanding of the relationship between sleep disturbance and daytime problems remains limited. Daytime behavioural sequelae have been demonstrated in children with obstructive sleep apnoea secondary to rhinitis, in children with nocturnal itch with eczema, and nocturnal cough and wheeze secondary to asthma. Sleep disturbance improves with treatment of all three sets of symptoms, with apparent ensuing beneficial effects on daytime behaviour.

Drugs used to treat the allergic symptoms may cause behavioural effects. There are substantial anecdotal reports but far less robust evidence. The one study examining the effect of nebulised salbutamol on behaviour showed no effect. Systemic corticosteroids do affect children's behaviour but only in the short term. First generation H-1 antagonists (but not second and third generation), have a sedative effect but their effects on behaviour have not been described.

There is evidence that both the child and parents' perception of symptoms and reaction to those symptoms is affected by certain psychological traits. It is not clear whether a child's eczema affects the mother's emotional state and her attitude to her child.

This review points to the need for further studies of non-clinic based populations of adults and children, employing objective measures of atopy and allergic disease, in vitro and in vivo measures of specific IgE, validated symptom-based questionnaires, lung function tests, and bronchial challenges. There is a similar need for validated measures of temperament, behaviour and psychological morbidity, supported with measures that are more objective where practical. This study aims to this.

1.6 General foods and behaviour

1.6.1 Background

In this small additional review I systematically examine the evidence for any short-term and long-term effects of foods, excluding food additives, as I have already reviewed this earlier in this introduction. I will include both the beneficial and detrimental effects of specific nutrients, foodstuffs, meals and eating patterns. I do not examine the research information that reports the detrimental cognitive and behavioural effect on children of poor nutritional status. I discuss some of the effects of breast or formula feeding upon sleep, but I do not examine any further the beneficial effects of breast-feeding. I examine some of the research around food and infantile colic given the interaction with temperament and and the continuity with later childhood behaviour. The work examining the effect of sucrose on infants is included for its insight into the possible effects later in childhood.

1.6.2 Search strategy

A MEDLINE search was carried out for relevant trials published from 1985 to 2005, EMBASE from 1974 to 2005, PsychInfo from 1985 to 2005, and the whole COCHRANE library. Key words and (MeSH) terms included food, behavior, autism, sleep or sleep disorders, hyperkinesis, attention deficit hyperactive disorder, food additives and behavior change. Search limits were placed with English Language and children. Manual searches were then performed of bibliographies.

1.6.3 Effects of foods on infants

There are three strands of research describing the behavioural effects of food on infants. The first is hospital-based research reporting the analgesic effects of sucrose upon infants undergoing painful procedures. The second concerns the sleep behaviour of breast and formula fed infants. The third examines associations between cow's milk protein and carbohydrate intolerance and infantile colic.

There is a continuum of behaviour from infancy through to childhood. Infants who had infantile colic continued to have more interactional and behavioural problems at the age of 3.[382] Successful behavioural interventions appear to have lasting effects[383] although there appears to be no evidence of the long term effects of successful dietary interventions.

There is good evidence, collated in a recent Cochrane Review that infants orally (but not nasogastrically) administered sucrose solutions during painful procedures exhibit less behavioural (the mean percentage time crying, total cry duration, duration of first cry, and facial action) pain indicators than control groups receiving placebo. This is thought to be mediated by the endogenous opioid and non-opioid systems.[384] There is no work examining the possible common mechanisms of the effect of sugar in this age group and later childhood.

There is a different pattern of crying and sleep exhibited by breast fed as compared to formula fed babies. This remains after controlling for maternal socio-economic background and age. Breast fed babies have been shown to increase their length and frequency of crying between 2 and 6 weeks, whereas formula fed babies peak in their crying at 2 weeks of age. At 6 weeks of age breast fed babies slept 80 minutes

less than formula fed babies every 24 hours. It is suggested that beta-casomorphins derived from beta-casein may sedate formula fed babies, or that hormones contained in breast milk including thyroxine may influence behaviour.[385] Other work exploring the differential risks posed by infant feeding practices for sudden unexpected death of infancy has examined sleep effects. Horne reported that breast fed babies were more arouseable in active sleep, but not quiet sleep, than formula fed babies.[386]

There is other work looking at the effects of composition of formula feed on the sleep patterns of low birth weight babies. It is suggested that brain serotonin levels, which are associated with increased amounts of quiet rather than active sleep, are increased following the flux of the precursor tryptophan across the blood-brain-barrier. This is related to the plasma concentration of tryptophan relative to other neutral large amino acids. Postprandial surges of insulin promotes the utilisation of large amino acids, except tryptophan. Thus following a higher carbohydrate meal the relative concentration of tryptophan increases. The amount of quiet sleep in a group of low birth weight babies was increased with increasing amounts of non-protein energy in their feed as in most formula milk, this was most noted if the baby was prone.[387] Again there is little continuum from this research to the possible effects of cow's milk in older children.

Infantile colic is characterised by excessive crying in healthy thriving infants in the first months of childhood and is estimated to affect between 5 and 19% of infants.[388] It is likely that infantile colic is a group of heterogenous conditions, all with excess crying as the final pathway. There are two main theories expounded one that it is associated with painful gut contractions, the other that it is the result of parent-child interaction, with difficult child temperament as part of this. It may also be associated with Western 'pulse' feeding and reduced carrying of infants. Crying associated with the presence of cow's milk either in infant formula[389] or breast milk[390] has been reported as a feature of cow's milk protein allergy. Casein and whey based hydrolysed formulae have both been shown to reduce crying in unselected populations with infantile colic.[391] A second cause of excess gastrointestinal gas, due to unabsorbed carbohydrates has been suggested. Apple and pear juices have higher sorbitol and fructose to glucose ratios than grape juice and are associated with higher concentrations of breath hydrogen and increased crying times and

reduced sleep times.[392] Given that the peak incidence is between 1 and 4 months, a time when few babies are given juice, it is unlikely that carbohydrate malabsorption is a significant cause of infantile colic.

1.6.4 General foods

There are only a few papers examining the effects of general foodstuffs upon children's behaviour, using the hypothesis of food allergy. Egger's study[219] from a UK based group gave some support for the adverse behavioural effects of general food stuffs. They employed a three stage methodology. Children diagnosed with hyperactivity had their behaviour assessed on a few foods diet based upon a limited selection of meat, fruit and vegetables (so called oligoantigenic). The children whose behaviour improved on this diet underwent open challenges. Thirdly they then underwent a double blind placebo controlled challenge with one foodstuff, chosen pragmatically. Global assessments by clinic staff and parents assessed the children's behaviour as worse during the active challenge than the placebo challenge, this was not corroborated by psychology tests. Carter, from the same group, more recently replicated Egger's findings.[229b] Foods implicated included; chocolate, cow's milk, cow's cheese, oranges and other fruit, wheat, tomatoes and egg. Both papers speculate on potential mechanisms, favouring an allergic hypothesis acknowledge that behavioural deteriorations may have been mediated by physical symptoms.

1.6.5 Epilepsy

Egger also reports on a mixed group of children with migraine and/or epilepsy and/or hyperkinetic behaviour.[393] None of the children with epilepsy alone improved. His results are vulnerable to the same criticisms as his earlier study of potentially inadequate blinding and/or placebo controls and problems with diagnostic criteria especially in the epilepsy and migraine group.[219] Uhlig with Egger more recently reported EEG changes on open challenge with foods, following a similar few foods diet.[394] They implicate a wide range of foods (sugar, wheat, cow's milk, banana, egg, citrus, cocoa, beef, pork and oats) and because of this claim that a immunological mechanism is the most likely, but with little more to support this mecanism. Double blind placebo-controlled trials are needed.

It is also worth mentioning epilepsy and the ketogenic diet, although this is evidence of a direct neurological effect of dietary consequences rather than behavioural effect of diet. It appears that a diet high in fat and low in carbohydrate will through the production of ketone bodies exert enable the control of some people's seizures. The exact method of action is still debated, and although Tallian in her review[395] reported uncontrolled studies confirming the diet's efficacy there remains also in this areas still a lack of good quality controlled studies.

1.6.6 Sugar, aspartame and behaviour

It is still a popular belief that sugar and/or the artificial sweetener aspartame adversely affects the behaviour of children with or without attention deficit disorder, or incarcerated adolescents.

It is hypothesised that aspartame affects behaviour by the resultant elevation in plasma phenylalanine from its metabolism thus altering the transport of essential amino acids to the brain. Suggested mechanisms of the effect of sugar include the immediate effects of a rise in blood sugar, or reactive hypoglycaemia several hours after ingestion. Mild reductions in plasma glucose and associated increases in epinephrine have been shown to have adverse effects on cortical functioning in healthy children as assessed by auditory cortical evoked potentials.[396] Girardi et al[397] hypothesised that the catecholamine surge (epinephrine) in response to the post prandial reduction in plasma glucose (3-5 hours post ingestion) may mediate behavioural deterioration. In their study children with attention deficit disorder and their controls both showed a similar deterioration in the continuous performance test (testing attention and impulsivity), however children with attention deficit disorder had only 50% of the epinephrine response of the control group.

Most earlier studies did not find adverse behavioural effects of sugar,[398-400 401 402;403] some studies have perhaps surprisingly shown small behavioural improvements.[404-406] Benton's team reported on two studies[407;408] that showed an improvement of attention, short-term memory and information processing following a glucose load. They proposed that this may be due to the rise in available cerebral glucose, an effect of the ensuing rise in insulin or the cholinergic agonist and opioid antagonist effect. There are a small number of studies that have shown a modest deterioration

in attention or behaviour following a sucrose challenge compared to placebo. Methodological differences explain some of the conflicting findings, including timing of assessment and the argument that sucrose or glucose may have different effects if given alone after fasting, or with varying amounts of protein, carbohydrate or fat, or if given as part of a calorie constant meal.

Work from juvenile delinquents has focused upon aggressive behaviour as an outcome measure. Virkkunen's work demonstrated increases blood glucose and insulin levels following glucose tolerance tests in prisoners with antisocial personalities.[409] Gans et al showed lower blood glucose levels and increased insulin levels following oral sucrose challenges in 'juvenile delinquents' as compared to non-delinquent controls.[410] There was no concomitant mood change, which made them doubt its clinical relevance. They also suggested that the biochemical changes might have been due to liver damage secondary to alcohol, drugs or infections.

Wolraich reported most recently no adverse response following the double blind administration of sucrose or aspartame to a group of 3-10 year olds, half of whom were unselected and half of whom were reported as being 'sensitive' to sugar. The study also reported the slight rise in phenylalanine levels following the ingestion of aspartame were unlikely to produce any behavioural effects.[411]

A review of the research to date in the late 1980s concluded that there was no effect of aspartame on the behaviour of children.[412] Shaywitz reviewed the literature which followed[406] uniformly also reporting no behavioural or cognitive effect and then in a carefully controlled trial confirmed his conclusions with a further group of children.[413] Zametkin examined whether loading boys with ADHD with D-phenylalanine would enable increased production of dopamine, and thus improve their behaviour, but he found no effect.[414]

1.6.7 Coeliac disease

Coeliac disease is a permanent gluten-sensitive enteropathy. The small bowel changes resolve on complete avoidance of gluten-containing foods, wheat, rye and barley and arguably oats. Catassi reviews the relatively recent development of sensitive serological markers for this condition (antigliadin, antireticulin and

antiendomyseal IgA antibodies) which have enabled epidemiological studies to be undertaken, and the recognition of atypical or even silent versions of this condition.[415]

The typical presentation is of a child between 6 and 24 months who presents with impaired growth, abnormal stools, abdominal distension and unhappiness or misery. It is likely in these cases that the behavioural disturbance with which these children present is mediated by the physical effects of the disease. Fabiani reported on an epidemiological study of Italian school aged children.[416] Some of the children with positive antibodies that appeared to be asymptomatic, on closer questioning did reveal decreased psychophysical well being; including a tendency to depression, fatigue, irritability and impaired school performance. Few studies claiming a behavioural effect of gluten or gluten-containing foods ensure that none of the participants have 'silent' coeliac disease. Other neurological connections with coeliac disease include rare reports of epilepsy with and without intracranial calcifications secondary to coeliac disease. Seizure control improved on adherence to a gluten free diet.[417]

1.6.8 Effects of gluten and casein on children with autism

Children diagnosed with autistic spectrum disorders are a specific group with a triad of impairments within social functioning, flexibility of thought and behaviour and communication.[418] The prevalence lies between 0.7 to 21.2 per 10,000 children.[419] It has been suggested that peptides from gluten and casein may have a causal or exacerbating role in the features of autism, due to excessive opioid activity linked to these peptides.[420] A Cochrane review from 2004[421] reported only one good quality randomised controlled trial by Knivsberg's team.[422] They reported a small randomised study, with blind assessment of outcomes after a year long trial of gluten and casein free diet with control children also with autism maintained on normal diet. Outcome measures included number of autistic traits, linguistic age in months, non-verbal cognitive level and motor problems. Only 'autistic traits' showed a significant improvement in the intervention group. Further, well designed adequately powered trials are needed before such diets can be recommended.

1.6.9 Micronutrients

Some have claimed an increase in IQ in children who have been given micronutrient supplements (vitamins and minerals).[423-425] Others have failed to replicate these findings.[426;427] More recent findings clarify this. It appears to be only children with a nutritionally inadequate diet who benefit from supplements, the mechanism of action being by reversal of the effects of poor nutritional status.[428-431]

1.6.10 Essential fatty acids (EFA)

The hypothesis that hyperactive behaviours may be at least partly due to essential fatty acid deficiency arose from a survey carried out by the Hyperactive Children's Support Group 20 years ago.[432] They reported that children with hyperactive behaviours had symptoms similar to essential fatty acids deficiency; dry skin and hair, excess thirst. Linoleic acid (n-3 or omega 3) and alpha-linolenic acid (n-6, or omega 6) are both essenial fatty acids from which long chain polyunsaturated fatty acids (LC-PUFAs) are generated including arachidonic acid (AA) and dihomogamma linolenic acid (DGLA) (n-6) and eicosapentaenoic acid (EPA) and docosohexanoic acid (DHA) (n-3). Neuronal membranes are largely made up of phospholipids. These in turn affect the structure of membrane bound receptors and thus neurotransmitter functioning. They are also converted into local hormones eicosanoids (including prostanoids and leukotrienes). There is animal model evidence of the interruption of neural integrity and function if a foetus or infant is deficient in these two EFAs.[433;434] There is also evidence that children with ADHD, compared to controls have lower plasma levels of n-3, and possibly n-6 LC-PUFAs.[435 433]

Evening primrose oil has been used as a source of n-6 and fish oil as a source of n-3 LC-PUFAs. Sources of both these EFA are relatively deficient in the Western diet, but why children with hyperactive behaviours, or a subgroup of them should be particularly deficient in them remains at the speculative level, and may be constitutional or/and environmental. Supplementation to unselected children with gamma linolenic acid (GLA n-6) appeared to have no[57] or only modest[437] benefit. Subsequent studies have suggested that n-3 LC-PUFAs may be more important in ADHD than n-6, and treatment may need to be as long as 3 months, to enable neurological repair.[434] More recent research with a combination of DHA, EPA, AA

and DGLA (weighted in favour of the n-3 fatty acids) was associated with a reduction in ADHD behaviours.(Burgess 1998 cited in[438]) Other work with only DHA reported no improvement in behaviour.[438;439] Richardson reported improved cognition and behaviour from a similar combination of n-3 and n-6 LC-PUFAs, placebo controlled, with children with diagnoses of specific learning disorders including ADHD, dyspraxia, autism and dyslexia. Most workers continue to conclude that the quality of the research is not adequate to as yet make any dietary recommendations.

1.6.11 Eating patterns

The only substantial body of work examining eating patterns has been work on the effects on learning of breakfast, reviewed recently.[440] Much of the work originates from socioeconomically deprived neighbourhoods in the USA, or from developing countries. Most focuses upon the effects of school feeding programmes. All the studies have found it difficult to control a nutritionally heterogeneous group. Gibson and Green particularly identify differing glycogen stores within the group as being one potential factor explaining differing outcomes.[441] There is no doubt that school feeding programmes improve school attendance, and performance, there remain significant gaps within the research to say whether this is a feature of the food and timing of eating, or other aspects of the programmes.

1.6.12 Summary

Infantile colic, with its continuity to difficult behaviour in later childhood can be as a result of exposure to cow's milk protein and is improved by change to a hydrolysed formula. Infantile colic may also be exacerbated by malabsorption of certain fruit juices. Infant sleep patterns are affected by feeding, with potential for longer-term effects.

Sucrose has been shown to reduce the crying of infants undergoing painful procedures. In older children sucrose has not been shown adversely affect behaviour, and may be associated with improved information processing and attention. The widely used artificial sweetener aspartame has not been shown to adversely affect behaviour.

There is now good evidence that children may have undiagnosed coeliac disease, which is likely to impact upon their learning and behaviour, although insufficient understanding of the natural history of silent or sub-clinical disease to recommend screening programmes.

The only work that supports supplementation of children's diets is that around the essential fatty acids alpha-linolenic and linoleic acid, and this area is also awaiting good quality controlled trials before dietary recommendations can be made.

Gluten and casein-free diets may result in less autistic behaviour in children with autism, the mechanisms being less clear. There is a need for more good quality trials in this area.

There is only a small amount of evidence that food allergy may cause behaviour problems, and/or exacerbate migraine or epilepsy. Any attempt to duplicate this research poses serious methodological challenges.

There is limited research that a minority of children with behaviour problems, such as ADHD may be intolerant of foods. Any attempt at a few food diet should be done with the supervision of a dietitian and a mental health professional. It seems that current research for all children can only recommend a regular, balanced, nutritionally adequate diet.

1.7 The effects of artificial food colourings and benzoate on hyperactivity and allergic symptoms

A study by Feingold reported behavioural improvement in a group of 25 children following adherence to a diet.[192;193] The diet was devised in the department of allergy in the Kaiser-Permanente Medical Center in San Francisco originally for the treatment of salicylate-sensitive patients. It is free of artificial colourings and preservatives, and several fruits and vegetables thought to be high in naturally occurring salicylates. Feingold's study was uncontrolled with a group of children with learning difficulties and behavioural problems. He claimed 68% improvement which was dramatic and immediate.

Conners places in context the political, industrial and medical response to Feingold's claims.[194] The 'National Committee on Hyperkinesis and Food Additives' was founded and sponsored by 'The Nutrition Foundation' an educational and research organisation supported by the USA food industry. They assembled a group of medical and behavioural scientists who expressed concern at Feingold's conclusions, mainly that the results could all be explained by the placebo effect but also the potential detrimental nutritional impact of the diet. To date there remains world-wide concern about the potential detrimental effects of artificial additives on children's behaviour and health. Parent support groups such as the Hyperactive Children's Support Group continue to advocate Feingold's Kaiser-Permanente diet.[195]

1.7.1 Mechanisms

Evidence to explain the effects of artificial additives on behaviour or allergic symptoms is sparse. In vitro studies show the biological activity of some food dyes[196] and their potential to affect neurotransmitters.[197] Red 3 has been reported as affecting neurotransmitter uptake in synaptosomal preparations.[198] Shaywitz et al found behavioural effects on rat pups, but with no dose-response.[199]

Most studies on the effects on children's behaviour have not found an association between response and atopy, leading to the conclusion that any effect is likely to be pharmacological rather than IgE mediated.[200] Research on urticaria demonstrated an associated between artificial food additives and non-IgE mediated histamine (and other mediator) release.[201] An in vitro study demonstrated that circulating basophils released histamine in a non-IgE dependent response on exposure to azo dyes; and in an in vivo study in which high doses of tartrazine were administered to normal subjects demonstrated significant histamine.[202] Despite this the public and professionals continue to link allergy, artificial food additives and behaviour disturbance.

1.7.2 The effects of artificial additives upon allergic symptoms

Food additives may be responsible for exacerbations of eczema, asthma and rhinitis, and provoke urticaria, even if the effects are not IgE mediated.[203] Sulphite additives

have been associated with serious asthmatic reactions.[204] Tartrazine has been shown in selected groups of children to increase bronchial reactivity.[205] Other dyes and preservatives (including sodium benzoate and sodium metabisulphite) are reported to provoke urticaria and asthma.[206] Fuglsang examined a population-derived sample to estimate the prevalence of reproducible reactions to food additives.[207] 6.6% of the total responding population suspected intolerance to food additives. After open and then double-blind challenges only 6 children proved to have positive reactions (4 with synthetic colourings, 1 to a preservative and 1 to citric acid) and none of these results reached statistical significance. The group estimated the prevalence in this paediatric population of true exacerbation of symptoms with artificial food additives at between 1-2%, making many population-derived challenge study potentially under-powered for investigating any effect upon allergic symptoms. There continues to be dispute over whether azo and non-azo dyes and benzoates provoke reactions.[208] There are methodological criticisms of much of the work but the probable low prevalence of between 0.15 and 2%[209] of reactions to food additives may explain some of the discrepancies between different groups' findings.

1.7.3 The effect of exclusion diets on behaviour

There are two methodological approaches that have been used to investigate the effects of artificial additives on behaviour. The first has been termed the dietary replacement method[210] the second a challenge design.

An early study from Australia examined the effect of the Feingold K-P diet on a small group of clinic-recruited children, some with learning difficulties some with behaviour problems, all with 'resistant' problems.[211] The method of selecting children using 'sublingual provocation' has since been widely discredited.[212] Although the study obtained statistically significant results these findings are limited by its open design.

In the same year Conners in North America published the results of his first study.[213] It was rigorously designed, in a double blind fashion, with a control diet. The children had all been referred for 'hyperkinetic syndrome' to a specialist clinic. Inclusion criteria included a confirmed diagnosis of 'hyperkinetic reaction of childhood', normal IQ and age from 6 to13 years. Out of their initial 37 children, 17 fulfilled these criteria and 15 completed the trial. The children spent 4 weeks on each diet. The children's

behaviour was assessed both by parents and by teachers; using Conners' abbreviated Parent-Teacher Questionnaire (P-TQ). Only the teachers' ratings of the children's behaviour during the K-P diet showed statistically significantly improvement. The authors urged caution because of the small study size and the possible inadequacy of blinding of the diet.[214] Sprague subsequently showed a marked order effect in their results, with the K-P diet only appearing more effective when it followed the placebo.[215]

Harley's study.[216] had two groups of boys, (n=36, aged 6-13 years; n=10, aged 3-6 years) clinic-referred with hyperactive behaviour with a subsequent confirmed clinical diagnosis of hyperkinetic syndrome. Close adherence to each double-blind administered diet was ensured. Following a two week baseline period the families spent three or four weeks on each diet. Parents were persuaded to think that there may be many different diets. Outcome measures included weekly completion of Conners' P-TQ by parents and teachers and neuropsychological tests, haematological and biochemical measures. There were no statistically significant differences between the two diets assessed by the teachers or neuropsychological tests. Parental measures did show an effect, but with an order effect (placebo followed by trial), possibly due to the instability of parental rating scales, with a tendency to reduce judgement of hyperactivity over time.[217] The pre-school group of children showed a significant improvement in their behaviour by parental report on trial diet, with no order effect. This subgroup was small (n=10) and in this age-group there were some problems with non-validation of the Conners' P-TQ. There was also lack of corroboration from the other more objective outcomes. Their conclusion was that any cause-effect relationship between Feingold's diet and behaviour change in school age children had been seriously over-stated, but that pre-school children may be different. The same group went on to challenge the children who had apparently responded to their dietary intervention with double blind placebo controlled artificial food colours, this is discussed later.[218]

Egger was investigating the wider hypothesis that many different foods affect certain children's behaviour.[219] Initially there were 76 children, referred to their clinic for dietary management of hyperactive behaviour. All the children scored ≥ 15 on the abbreviated Conners' P-TQ. Just under half of the children had allergic disorders and were atopic. The children were placed upon an open 'few-food' (oligoantigenic)

diet. 62 of the children improved as a result of this intervention. Following a positive open challenge of orange squash 34 children underwent a double-blind placebo-controlled challenge of 150mg daily of tartrazine in capsules for a week. Benzoic acid was also given at a dose of 150mg daily in capsules for a separate week. The authors claimed 27 (79%) out of 34 children had a deterioration of behaviour with the tartrazine or sodium benzoate capsules as compared to the placebo. There was a marked order effect with no break down of the results for artificial additives.

A further study examined 24 boys (aged 3-6 years) population-derived, but with a clinical diagnosis of attention deficit disorder with hyperactivity.[220] Children with somatic symptoms and sleep complaints were excluded as the authors claimed that they were less likely to respond. The experimental diet was free of artificial food dyes, flavours, preservatives, monosodium glutamate, chocolate and caffeine, and had reduced simple sugars. The study period was 10 weeks. The study suggested, from parental ratings (Conners' P-TQ) but not from psychological tests, that the study diet resulted in improved behaviour. There was no order effect. Parents also reported an improvement in sleep.

1.7.4 The effect of additive challenges on behaviour

Studies in which the diet excludes many foodstuffs make it difficult to say which element of the intervention resulted in improved behaviour.[216;219;220] Some diet studies designed to examine the impact of the K-P/Feingold diet eliminated artificial colourings and preservatives but also restricted the foods which were thought to contain natural salicylates[211;213] some made wider eliminations.[216;220] Challenge studies using artificial colourings and preservatives are better placed to more clearly investigate their specific behavioural effect. Conners' next study examined two groups of children (n=16,aged 4 –11 years;n=13, aged 3-10 years). [221] The first group fulfilled the diagnostic criteria for hyperkinesis and improved with an open artificial additive free diet, the second group was less stringently selected. The children underwent a double blind placebo controlled challenge (DBPCC) with half the average adult daily intake of all the synthetic colours approved then by the FDA (estimated at 26mg/day), in two chocolate cookies. The child had two week alternating sequences of active cookie or placebo, randomly assigned to APAP or PAPA (A=active P=placebo). The older children showed no significant differences in

parent or teacher reported behaviour. The reported deterioration measured by a tracking task 1 to 2 hours after active cookie did not reach statistical significance. In the second group, parents were asked to rate their child's behaviour during the 3 hours after ingestion of the cookie. These children completed a single two-week cross over trial. There was a significant treatment effect and no order effect.

Harley also further investigated the 'responders' from their dietary intervention study[216] who underwent DBPCC with artificial colours.[218] There were 9 weeks of multiple crossovers of challenge material and placebo. There were two patterns; PPAAPPAAA and AAPPAAPPP. The active challenge consisted of 27mg of 'certified' food colours daily, hidden in either a candy bar or a cookie. The parents and teachers assessed the child's behaviour using Conners' P-TQ for 2 days of each of the 13 weeks. The children also had 2 days each week of classroom observations using a validated index. The children completed neuropsychological tests, at the end of the baseline period at the end of the first 2 experimental fortnights, and at the end of the study. No outcome measures showed a statistically significant difference.

As their previous trials had been inconclusive,[213;221;223] Conners and Goyette undertook a fifth trial.[222] They aimed to demonstrate a pharmacological dose-time effect. Of the 9 children (aged 5 -10 years), 8 had been shown to respond to the Feingold diet and 1 had a marked clinical response; all fulfilled the diagnostic criteria for either 'hyperkinetic reaction of childhood' (DSMII)[224] or 'attention deficit of childhood' (DSMIII)[9]. On the Feingold diet each child's behaviour was assessed at intervals for 180 minutes after eating either placebo or active cookie (15mg of artificial colours). The children's activity level increased, similarly after active and placebo, reaching a peak at about 2 hours and then returned gradually to baseline. Their preliminary results were positive, but were not confirmed by subsequent results. They speculated that the practice effect may have masked any detrimental effect of artificial colours, or that the challenge dose had been too low.

A further study addressed concerns about too low challenge doses.[225] Children referred for assessment of hyperactive behaviour were placed on the Feingold diet and challenged with 100 or 150mg of 9 food dyes. Swanson subsequently analysed the 40 children (36 boys and 4 girls; mean age of 10 years) in two groups. They termed the first a 'non hyperactive' group with a history of adverse response to

stimulant medication, and whose problems were below the accepted cut off of 15 on Conners' P-TQ. The second group were termed 'hyperactive' and reported a favourable response to stimulant medication, and an average score of 16.2 on Conners' P-TQ. In hospital, over 3 days they were placed upon the Feingold diet and for the last 2 days they received either placebo or active capsules. 20 of the children received a total colouring dose of 100mg, and 20 received 150mg. The children completed a paired-associate learning test before and after the capsules. They reported significant impairment of the task during the active capsules, but with no effect of dose. The colours took 30 minutes to take effect and were still effective at 210 minutes. Subsequent sub-group analysis showed only a statistically significant detrimental effect of the challenges on the 'hyperactive' group, and not on the 'non-hyperactive group'. They showed no change in a twice-daily completed Conners' P-TQ. Their subgroup analysis was post-hoc and weakens their conclusions. Although they suggested that the children who had responded to stimulant medication might have had a common neurochemical disturbance making them vulnerable to the effects of the colours, there was no a priori rationale given for this. They did not define 'improvement' or 'adverse reaction' to stimulant medication.

Weiss reported a study which included 22 children, (15 boys and 7 girls, aged 2-7 years) who underwent a 77-day double blind placebo controlled crossover trial. [226] The children received a soft drink daily. On 8 days distributed randomly from day 15 to day 70 each child received the challenge drink (35.26mg of 7 colours). The children were either on the full K-P diet throughout this time, or a modified version with no exclusion of fruit and vegetables. Each parent developed an individualised rating scale from several standardised behaviour inventories. They were asked to report globally on the child's behaviour for two separate periods each day, one within 3.5 hours of the drink and one at some other time. They were also asked to keep a record of sleep data and complete the short Conners' P-TQ. An actometer was used when any of the aversive behaviours were observed. Each child's data was analysed separately; Although 20 children showed no evidence of sensitivity to colours, 2 did, a three-year-old boy and a slight 34-month old girl (13 kg; 25th centile[239]). This group also had concerns whether their selected dose was large enough.

Mattes and Gittelman chose a larger dose (76mg/day) based upon revised estimates of the consumption of colourings of US children.[227] They recruited children (aged 4-

13 years) who had responded to an open trial of the Feingold diet. This was a five-week design, the first baseline week was followed by an open trial of the placebo cookie; children that had an adverse reaction to the placebo cookie were excluded. There was an active and a placebo challenge week with a washout week in between. The child received one cookie (13mg of artificial colouring) on the first day, increasing gradually to a maximum of 76mg on the sixth and seventh day. Outcomes were measured using the Conners' P-TQ[223] and the groups own. A test of distractibility was used 1.5 hours after ingestion of 26mg of colours. Of the 11 children there were only clinic test measures on 5 children. None of their outcome measures demonstrated statistically significant differences between active and placebo cookies, with no order effect and no effect of the clinical characteristics of the children including age. The parents' ratings did report large differences in six children, three children during the active and three children during the placebo week. Although firmly stating their negative conclusions these authors expressed concerns as to whether their study was adequately powered.

Boris and Mandel reported their study examining the behavioural effects of many foodstuffs including artificial colours.[228] All the children were referred for assessment of hyperactivity (aged 5-9 years). They had claimed that 'atopic' children were more likely to respond to elimination diets, but used now discredited methods of defining atopy (intradermal tests). Finally 4 out of the original 26 children were challenged with 100g of colours over a week, with random placebo or active days. Statistically significant differences were reported on the parent Conners' P-TQ for all the foods with no separate reports of the colouring challenge results.

David examined the effects of tartrazine and benzoic acid with 24 children (aged 1.6-12.4 years) who on parental report had behavioural reactions to either of the substances. [229] Any child who had exacerbation of allergic symptoms on challenge with these substances was excluded. All the children were already maintained upon diets that were free of artificial colourings and preservatives, with some on more exclusive diets. 11 of the children had a history of allergic disease. 6 children fulfilled the DSM-III criteria for attention deficit disorder with hyperactivity.[9] They were challenged double blind, 12 as inpatients and 12 as outpatients. All 24 received 50mg of tartrazine followed 2 hours later by 250mg, in a drink. On a separate day 20 children were challenged with benzoic acid. The nursing staff and parents globally

assessed the children, with no formal rating scales or psychological tests. In no patient was any change in behaviour observed associated with placebo or active challenge. As part of the general clinical management of the child 22 out of the 24 children subsequently returned to a normal diet. At follow up (time not stated) all children had no food related problems, countering to some extent the two drawbacks of this study; the hospital setting and the lack of objective measures of changes in the child's behaviour.

Rowe looked at a further clinical group of children.[230] Out of 220 children referred for assessment of 'hyperactivity', 55 were placed on an open Feingold diet (aged 3-15 years). 40 were said to have improved but 26 had no deterioration on reintroduction of artificial colourings. 9 of the remaining 14 children underwent a DBPCC (7 boys, aged 3-15 years). One child was excluded from the study as he tampered with the capsules. The study period lasted 18 weeks, with daily challenges. There were four separate weeks throughout these 18 weeks that each child was challenged with either 50mg of carmoisine or tartrazine. Parents scored the child with 8 behaviour variables daily. If 4 or more of these variables were rated as a 'bad day' the whole day was rated as a 'bad day'. Two children reacted significantly, neither diagnosed as 'hyperactive', both clinically atopic but their behaviour changes were said not to have been mediated by an exacerbation of their allergic symptoms. These authors expressed concern that the previously employed outcome measures had limited themselves to hyperactive behaviours assessed usually by Conners' P-TQ and had not measured what they felt were important behavioural changes; 'irritability', 'restlessness' and 'sleep disturbance'.

Moving in to the 1990s there were several more papers published. Pollock and Warner studied 39 children (aged 2-15 years) recruited from a paediatric allergy practice and from a general population survey of food additive intolerance.[200] The children were already on a diet that excluded artificial food colours and some other artificial additives. 41% of the children were atopic (on skin prick test), but did not with hyperactive behaviour problems. Nineteen children completed a seven week DBPCC with two active (125mg of artificial food colourings within opaque capsules) and five placebo weeks (APPPAPP or PPAPPPA). Parents rated daily and weekly their child's behaviour (Conners' P-TQ) and also any allergic symptoms. Four children failed to complete the trial because of unacceptable behavioural changes,

two during active stage and two during placebo stage. They reported a small but statistically significant behavioural deterioration during the active weeks with no significant order effect. There was no evidence of any cumulative behavioural effect of additives. No changes were reported in allergy symptoms and there was not association with the child's baseline behavioural or atopic status.

Carter reported a study of multiple food elimination followed by double blind challenges with the implicated foods.[231] Their study included 19 children (aged 3-12 years) with behavioural changes on open challenges. All had been referred to a special diet and behaviour clinic and met DSM III criteria for ADHD[9]. The data are difficult to interpret as they were testing the behavioural effects of many different food stuffs. 16 of the 19 children underwent a DBPCC with increasing amounts of artificial colours up to a total of 26mg, hidden within opaque capsules, or chocolate or carob bars. 3 children were not affected. 2 children had behavioural and physical symptoms, 8 had behavioural problems only and 3 had physical symptoms only. Artificial additives alone affected only 4 children. A DBPCC was administered of sodium benzoate (25mg and then 50 mg) in a fizzy drink. 16 of the 19 children had reported problems with sodium benzoate containing drink. Carter adds that the parents identified irritability as being the characteristic most affected by the provoking foods. Unfortunately there is no statistical analysis of the outcomes following the additive challenges.

Rowe and Rowe examined 200 children referred for assessment of suspected hyperactivity.[232] They identified 150 who responded to an open artificial food colouring free diet with deterioration in behaviour upon open exposure to artificial colourings, of whom 34 were subsequently challenged. They collected parents' accounts of the types of behaviour most affected by dietary infractions, irritability, restlessness and sleep disturbance being most often identified. They do not break down the children's clinical diagnoses and had no strict entry diagnostic criteria. They commented that younger children (aged 2-6 years) had a different cluster of behaviours than the older ones (aged 7-14 years). The younger children were more likely to have problems with constant crying, tantrums, irritability, restlessness and severe sleep disturbance. The older group was described as irritable and aimlessly active, but was less likely to have sleep problems; lacked self-control and were described as unhappy. They finally used 5 clusters of behaviours: 1)

irritability/control 2) sleep disturbance 3) restlessness 4) aggression 5) attention span but also administered Conners' P-TQ. 54 children (34 from the original group and 20 with no behaviour concerns) (38 boys, aged 2-14 years) then underwent a DBPCC. Children were classified as atopic based upon a history of eczema, asthma or allergic rhinitis and a positive skin prick test. The children had spent at least 6 weeks on the additive free diet. The challenge period was 21 days, the children received a capsule or a carton of orange juice each morning. The tartrazine was administered randomly at 1, 2, 5, 10, 20, and 50mg doses for each child, with the higher doses administered towards the end of the study. There was a placebo period of at least 2 days between each dose. At least 5 of the 6 dose challenges affected the behaviour of 24 of the 54 children. There was a dose effect evident, but no effect of age or gender. All the reactors were atopic, and they state that the behavioural changes were independent of changes in symptoms, although do not provide the data to support this.

1.7.5 The effects of artificial additives on behaviour - summary

I can conclude from the results of studies using exclusion diet methodology that there is appears to be a deleterious effect of artificial additives.[213;216;220] None of the studies examined large groups of children (range of n;10-24), and were probably under powered, with reported small effect size.[216] Effects were only shown by parental report, and not replicated by teacher report or clinic testing. One study only showed an effect on younger children. [216]

The results of studies using challenges are less conclusive. Pollock showed a small but statistically significant deterioration in children's behaviour measured by parental ratings.[200] The studies that used multiple cross over designs also showed a deleterious effect on a minority of children's behaviour.[226;232;233] Swanson's group that used a post hoc subgroup analysis showed a deleterious effect on children with more baseline behavioural problems.[225] Conners' group only showed an effect on their younger group of children.[221] Most of these studies only showed an effect when measured by parental ratings. A further group of studies reported no effect of artificial additives on children's behaviour.[218;222;227;229]

The studies that examined the effects of many foodstuffs seldom reported the effect of artificial additives alone making them of little use.[219;228;229b]

I have described three areas of research that have examined the risk factors associated with childhood behaviour problems. 1. Socioeconomic adversity adversely affects parenting, making childhood behaviour problems more likely to occur and persist. 2. Associations between allergic disease, particularly respiratory disease, and behaviour problems are important but need careful control of such environmental factors, to avoid confounded relationships. 3. Artificial additives may affect children's behaviour and are unlikely to only affect atopic children or those with symptomatic allergic disease. As the literature suggests a more consistent effect in younger children a careful study is needed in preschool children, with age-appropriate outcome measures.

Chapter 2

Research questions

2.1 General aims

1. To examine the links between behaviour and allergic disease, by using a whole population of 3-year-olds, after having characterised and controlled for confounding environmental factors.
2. To examine the effect of artificial additives on children's behaviour by a randomised placebo controlled cross over trial on a group of these children, with sufficient power to detect a clinically significant effect.

2.2 Specific aims

2.2.1 Environmental factors and behaviour problems

1. To report the point prevalence of hyperactivity and behaviour problems in a geographically defined group of 3-year-olds.
2. To quantify the contribution of material deprivation and family social environment to the variation in pre-school children's behaviour.
3. To quantify the contribution of other factors not directly reflecting physical environment (social factors) to the variation in pre-school children's behaviour.

2.2.2 Allergic symptoms and atopy

1. To report the point prevalence of symptoms of asthma, eczema, rhinoconjunctivitis and food allergy and their coexistence in three year olds.
2. To describe the strength of association between atopy and these symptoms.
3. To describe the association of atopy with birth order and socioeconomic conditions.
4. To describe the association of allergic symptoms with tobacco smoke exposure, perinatal adversity and socioeconomic conditions.

2.2.3 Allergy and behaviour

1. To estimate the association between atopy and current allergic symptoms (wheeze, rhinitis or itchy flexural rash), and both general behaviour problems measured by parental questionnaire (PQ), and behaviour problems associated with hyperactivity (PQ), having controlled for significant environmental factors.
2. To estimate the assocation between atopy and current allergic symptoms (wheeze, rhinitis or itchy flexural rash) and behaviour problems associated with hyperactivity, measured by direct observation (DO), having controlled for significant environmental factors.

2.2.4 Randomised controlled trial

1. To examine the effect of artificial colours and sodium benzoate on the behaviour of 3-year-olds supported by parental questionnaire and direct observation.
2. To examine the effect of artificial colours and sodium benzoate on the symptoms of asthma, eczema and rhinitis of 3-year-olds by parental questionnaire.
3. To examine whether pre-existing hyperactivity makes the child's behaviour more vulnerable to the effects of artificial additives.
4. To examine whether atopic status makes the child's behaviour more vulnerable to the effects of artificial additives.

Chapter 3

Methodology

This study is divided in two; firstly a whole population examination of the association between allergy and behaviour problems in 3 year olds, secondly a randomised controlled trial testing the hypothesis that food additives have a detrimental effect on the behaviour of children.

The study was approved by the local Research Ethics Committee (Isle of Wight) (Reference Number 40/96) and written informed consent was obtained from the parents at each stage, and full verbal explanations given to the child, and verbal consent taken.

3.1 Plan of investigation

There were three sequential phases to the study:
Phase I:
Screening of a geographically defined population of 3 year olds for hyperactivity and behaviour problems
Phase II:
Assessment of each child's general health and symptoms of allergic disease, using a doctor-administered questionnaire.
Skin prick testing of each child to a range of common aero and food allergens.
Phase III:
A double blind placebo controlled crossover trial with artificial food colourings and the preservative sodium benzoate, on a sub group of the 3-year-olds.

3.2 Population

The study population was 2692 3 year olds (dates of birth 01/09/94 to 31/08/96), resident within a geographically defined area (Isle of Wight). All children were included whatever their medical or developmental problems. Their names and addresses were obtained at 6 weekly intervals throughout the study from the Central Health Register. The local GPs and health visitors were informed and supportive of

the study. Nurseries and playgroups were contacted. The study was advertised in local clinics, surgeries and nurseries and playgroups.

The parents or guardians of each child were contacted by mail the month after the child's 3rd birthday, in monthly batches. The letter sent to parents requested their help in a study looking at the behaviour of 3 year olds (Appendix A). The parents were offered a variety of places where they could answer a 15-minute questionnaire about their child's behaviour, with no mention of artificial food colourings or preservatives. The letter was addressed from 'The David Hide Asthma and Allergy Research Centre', St Mary's Hospital, Newport, Isle of Wight, and signed by the research paediatrician (BB). A pre-paid addressed envelope was enclosed, and parents were given the opportunity to decline consent. If the parents did not reply to the first contact they received up to three reminders at fortnightly intervals (Appendix B).

3.3 Phase I

Following the parents' agreement to participate in the study they were contacted. A 15-minute questionnaire (Appendix C) was administered by one of the members of the team. The child's activity, attention and impulsivity were assessed using validated questionnaires: 1) The activity component of the Emotionality, Activity and Sociability Temperament questionnaire (EAS)[3]; 2) Weiss-Werry-Peters Activity Scale (WWP)[2]. Their general behaviour was assessed using the Behaviour Checklist (BCL)[1]. Parental perception of their child's behaviour was assessed, by yes or no responses to the presence of various features of hyperactivity. Parents were also asked to respond yes or no to a selection of factors which might affect their child's behaviour, including, food and drink. Maternal educational level was also recorded, as 'age at leaving full-time education'.

The child was defined as hyperactive if they scored 20 or more on the WWP activity questionnaire and a mean of 4 or more on the EAS Temperament questionnaire. In line with other epidemiological studies[263] more stringent criteria were applied when examining prevalence; 20 or more on WWP, and a mean of 4.2 or more on the EAS Temperament questionnaire. Children who scored 11 or more on the BCL were

defined as having a behaviour problem. At the end of the assessment parents were invited to join Phases II and III of the study.

3.4 Phase II

All children whose parents consented to Phase II were invited to attend the David Hide Asthma and Allergy Research Centre.

Skin prick testing was undertaken to a panel of allergens; house dust mite (D.pteronyssinus), a mix of grass pollens, cat, egg, milk and peanut (ALK, Hørsholm, Denmark) and a negative (normal saline) and positive (histamine 10mg in 1ml) control on the volar aspect of the child's forearm using Pepy's method[5], with 1mm standardised point skin prick test lancets (Dome-Hollister-Stier). (Appendix D)

A questionnaire was administered to the child's carer eliciting past and current medical history, socio-demographic details, and the ISAAC questions to ascertain the presence of allergic symptoms[234]. The child was weighed, measured and had a general examination. (Appendix E)

The child was defined as atopic if they had at least one positive skin prick test of a mean wheal diameter greater than or equal to 2mm, in the presence of a positive histamine control and negative saline control. The parents of children who were skin prick positive to a particular allergen were given commonly available allergen avoidance advice if the child was felt to have relevant symptoms. Children who were positive on skin prick testing to food allergens (namely peanut) who had had no known exposure were referred to a paediatrician for clarification. The GP was informed of any positive findings elicited from the history and examination and of positive skin prick tests.

3.5 Phase III

This was a randomised placebo controlled cross over study. The children were selected in a nested case controlled fashion with defining characteristics of hyperactivity and atopy, resulting in 4 cells:

Hyperactive *and* atopic - these children were the 'index' child. They were matched with one child from each of the three other nests.
Hyperactive, *not* atopic
Not hyperactive, atopic
Not hyperactive, *not* atopic

In order to improve the power of the study children were also recruited to the other two or three cells, without an index case, using the hyperapactive, not atopic child as the index child. This produced groups containing 2 or 3 children, as well as the original groups of 4 children. Children were matched as closely as possible, using the following matching hierarchy; gender, month of birth (the child with the closest date of birth within 3 months of their match), maternal age at leaving full-time education and sibship position.

3.6 Power calculations

Power calculations estimated that 60 children were needed in each cell, to examine the combined effect of hyperactivity and atopy. Analysis was to centre on testing changes within each cell in the level of hyperactivity when the children received placebo or active challenge. Within each cell and setting a significance level of <0.01 (one tailed), it was estimated that there would be 80% power to detect an effect size equivalent to 0.6 of a standard deviation unit change in mean hyperactivity scores. This degree of change was felt to be feasible to achieve, comparing the degree of change in hyperactivity in response to methylphenidate, and clinically relevant in relation to, for example behaviour in the nursery or infant class. A similar power would hold for comparison in the degree of changes seen in two groups. For example if the additives had a greater effect (compared to placebo) for the hyperactive and not atopic group a difference of 0.6 in the standard deviation units of change would be detected with this power.

3.7 Randomisation and blindness

Randomisation took place on site by the dietitian. Prior to the start of the trial 500 sealed envelopes were prepared by myself and the dietitian. In these envelopes we randomly placed pieces of paper (written either Placebo-Active or Active-Placebo). When the child attended for visit 1 of phase III they were allocated the next number from a random number table, generated in Excel, containing numbers from 1-500, identifying the child's envelope, and order of randomisation. The dietitian carried out this allocation of drink order. Occasionally if she was away, she would leave a plastic bag in the freezer containing the child's drinks, only labelled with their name and week.

A preliminary test showed that the drinks could not be accurately differentiated on blind testing and that they were generally palatable to children of this age. Blind tasting of the placebo and active drinks by 34 adults showed that they were no more likely to identify the drink than expected by chance. 15 of the 59 parents who withdrew their child from the study did so due to perceived adverse behavioural changes. 9 of these withdrawals occurred during an active week and 6 during a placebo week. At the end of the study period the parents of the children who completed the study were equally divided into those who correctly identified the drink order (96;35%), those who did not (80;29%), and those who did not know (101;36%). All the study team and the family were blind, apart from the dietician.

3.8 RCT

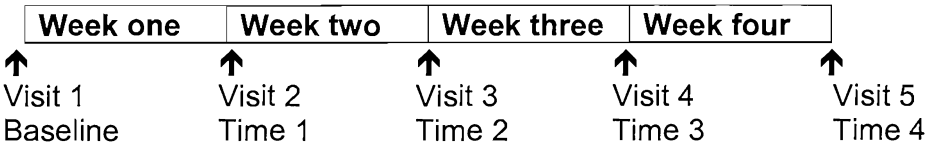


Figure 1 Phase III – challenge month

In the course of the study a small group of the children refused the fruit juices and alternatives of active or placebo chocolate cakes and biscuits were made to the individual child's requirements. These children are not analysed separately, despite considerations of differing bioavailability to this group of the additives. The main

group, the drinks group had widely differing patterns of consumption. Some drank all their drink first thing in the morning, other throughout the day, which it was felt accounted for greater variability than the vehicle for the additives (drink or food).

The period of four weeks was chosen pragmatically to suit the families and the study team, with a one week wash out period. In the challenge month the children followed an artificial colouring and sodium benzoate free diet, with the support of the research dietitian and relevant literature. (Appendix F) During week two and week four they received, daily, 300mls of mixed fruit juice, (placebo or active randomly assigned) in identical, sealed bottles. The active drink included 20mg in total of artificial food colourings (sunset yellow, tartrazine, carmoisine and ponceau 4R) *(Forrester Wood, Oldham, UK)* and 45mg of sodium benzoate *(J. Loveridge, Southampton, UK)*. The placebo drinks had the natural colourings turmeric and betanine added (APPENDIX F/2). In the challenge weeks an attempt was made to ensure that the child received 100mls (one third) of their placebo or active drink no more than two hours before the assessment, occasionally in addition to their daily 300mls.

The dose of additives selected addressed issues raised in previous studies. The early studies selected doses based upon half the average estimated USA daily adult intake[216;222] (15-27mg). They had followed the recommendations of the interagency collaborative group of the National Institute of Mental Health. Weiss used a dose estimated from dietary histories of 80 children similar to their study population 'relying on published industry practices as the basis for the calculations' and used a total of 35mg of mixed colours.[235] Mattes and Gittelman estimated that under 11 year olds in the USA were consuming 50-60mg/day of artificial colours, and used a higher challenge dose of 78mg/day.[236] Later teams used even higher amounts, Boris[237] used 100mg and Pollock and Warner[238] used 125mg of colours/day. Although this dose was lower previous studies had examined mainly school age children. If we consider the average UK 11 year old girl of 35kg[239]; the dose/kg previously used ranges from 0.4mg/kg[222] to 3.6mg/kg[200]. The mean weight for a UK child aged 3 years and 4 months is 15kg,[239] 20mg translates to 1.3mg/kg. Also these children were too young to tolerate capsules and so the colours had to be hidden within fruit drinks. This dose proved to be the maximum that could be hidden effectively, and still not look different than the placebo drink.

3.9 Outcome measures

3.9.1 Clinic Tests

The children were assessed by one of three research psychologists. Most children saw the same psychologist each week, except during staff leave, with or without the child's carer. The first baseline assessment was at the beginning of the four week period, and the child had four subsequent assessments (time 1 – time 4). Each assessment lasted about 30 minutes. The clinic tests[240-242] had been validated individually, but had not been administered before in a battery. We aimed to have measures that would be sufficiently sensitive to detect clinically relevant behaviour change.

Actometer

This estimated of the child's gross motor activity using a modified wristwatch, an actometer, placed upon the same wrist each week, thus measuring the movement of one limb. The child was allowed a few minutes of unobserved 'warm up' play before moving onto observed free play.

'Free play'

This first task involved free play, with 9 toys spread throughout the room; a ball, a simple 'push' bike, a clothed doll, a teddy bear, a 16 piece jigsaw puzzle, a wooden train and circular track, a miniature car and a selection of plastic body parts which make up a person or animal. Over a 5 minute period, every 15 seconds, the main toy and ancillary toys with which the child was playing was recorded. Other qualitative aspects of the child's play were also recorded, in a systematic way[240]. The toys were then placed out of sight and the child moved onto the next task.

'Puppet game'

The puppet game was in the style of a 'Simon-says' game, and measured the child's ability to inhibit their behaviour.[241] The child was instructed that they were to touch a particular body part (head, tummy, leg) if the 'good' puppet ('bubble' - the pig) told them to and not to touch it if the 'naughty' puppet told them to ('squeak' - the cow). Correct moves, half moves, incorrect moves and no moves were all recorded.

'Sticker game'

The child's ability to inhibit behaviour was also measured using a 'sticker game'.[241] This used a simple scene with characters from one of two well-known children's books ('Postman Pat' and 'Thomas the Tank Engine'). The child watched while a sticker was hidden under one of three cups. They then had to wait for varying amounts of time, randomly presented; 5 seconds, 15 seconds, 25 seconds, 35 seconds and 45 seconds. When the time had elapsed the tester clapped, the child had been previously taught that this was the cue to retrieve the sticker and stick it on the scene. The length of time the child was able to wait each separate time was recorded. This enabled the recording of impulsive and non-impulsive searches. Whether the child remembered correctly or incorrectly was also recorded.

Slow drawing and walking

The psychologist then moved on to further measure the child's ability to inhibit both gross motor activity and fine motor activity.[242] They were instructed to draw a line between two telegraph poles, to let 'Sally the squirrel get to her friend'. They were first asked to perform a practice draw, followed by a slow one and a fast one. A similar task was then introduced with a cat that wanted to walk around a circular path, the child was asked to draw 3 separate times around a printed circle, first as a practice then twice as slowly as possible. The child was then asked to walk along a floral fabric path, 2½ inch by 12 foot (as per the test), firstly as a practice and then as slowly as possible.[242] All the trials were timed.

3.9.2 Parent completed assessments – behaviour and allergic symptoms

There are no validated parent-completed questionnaires to measure behaviour changes in this age group. The screening questionnaire was thus modified to measure change. The parents rated changes within their child's behaviour daily, and weekly, with a 5 point Likert scale, using behaviours from the WWP[2]: 1. Switching activities; 2. Interrupting or talking too much; 3. Wriggling; 4. Fiddling with objects or own body; 5. Restless; 6. Always on the go; 7. Concentration. (Appendix H & J). Parents also rated changes within their child's allergic symptoms weekly, using wording from the ISAAC study.[6] This consisted of 8 questions; 3 questions about the child's skin, including any impact it may have had upon their sleep, 3 questions about the child's symptoms of wheeze and cough, including any impact it may have

had upon their sleep, one question about any symptoms of rhinoconjunctivitis and a question about antihistamine use. The child's allergic symptoms and the weekly summary of the child's behaviour symptoms were reported with a 5-point Likert scale; 'much worse, worse, same, better, much better'.

Parents kept a daily 'snack' diary to allow an estimate of their compliance with the consumption of the challenge drinks as well as with the diet over the four week study period. Each time a portion of drink or food was recorded containing sodium benzoate or an artificial colour this was counted as one 'mistake' (Appendix I).

Domain	Task
inattention 1	free play - rate of toy change
inattention 2	free play – quality of attention (5 measures)
inattention 3	stickers - % of time waited spent 'off task'
activity 1	free play – quality of activity (3 measures)
activity 2	stickers - amount of time spend out of seat
activity 3	actometer
impulsivity 1	puppet - % tasks correctly inhibited
impulsivity 2	puppet - score from levels of inhibition
impulsivity 3	stickers - amount of time successfully waited
impulsivity 4	draw a line slowly – difference between fast and slow trial
impulsivity 5	draw a line slowly – mean of two slow circle trials
impulsivity 6	walk a line slowly – mean of two walking trials

Table 1 Variables derived from clinic tests

3.9.3 Clinic tests – generation of outcome measures

The clinic-based tests produced 12 measures for each visit based upon task performance and tester recordings of behaviour: 3 of inattention, 3 of activity and six of impulsivity (table 1). Three measures were taken from the 5 minutes of free play. 'Toy change' was the number of times the children changed their main toy during the free play period, recorded using 15 second sampling periods. The tester also systematically rated the quality of the child's play during these 5 minutes. 3 of the scores were amalgamated to produce a measure of activity and 5 to produce a measure of attention. Two measures were taken from the puppet inhibition task. Both measures referred to the child's success at inhibiting their behaviour when requested. The first was the proportion of all responses that were correctly inhibited. The second was an attempt to differentiate the child's responses more finely. Each response was 'scored' from 0- 3; with a score of 3 for no movement in response to an inhibition trial (ie. correct response). Children scored 0 if they responded to an inhibition trial by touching the named body part (ie. incorrect response). Scores of 1 and 2 were awarded for a full movement but to the incorrect body part and for a

partial movement respectively. These scores were used to calculate the child's mean response. A further task, the stickers game, involved delay aversion, with measures of the child's associated behaviour while engaged in this task. The first was a measure was of the ability to delay reward, with successful delay being expressed in seconds of successfully waited time, with a maximum possible total of 125 seconds. The total time spent out of seat throughout the task was recorded, and the time spent 'off task', looking at other things or engaged in other tasks was expressed as a proportion of the time they managed to wait for the reward. Control of fine motor activity was assessed by the drawing of a straight line between two printed telegraph poles, first fast and then slowly, and then slowly around a large printed circle. The difference between the fast and slow trial was recorded for the poles task, and the mean of the two slow trials for the circle. The child's ability to control gross motor activity was assessed by walking slowly along a fabric path. The mean of two slow walking trials was recorded. The actometer provided a measure of arm activity.

The three attention and three activity scores were aggregated into a single index since these aspects of behaviour were so highly correlated (Reliability analysis (Alpha (Cronbach model)). The six impulsivity measures were also aggregated. They were calculated as a mean of the available constituent measures. An overall Aggregate Test Hyperactivity (ATH) index was also calculated using the same methodology.

There were 277 children who completed the trial and for whom test data was available at all 5 measurement time points (chapter 7 - table 3). Inevitably with studies on children as young as three years, there were missing data in the testing. To deal with this two procedures were adopted. If the scores were aggregated across a number of measures the mean score was taken for those on which the participants had data. If a child had sporadic missing data they were replaced by the modal value for that variable. By this means it was possible to achieve an N of 277 for each of the three measures (Aggregated Test Hyperactivity, Test Impulsivity and Test Activity and Attention) at each of the 5 time points.

Each of the measures was based on a different scaling and therefore had different mean values and variances. To facilitate the interpretation of the data analysis, all

measures were standardised such that each score was expressed as deviation from the baseline mean divided by the standard deviation at baseline.

To avoid inflating Type I errors two primary outcome variables were identified – Aggregated Test Hyperactivity (ATH) and Aggregated Parental Hyperactivity Ratings (APHR). This was made after standardisation and resulted in the standard deviations of the aggregated measures being less than unity.

3.9.4 Parental ratings of behaviour – generation of outcome measures

From parents global rating of their child's behaviour an aggregate general behaviour rating (APGBR) was produced for each child.
Three parental ratings were calculated from the weekly behaviour questionnaire. This was available at the same 5 time points as the clinic tests, and thus this was used as the main parental rating outcome measure. We had measures of activity (items 1, 3, 4, 5 and 6), attention (item 7) and impulsivity (item 2). The sum of these three measures was aggregated to form the Aggregated Parental Hyperactivity Ratings (APHR). There was also a question about settling down to sleep.d for the 28 days of the trial.

3.9.5 Parental ratings of allergic symptoms – generation of outcome measures

It was hypothesised that changes in symptoms of eczema, rhinitis and asthma in response to additives could mediate behavioural changes. David's group dealt with this problem by excluding children with allergic symptoms[355], Warner and Pollock found no evidence of an effect upon somatic symptoms[238]. The most common outcome measures used in pre-school childhood asthma are symptom based, particularly when the time-scale of interest is days.[364] This is limited by the reliance upon information from caregivers, who are known to under-report nocturnal symptoms and exercise induced symptoms.[365]

All parents completed 8 questions about their child's allergic symptoms at baseline, and the subsequent 4 visits. This was based upon a 5 point Likert scale and was related to the last 7 days. Questions 1-3 worsening or extension of the child's eczema, and whether it had disturbed sleep or required increased medication.

Questions 4 and 5 solicited information on the frequency or worsening of rhinoconjunctivitis symptoms, and whether this had necessitated increased medication. Questions 6-8 addressed whether the child had experienced more frequent or worse wheeze or cough, whether these symptoms had disturbed their sleep, or resulted in increased medication. 'Eczema score' and 'Asthma score' had a range from 3-15, and 'Rhinitis score' from 2-10 (chapter 7 - table 4). These symptom changes are limited by lack of corroboration by more objective measures such as examination[86], or changes in inflammatory markers[364], neither of which proved practical within the constraints of the study.

3.9.6 Reliability of measures

The test-retest and inter-rater reliabilities were examined using data from a separate group of 10 children who completed the clinic tests twice, a week apart (table 2). The children were assessed by the same tester, while the second tester scored their performance simultaneously. Inter-rater reliabilities were high (range 0.91 - 0.99). The intraclass test-re-test reliabilities[243] were less good (range 0.002 – 0.65). The Pearson product moment test-retest correlations for this sample were somewhat higher (Impulsivity, 0.57; Hyperactivity ,0.24; Activity and Attention, 0.72) and were confirmed by the correlations for the N= 277 sample between the Baseline and Time 1 testing (Impulsivity, 0.70; ATH ,0.64; Activity and Attention, 0.45) (Chapter 7 - table 3). The delay aversion 'hiding-stickers' off task and Actometer measures were excluded on this basis. The lower intraclass correlations reflect the influence of mean level changes in scores between tests. It should be noted that these test-retest reliabilities are comparable to those obtained previously with this age group on cognitive and behavioural measures and and superior to some physiological measures such as blood pressure reactivity (e.g. 0.25-0.50).[244;245]

3.10 Ethical issues

McIntosh chaired the writing of ethical guidelines for research involving children for the Royal College of Paediatrics and Child Health in 2000.[245b] This was published after the start of this research, but is useful as a template to reflect upon the positive sides of this research, and reflect upon any gaps.

It is not difficult to justify that this work was carried out with children rather than adults. All the studied conditions, both those involving allergy and atopy and those involving behaviour are at a different stage in their natural history and specific socioeconomic associations than if these conditions had been examined in adults. The claims about the effects of additives have been made specifically about children's behaviour, with a question as to whether young children's behaviour particularly is vulnerable. It was thus imperative that this research was carried out with specific design for this age group of children.

This research carried little benefit for the individual children's and family, but largely benefited children as a whole. This does not detract from the ethics of this research.

The majority of members of the research team were trained in the health care of children. This was vital for both design and sensitive carrying out of research in particular procedures which carry some minor discomfort, and require the co-operation of young children such as skin prick tests, examinations and psychological tests. There was also a positve secondary effect; ensuring that a wide base of child health care professionals are trained in research methodology is essential for the ongoing health of their academic base.

Any potential harms from this study were identified as 'low risk' as defined by RCPCH paper.[245b] Skin prick testing does involve a small amount of discomfort. This was carried out with sensitivity and skill by the research nurse, it involved persuasion but never coercion. The best endorsement of her skills were requests she received from parents several times; 'can you look at their teeth, cut their nails and hair and fit their shoes at the same time'. The time given and disruption tolerated by study participants was considerable, and should not be underestimated. The study diet was not estimated to be more expensive, but involved more thought in shopping. Travel expenses were given, but not uniformly. Only token presents were given to children. I think that more financial compensation should have been offered to families.

It should be noted that Isle of Wight children have been involved in many large studies before, starting with Rutters in the 1960s[273b] to more recent allergy ones from the same centre[381]. None of this group of children had been involved in any

studies, although the families may have been. We must beware 'over researching' what is a small population. Written Consent was obtained following written information to the parents for each phase of the study. The information leaflets could have been more extensive, and in retrospect I would have liked to develop picture information sheets for the children. Verbal consent was always taken from the children.

There is an issue of recruitment. The names and addresses were supplied by the NHS. I would query as to whether now our LREC, with Caldicott in mind, would have allowed us direct access to these families' addresses. We would have used a 'middle man' to manage the approach to families, although with resultant lower coverage of the population.

This study had received LREC approval and was registered with the NHS Trust R&D department. The paper research findings have been securely archived. Confidentiality was addressed throughout the study. There was separation of all identifiable information from the outcome measures of study and electronic storage of date was on secure, backed up regularly by the NHS Trust server.

Finally I wish to discuss dissemination. This was promised to families throughout the study, and occurred as promised by letter. A public presentation of the findings would have been more accessible, although difficult when members of research teams move on. The majority of the findings have been published in peer-reviewed journals. The findings were also published as a report to funders Food Standards Agency (formerly MAFF), and has entered the public domain through their publically accessible library.

3.11 Rescheduling of missed visits

Every effort was made to ensure that the child was not away during the month but there were unforeseen events, which were dealt with by extending baseline weeks or wash out weeks, or by repeating wash out weeks and the subsequent challenge week. The weeks could be extended from 7 days to up to 14 days, all changes to the timetable were recorded.

Visit missed	Action
One	Visit one rescheduled
Two	Week one extended to two weeks
Three	Repeat washout week (Wk 1) – child randomised again, week 2 repeated
Four	Week three extended to two weeks
Five	Repeat washout week (Wk 3) – wk 4 repeated (not randomised again)

Travel expenses to and from the centre were offered to all families. A simple present and certificate was awarded to the child at the end of the study. The parents were made aware that none of the team would be able to 'break the code' for their individual child while the study was ongoing, but that it would be broken at the end. I initially waited for peer-reviewed publishing of the findings of the study, however as this was somewhat delayed, the findings of the study were released to participating parents by letter in August 2001.

3.12 Data management and statistical analysis

Data was double entered, cleaned and analysed using SPSS.[246]
Statistical analysis of phase III (the randomised controlled trial) initially was based on the pooled data for all subjects. The effect of the order with which the active and placebo supplements were administered was tested in an analysis of variance (ANOVA) by the interaction of the between subject factor of order and the within subject 5-level factor of time of measurement. Subsequent analyses pooled subjects across order and were concerned with detecting a difference between the changes in scores in the placebo and active periods. This was tested using a repeated measures ANOVA and shown by the interaction between the two within subject two level-factors of period (active/placebo) and time (pre- and post).

The initial sample selection was designed to allow a mixed ANOVA analysis with 2 two-level between subject factors: - Hyperactive/Non-hyperactive and Atopic/Non-atopic. The interaction between subject factors and the within subject factors of period (active/placebo) x time (pre-/post) interaction effect was tested. These analyses were based on the total sample of 277 subjects. To take advantage of the

matching of cases it was possible to repeat the analysis using 35 matched quartets in the 2x2 design with N=140.

There were pre-period inequalities in APHR for the active and placebo periods. The analysis was repeated casting the active and placebo periods as a between subject factor. The post-period scores were the dependent variable and the pre-period scores a covariate. The main effect of period in this analysis of covariance indicates differential change in behaviour in the active and placebo periods with the initial level of hyperactivity controlled.

Treating the study as a crossover challenge with two treatments with a total of 240 children the probability is 94% that the study will detect a challenge difference at p=0.05, if the true difference between the treatments is 0.3 standard deviation units of pre to post-treatment change scores. As a 2x2 design with 30 subjects per cell the main effects of each factor of 0.35 could be detected with power greater than 0.80 and p=0.05.

Analysis of changes in allergic symptoms similarly pooled subjects across order. Paired t tests were used to compare the changes that occurred during the placebo period with those that occurred during the active period. It was possible that children who did not normally complain of these symptoms would experience them during the trial and so three groups of children were also examined separately. The 'eczema score' was examined for the group of children whose parents said that they had had flexural itchy rash within the last 12 months (n=58). 2) and similarly for the 'rhinitis score' (n=92) and the 'asthma score'.

3.13 Project timetable

Initial contact by mail

This occurred in the month immediately following the child's 3rd birthday. If the parent failed to respond it was followed by up to three reminders (sent at fortnightly intervals).

Date of commencement: November 1997

Date of completion: September 1999

Phase I (Behaviour questionnaire)

Each child was screened at the age of 3 years and 3 months, plus or minus 6 weeks.

Date of commencement: November 1997

Date of completion: October 1999

Phase II (Medical assessment)

Date of commencement: March 1998

Planned date of completion: November 1999

Phase III (Challenge month)

Each child entered Phase III between the age of 3 years and 3 months and 3 years and 11 months.

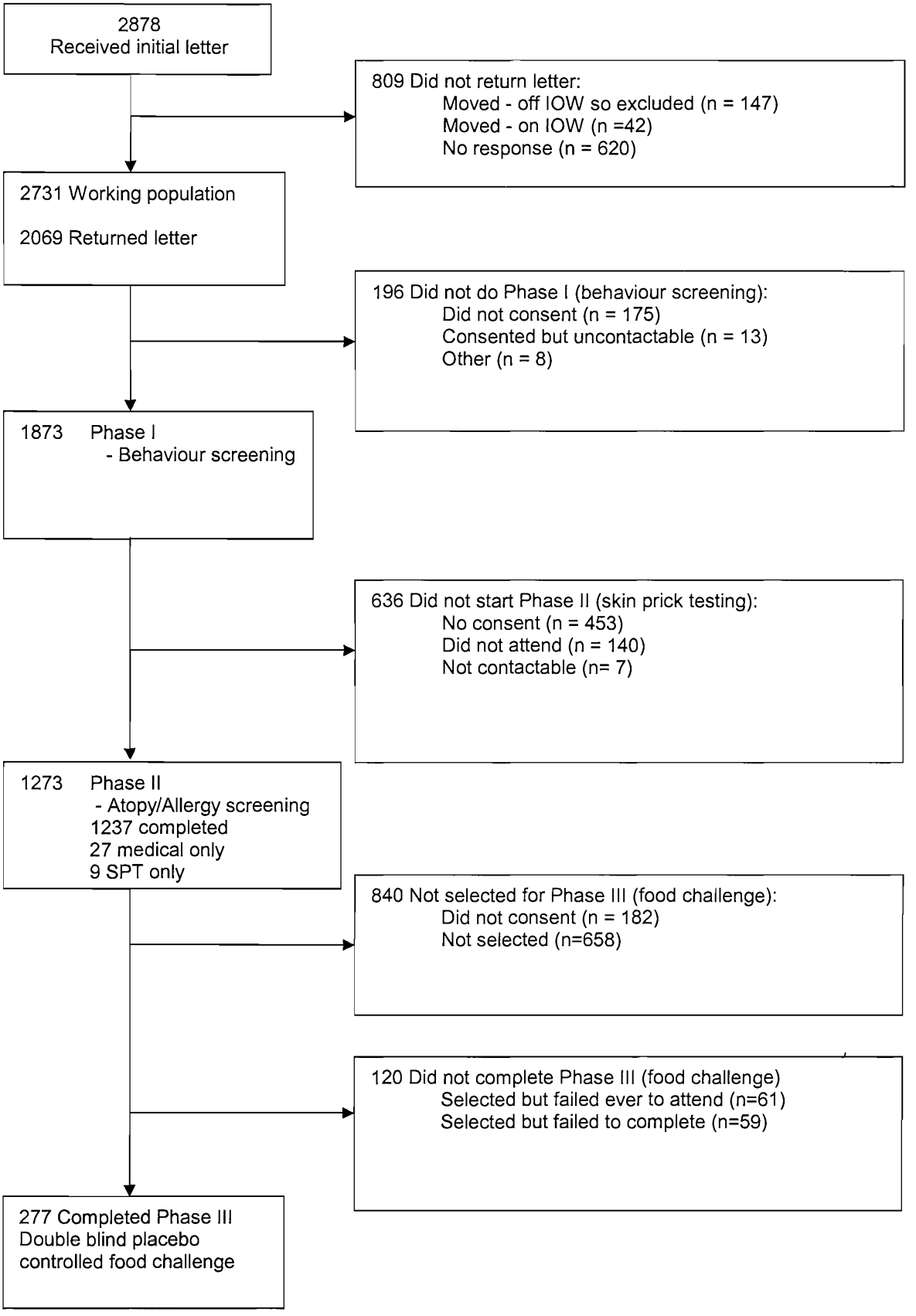
Date of commencement: April 1998

Date of completion: December 1999

	Test retest (intraclass)			Test retest (tester)			Test retest (observer)			Interrater (time 1)			Interrater (time 2)		
	n	r	p	n	r	p	n	r	p	n	r	p	n	r	p
Testing Aggregated hyperactivity (ATH)	10	0.237	0.314	10	0.242	0.501	10	0.521	0.122	10	0.944	<0.001	10	0.910	<0.001
Impulsivity	9	0.481	0.040	9	0.571	0.108	9	0.375	0.320	10	0.995	<0.001	10	0.930	<0.001
Activity & inattention	10	0.649	0.002	10	0.716	0.020	10	0.683	0.030	10	0.933	<0.001	10	0.931	<0.001
Attention (Stickers off-task)	9	0.002	0.994	9	0.063	0.872	9	0.089	0.820	10	0.959	<0.001	10	0.985	<0.001
Actometer	7	0.062	0.834	7	0.262	0.570	7	0.542	0.209	7	0.673	0.067	7	0.301	0.512

Table 2 **Sub group of children - Test-retest reliability & inter-rater reliability**

Figure 2 Population flow chart



Chapter 4

Environmental factors and behaviour problems

4.1 Background

This chapter will examine the point prevalence in the pre-school child of general behaviour and hyperactive behaviour problems and the associated environmental factors.

4.2 Hypotheses and aims

Hypotheses

1. Environmental influences have a greater effect upon general behaviour problems (GBP) than the specific behaviours associated with hyperactivity (HB).

Aims

1. To report the point prevalence of hyperactivity and behaviour problems in a geographically defined group of 3-year-olds.
2. To quantify the contribution of material deprivation and family social environment to the variation in pre-school children's behaviour.
3. To quantify the contribution of biological factors to the variation in pre-school children's behaviour.

4.3 Environmental influences

Ten variables represent different, but interrelated environmental influences (figure 1). Two broad aspects of the child's environment are examined. The first includes those influences that are assumed to more directly reflect material environment; annual household income, tenure of housing and ownership of vehicle. The second aspect includes factors more strongly associated with family social environment; maternal age at leaving full-time education, maternal employment status, maternal and paternal age, the presence of one or two parents in the family, the birth order of the child and current exposure to smoke.

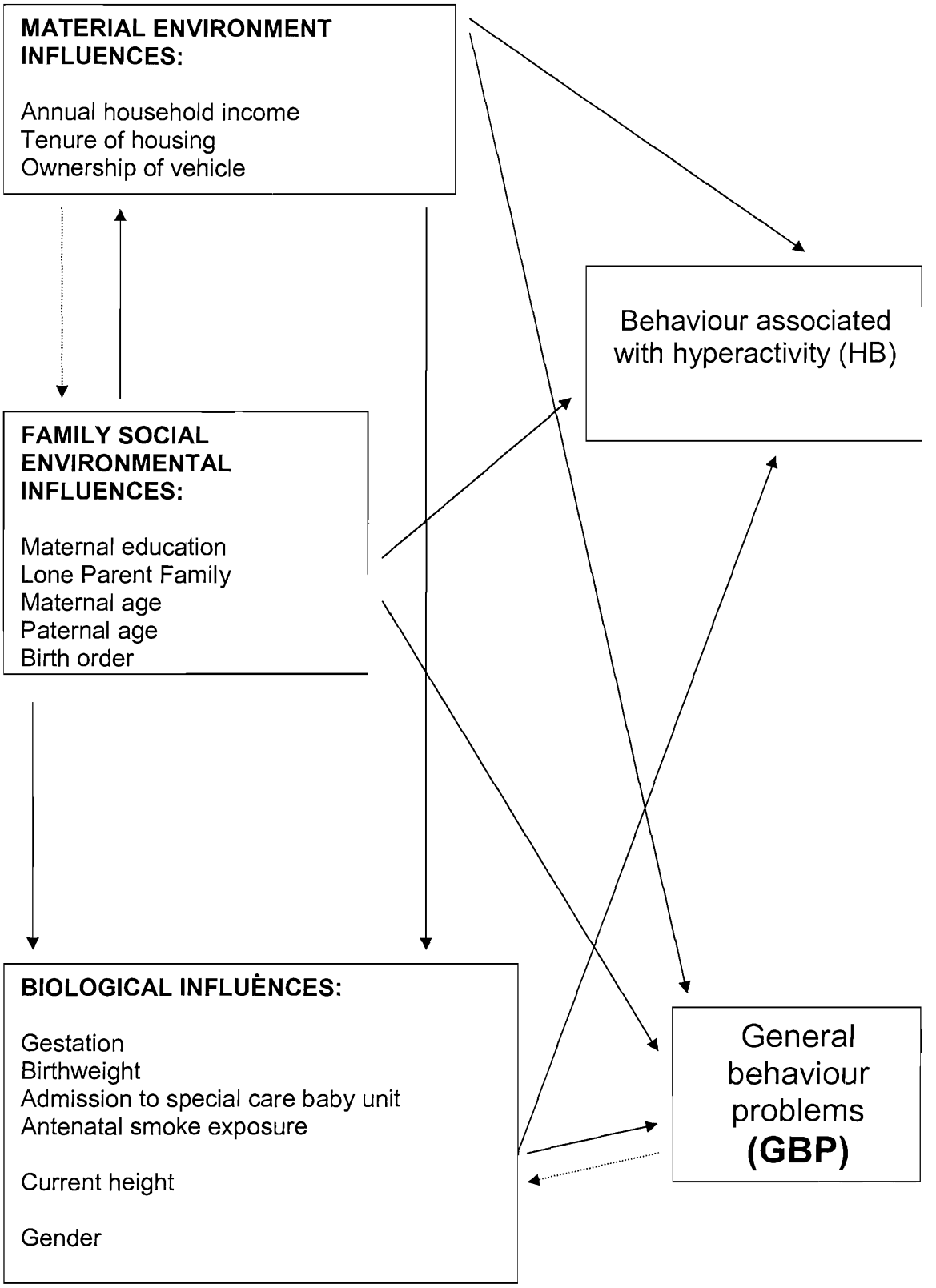


Figure 1 **Hypothesised environmental and biological influences on behaviour**

The effect of some of these independent environmental variables may well be mediated by a biological mechanism. Maternal age is associated with an increased risk of chromosomal problems.[256] Birth order, maternal age, socioeconomic conditions, and maternal smoking all have an effect on birth weight.[257] Figure 1 diagrammatically represent the potential interrelationships.

Material environment

1. Annual household income
2. Tenure of housing
3. Ownership of vehicle

Family social environment

4. Maternal age at leaving full-time education (Maternal education)
5. One or two parents in the family (Lone Parent Family - LPF)
6. Maternal age
7. Paternal age
8. Birth order
9. Maternal employment
10. Current exposure to smoke (living with a smoking adult)

Figure 2 Indicating environmental factors

4.4 **Biological influences** (figure 3)

It is likely that perinatal adversity affects behaviour. Developmental brain problems result from antenatal and postnatal events, possibly directly caused by antenatal smoke exposure, and adversity indicated by birth weight, gestation at delivery, and admission to the special care baby unit. Low birth weight has been proposed as one of the mediating factors between socio-economic adversity and cardiovascular adult morbidity.[258;259]

1. Birth weight
2. Gestation
3. Antenatal smoke exposure
4. Admission to special care baby unit
5. Current height
6. Gender

Figure 3 Indicating biological influences

I propose common mechanisms in the link with childhood behaviour problems. There are problems of confounding with gestation and genetic problems. Swanson suggests that perinatal complications may only lead to negative behavioural

outcomes when present in conjunction with subsequent environmental adversity.[21] Current height is examined as a proxy for subsequent central nervous system development. Short stature has been shown to be associated with low socioeconomic status in adulthood[260] and childhood.[261] Behaviour problems could arise by a common mechanism to that resulting in short stature. I will examine the interaction of low birth weight and height with other measures of current socioeconomic adversity.

4.5 Results – univariate analysis

4.5.1 Population

This chapter is based upon data collected from two groups, one large and the other a sub group of the first (figure 2 Chapter 3 Methodology - Population Flow Chart). The larger group (n=1873) comprises 70% of the 'working population', and includes data collected from Phase I of the study. The smaller subgroup (n=1264) is 46% of the 'working population' and is made up of the children who completed Phase II.

Parents were asked to specify a choice of venue when returning their consent for the study. Subsequent contact was usually then by telephone, when possible, and the majority of parents (more commonly mothers) completed the questionnaire over the telephone (Phase I) (table 1). Phase II was always completed in the clinic, to safely accommodate skin prick testing. Again mothers were the most common interviewees (80%). Only a small number of Phase II clinics were run outside office hours, partly explaining the preponderance of mothers. For a small number of children specific pieces of data are missing, due to interviewer error in completion of the questionnaire, therefore n is sometimes less than 1873 (Phase I) or 1264 (Phase II). The sociodemographic and socioeconomic data show no consistent differences based upon the gender of the child and are not reported.

4.5.2 Environmental influences

Material environment (table 2)

The parents were asked to estimate their annual income before tax, in 5 broad income bands. Nearly a third (27%) of parents estimated their income at less than

£12,000, and most (84%) with incomes less than £29,999, including families on state benefits, this is a similar number as comparable studies of families with pre-school children. The majority of children (74%) lived in owner-occupied dwellings, again comparable to other studies. The majority of parents of the children owned a vehicle (90%). This is higher than the General Household Survey from 1991.[264] Anecdotally public transport on the Isle of Wight is relatively expensive, and families can 'run' a relatively old, unreliable and therefore cheap car as the distances are small. This may partly explain the higher rate of car ownership.

	Prevalence n (%)
Phase I	
Interviewee	
Mother	1674 (90%)
Father	140 (8%)
Both parents	29 (2%)
Other carer	13 (<1%)
Place of interview	
Telephone	1552 (83%)
Clinic	106 (6%)
Home	199 (11%)
Other	4 (<1%)
Phase II	
Interviewee	
Mother	1005 (80%)
Father	51 (4%)
Both parents	187 (15%)
Other carer	14 (1%)

Table 1 Interview - Phase I & II

Annual household income (£)	Prevalence n (%)
<12,0000	347 (27%)
12-17,999	338 (27%)
18-29,999	383 (30%)
30-41,999	133 (11%)
>42,000	60 (5%)
Housing type	
House or bungalow	1158 (92%)
Flat	98 (8%)
Other	6 (<1%)
Housing tenure	
Owner occupier	935 (74%)
Other	4 (<1%)
Rented	324 (26%)
Privately rented	145 (12%)
Social housing	179 (14%)
Vehicle ownership	
vehicle	1134 (90%)

Table 2 Child's material environment

Family social environment (table 3)

Phase I included a question on 'maternal age at leaving full time education'. These were divided into three groups. Just over half of the children had mothers who left school after the age of 16 years, comparable to other studies.[272]

88% of children lived in a two-parent household, 84% with both their biological parents, and 4% with their mother and mother's partner. Only 1% of children lived with mothers and adults other than her partner. Only 6 children lived with carers other than their parents and one child lived alone with his father. The number of children living in lone parent families was lower than expected (12% as compared to the national estimate of 22%[265]). This may be due to selection bias, a true representation of different living circumstances of this population or partly explained

by parents being more willing to verbally describe themselves as living with their partner than on more formalised closed questionnaires.

	Prevalence n (%)
Maternal age at leaving education	
<=16	554 (44%)
17-20	547 (43%)
>=21	171 (13%)
Adults present in child's home	
Two parent household	1107 (88%)
Mother and Father	1060 (84%)
Mother and Partner	46 (4%)
Father and Partner	0
One parent household	156 (12%)
Mother and adult(s)	14 (1%)
Mother alone	136 (11%)
Father alone	1(<1%)
Other carers	6 (<1%)
Parental age (mean and range)	
Mother	32 (18-51)
Father	35 (20-64)
Birth order (range)	(1-9)
no 1	519 (41%)
no 2	462 (36%)
no 3	195 (15%)
no >3	87 (7%)
Mother's employment situation	
F/T employed	160 (13%)
P/T employed	547 (43%)
Maternity leave (F/T or P/T)	20 (2%)
F/T student	14 (1%)
P/T student	41 (3%)
Not employed or student	480 (38%)
Out of home F/T (student/employed)	174 (14%)
Out of home P/T (student/employed)	588 (47%)
In home F/T	500 (40%)

Table 3 Child's family social environment

The description of maternal employment status was not simple. Mothers often described themselves as having two forms of occupation e.g. some were both part time employed as well as being a part time student. Here I report the *main* occupation of the mother, in a hierarchical fashion. If the mother reported herself as full time employed or a full time student that is regarded as her main occupation. For the mothers in part time paid employment this is reported as their main occupation even if they were also part time students. Over half of the mothers were employed, 13% full time and 43% part time. A further 2% were on maternity leave from full or part time employment. 4% of mothers were students, only 1% full time. Thirty eight per cent of the mothers were neither in paid employment nor students. For subsequent analysis the mothers are divided into three simpler groups: out of the home full time (employed or student), out of the home part time (employed or student), in the home full time. Despite these problems in categorisation they are remarkably similar to the findings from two other studies. [264; 267]

	Prevalence n (%)
In any child care	1217 (96%)
No of half days (mean)	4.9
Nursery/playgroup	1195 (95%)
No of half days (mean)	3.6
Other carer	577 (46%)
No of half days (mean)	2.9
Place of care	
Child's home	63 (11%)
Carer's home	381 (66%)
Both	131 (23%)
Other carer*	
Nanny	17 (3%)
Childminder	131 (23%)
Grandparent	403 (70%)
Other relative	81 (14%)

Table 4 Child care
***Some children had more than one carer providing care throughout the week – hence this total more than 100%.**

Childcare (table 4)

Nearly all the children (97%) were in some form of childcare, usually playgroup or nursery (95%), with just less than half of the group (46%) also experiencing more individual care provided by family members or childminders/nannies. One third of the whole group were looked after by grandparents or another family member sometime in the week, reflecting a fairly geographically immobile population. Children spent on average half of their week (5 half days) cared for by someone other than their parents (biological and 'step'). Childcare practice has changed over the last decade in the UK since the introduction of funded nursery places for over 3-year-olds. This is the likely explanation for nearly the whole group (95%) attending nursery or playgroup, compared to the national figure of 10% in 1990. As virtually all the children in the study received some care from other adults there was insufficient power to meaningfully analyse this with regard to the observed variation in behaviour.

Biological influences (table 5)

Indicating biological influences	
Birth weight (kgs) mean (sd)	3.39 (0.56)
Gestation (weeks) mean (sd)	39.5 (2.0)
Antenatal smoke exposure n (%)	279 (22.2%)
Current home smoke exposure n (%)	536 (42.5%)
Admission to SCBU n (%)	230 (18.2%)
Current height (cms) mean (sd)	98.01 (4.01)

Table 5 Indicating biological influences

The mean birthweight of the children was 3.39 kg (UK mean 3.6kg[239]), and mean gestation 39.5 weeks. The mean maternal age for all births in 1991 in the UK was 27.5 years.[271] Just over a fifth (22.2%) of the children had been exposed to cigarette smoke antenatally. 42% of the children were living in households with smoking adults. The mothers' mean age at interview was 32 in this group, 29 years of age when their 3- year-old was born, slightly older than expected. This group of children was comparable to other groups of UK preschool children (table 6). The prevalence of behaviour problems in our population of children was strikingly similar to that reported in other studies. Rural-urban differences were reported in the prevalence of behaviour problems and reading problems in the classical Isle of Wight studies from thirty years ago.[273b] This is also, a largely white, rural population. There is some evidence of what is probably selection bias these children had slightly older mothers, more likely than the national average to have stayed on for further education, be less likely to be living in rented housing and very likely to have access to a vehicle.

	Study population Isle of Wight UK 1997-99	**Comparable UK groups**
General behaviour problems	12.2%	13.5%[263]
Hyperactive behaviour	11.5%	11.4%[263]
Mother's age at birth of child	29 years	27.5 years[271]
Living in lone parent families	12%	9% in New Forest[263] 19% 1991[264] 22% 1999[265]
Mother in full time employment	13%	13% 1991[264] 18% 2000[267]
Mother in part time employment	43%	30% 1991[264] 36% 2000[267]
Living in owner-occupied homes	74%	67% 1991[264]
Own car	90%	67% 1991[264]
Attends nursery/playgroup	95%	10% 1990[270]
Maternal education >16 years	56% 1979 - 1986	35% 1974 49% 1983 52% 1990[272]
Annual household income	27% <£12,000 (included those on state benefits) 84% <£29,999	20% <£12,500 (only in full time work)[273] 75% <£24,000[273]

Table 6 Comparison of socio-demographics of study group

4.5.3 Environmental influences and general behaviour problems (GBP) and behaviour problems associated with hyperactivity (HB)

General behaviour problems are reported in two ways; the distribution of continuous BCL scores for different groups (GBP); and the prevalence of children with more extreme behaviour, who fell above a pre-defined cut-off of 11 (extreme GBP). Hyperactivity is similarly reported in two ways, the distribution of WWP scores for different groups (HB), and the prevalence of children with more extreme behaviour, who fell above a pre-defined cut off of 20 on the WWP, and 4 on the EAS (extreme HB).

Annual family income, the most direct measure of physical environment (material circumstances), showed a clear correlation with behaviour problems. GBP showed a statistically significant gradient across the 5 income bands, with a 2.38 difference between the mean score of the highest and lowest income band (table 7). The prevalence of extreme behaviour problems was over three times higher in the bottom income band (18.4%) than the top income band (5.0%) (table 8). Both HB and the prevalence of more extreme HB showed a similar trend across the 5 family income bands (table 7 and 8).

Indicating environmental influences	Behaviour problem BCL SCORE (GBP)	Hyperactive WWP SCORE (HB)
Sub group total (Phase II) (n=1263)		
Income mean (sd)		
>£42,000	6.18 (2.76)	9.97 (6.56)
£30-41,999	6.82 (2.95)	11.99 (9.01)
£18-29,999	7.12 (3.18)	13.48 (9.15)
£12-17,999	7.60 (3.23)	14.92 (9.71)
<12,000	8.56 (3.47)	17.34 (10.50)
one way ANOVA F (significance)	14.34 (p<0.0001)	14.48 (p<0.0001)
Housing tenure mean (sd)		
owned (n=935)	7.18 (3.13)	13.41 (9.25)
rented/other (n=328)	8.68 (3.60)	17.95 (10.47)
t	-6.706	-6.97
df	510.029	517.002
sig. (2-tailed)	<0.0001	<0.0001
mean difference (95% CI)	-1.50 (-1.94 to -1.06)	-4.55 (-5.83 to -3.27)
Vehicle ownership		
vehicle (n=1134)	7.40	14.20
no vehicle (n=126)	9.10	18.05
t	-5.53	-4.21
df	1258	1258
sig. (2-tailed)	<0.0001	<0.0001
mean difference (95% CI)	-1.71 (-2.31 to -1.10)	-3.84 (-5.63 to -2.05)

Table 7 Physical environmental influences by GBP and HB score

Indicating environmental influences	Prevalence	
	Extreme GBP (BCL>11)	Extreme HB (EAS>4 &WWP≥20)
Sub group total (Phase II) (n=1263)	154 (12.2%)	146 (11.5%)
Income		
<12,0000 (n=347)	64 (18.4%)	53 (15.3%)
12-17,999 (n=338)	42 (12.4%)	45 (13.3%)
18-29,999 (n=383)	34 (8.9%)	36 (9.4%)
30-41,999 (n=133)	11 (8.3%)	11 (8.3%)
>42,000 (n=60)	3 (5.0%)	1 (1.7%)
Mann-Whitney U sig. (2 tailed)	p<0.0001	p<0.0001
Housing tenure		
owned (n=935)	83 (8.9%)	90 (9.6%)
rented/other (n=328)	71 (21.6%)	56 (17.1%)
Odds Ratio (95% CI)	2.84 (2.01 to 4.01)	1.93 (1.35 to 2.77)
X^2 (sig. – Pearson's 2 tailed)	36.98 (p<0.0001)	13.17 (p<0.0001)
Vehicle ownership		
vehicle (n=1134)	126 (11.1%)	123 (10.8%)
no vehicle (n=126)	28 (22.2%)	22 (17.5%)
Odds Ratio (95% CI)	2.29 (1.44 to 3.62)	1.74 (1.06 to 2.86)
X^2 (sig. – Pearson's 2 tailed)	13.05 (p=0.001)	4.87 (p=0.027)

Table 8 Physical environmental influences by extreme GBP and extreme HB

Children living in a rented house were more likely to have GBP and extreme GBP than those in owner-occupied dwellings (table 8). Housing tenure was also similarly significantly associated with hyperactive behaviours, although with smaller odds ratios (table 7 and 8) (OR (95% CI): extreme GBP = 2.84 (2.01 to 4.01), extreme HB = 1.93 (1.35 to 2.77)). The parents who did not own a vehicle were more likely to have a child with both more general and hyperactive behaviours (OR (95% CI): extreme GBP = 2.29 (1.44-3.26), extreme HB = 1.74 (1.06 to 2.86)) (tables 7 and 8).

Maternal age at leaving full time education was the only environmental variable available for the larger group from Phase I (n=1873). GBP showed a statistically significant gradient across the three maternal education bands, with a 1.60 difference between the mean for the highest and lowest bands (table 9). The children with more extreme behaviour problems were three times more prevalent in the lowest education band (14.9%) than the highest education band (4.8%) (table 9). A similar association with maternal education was seen for hyperactive behaviours (table 9,10 and 11). 13.1% of the boys had GBP and 10.1% of the girls (X^2 =3.98, p=0.046, OR (95% CI) =0.75 (0.56 to 1.00)), this was supported by the significant difference between the two groups' mean scores. The parents of girls were less likely to report more extreme HB (OR (95% CI) = 0.66 (0.49 to 0.90). This only applied for the more extreme end of behaviour, and there was no significant difference in the mean scores of boys and girls (table 9).

Socio-demographic variable		Behaviour problem BCL SCORE (GBP)	Hyperactive WWP SCORE (HB)
Total	**(Phase I) (n=1873)**		
Gender mean (sd)			
	Girls	7.26 (3.24)	13.91 (9.68)
	Boys	7.67 (3.28)	14.26 (9.52)
	t	2.712	0.804
	df	1871	1871
	sig (2-tailed)	0.007	ns
	mean difference (95% CI)	0.41 (0.11 to 0.70)	0.36 (-0.51 to 1.23)
Maternal age at leaving education mean (sd)			
	21 yrs or over	6.37 (2.64)	10.75 (7.41)
	16-21 yrs	7.51 (3.29)	14.50 (9.70)
	16yrs or less	7.97 (3.44)	15.86 (10.17)
	one way ANOVA F (significance)	15.78 (p<0.0001)	18.36 (<0.0001)
		Prevalence	
		Extreme GBP (BCL>11)	**Extreme HB (EAS>4 &WWP≥20)**
Total	**(Phase I) (n=1873)**	218 (11.6%)	195 (10.4%)
Gender			
	Girls	93 (10.1%)	78 (8.5%)
	Boys	125 (13.1%)	117 (12.3%)
	Odds Ratio (95% CI)	0.75 (0.56 to1.00)	0.66 (0.49 to 0.90)
	X^2 (sig. – Pearson's 2 tailed)	3.98 (p=0.046)	7.07 (p=0.008)
Maternal age at leaving education (yrs)			
	<=16	132 (14.9%)	109 (12.3%)
	17-20	75 (9.9%)	71 (9.4%)
	>=21	11 (4.8%)	15 (6.6%)
Mann-Whitney U sig. (2 tailed)		p=0.006	p<0.0001

Table 9 **Phase I – Gender and Maternal education and GBP and HB score extreme GBP and extreme HB**

Children who lived in a single parent household were statistically significantly more likely to have a higher GBP (table 10). 19.7% of children who lived with only one adult had more extreme behaviour problems as compared with 11.1% of children who lived with two adults (table 11). Although HB score was significantly higher in the single parent group than the two parent group (p=0.001) (table 10) this association was not seen for extreme HB (table 11).

Parental age was significantly associated with the children's behaviour, with younger parents more likely to report a higher GBP and HB, and a higher prevalence of more extreme GBP, although not extreme HB (tables 10 and 11). There was no significant effect of birth order upon general or hyperactive behaviours, or the more extreme groups. Maternal full time and part time employment significantly reduced the risk of HB and GBP and also extreme GBP, but not extreme HB (tables 10 and 11).

Indicating environmental influences	Behaviour problem BCL SCORE (GBP)	Hyperactive WWP SCORE (HB)
Maternal age at leaving education mean (sd)		
21 yrs or over	6.37 (2.64)	10.75 (7.41)
16-21 yrs	7.51 (3.29)	14.50 (9.70)
16yrs or less	7.97 (3.44)	15.86 (10.17)
one way ANOVA F (significance)	15.78 (p<0.0001)	18.36 (p<0.0001)
Single parent household mean (sd)		
one parent (n=157)	8.61 (3.77)	16.92 10.31)
two parents (n=1106) (mother&father/partner)	7.41 (3.24)	14.26 (9.66)
t	-4.216	-3.189
df (significance – 2-tailed)	1261(p<0.0001)	1261 (p=0.001)
mean difference (95% CI)	-1.19 (-1.74 to -0.64)	-2.66 (-4.29 to -1.02)
Maternal age		
Pearson correlation (2 tailed) (significance)	-0.156 (p<0.0001)	-0.16 (p<0.0001)
Paternal age		
Pearson correlation (2 tailed) (significance)	-0.096 (p=0.011)	-0.091 (p=0.001)
Birth order		
no 1	7.55 (3.21)	14.47 (9.43)
no 2	7.50 (3.31)	14.38 (9.59)
no 3	7.72 (3.53)	15.30 (10.70)
no >3	7.69 (3.58)	14.94 (10.87)
one way ANOVA F (significance)	0.25 (ns)	0.47 (ns)
Maternal employment mean (sd)		
Out of home F/T	13.94 (9.05)	13.94 (9.05)
Out of home P/T	13.97 (9.24)	13.97 (9.24)
In home F/T	15.52 (10.55)	15.52 (10.55)
one way ANOVA F (significance)	3.70 (p=0.025)	3.84 (p=0.022)

Table 10 Indicators of family social environment compared with GBP score and HB score

Indicating environmental influences	Prevalence			
	Extreme GBP (BCL>11)		Extreme HB (EAS>4 &WWP≥20)	
	GBP	No GBP	HB	No HB
Maternal age at leaving education n (%)				
21 yrs or over	8 (4.7%)		12 (7%)	
16-21 yrs	59 (10.8%)		59 (10.8%)	
16yrs or less	87 (15.7%)		75 (13.5%)	
Mann-Whitney U significance (2 tailed)	p<0.0001		p=0.018	
Single parent household				
one parent (n=157)	31 (19.7%)		23 (14.6%)	
two parents (n=1106) (mother&father/partner)	123 (11.1%)		123 (11.1%)	
Odds Ratio	1.966 (1.27-3.04)		1.372 (0.85-2.22)	
X^2 (significance – Pearson's 2 tailed)	9.55 (p=0.004)		1.67 (ns)	
Maternal age (yrs) mean (sd)	30.38 (5.58)	32.73 (5.24)	31.58 (5.50)	32.56 (5.31)
t	-5.16		-2.08	
df	1260		1260	
sig (2-tailed)	p<0.0001		p=0.04	
mean difference (95% CI)	2.35 (1.45-3.24)		0.97 (0.05-1.89)	
Paternal age (yrs) mean (sd)	33.93 (7.19)	35.68 (6.52)	34.50 (6.53)	35.60 (6.64)
t	-3.06		-1.88	
df	1241		1241	
sig (2-tailed)	0.002		0.06	
mean difference (95% CI)	1.75 (0.63-2.87)		1.10 (0.05-2.25)	

Table 11 Indicators of family social environment compared with extreme GBP and extreme HB

4.5.4 Physical environment and general behaviour problems (GBP) and behaviour problems associated with hyperactivity (HB)

Birth weight was only weakly inversely associated with both continuous GBP score and the continuous HB score. Neither the children with more extreme GBP nor HB had different birth weights. Gestation was not associated with any of the behavioural measures. Being exposed to cigarette smoke both antenatally and currently was associated with GBP and HB and an increased risk of more extreme GBP and HB. Having been admitted to a Special Care Baby Unit did not significantly increase the risk of GBP or HB. Current height was significantly associated with both the continuum and the extremes of GBP, but not HB (table 12).

	Behaviour problem BCL SCORE (GBP)	Hyperactive WWP SCORE (HB)
Antenatal smoke exposure mean (sd)		
Yes (n=279)	8.64 (3.54)	17.24 (10.58)
No (n=977)	7.28 (3.19)	13.86 (9.41)
t (significance – 2-tailed) (df)	5.81 (p<0.0001) (415.746)	4.82 (p<0.0001) (411.781)
mean difference (95% CI)	1.37 (0.90-1.83)	3.38 (2.01 to 4.76)
Current smoke exposure mean (sd)		
Yes (n=536)	8.23 (3.40)	16.33 (10.04)
No (n=724)	7.07 (3.18)	13.29 (9.40)
t (significance – 2-tailed) (df)	6.19 (p<0.0001) (1258)	5.50 (p<0.0001) (1258)
mean difference (95% CI)	1.15 (0.79 to 1.52)	3.03 (1.95 to 4.11)

	Extreme GBP (BCL>11)		Extreme HB (EAS>4 &WWP≥20)	
	GBP	**No GBP**	**HB**	**No HB**
Birth weight (kgs) mean (sd)	3.34 (0.58)	3.40 (0.56)	3.37 (0.57)	3.39 (0.56)
t (significance – 2-tailed)	-0.31 (ns)		-0.53 (ns)	
df	1248		1248	
mean difference (95% CI)	-0.06 (-0.16 to 0.03)		-0.03 (-0.12 to 0.07)	
Gestation (weeks) mean (sd)	39.3 (2.3)	39.6 (2.0)	39.7 (2.0)	39.5 (2.0)
t (significance – 2-tailed) (df)	-0.39 (ns) (1261)		0.97 (ns) (1261)	
mean difference (95% CI)	-0.24 (-0.57 to 0.10)		0.17 (-0.17 to 0.51)	
Antenatal smoke exposure				
Yes	52 (18.6%)		45 (16.1%)	
No	102 (10.4%)		101 (10.3%)	
Odds Ratio (95% CI)	1.97 (1.37 to 2.83)		1.67 (1.14 to 2.44)	
X^2 (sig. – Pearson's 2 tailed)	13.56 (p<0.0001)		7.09 (p=0.008)	
Current smoke exposure				
Yes	86 (16.0%)		81 (15.1%)	
No	68 (9.4%)		65 (9.0%)	
Odds Ratio (95% CI)	1.84 (1.31 to 2.59)		1.81 (1.28 to 2.56)	
X^2 (sig. – Pearson's 2 tailed)	12.71 (p<0.0001)		11.31 (p=0.001)	
Admission to SCBU				
Yes	25 (10.9%)		23 (10%)	
No	129 (12.5%)		123 (11.9%)	
Odds Ratio (95% CI)	0.85 (0.54 to 1.35)		0.82 (0.51 to 1.31)	
X^2 (sig. – Pearson's 2 tailed)	0.467 (ns)		0.68 (ns)	
Current height (cms) mean (sd)	97.22 (4.16)	98.12 (3.98)	97.52 (3.91)	98.08 (4.03)
t (significance – 2-tailed)	-2.55 (p=0.011)		-1.57 (ns)	
df	1212		1212	
mean difference (95% CI)	-0.90 (-1.59 to -0.21)		-0.56 (-1.25 to 0.14)	

Table 12 Physical environment compared with GBP and HB and extreme GBP and HB

4.6 Results - multivariate analysis

As in the univariate analysis, multivariate analysis was used to examine the relationship between both environmental and biological independent variables and the two dependent variables; both the continuous and extreme GBP and HB. Logistic regression was used to examine binary dependent variables and multiple regression for continuous dependent variables. Three measures were taken to most directly reflect the physical environment of the family; household income (5 bands), housing tenure (owner occupied or rented), and ownership of a vehicle. Seven environmental measures assumed to be more associated with family social environment were then added to the model in turn. These were maternal education, lone parent family, maternal age, paternal age, birth order, maternal employment and current smoke exposure. Independent biological variables were then added to the model consisting of the significant environmental independent variables. These were factors associated with perinatal adversity; birthweight, gestational age, antenatal smoke exposure and admission to a special care baby unit. Gender and current height were also examined.

4.6.1 Environmental influences and general behaviour problems (GBP)

Firstly the continuous score of GBP was examined, with sequential multiple regression. There was a good model fit on the basis of the three physical environmental factors alone (ANOVA, $F=26.29$, $p<0.0001$, $R^2 = 0.059$).

	GBP score as a function of all environmental measures		GBP score as a function of significant environmental measures	
	β	significance (p)	β	significance (p)
household income	0.195	0.058	0.23	0.018
Vehicle	0.566	0.118	0.623	0.063
Housing tenure	0.694	0.006	0.675	0.006
maternal education	0.346	0.017	0.358	0.011
lone parent family	0.221	0.505		
maternal age	-0.051	0.034	-0.039	0.032
Paternal age	-0.004	0.821		
birth order	0.131	0.238		
mat. employment	-0.022	0.876		
current smoke expos	0.622	0.002	0.622	0.001
constant	6.868	-	6.687	-

Table 13 **Multiple regression analysis of GBP score as a function of environmental measures**

Four out of the seven variables associated with family social environment (lone parent family, birth order, paternal age and maternal employment) did not significantly improve the model fit. Three variables did, maternal education (R^2 = 0.067, R^2 change = 0.008, p=0.001), maternal age (R^2 = 0.073, R^2 change = 0.005, p = 0.01) and current exposure to smoke (R^2 = 0.079, R^2 change = 0.008, p = 0.001).

The R^2 with all these physical environment factors and the four significant family social environment factors was 0.079.

4.6.2 Environmental influences and children with more extreme general behaviour problems (GBP)

Sequential logistic regression was then used to examine extreme GBP as a binary dependent variable. This analysis produced slightly different results. There was a good model fit on the basis of the three material environmental factors (household income, vehicle ownership and housing tenure) alone X^2 = 37.82, df 3, log-likelihood ratio 897.41. Four out of seven variables associated with family social environment (lone parent family, paternal age, maternal employment and current smoke exposure) did not significantly improve the model. Three of the family social environment variables were important. Maternal education improved the model fit significantly (X^2 = 46.94, df 4, log-likelihood ratio 888.29 (X^2 change 9.12, df1, p = 0.003)), as did birth order (X^2 = 64.16, df = 8, log-likelihood ratio 856.65 (X^2 change 6.68,df1, p=0.01)) and maternal age (X^2 =62.78, df 9, log-likelihood ratio 858.82 (X^2 change 7.79, df1, p = 0.005)).

	All environmental measures	Significant environmental measures
	Exp (B) (Odds ratio) (95% confidence intervals)	
household income	0.97 (0.79 – 1.20)	1.04 (0.85 – 1.27)
vehicle	1.13 (0.65 – 1.99)	1.18 (0.69 – 2.00)
housing tenure	1.91 (1.23 – 2.98)	1.91 (1.24 – 2.92)
maternal education	1.42 (1.05 – 1.93)	1.43 (1.06 – 1.92)
lone parent family	1.36 (0.79 – 2.33)	
maternal age	0.93 (0.89 – 0.98)	0.94 (0.90 – 0.97)
paternal age	1.00 (0.97 – 1.04)	
birth order	1.31 (1.07 – 1.62)	1.27 (1.04 – 1.56)
maternal employment	0.98 (0.74 – 1.28)	
current smoke exposure	1.21 (0.83 – 1.76)	
constant	0.23	0.21

Table 14 **Logistic regression analysis of extreme GBP as a function of environmental measures**

4.6.3 Environmental influences and behaviour problems associated with hyperactivity (HB)

	HB score as a function of all environmental measures		HB score as a function of significant environmental measures	
	β	significance (p)	β	significance (p)
household income	0.786	0.009	0.092	0.005
vehicle	0.582	0.584	0.010	0.739
housing tenure	2.350	0.002	0.107	0.001
maternal education	1.127	0.008	0.082	0.005
lone parent family	-0.084	0.931		
maternal age	-0.175	0.014	-0.073	0.013
paternal age	0.023	0.664		
birth order	0.483	0.179		
mat. employment	0.049	0.905		
current smoke expos	1.209	0.038	0.068	0.020

Table 15 **Multiple regression analysis of HB score as a function of environmental measures**

The continuous score of HB, derived from the WWP questionnaire was examined, with sequential multiple regression. There was a good model fit on the basis of the three material environmental factors alone (ANOVA, $F=26.36$, $p<0.0001$, $R^2 =0.059$). Four out of the seven variables associated with family social environment (lone parent family, birth order, paternal age and employment of mother) did not significantly improve the model. Three of the seven variables did, maternal education ($R^2 = 0.068$, R^2 change = 0.009, $p=0.001$), maternal age ($R^2 = 0.074$, R^2 change = 0.006, $p = 0.016$) and current smoke exposure ($R^2 = 0.078$, R^2 change = 0.003, $p = 0.038$)

4.6.4 Environmental influences and children with more extreme behaviour problems associated with hyperactivity (HB)

Sequential logistic regression was then used to examine extreme HB as a binary dependent variable. This analysis produced slightly different results. There was a less good model fit on the basis of the three material environmental factors (household income, vehicle ownership and housing tenure) alone ($X^2 = 18.80$, df 3, log-likelihood ratio 880.365) (table 20). Household income and housing tenure only just significantly explained the variance in extreme HB.

None of the seven variables associated with family social environment (lone parent family, birth order, paternal age, employment of mother, maternal education,

maternal age and current smoke exposure) significantly improved the model (table 17).

		95% Confidence Intervals	
Variable	Exp (B) (Odds ratio)	Lower	Upper
household income	1.25	1.04	1.52
vehicle	1.11	0.63	1.93
housing tenure	1.53	1.00	2.35

Table 16 **Logistic regression analysis of extreme HB as a function of environmental measures related to material deprivation**

4.6.5 Biological factors and general behaviour problems (GBP)

The contribution of biological factors (birthweight, gestation, antenatal smoke exposure, admission to special care baby unit or current height) to behaviour problems was then examined, controlling for the environmental factors previously found to be associated. Firstly, the continuous score of GBP was examined, with sequential multiple regression. The three material environmental factors and the three variables associated with family social environment that had previously been shown to significantly improve the model (maternal education, maternal age and current smoke exposure) were first added to the model.

	GBP score as a function of significant environmental and all biological measures		GBP score as a function of significant environmental and biological measures	
	β	significance (p)	β	significance (p)
household income	0.077	0.021	0.079	0.017
vehicle	0.058	0.060	0.053	0.079
housing tenure	0.075	0.023	0.085	0.009
maternal education	0.065	0.031	0.072	0.014
maternal age	-0.057	0.059	-0.056	0.057
current smoke	0.049	0.145	0.045	0.170
birth weight	-0.050	0.157	-0.066	0.018
gestation	-0.011	0.764		
antenatal smoke	0.089	0.008	0.081	0.013
admisison to SCBU	-0.003	0.923		
current height	-0.050	0.087		
gender	-0.075	0.008	-0.078	0.004

Table 17 **Multiple regression analysis of GBP score as a function of significant environmental measures and biological factors**

Of the antenatal variables added neither gestation nor 'admission to a special care baby unit' significantly improved the model. Birthweight did however improve the model (R^2 = 0.085, R^2 change = 0.005, p=0.012). Antenatal smoke exposure also significantly improved the model (R^2 = 0.091, R^2 change = 0.006, p = 0.007).

Gender significantly improved the model (R^2 = 0.098, R^2 change = 0.006, p=0.008) (table 17) whereas current height had no effect (table 17).

4.6.6 Biological factors and children with more extreme general behaviour problems (GBP)

Sequential logistic regression was used to examine the effects of the biological variables upon these extremes GBP as a binary dependent variable. None of the biological variables significantly improved the model (table 18).

		95% Confidence Intervals	
	Exp (B) (Odds ratio)	Lower	Upper
household income	1.04	0.84	1.28
vehicle	1.25	0.72	2.16
housing tenure	1.78	1.14	2.80
maternal education	1.30	0.96	1.77
maternal age	0.94	0.90	0.98
birth order	1.22	0.98	1.52
birth weight	0.89	0.57	1.39
gestation	0.94	0.83	1.05
antenatal smoke	0.73	0.48	1.10
admission to SCBU	1.53	0.87	2.70
current height	0.97	0.92	1.01
gender	0.71	0.49	1.03

Table 18 **Logistic regression analysis of extreme behaviour problems as a function of significant environmental measures and all biological measures**

4.6.7 Biological factors and behaviour problems associated with hyperactivity

The contribution of the biological factors to the variation in the continuous score of HB was examined. The model included the significant material and family social environment environmental factors. None of the biological factors significantly improved the model (table 19).

	HB as a function of significant factors		HB as a function of significant environmental and biological factors	
	β	significance (p)	β	significance (p)
household income	0.100	0.003	0.098	0.004
vehicle	0.002	0.942	0.004	0.888
housing tenure	0.092	0.006	0.095	0.005
maternal education	0.080	0.009	0.082	0.007
maternal age	-0.072	0.018	-0.070	0.019
current smoke	0.042	0.217	0.043	0.203
birth weight	-0.051	0.152		
gestation	-0.001	0.970		
antenatal smoke	0.055	0.099	0.063	0.057
admisison to SCBU	0.042	0.170		
current height	-0.007	0.806		
gender	-0.029	0.311		

Table 19 **Multiple regression analysis of HB as a function of significant environmental measures and biological factors**

4.6.8 Biological factors and children with more extreme behaviour problems associated with hyperactivity (HB)

Sequential logistic regression was then used to examine the effect of biological variables upon the extremes of HB as a binary dependent variable. Most of the biological variables did not significantly improve the model (table 16). Gender was the exception (X^2 = 32.88, df 9, log-likelihood ratio 843.618 (X^2 change 9.41, df1, p = 0.002)).

		95% Confidence Intervals	
	Exp (B) (Odds ratio)	Lower	Upper
household income	1.23	1.01	1.49
vehicle	1.00	0.57	1.77
housing tenure	1.41	0.91	2.19
birth weight	0.85	0.56	1.29
gestation	1.05	0.93	1.19
antenatal smoke	0.75	0.50	1.14
admission to SCBU	1.15	0.68	1.94
current height	0.97	0.92	1.01
gender	0.57	0.39	0.82

Table 20 **Logistic regression analysis of more extreme HB as a function of significant environmental measures and all biological factors**

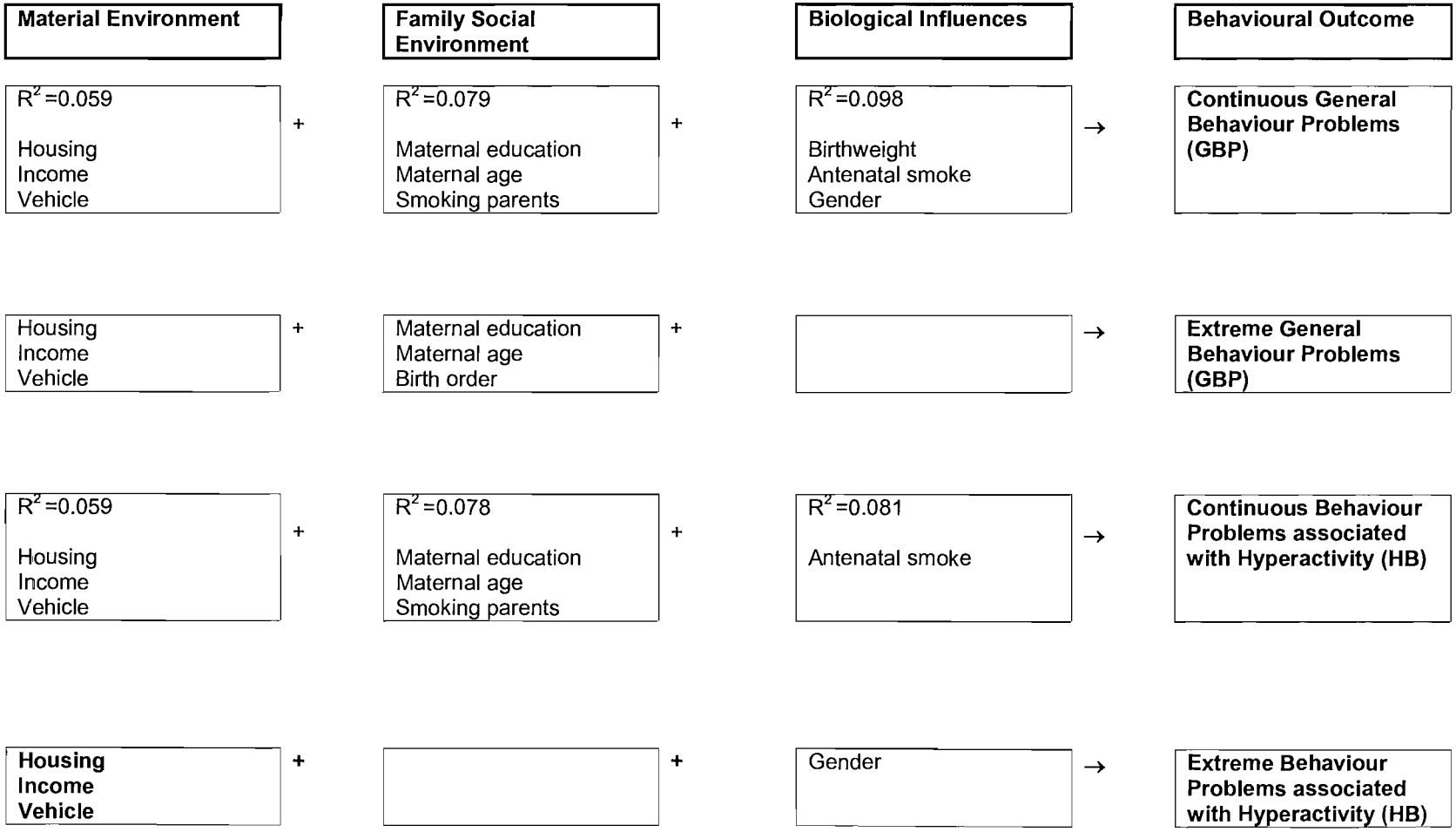


Figure 4 **Significant environmental and physical influences on the various dependent behavioural variables**

4.7 Discussion

This group of children illustrate that many measures of psychosocial adversity are associated with adverse behavioural outcomes, but only a small effect of the measured biological influences (low birth weight, antenatal smoke exposure and male gender).

There was a general pattern of:
a) a weaker association between environmental factors with hyperactive than general behaviour problems, most striking for extreme hyperactivity
b) a smaller number of any variables associated with hyperactive behaviour.

There was no evidence that biological factors had a differential effect upon hyperactive behaviours, and in fact, they had a greater effect upon general behaviour problems.

4.7.1 Environment influences

To what extent was psychosocial adversity associated with adverse behavioural outcomes and what mechanisms may have been at play? Socioeconomic deprivation explained nearly 6% of the variance in behaviour in this sample which dovetails well with estimates of 0.5 – 0.9 of the effects of heritability on attention deficit hyperactivity disorder.[249;274;20] There was little evidence of an association of socio-economic circumstances with *extreme* general and hyperactive behaviours.

Adverse family environment was associated with an increased risk of general but not hyperactive behaviour problems. Maternal factors have been shown to have the strongest effect upon general child health outcomes worldwide.[29] This group showed no adverse effect of maternal employment. Maternal employment has been reported as adversely affecting children's behaviour only when associated with poor parenting[275] and substandard childcare[276]. There was insufficient power to examine the effect of living in a lone parent family on the children's behaviour as this was so closely associated with household income. There were very few wealthy lone parent families (87% of the LPF had incomes in the bottom band, <£12,000).

Figure 4 summarises the aspects of social and family environment that explain nearly 10% of the variation in the number of general behaviour problems and 8% of the variation in hyperactive behaviours. There follows a discussion of possible mechanisms by which these factors may have been influencing children's behaviour.

4.7.2 Differential effect of environment on GBP and HB

There was a similar effect of the same material and family social environment variables upon the continuous measures of general and hyperactive behaviours. This is somewhat surprising. We may have expected a stronger effect of environment upon the heterogeneous problems associated with a higher score for general behaviours than the more specific behaviours associated with hyperactivity. The children who were identified as having a high score on the BCL[301] checklist were likely to be a heterogeneous group. This checklist contained questions about many aspects of behaviour. The WWP[2] and EAS[3] questionnaire accessed specific elements of the child's behaviour, impulsivity, activity and attention.

There was no evidence of a differential effect of any of the biological variables upon hyperactive behaviours. Gender did have an effect on the behaviour outcomes but not differentially. The only other biological variable that affected the continuous hyperactive behaviour score was antenatal smoke exposure, and this also was associated with the continuous general behaviour problems.

Environmental associations with more extreme hyperactive behaviours were noteable less important (see figure 4). This has been reported elsewhere,[20] and is evidence that factors not measured, such as genetics may largely explain the variability in extreme hyperactive behaviours in this age group.

4.7.3 Parenting

Researchers have recognised three sources of influence upon parental functioning, the personality and psychological well being of the parent, characteristics of the child and contextual sources of stress and support.[277;278] The demographic variables collected here may be proxy measures for all three of these sources, and are likely to remain highly correlated and confounded. Most of the social and family

environmental measures can be understood as intermediate factors affecting the child's behaviour mediated by parenting functioning.[35]

Family social environment was assumed to more directly adversely affect parenting and family style, conferring a risk of childhood behaviour problems. Young parental age is associated with behaviour problems throughout childhood. In the multivariate analysis maternal age explained 0.5% of the variance in all behaviour problems, but paternal age was not associated with adverse behavioural outcomes. Younger mothers may have less realistic expectations of infant development, and be less responsive to their child's needs. In a UK study of infant feeding practices maternal age and maternal education were found to be more important predictors than social class of whether a mother both started and continued to breast-feed.[279] Mothers of these Isle of Wight children were at least a year older than the national average, partly due to selection bias, weakening any associations. The observed effect of maternal education was similarly significant but small. In the univariate analysis there were 2-3 times the prevalence of behaviour problems the less education group of mothers compared to the most educated group. This effect held in the multivariate analysis (apart from extreme hyperactive behaviours) explaining 0.5% of the variance in behaviour. It is possible that the skills entailed in staying at school are common to some of those involved in consistent, positive parenting. Little is known about the direct effect of parental IQ upon parenting ability.[15] There is also a possibility of a genetic effect, the mothers of children with behaviour problems may themselves have had childhood behaviour problems. Children with preschool behaviour problems have been shown to have a strong likelihood of persistence of these problems into school years,[280] making them more likely to leave school earlier.

Children of higher birth order were more likely to have extreme GBP, but this was not associated with any of the other behaviour outcomes. There are other reports of children of higher birth order (>5 children), with later language development[1] and with lower educational achievement.[281]

4.7.4 Material deprivation

Rutter maintains that the main effect of socioeconomic adversity upon the incidence of behaviour problems is due to poverty frustrating the attempts at good parenting.[7]

The measures of material deprivation supply most to the models explaining variance in this group of children's behaviour. In the univariate analysis across the five household income bands there was a significant dose relationship with all 4 behavioural measures, indicating that it was not only absolute poverty affecting the behaviour of the child, but relative material adversity. Housing tenure was the most robust predictor of all four measures of behaviour problems. Housing tenure has been proposed as one of the most predictive socioeconomic measures of ill health and health behaviour.[282;283] It is less clear whether there is a direct behavioural effect of the quality of immediate housing and/or wider environment or whether housing is simply the best proxy measure of some other adverse environmental effect. Overcrowding is predictive of childhood behaviour problems.[263] Housing tenure may be more specifically identifying families in worse material circumstances than estimates of household income. Data were not collected on dependence upon state benefits of the household, just those households whose income, from whatever source, was below £12,000. We may have inadequately differentiated this group. Those in rented housing in the UK have been shown to be more likely to be in receipt of state benefits, and for more of their adult life and be more likely to have debts.[34]

The other measures assumed to be reflecting family social environment may also have been measuring material circumstances. The presence of smoking parents was significantly associated with general and hyperactive behaviours. Parental smoking is associated with a number of negative health outcomes for children,[284] the strength of association reduced after controlling for other socio-economic and parental factors. Smoking however has been regarded as a potent 'residual confounder' in many studies on the effects of poverty on ill health. It seems to identify the people who are not only in more extreme poverty but those who have been in poverty longer.[284b;285] Marsh and McKay concluded that smoking was able to differentiate couples with less available money for essential items.[286] Some of the association seen between smoking and behaviour problems may have been due to more extreme material disadvantage.

Twenty two per cent of the mothers smoked during pregnancy. This compares with other estimates of the prevalence of smoking during pregnancy.[287] Antenatal smoke exposure was independently associated with behaviour problems after controlling for

current parental smoking. The direct toxic effect of smoking upon the foetal brain will be discussed later, but smoking during pregnancy has also been linked with deprivation and has been shown to be associated with the length of time dependent upon state benefits.[282;284b] Women smokers are also more likely to have unemployed partners.[286] Unemployed families probably formed a large proportion, but not the whole of the study's lower income band (£12,000), smoking may have been identifying this poorer group, on state benefits.

Birthweight was associated with the continuous measure of GBP, bot not the other three dependent behaviour measures. Birth weight is made up of genotype, gestational age at delivery (controlled for in the subsequent analyses) and in utero environment. Several studies have confirmed Barker's reported associations between low birth weight and adult health problems, in particular ischaemic heart disease and impaired glucose tolerance.[286a] There are also reported associations between low birth weight and neurological problems. Swedish conscripts who are shorter are more likely to have sensorineural hearing loss.[286b] Carefully controlled studies have also shown that cognitive ability at ages 8, 11, 15 and into adulthood has also been shown to be associated with lower birth weight within the normal range (>2.5kg).[286c,286d] A mechanism proposed suggests that as insulin-like growth factors (IGF) play a critical role in determining overall somatic body growth it is also likely that they play a role early in life in the development of the areas of the brain responsible for learning and memory. This reduction in brain growth may have a direct effect upon behaviour or indirectly hearing and cognitive functioning have been shown to have an effect upon general behaviour, and behaviour associated with hyperactivity.

4.7.5 Maternal depression

Unfortunately none of the independent variables directly measured parental personality and psychological well being, but clearly at least part of the reported associations may be secondary to parental mental health problems. Maternal mental health has been suggested as one of the mediating mechanisms linking psychosocial adversity and childhood behaviour problems. There is good evidence of the link between socioeconomic deprivation and women's mental health.[289] Professional evaluation and maternal self-report of infants of depressed women

record an increase in infant behavioural and health difficulties.[290] Breznitz and Friedman showed that depressed mothers were more likely to be use a rapid attentional switching behavioural style towards their child, associated with subsequent behaviour problems.[291] Campbell in a study of low risk mothers however failed to find clear differences in the behaviour of the infants of well and depressed mothers.[248] In a meta-analysis O'Hara reported that indicators of low social status showed a small but significant predictive relationship with post-partum depression.[292] It may be that maternal depression is not sufficient in itself, but has an effect when present with other difficulties. Maternal mental state has been shown to interact with other child factors including temperament[294] and gender[295]. Murray concluded that maternal depression only affected early infant interaction when there was concurrent socio-economic adversity.[293]

Within this population it is possible that maternal smoking was a proxy for poor maternal mental health, providing an alternative explanation for the observed association between both current and antenatal smoking and the two continuous behaviour measures. Several workers have reported poorer psychosocial health in women that smoke[295b;282;296] Smokers have also been reported to have both greater caring responsibilities and poorer social support.[295b]

4.7.6 Biological variables

These were the only measures of child characteristics available to us. In retrospect it would have been useful to access child 'temperament'.[263;295] This study gives only weak evidence that perinatal adversity causes behaviour problems, supporting others' findings.[295] All the perinatal variables were limited as they relied upon parental report, and were retrospective and subject to recall bias. The study was under-powered to comment on the effect of prematurity on behaviour problems, only 35 children (2.8%) were born at 34 weeks or less gestation, none born at less than 28 weeks gestation. A second measure of perinatal adversity, admission to SCBU, had no effect. there is a higher rate of admission to SCBU (18.2%) than the UK national average (10%), but this concurs with their declared admission rate, and suggests that relatively well babies are admitted to this small unit, rendering this variable a poor marker of perinatal adversity. Birthweight only had an effect upon the continuous general behaviour problem score (GBP). It is associated with poorer

cognitive and behavioural outcomes at the extreme end of children born less than 1500g.[252] Again power was a problem. only eleven children were born at less than 1500g (<1%). A German study has shown an interactive effect of low birth weight with maternal mental health on children's behaviour.[253]

Antenatal smoke exposure was associated with higher scores on both behavioural measures. There may have been a direct biological effect, there is evidence that antenatal smoke exposure is causally associated with low birth weight.[288] As well as the effect of maternal smoking on birth weight, paternal smoking has been associated with increased rates of congenital abnormalities.[297;298] There is speculation whether this is due to a toxic effect upon sperm or through the effects of passive smoking on the mother and foetus. Diet may be a further confounder when examining the effect of smoke exposure on the foetus. Maternal diet is known to affect the likelihood of some malformations, the link between folic acid and neural tube defects is now well established.[299] Women who smoke, of all ages and social groups have been shown to eat less fruit and vegetables, and drink more tea.[300]

Gender has been shown previously to have little effect upon the risk of general behaviour problems in this age group.[263] Earls argued that a gender difference is apparent if behaviour problems are differentiated into externalising and internalising problems.[295] In our population boys were more likely to be represented in the group that had extremes of HB, but gender did not affect the continuous HB score. Gender affected the continuous general behaviour problem (GBP) score but not the extreme GBP. Parents may well have different expectations of the behaviour of girls and boys.

4.7.7 Limitations of cross sectional study

This was a cross sectional study and essentially gave us a point prevalence of general and hyperactive behaviour problems when this population had just passed their third birthday. This point prevalence will be influenced by factors influencing the onset of problems as well as factors enabling the resolution of problems. It is unfortunate that we can only speculate on the mode of action of the measured environmental and biological factors. Longitudinal cohort studies may offer greater insight into useful therapeutic interventions.

4.8 Conclusions

The conclusions that can be drawn from this cross-sectional study must be treated with caution. Although the initial response rate was over 70% most of these conclusions are based upon 45% of the population. They rely upon parental (largely maternal) reports of the child's behaviour, socioeconomic circumstances and perinatal details.

The study has shown that environmental factors account for nearly 10% of the variance in the total number of general behaviour problems in these three year olds, and just over 8% of the variance in more specific behaviour problems associated with hyperactivity. The environmental factors were not just those more obviously associated with material circumstances, but those affecting what I have termed the family social environment, including young maternal age, lower maternal education, the presence of smoking in the household, and, to a small extent, later birth order. The social context that children are living within is clearly complex and these factors are highly correlated and incomplete. More specific measures of parental mental health and social support would have been useful.

There was little good evidence of biological factors affecting the child's behaviour, although the number of premature or extreme low-birth-weight babies were too low to explore this hypothesis. Lighter babies were shown to be more likely to have a greater number of general behaviour problems, although this should be interpreted with caution. As with the association with smoking there is the potential for residual confounding and we may have been seeing an ongoing effect of socio-economic adversity. The exception was gender. Boys were more likely to have a higher number of general behaviour problems, and boys were more likely to be represented in the group with extreme hyperactive behaviours.

The total number of general behaviour problems and behaviour problems associated with hyperactivity were similarly affected by environmental influences, although the behaviours associated with hyperactivity were slightly less so. Environmental factors also predicted the prevalence of the more extreme general behaviour problems.

A different picture emerges when we examine extreme behaviours associated with hyperactivity. In the multivariate analysis, household income and housing tenure just remained significant, with the 95% confidence intervals of their odds ratios close to 1.00. No other environmental influences were significant. This study does provide good evidence of the lack of environmental influence upon the prevalence of more extreme behaviours associated with hyperactivity.

Chapter 5

Allergic symptoms and atopy

5.1 Background

This chapter addresses the point and lifetime prevalence in 3-year-old children of symptoms associated with asthma, eczema, rhinitis and food intolerance and allergy and atopy and other associated environmental factors.

5.2 Hypothesis and aims

Hypothesis

Atopy only partly explains the risk of wheeze, rhinitis, eczema and food intolerance in the pre-school child. Other environmental factors are important in determining the likelihood of these symptoms and their persistence.

Aims

1. To report the point prevalence of symptoms of asthma, eczema, rhinoconjunctivitis and food allergy and their coexistence in three year olds.
2. To describe the strength of association between atopy and these symptoms.
3. To describe the association of atopy with birth order and socioeconomic conditions.
4. To describe the association of allergic symptoms with tobacco smoke exposure, perinatal adversity and socioeconomic conditions.

5.3 Results

This analysis is based upon the 1273 children from Phase II (46.6% of the population - Population flow chart, figure 2, Chapter 3). There were complete data on allergic symptoms, skin prick test and demographic factors from 1237 of the population. 28 children declined skin prick testing, and 9 children were skin prick tested but did not have either allergic symptom or full demographic data collected. The mean age of testing was 3 years and 2 months (range; 3 years 0 months to 3 years and 8 months). The denominators for prevalence vary slightly from question to question but missing values for any one question did not exceed 0.5%.

The socio-demographic and biological independent variables have been fully described in Chapter 4. Environmental variables include; annual household income,

tenure of housing, ownership of vehicle, maternal age at leaving full time education, lone parent family, parental age, birth order, maternal employment, current exposure to smoke. Biological variables include; gestation, birth weight, admission to a special care baby unit, antenatal exposure to smoke, current height, and gender.

The child was defined as atopic if they had a reaction to at least one of the six allergens, which was at least 2mm mean wheal diameter, in the presence of a positive histamine and negative saline control (Appendix D). Parents were asked to complete the ISAAC questions[89], identifying their child's current and lifetime experience of allergic symptoms; wheeze, rhinitis or symptoms of eczema (chronic itchy rash). There were additional questions addressing food allergy and intolerance whether their child had experienced other symptoms (diarrhoea and vomiting, abdominal pain, urticaria, other cutaneous and mucous membrane symptoms, wheeze and collapse) and whether the symptoms were food-associated (Appendix E).

Standardised examination may have improved the specificity to the parental responses for current eczema. A systematic review found 13 assesment scales for atopic eczema[86a], including, the six area six sign atopic dermatitis severity score (SASSAD), Rajka and Langeland scoring system, and dermatology life quality index and SCORAD[86] . There has only been wide publication of SCORAD's validity, reliability, sensitivity and acceptability. The single medical assessor would have negated the inter-rater reliability concerns[86a], but the time constraints of an additional 10 minutes per child would have added at least 200 hours of medical time to the project. Eczema is a relapsing and remitting condition. Interest was not only in point prevalence, but also prevalence over the last 12 months, and lifetime prevalence. A Scottish study from the mid 1990s estimated a point prevalence of visible eczema in 2-11 year olds as 2.5%, but of 1-year period prevalence as 8.1%.[316]

Most population surveys rely upon physician-diagnosed rhinitis, which is likely to underestimate the prevalence. The symptom-based questions of the ISAAC questionnaire attempt to circumvent this, a more complex questionnaire-based tool such as SFAR (score for allergic rhinitis)[86b] may have been more sensitive, but has not been validated in children. Examination of the children, for what is often a seasonal condition would have been unlikely to have been useful.

5.3.1 Prevalence

Respiratory symptoms

These results are reported in table 1. Respiratory symptoms were common in this group. The parents of half of the children reported that their child had experienced wheeze at some stage in their life, with a third of the whole group reporting wheeze within the last 12 months. Current exercise induced wheeze was less common, reported in 16% of the group. 9.5% of the children had experienced the isolated symptom of nocturnal cough in the last 12 months. Half of the children who experienced current wheeze also had nocturnal cough. The parents of a fifth of the group reported that their child had asthma. Children with current wheeze were more likely to report asthma than those with a lifetime history of wheeze (55% vs 37%) Children with isolated current nocturnal cough had no increased risk of reporting asthma (table A1).

Table 2 reports the severity and frequency of respiratory symptoms, the majority reporting infrequent symptoms. Of those children reporting current wheeze most (64%) reported 1-3 attacks in the last 12 months, and only a minority (16%) had had a sufficiently severe attack to cause speech limitation, significantly more likely in boys. The majority of the wheezers reported sleep disturbance with 29% being awoken once a week or more frequently.

	Ever wheezed or whistled	Wheeze or whistle last 12 months	Wheeze or whistle last 12 months & noct cough	Ever asthma	Wheezy during/after exercise last 12 months	Nocturnal cough last 12 months (no wheeze)
	N=1264	N=1264	N=1258	N=1262	N=1260	N=1258
Total	628	417	202	242	202	120
n (%)	(49.7)	(33)	(16.1)	(19.2)	(16)	(9.5)

Table 1 Whole group respiratory symptoms

	No of attacks N=416				Sleep disturbance N=414			Speech limitation N=415
	0	**1-3**	**4-12**	**>12**	**never**	**<1/wk**	**≥1/wk**	
Boys	1	144	74	9	74	100	55	44
n=228 (%)		(63)	(32)	(4)	(32)	(44)	(24)	(19)
Girls	1	122	53	12	49	72	65	22
n=188 (%)		(65)	(28)	(6)	(26)	(38)	(35)	(12)
	ns				ns			X^2 = 4.28 p=0.039 OR 1.78 (1.03 - 3.10
Total	2	266	127	21	123	172	120	66
n (%)	(0.5)	(64)	(30)	(5)	(30)	(42)	(29)	(16)

Table 2 Severity of respiratory symptoms (group with symptoms in last 12 months)

Rhinitis

The parents of just under a third of the children reported that their child had experienced symptoms of rhinitis at some stage in their life, most of them also reported symptoms within the last 12 months. Only half of this group had experienced accompanying eye symptoms. Of the symptomatic children more than half of them had perennial symptoms, with just less than half experiencing symptoms in Summer only and a minority suffering Winter symptoms. Only 9% of the parents reported that their child had hayfever (table 3). When the parents of the symptomatic children were asked whether their symptoms interfered with their daily activities, more than half were not affected and only 3% of the parents said that their child was affected 'a lot' (table 4).

n (%)	lifetime rhinitis	current rhinitis	current rhino-conjunctivitis	timing of symptoms				lifetime hayfever
	N=1264	N=1264	N=1264	N=335				N=1261
				Summer	Winter	All year	Other	
Total	362 (29)	337 (27)	163 (13)	92 (28)	36 (11)	192 (57)	15 (5)	119 (9)

Table 3 **Whole group rhinitis symptoms**

n (%)	In last 12 months - nose problem interfered with daily activities N=336			
	Not at all	A little	A moderate amount	A lot
Total	185 (55.1)	105 (31.3)	36 (10.7)	10 (3.0)

Table 4 **Severity of nasal symptoms in the group with nasal symptoms in last 12 months**

Eczema

The parents of 23% of the children reported that their child had experienced a chronic itchy rash at some stage in their life, and 19% reported symptoms within the last 12 months. Many more (45%) said that their child had had eczema at some time in their life. There appeared to be different parental behaviour regarding symptoms and the diagnostic label. Of the parents who had said that their child had had lifetime eczema, over half of them did not identify it as a lifetime chronic itchy rash (table A11). This contrasts with the other allergic conditions where parents were more likely to identify relevant symptoms in their child than give the 'matching' diagnosis.

n (%)	Lifetime itchy rash coming and going for 6 months N=1264	Current itchy rash N=1261	Current itchy rash site specific N=1261	Lifetime eczema N=1264
Total	297 (23%)	242 (19%)	204 (16%)	574 (45%)

Table 5 Whole group eczema symptoms

Of those with a current chronic itchy rash, the majority of the children's symptoms (72%) started at age less than one year, and only a minority (9%) reported symptoms starting within the last 12 months (table 6). More than half of the children had no sleep disturbance, still leaving a significant minority (21%) awoken at night at least once a week.

n (%) n=241	Current itchy rash – age when started			Not cleared completely in last 12 months	Sleep disturbance in last 12 months		
	<1 yr	1-2 yrs	2-4 yrs		never	<1/wk	≥1/wk
Total	174 (72%)	45 (19%)	22 (9%)	87 (36%)	143 (59%)	47 (20%)	51 (21%)

Table 6 Current eczema group – severity

Atopy

1074 children (86%) were assessed by the main research nurse (JG), 169 (14%) were carried out by 4 research nurses primarily working within the NHS or on other studies. All nurses were regularly carrying out skin prick testing. The practical and ethical implications in this age group of carrying out duplicate tests prevented us from adhering to recommendations given for research studies.[5] A mean wheal diameter of greater than or equal to 2mm was used as the cut off to define a positive skin prick test. International recommendations are now to use greater than of equal to 3 mm.[5] The use of 2mm, with its effect of increasing sensitivity but reducing specificity to clinical disease was a pragmatic one, to increase the recruitment for the randomised controlled trial. This decision is likely to have weakened the associations both in the epidemiological part of the study, and the randomised controlled trial, and in retrospect was a poor one. I report the results below with a cut off of 3mm for comparison. All children reacted to the positive control, and none to the saline control. Nineteen per cent of the children were defined as atopic (table 7). House dust mite was the most common cause of sensitivity, with 14% of the whole group sensitised. There were smaller numbers of children sensitised to grass pollen and

cat dander (although still a third of the atopic group). The prevalence of sensitisation to food allergens tested was lower, less than 5% of the group were sensitised to milk, egg or peanut.

Total n (%)	House dust mite*	Grass pollen	Cat dander	Milk	Egg	Peanut	Atopic
	n=1243	n=1243	n=1243	n=1242	n=1240	n=1241	n=1241
≥ 2mm	172 (14)	87 (7)	81 (6)	20 (2)	29 (2.3)	45 (4)	236 (19)
≥ 3mm	125 (10)	58 (5)	61 (5)	9 (1)	17 (1.4)	38 (3)	174 (14)

* D.pteronyssinus

Table 7 Skin prick test - individual allergens

Food intolerance and allergy

These data are limited by several factors. These questions had not been validated and were dependent upon historical recall and vulnerable to parental attributions. Parents quickly blame common symptoms such as vomiting and diarrhoea on foods. Detailing the potential signs and symptoms of the stages of anaphylaxis is complex. Even in the acute clinical situation it is not always easy to assess whether children with urticaria and oedema have reacted to foods. The gastrointestinal symptoms were only recorded if a parent felt that food had caused the symptoms, and were mostly likely to be food intolerance rather than allergy. All events of urticaria and serious allergic symptoms including anaphylaxis were recorded, and then subdivided according to their attributed cause, that may have included a food ingredient.

Gastrointestinal symptoms

16% of parents reported that their child had had gastrointestinal symptoms associated with food at some stage in their life, most commonly milk (table 8). Nearly 7% of all the children were reported to have had symptoms within the last 12 months (table 9). Other foods implicated were; tree nuts, wheat (and more specifically gluten), oats, squash and fruit juices, fatty foods, soya, formula milk, breast milk, ice-cream, breakfast cereal, cheese, peas and beans, meats, drugs, chips, colours and flavours, sweets and chocolate, vegetables and fruit, and tap water.

Cutaneous and mucous membrane symptoms

Eighteen per cent of the children had a history of *any* cutaneous (excluding eczema) or mucous membrane symptoms at some stage in their life. Over two thirds of these

children (165 out of 230, 72%) had experienced only urticaria without any other symptoms. A much smaller number of children (65 (5%)) had had other associated symptoms, but only 8 children, 0.6% of the whole group had suffered parentally-reported life-threatening symptoms (table A19).

n (%)	Lifetime GI symptoms associated with food N=1263	milk	eggs	fish	nuts	other	no provoking food identified
Total	199 (16)	133 (11)	21 (2)	6 (<1)	3 (<1)	30 (2)	9 (<1)

Table 8 Food allergy and intolerance (GI symptoms) - lifetime

n (%)	Current GI symptoms associated with food N=1262	milk	eggs	fish	nuts	other	no provoking food identified
Total	84 (7)	48 (4)	12 (1)	2 (<1)	2 (<1)	32 (3)	9 (<1)

Table 9 Food allergy and intolerance (GI symptoms) – current

13% of children had experienced the isolated symptoms of urticaria at some time in their life. It was more likely to occur in a child's second year of life than their first. Most of the children were only 3 months into their third year at the time of the interview, skewing these results. Half of the children had only experienced one episode, although a fifth of them (21%) did report more than three episodes. Over half of the parents (60%) were not able to identify a precipitant, and just less than a quarter of them (23%) identified a non-food precipitant (including infection, drugs, animals and plants). The food precipitants identified included nuts, milk, egg, fruit or vegetables, bottled-sauces, fish, crisps, additives, ice-cream, chocolate and desserts, (table A21).

Parents of children who reported more significant symptoms were more likely to identify a precipitant (table A22 and table A23). Those children who had had symptoms defined as life threatening identified mainly food precipitants; only one child had no identified precipitant. One child had symptoms triggered not only by food, but also by contact with a furred animal. All of the children in the life-threatening group had experienced 3 or more episodes.

The children who reported symptoms of allergic reactions. regardless of severity, were all more likely to experience other current allergic symptoms (table A24). Urticaria was not associated with an increased likelihood of eczema, but of rhinitis and wheeze. 36 (55%) of the children with serious allergic symptoms also reported current wheeze.

This group of 3-year-olds on the Isle of Wight, had easy access to a local NHS provision for outpatient investigation and treatment of allergies which is unusual for a small district general hospital. Despite this, only 2 out of the 8 children who had experienced life-threatening symptoms had had adrenaline (epinephrine) prescribed. This contrasts with the concerns raised by some authors about possible over-prescription of epinephrine.[48] Half of each group had experienced wheeze within the last 12 months (table A24), and a third of each group had a bronchodilator prescribed.

Coexistence of allergic disorders

The current symptoms of wheeze, chronic rash and rhinitis were examined for their coexistence (table 48 and figure 1). Twenty-nine children (2%) had all three conditions, and 141 (11%) of the children had two conditions. The frequent association between the three conditions of wheeze, rhinitis and eczema has been widely reported.[64;44] A small number of studies have shown a relationship independent of atopy,[51] although it is widely recognised that an atopic disposition explains some of the comorbidity. The relationship between these 3 conditions, independent of atopy, after controlling for confounding environmental factors, was explored.

Sequential logistic regression was used to examine the predictive effect in turn, of current wheeze, symptoms of rhinitis and itchy rash as independent variables on, in turn current wheeze, symptoms of rhinitis, and itchy rash as binary dependent variables, after controlling for atopy, and the other significant environmental and biological variables that are discussed later in this results section.

Current wheeze was examined as a dependent variable, having controlled for atopy, household income, housing tenure and gestation. Current rhinitis improved the model fit (X^2 = 110.44, df 5, log-likelihood ratio 1443.92 (X^2 change = 76.00, df 1,

p<0.0001)). Current itchy rash also improved the model fit (X^2 = 115.58, df 6, log-likelihood ratio 1438.79 (X^2 change = 5.13, df 1, p=0.023)).

Current rhinitis was examined as a dependent variable, having controlled for atopy, household income, gender and current height. Current wheeze improved the model fit (X^2 = 112.37, df 5, log-likelihood ratio 1260.79 (X^2 change = 68.94, df 1, p<0.0001)). Current itchy rash did not improve the model fit.

Current eczema (itchy rash) was examined as a dependent variable, having controlled for atopy. Current wheeze improved the model fit (X^2 = 69.18, df 2, log-likelihood ratio 1125.69 (X^2 change = 8.92, df 1, p=0.03)). Current rhinitis did not improve the model fit.

In summary there proved to be a persisting association between current rhinitis and wheeze, independent of atopy and confounding environmental factors. The relationship between current eczema and wheeze also persisted. After controlling for atopy and environmental factors there was no persisting association between symptoms of eczema and rhinitis.

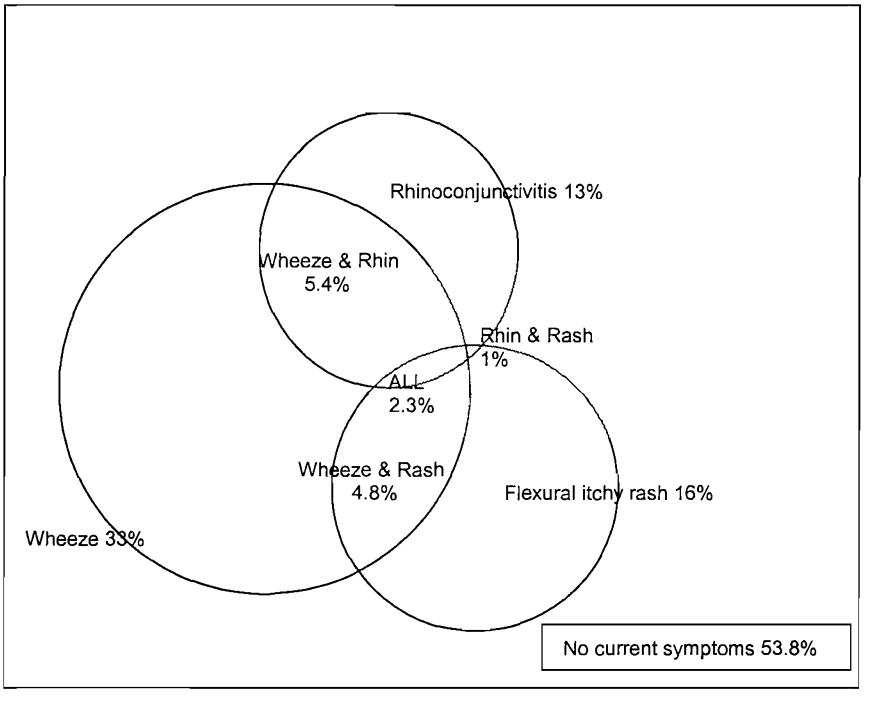


Figure 1 Coexistence of current allergic symptoms
The areas of the circles, and their overlap are proportional to the various prevalences

Current allergic symptoms	FAB n (%)	NE England (ISAAC) [44]
wheeze	417 (33%)	
rhinoconjunctivitis	163 (13%)	
flexural itchy rash	204 (16%)	
no current symptoms	677 (53.8%)	52.4%
wheeze alone	259 (20.6%)	17.9%
rhinoconjunctivitis alone	52 (4.1%)	5.5%
flexural itch alone	101 (8.0%)	5.7%
wheeze & rhinoconjunctivitis	68 (5.4%)	6.2%
wheeze & flexural itch	60 (4.8%)	4.2%
rhinoconjunctivitis & flexural itch	13 (1.0%)	2.0%
wheeze, flexural itch & rhinoconjunctivitis	29 (2.3%)	4.0%

Lifetime diagnoses	FAB n (%)	NE England (ISAAC)[303]
asthma	242 (19.2%)	
hayfever	119 (9%)	
eczema	574 (45%)	
no lifetime diagnosis	564 (44.6%)	46.1%
asthma alone	6.7%	6.2%
hayfever alone	2.5%	16.3%
eczema alone	30.3%	8.7%
asthma & hayfever	0.7%	6.5%
asthma & eczema	9.0%	2.3%
hayfever & eczema	3.3%	5.8%
asthma, eczema & hayfever	2.9%	4.9%

Table 10 Coexistence of current allergic symptoms and lifetime diagnoses

5.3.2 Univariate analyses

The effect of social and physical environment upon both current and lifetime allergic symptoms was examined. The associations with current symptoms are reported in tables 11 and 12 and discussed in more detail as they are less vulnerable to recall bias than lifetime symptoms, and not influenced by access to health care.

	current wheeze	current rhinitis	current itchy rash	atopy (2mm)
Income (£)				
<12,0000 (n=347)	132 (38.0)	102 (29.4)	71 (20.6)	50 (14.8)
12-17,999 (338)	117 (34.8)	91 (26.9)	71 (21.0)	66 (20.0)
18-29,999 (n=383	107 (27.9)	106 (27.7)	60 (15.7)	69 (18.4)
30-41,999 (n=133	43 (32.3)	24 (18.0)	24 (18.0)	24 (18.3)
>42,000 (n=60)	15 (25.0)	13 (21.7)	12 (25)	23 (39.7)
Mann-Whitney U sig. (2 tailed)	158163.00 (p=0.004)	144345.00 (p=0.045)	117717.00 (ns)	1.3786.00 (p=0.011)
Housing tenure				
owned (n=935)	285 (30.5)	231 (24.7)	174 (18.6)	183 (20.1)
rented/other (n=328)	131 (39.9)	105 (32.0)	68 (20.8)	50 (15.6)
Odds Ratio (95% CI)	1.51 (1.16 to 1.96)	1.43 (1.09 to 1.89)	1.15 (0.84 to 1.57)	0.73 (0.52 to 1.03)
X^2 (sig. – Pearson's 2 tailed)	9.68 (p=0.002)	6.64 (p=0.01)	0.72 (ns)	3.15 (ns)
Vehicle ownership				
vehicle (n=1134)	367 (32.4)	297 (26.2)	218 (19.3)	210 (19.0)
no vehicle (n=126)	49 (38.9)	39 (31)	24 (19.0)	22 (18.0)
Odds Ratio (95% CI)	1.33 (0.91 to 1.94)	1.26 (0.85 to 1.89)	0.99 (0.62 to 1.57)	0.94 (0.58 to 1.53)
X^2 (sig. – Pearson's 2 tailed)	2.14 (ns)	1.32 (ns)	0.01 (ns)	0.06 (ns)
Maternal age at leaving education				
<=16 n=549	196 (35.8)	152 (27.7)	115 (21.0)	98 (18.1)
17-20 n=545	171 (31.4)	144 (26.4)	97 (17.8)	98 (18.4)
>=21 n=170	50 (29.4)	41 (24.1)	30 (17.6)	40 (24.0)
Mann-Whitney U (sig - 2 tailed)	165829.5 (ns)	151574.5 (ns)	116893.5 (ns)	113182.0 (ns)
Single parent household				
one parent n=156	59 (37.8)	48 (30.8)	33 (21.2)	22 (14.9)
two parents n=1107	357 (32.3)	288 (26)	209 (18.9)	211 (19.5)
Odds Ratio (95% CI)	1.27 (0.90 to 1.80)	1.26 (0.88 to 1.82)	1.15 (0.76 to 1.74)	0.72 (0.45 to 1.16)
X^2 (sig. – Pearson's 2 tailed)	1.88 (ns)	1.58 (ns)	0.44 (ns)	1.80 (ns)
	yes **no**	**yes** **no**	**yes** **no**	**yes** **no**
Maternal age (years) mean (sd)	32.0 (5.54) 32.66 (5.23)	31.84 (5.23) 32.66 (5.36)	32.72 (5.48) 32.39 (5.30)	33.21 (5.18) 32.26 (5.37)
t	-2.04	-2.44	0.87	-2.44
df (sig (2-tailed))	1258 (p=0.042)	1260 (p=0.015)	1257 (ns)	1229 (p=0.015)
mean difference (95% CI)	-0.65 (-1.28 to -0.02)	-0.83 (-1.49 to -0.16)	0.33 (-0.42 to 1.08)	-0.95 (-1.71 to -0.19)
Birth order				
no 1 n=519	172 (33.1)	128 (24.7)	97 (18.8)	113 (22.4)
no 2 n=462	151 (32.8)	138 (29.9)	83 (18.0)	77 (17.1)
no 3 n=194	61 (31.4)	50 (25.8)	47 (24.2)	36 (18.8)
no >3 n=87	32 (37.2)	19 (21.8)	15 (17.2)	7(8.2)
X^2 (sig. – Pearson's 2 tailed)	0.80 (ns)	4.61 (ns)	3.92 (ns)	11.04 (p=0.01)

Table 11 Current symptoms and atopy and social environment

Biological influences	current wheeze		current rhinitis		current itchy rash		atopy (2mm)	
	no	yes	no	yes	no	yes	no	yes
Birth weight (kgs) mean (sd)	3.40 (0.56)	3.38 (0.56)	3.41 (0.55)	3.34 (0.58)	3.38 (0.57)	3.42 (0.52)	3.37 (0.55)	3.46 (0.59)
t (df)	0.67		2.06		-0.97		-2.05	
df (sig (2-tailed))	1246 (ns)		1248 (p=0.040)		1245 (ns)		1218 (p=0.041)	
mean difference (95% CI)	0.02 (-0.04 to 0.09)		0.07 (0.00 to 0.14)		-0.04 (-0.12 to 0.04)		-0.08 (-0.16 to 0.00)	
Gestation (weeks) mean (sd)	39.62 (1.96)	39.46 (2.12)	39.61 (1.91)	39.30 (2.21)	39.50 (2.03)	39.65 (1.83)	39.51 (1.95)	39.61 (2.15)
t	2.37		2.26		-1.11		-0.73	
df (sig (2-tailed))	1259 (p=0.018)		529.067 (p=0.024)		1258 (ns)		1230 (ns)	
mean difference (95% CI)	0.28 (0.05 to 0.52)		0.31 (0.04 to 0.57)		-0.16 (-0.44 to 0.12)		-0.11 (-0.39 to 0.18)	
Antenatal smoke exposure								
Yes n=279	165 (59.1)		89 (31.9)		46 (16.5)		31 (11.4)	
No n=977	461 (47.8)		247 (25.3)		195 (20.0)		198 (20.8)	
Odds Ratio (95% CI)	1.62 (1.24 to 2.12)		1.38 (1.04 to 1.85)		0.79 (0.56 to 1.13)		0.49 (0.33 to 0.74)	
X^2 (sig. – Pearson's 2 tailed)	12.41 (p<0.0001)		4.85 (p=0.028)		1.66 (ns)		12.25 (p<0.0001)	
Current smoke exposure								
Yes n=536	292 (54.5)		187 (25.8)		99 (18.5)		85 (16.3)	
No n=724	333 (46.0)		148 (27.6)		143 (19.8)		148 (21.0)	
Odds Ratio (95% CI)	1.41 (1.12 to 1.76)		1.10 (0.85 to 1.41)		0.92 (0.69 to 1.23)		0.73 (0.55 to 0.98)	
X^2 (sig. – Pearson's 2 tailed)	8.87 (p=0.003)		0.50 (ns)		0.30 (ns)		4.34 (p=0.037)	
Admission to SCBU								
Yes n=230	85 (37.0)		64 (27.8)		36 (15.7)		47 (21.1)	
No n=1032	332 (32.2)		273 (26.5)		206 (20.0)		186 (18.5)	
Odds Ratio (95% CI)	1.23 (0.92 to 1.66)		1.07 (0.78 to 1.48)		0.74 (0.50 to 1.09)		0.85 (0.59 to 1.21)	
X^2 (sig. – Pearson's 2 tailed)	1.90 (ns)		0.67 (ns)		2.31 (ns)		0.82 (ns)	
Current height (cms) mean (sd)	98.13 (3.98)	97.82 (4.07)	98.18 (4.04)	97.59 (3.90)	98.05 (3.99)	97.96 (4.09)	97.98 (4.02)	98.04 (3.90)
t	1.26		2.28		0.30		-0.22	
df (sig (2 tailed))	1207 (ns)		1209 (p=0.023)		1207 (ns)		1194 (ns)	
mean difference (95% CI)	0.31 (-0.17 to 0.79)		0.59 (0.08 to 1.10)		0.09 (-0.49 to 0.66)		-0.06 (-0.65 to 0.52)	
Gender								
Girls n=609	187 (30.8)		141 (23.2)		113 (18.6)		97 (16.1)	
Boys n=655	230 (35.2)		196 (29.9)		129 (19.7)		139 (21.7)	
Odds Ratio (95% CI)	0.82 (0.65 to 1.04)		0.71 (0.55 to 0.91)		0.93 (0.70 to 1.23)		0.69 (0.52 to 0.93)	
X^2 (sig. – Pearson's 2tailed)	2.77 (ns)		7.40 (p=0.007)		0.25 (ns)		6.26 (p=0.012)	
Age at solids mean (sd)	2.97 (2.57)	3.06 (2.46)	2.97 (2.61)	3.15 (2.22)	2.98 (2.56)	3.15 (2.35)	2.91 (2.71)	2.99 (2.72)
t	-0.62		-1.16		-0.91		-0.41	
df (sig (2-tailed))	1262 (ns)		1262 (ns)		1259 (ns)		1239 (ns)	
mean difference (95% CI)	-0.09 (-0.36 to 0.19)		-0.19 (-0.50 to 0.13)		-0.16 (-0.52 to 0.19)		-0.08 (-0.46 to 0.30)	
Atopy (2mm)								
Yes n=233	101 (43.3)		96 (41.2)		90 (38.6)			
No n=1000	312 (31.2)		236 (23.6)		145 (14.5)			
Odds Ratio (95% CI)	1.69 (1.26 to 2.26)		2.27 (1.68 to 3.06)		3.70 (2.69 to 5.08)			
X^2 (sig. – Pearson's 2 tailed)	12.45 (p<0.0001)		29.75(p<0.0001)		70.87 (p<0.0001)			

Table 12 Current symptoms, atopy and physical environment

Respiratory symptoms

Social environment (table 11 and A3)

Wheeze was associated with a more materially deprived lifestyle. There was an increased risk of lifetime and current wheeze, and nocturnal cough in children living in rented housing. Younger mothers were more likely to report lifetime and current wheeze, and also asthma in their child, but not nocturnal cough.

Physical environment (table 12 and A4)

There was no effect of gender respiratory symptoms, but boys were more likely to have reported asthma (table A4). Some measures of perinatal adversity were associated with respiratory symptoms. Birth weight showed no association, but children with current wheeze and reported asthma were more likely to have been born at an earlier gestation. Antenatal smoke exposure was associated with lifetime and current wheeze, and asthma but not nocturnal cough. Current smoke exposure was associated with all the respiratory symptoms and asthma.

Atopy (table A2)

Being atopic was significantly associated with lifetime and current wheeze, and having asthma but not significant associated with nocturnal cough.

Rhinitis

Social environment (table 11 and A8)

Although children from a more materially deprived lifestyle, with younger parents were more likely to have simple rhinitis reported, they were not more likely to have rhinoconjunctivitis or lifetime hayfever.

Physical environment (table A9)

Boys had more lifetime and current rhinitis and rhinoconjunctivitis than girls, but were no more likely to have hayfever. Measures of perinatal adversity were associated with an increased risk of nasal symptoms; babies with lighter birth weight and lower gestation were more likely to have current rhinitis, but not rhinoconjunctivitis or hayfever. Antenatal but not current smoke exposure was associated with lifetime and current rhinitis and rhinoconjunctivitis, but not hayfever.

Atopy (table A7)

Atopy was highly significantly associated with lifetime and current rhinitis, rhinoconjunctivitis, and hayfever.

Eczema

Social and Physical environment and Atopy (table A12, A13 and A14)

In contrast to respiratory and nasal symptoms, lifetime and current symptoms of eczema were not significantly associated with any of the environmental and biological influences. Eczema appears to be a much 'purer' atopic disease.

Atopy

Social environment (table 11,12 and figure 2,3)

There was a striking effect of affluence upon the likelihood of a child being. Older mothers, but not fathers were more likely to have an atopic child. Children of lower birth order were also significantly more likely to be atopic.

Physical environment (table 12)

Atopic babies were more likely to have been heavier but there was no association with any other perinatal measures. Antenatal and current smoke exposure appeared protective against atopy. Boys were significantly more likely to be atopic than girls.

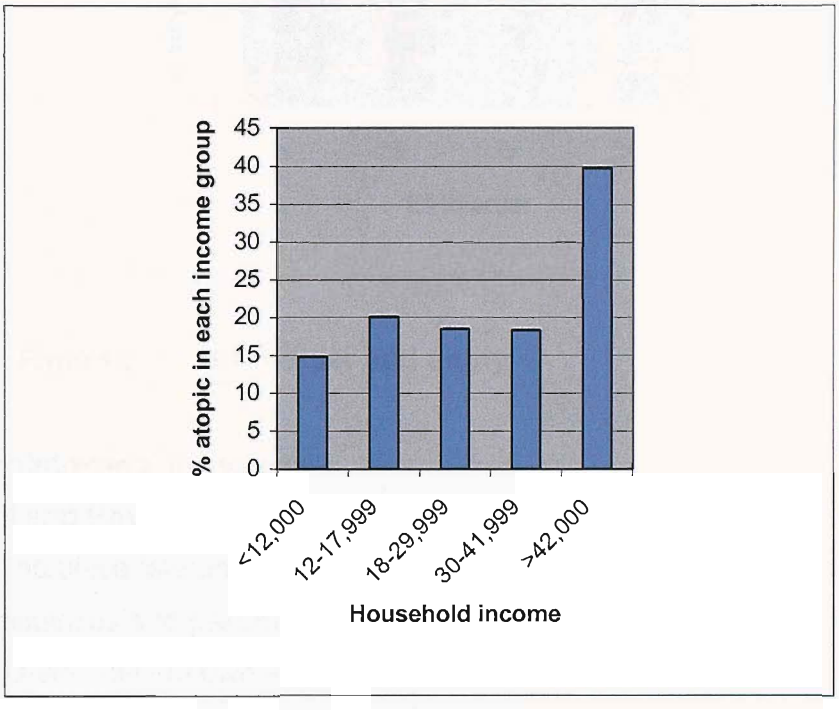


Figure 2 Income and atopy

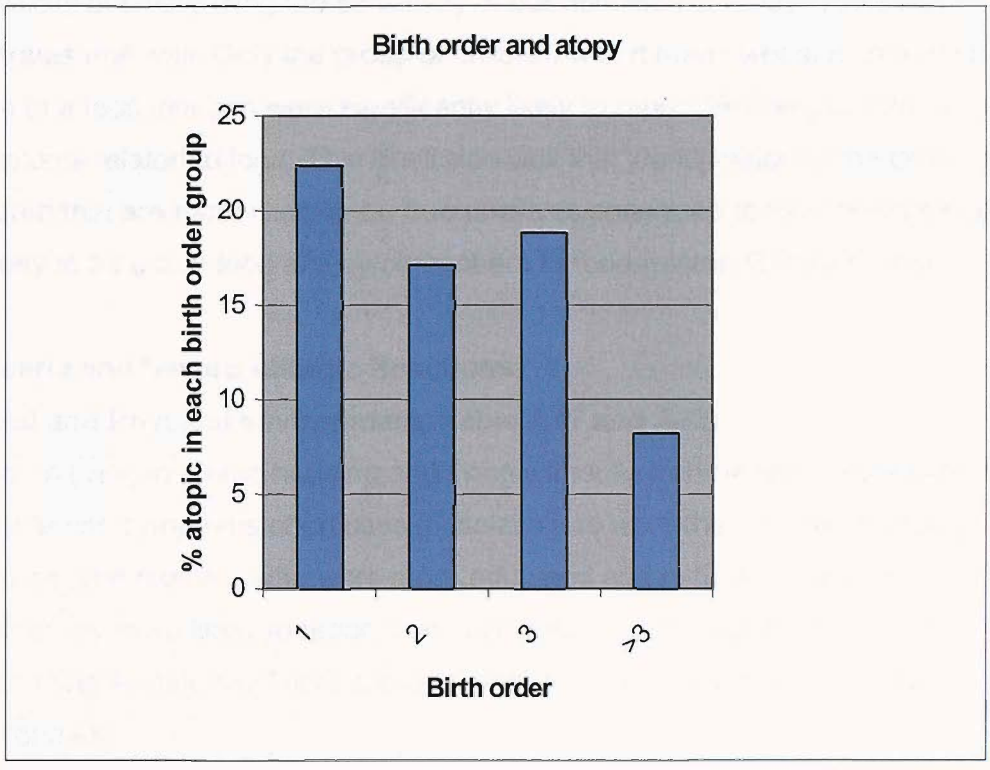


Figure 3 Birth order and atopy

Gastrointestinal symptoms

Social and Physical environment (table A29)

From the univariate analysis there was little association between material circumstances and gastrointestinal symptoms of food intolerance. The children of parents who did not own a vehicle and those living in single parent families were significantly more likely to report a lifetime, but not current history of gastrointestinal food intolerance (table A29). Children with current and lifetime gastrointestinal symptoms were shorter.

Atopy

There was no association between atopy and either current or lifetime gastrointestinal symptoms. In contrast atopy, and sensitisation to aero and food allergens were all significantly associated with a lifetime history of any allergic symptoms, (significant and life threatening). Urticaria in isolation was also more commonly reported in atopic children (table A28). The most striking finding was that 7 of the 8 children, who had experienced life-threatening symptoms, were atopic and 6 of them were sensitised to foods. I discussed earlier the problems with having chosen to use greater than or equal to 2mm mean wheal diameter in reducing the

specificity but increasing the sensitivity of our definition of atopy. Table A27 illustrates that well. Only the group of children with a mean wheal diameter of at least 3mm to a food allergen were significantly likely to report lifetime gastrointestinal symptoms related to food. This illustrates well that identification of the group of children that are more likely to be true positives sensitised to food reveals that there is likely to be a true food allergy component to food-related GI disturbance.

Urticaria and Severe Allergic Reactions

Social and Physical environment (table A31 and A32)

Children living in rented housing and living without a vehicle were more likely to have experienced symptoms of urticaria in isolation as were the children of younger mothers. The mothers who were more educated and in full-time work were significantly more likely to report that their child had had significant and life threatening symptoms. There are no significant associations with physical environment.

5.3.3 Multivariate analysis

Many of the environmental and biological variables are associated. To try and assess more specifically which aspects of the child's environment was associated with their symptoms, the independent association between the variables and the child's symptoms was examined.

Respiratory symptoms

Sequential logistic regression was used to examine lifetime and current respiratory symptoms as binary dependent variables, having controlled for atopy. The independent variables associated with first material and then family situation were examined in the model. Although atopy was important in increasing the risk of respiratory symptoms in this age group there was good evidence of the independent association of material deprivation with respiratory symptoms, and also antenatal smoke exposure. Boys were more likely to have nocturnal cough reported, and admission to SCBU appeared to be protective against a diagnosis of asthma.

Social environment (tables A5, A6 and figures 4,5)

Household income (X^2 = 19.417, df 2, log-likelihood ratio 1681.559 (X^2 change = 9.248, df 1, p=0.002)), and housing tenure (X^2 = 10.058. df 2, log-likelihood ratio

1677.410 (X^2 change = 4.149, df 1, p=0.042)) produced a good model fit for lifetime wheeze. When examining current wheeze, household income (X^2 = 22.478. df 2, log-likelihood ratio 1540.096 (X^2 change = 10.444, df 1, p=0.001)) and housing tenure (X^2 = 27.487. df 3, log-likelihood ratio 1535.087 (X^2 change = 5.009, df 1, p=0.025)) produced a good model fit. When nocturnal cough was examined housing tenure significantly improved the model (X^2 = 7.834. df 3, log-likelihood ratio 762.578 (X^2 change = 7.834, df 1, p=0.005)) but household income and vehicle ownership did not. When examining lifetime asthma, household income (X^2 = 25.282, df 2, log-likelihood ratio 1181.044 (X^2 change = 7.031, df 1, p=0.008)) and housing tenure (X^2 =33.664, df 3, log-likelihood ratio 1172.662 (X^2 change = 8.381, df 1, p=0.004)) significantly improved the model.

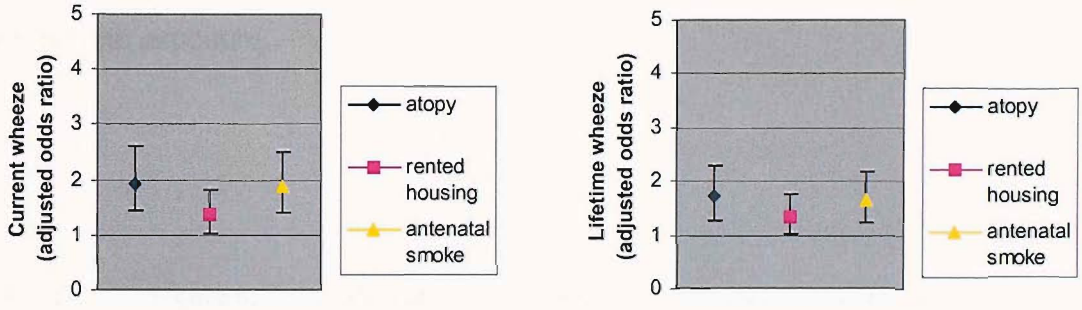


Figure 4 **Risk of current and lifetime wheeze (adjusted odds ratios with 95% confidence intervals)**

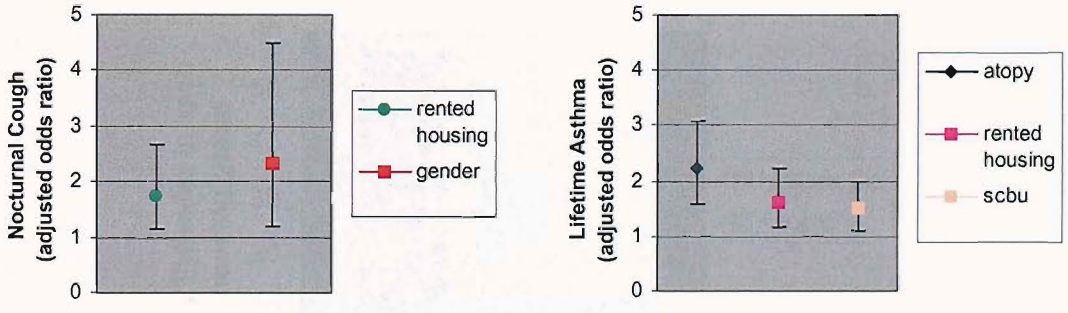


Figure 5 **Risk of nocturnal cough and lifetime asthma (adjusted odds ratios with 95% confidence intervals)**

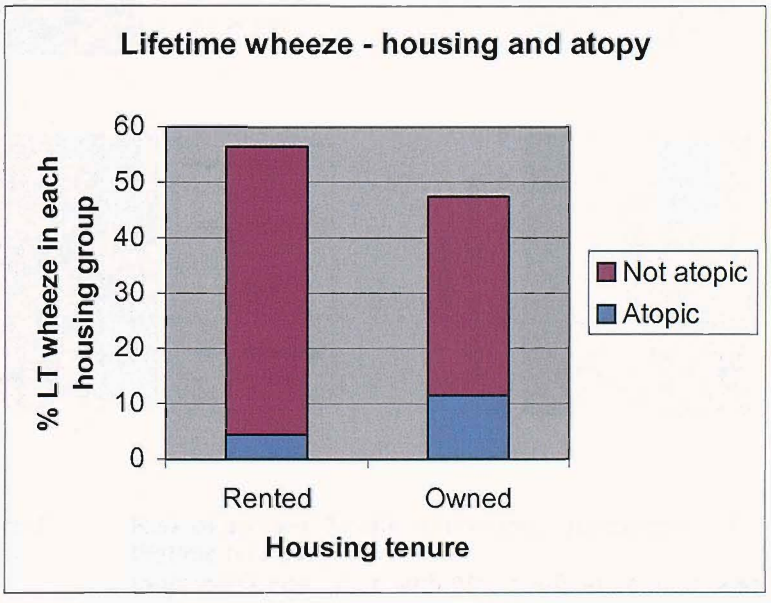
Physical environment

Longer length of breast-feeding was only correlated with a reduced likelihood of lifetime wheeze (X^2 =27.419, df 1, log-likelihood ratio 1674.947 (X^2 change = 4.201, df 1, p=0.040)). Boys were more likely to have reported- asthma, but not respiratory symptoms (X^2 =40.171, df 4, log-likelihood ratio 1167.449 (X^2 change = 4.422, df 1,

p=0.011)). There was only limited evidence of perinatal adversity increasing the risk of respiratory symptoms. Lower gestation babies were more likely to have current wheeze (X^2 = 34.784, df 5, log-likelihood ratio 1509.158 (X^2 change = 7.731, df 1, p=0.005)). The model for nocturnal cough was significantly improved by longer gestation (X^2 = 13.319, df 4, log-likelihood ratio 756.062 (X^2 change = 4.574, df 1, p=0.032)) and admission to SCBU (X^2 = 20.992, df 5, log-likelihood ratio 748.389 (X^2 change = 7.674, df 1, p=0.006)) which were protective. Older mothers were more likely to report that their child had asthma (X^2 = 46.344, df 5, log-likelihood ratio 1160.845 (X^2 change = 4.950, df 1, p=0.015)).

Lifetime wheeze (X^2 = 37.706, df 5, log-likelihood ratio 1160.801 (X^2 change = 9.404, df 1, p=0.002)) and current wheeze (X^2 = 46.774, df 6, log-likelihood ratio 1484.904 (X^2 change = 15.866, df 1, p<0.0001)) both remained associated with antenatal but not smoke exposure.

Figure 6 **Lifetime (LT) wheezing, housing tenure and atopy**



Rhinitis (table A10 and figure 7)

Sequential logistic regression was similarly used to examine lifetime and current rhinoconjunctivitis as binary dependent variables, having controlled for atopy. The independent variables associated with first material and then family situation were examined in the model. The adjusted odds ratios are illustrated in figure 7 with atopy evident as the main risk factor, but with some effect of male gender and deprivation.

Social environment

Household income remained significantly associated with lifetime (X^2 =35.126, df 2, log-likelihood ratio 1439.264 (X^2 change = 6.195, df 1, p=0.013)) and current rhinitis (X^2 =35.239, df 2, log-likelihood ratio 1395.501 (X^2 change = 6.464, df 1, p=0.011)). The fit for the models of both current rhinoconjunctivitis and lifetime hayfever was not improved by any of the material variables.

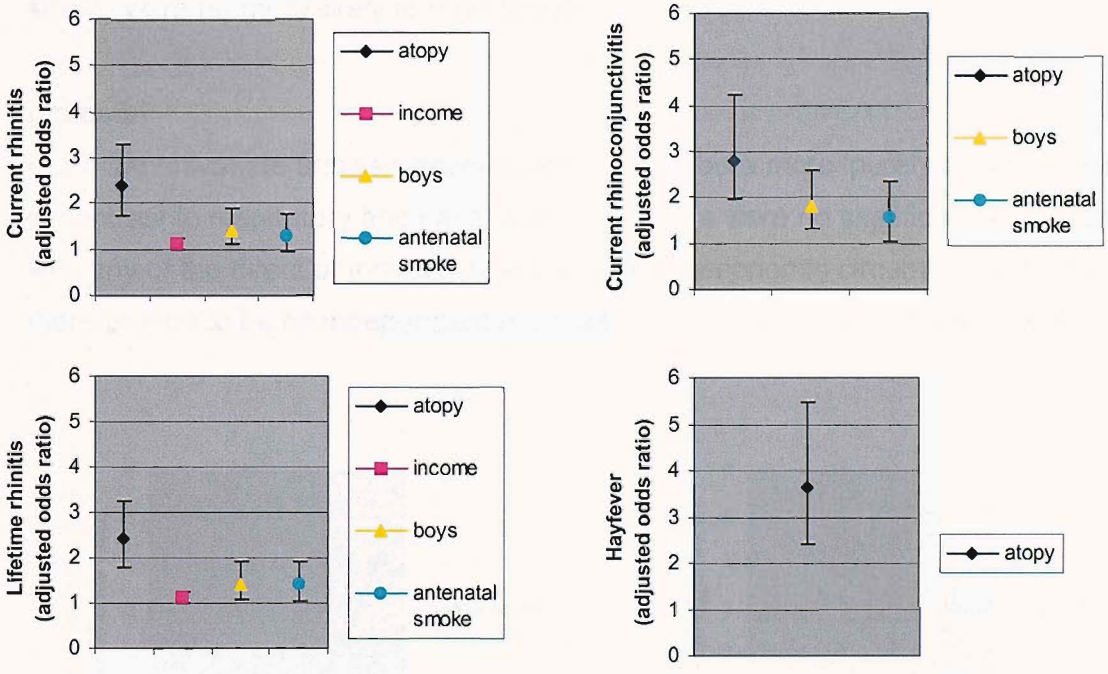


Figure 7 **Risk of current rhinitis and rhinoconjunctivitis and lifetime hayfever (adjusted odds ratios with 95% confidence intervals)**

Physical environment

Sequential logistic regression was then used to examine the effect of biological variables, first controlling for atopy and household income where significant. Boys

were persistently more likely than girls to have lifetime (X^2 =42.373, df 3, log-likelihood ratio 1434.056 (X^2 change = 7.329, df 1, p=0.007)), and current rhinitis (X^2 =35.170, df 2, log-likelihood ratio 1397.454 (X^2 change = 6.658, df 1, p=0.010)), and rhinoconjunctivitis (X^2 =39.150, df 2, log-likelihood ratio 912.577 (X^2 change = 7.831, df 1, p=0.005)), but not hayfever. Lower birthweight was associated with current rhinitis (X^2 = 44.297, df 4, log-likelihood ratio 1373.551 (X^2 change = 4.235, df 1, p=0.040)). The model predicting lifetime symptoms of rhinitis was not improved by current smoke exposure, but it was by antenatal smoke exposure (X^2 = 48.314, df 4, log-likelihood ratio 1417.019 (X^2 change = 4.950, df 1, p=0.026)). The model predicting current symptoms of rhinitis and rhinoconjunctivitis also was not improved by current smoke exposure but was by antenatal smoke exposure (rhinitis; X^2 = 51.646, df 6, log-likelihood ratio 1356.560 (X^2 change = 4.866, df 1, p=0.027)) (rhinoconjunctivitis; X^2 = 46.507, df 4, log-likelihood ratio 890.450 (X^2 change = 5.910, df 1, p=0.015)). Children who had been exposed antenatally or to current smoke were no more likely to report hayfever.

Eczema

From the univariate analysis eczema appeared to be a more 'purely' atopic disease, in contrast to respiratory and nasal symptoms there were no significant associations with any of the direct or indirect measures of socioeconomic circumstances, and there proved to be no independent association with any environmental factors.

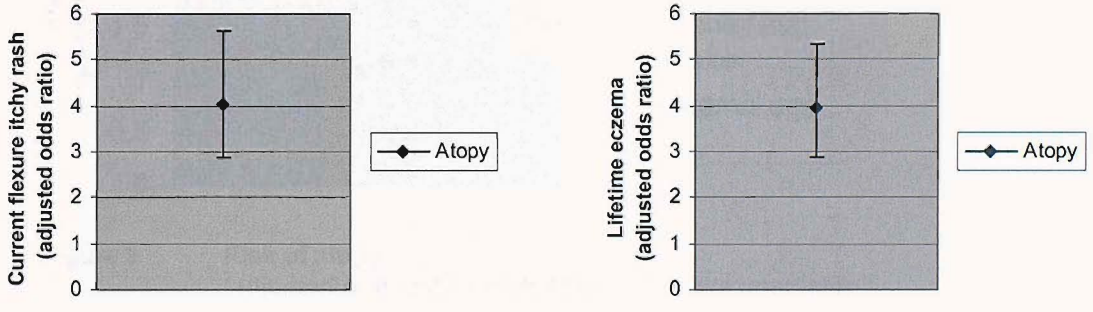


Figure 8 **Risk of current flexural itchy rash and lifetime eczema (adjusted odds ratios with 95% confidence intervals)**

Social and Physical environment (table A15 and figure 8)

Sequential logistic regression was used to examine lifetime and current symptoms of eczema as binary dependent variables, after controlling for atopy. The independent variables associated with first material and then family situation and then biological variables were examined. When examining lifetime and current itchy rash, current flexural itchy rash and lifetime eczema none of the material environmental factors provided a good model fit, refuting any independent relationship with eczema of affluence or deprivation. Maternal education did improve the model fit, less educated mothers were more likely to report that their child had a current flexural itchy rash (X^2 = 66.330, df 2, log-likelihood ratio 1015.921 (X^2 change = 4.887, df 1, p=0.027)).

Atopy (figure 9)

Sequential logistic regression was used to examine atopy as a binary dependent variable. The independent variables associated with material situation were first examined in this model and then measures of family situation. The evidence of association reported in the univariate analysis between affluence and atopy persisted. Lower birth order, heavier birth weight and no antenatal smoke exposure all predict atopy.

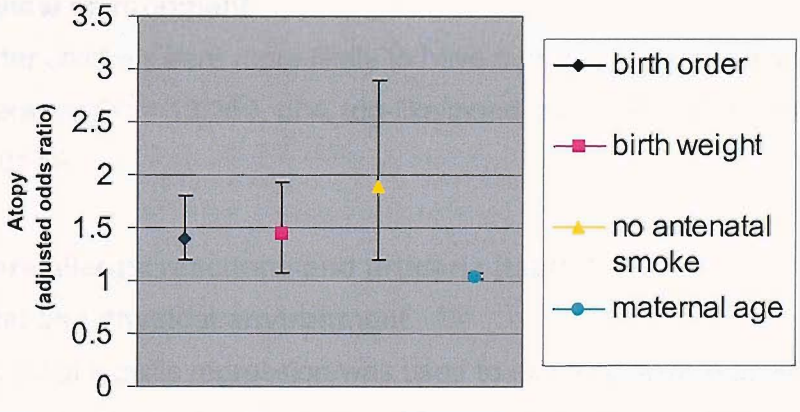


Figure 9 **Risk of atopy**
(adjusted odds ratios with 95% confidence intervals)

Social environment

Of the material independent variables household income (but not housing tenure or vehicle ownership) produced a good model fit (X^2 =8.496. df 1, log-likelihood ratio 1178.494). Children earlier in the sibship position were persistently more likely to be atopic after controlling for household income (X^2 = 16.736, df 2, log-likelihood ratio

1174.009 (X^2 change = 7.886, df 1, p=0.005)). Boys were also more likely to be atopic (X^2 = 22.518, df 3, log-likelihood ratio 1168.227 (X^2 change = 5.782, df 1, p=0.016)).

Physical environment

The only significant perinatal association was that heavier babies were more likely to be atopic (X^2 = 26.858, df 4, log-likelihood ratio 1152.195 (X^2 change = 5.228, df 1, p=0.022)). Babies exposed antenatally but not currently to tobacco smoke were less likely to be atopic (X^2 = 34.538, df 6, log-likelihood ratio 1129.073 (X^2 change = 6.407, df 1, p=0.011)). Children with older mothers were more likely to be atopic (X^2 = 40.692, df 6, log-likelihood ratio 1105.361 (X^2 change = 7.167, df 1, p=0.007)).

Gastrointestinal symptoms (table A33)

Sequential logistic regression was used to examine gastrointestinal symptoms of food intolerance, first controlling for atopy. In summary when examining lifetime gastrointestinal symptoms associated with food, after controlling for atopy, the only persisting significant association was with household income and height.

Social environment

Parents of children with lower household incomes were more likely to report symptoms (X^2 = 9.530, df 2, log-likelihood ratio 1054.693 (X^2 change = 6.411, df 1, p=0.011)).

Physical environment

Shorter children were more likely to have current gastrointestinal symptoms of food intolerance (X^2 = 13.259, df 4, log-likelihood ratio 567.776 (X^2 change = 5.713, df 1, p=0.017)).

Severe allergic reactions and urticaria (table A34)

Social and physical environment

Sequential logistic regression was used to examine severe allergic reactions and urticaria as binary dependent variables, after controlling for atopy. When examining lifetime and current urticaria and severe allergic reactions there was no good model fit based only upon environmental factors reflecting material or family environment. There was an association with younger mothers both with severe allergic reactions (X^2 = 30.042, df 2, log-likelihood ratio 1142.200 (X^2 change = 4.454, df 1, p=0.035)) and 'urticaria only' (X^2 = 8.421, df 2, log-likelihood ratio 949.760 (X^2 change = 4.538, df 1, p=0.033)).

5.4 Discussion

5.4.1 Prevalence

All the three major allergic symptoms are common within this population. Respiratory symptoms are extremely common. Comparisons with other populations are interesting but made difficult by their differing ages, and diagnostic criteria (table 13). Nearly half of the FAB children had had a wheezing illness at some stage, with just over a third with wheeze in the last 12 months. The prevalence of lifetime asthma (19.2%) is very similar to that reported by Shamssain in UK 6-7 year olds (22.7%), using the same ISAAC questionnaire.[91] However the parents of these younger FAB children reported a higher prevalence of respiratory *symptoms,* reporting similar prevalences to those from 12-13 year olds across the whole UK ISAAC data.[44;303]

It is now accepted in the younger child that even correctly labelled wheeze is not necessarily asthma.[57;305] The Tucson group has divided children with wheeze into three groups; 'transient wheezers', 'persistent wheezers' and 'late onset wheezers'.[61]The high prevalence of respiratory symptoms in this group is explained partly by the inevitable inclusion of some 'transient wheezers', who are unlikely to go on to have asthma. A third of the group of children with reported lifetime wheeze appeared to have had resolution of their symptoms, with none in the previous 12 months. The prevalence rates of respiratory symptoms are still higher than comparable populations. De Jong reported 10.9% of their 5-year-old population had experienced wheeze in the last 12 months, but this prevalence may have been affected by the affluence of this breast feeding population.[306] It is possible that selection bias also resulted in some degree of overestimate of the prevalence in symptoms, the FAB study was only able to recruit half of the Isle of Wight's three year olds.

There is no well-validated questionnaire available for use in the preschool age group.[308] The ISAAC questions have not been validated in this age group, although were validated for parental report for the 6-7 year old age group.[309] Some parents may have misreported wheeze. Elphick and team[310] described the noisy breathing originating in the upper airway, experienced commonly in infancy, in Yorkshire dialect as 'ruttles'. Their study showed that parents of infants were likely to mistakenly describe this as wheeze; one third of them changing their label once

more closely questioned with video demonstration. As this noisy upper airway breathing appears to be confined to infants under 18 months, some of our 3 year olds may have grown out of 'ruttling', and in fact never have wheezed, overestimating the prevalence of lifetime wheeze, but having little effect on current wheeze.

	FAB (3yrs)	N. East England (ISAAC) (6-7yrs)[91]	UK (ISAAC) (12-14yrs)[303]	IOW (4yrs)[45]	Aberdeen (10yrs)[55]		Sheffield (8-9yrs)[307]		Utrecht BOKAAL (5yrs)[306]
					1989	1994	1991	1999	
wheeze in last 12 months	33%	18.0%	33.3%		19.8%	25.4%	17.0%	19.4%	10.9%
nocturnal cough in last 12 months	25.6%	27.7%			14.0%	31.9%			
exercise wheeze in last 12 months	16%	13%	28.5%						
lifetime wheeze	49.7%	29.6%	48.8%				30.3%	35.8%	
lifetime asthma	19.2%	22.7%	20.9%	16.4%	10.2%	19.6%	17.9%	29.7%	

Table 13 Comparison of respiratory symptoms with other studies

Cane's team[311] similarly reported that 30% of parents of older children, irrespective of whether or not their child had been diagnosed with asthma, when shown a video of a child wheezing, identified it with words other than wheeze, and 30% incorrectly labelled other sounds as wheeze. Parents were more able to correctly label the location of sound than name it as wheeze. The ISAAC questions do at least partly address this, as the question posed does refer to location, 'wheeze or whistling in the chest'. Use of a supporting video may have increased the accuracy of our reporting.

It is unlikely that the high rates of symptoms can be explained by some peculiarity of the children of the Isle of Wight. In the 12-14 year old ISAAC data there was very little geographical variation across the UK.[303] Arshad et al reported a lower prevalence of current wheezing illness in 4 year olds, born 5 years earlier than these children, also on the Isle of Wight.[45] This data may reflect a real subsequent increase in the prevalence of wheeze. Anderson[312] suggested that the rise in reported wheeze reached a plateau in the mid 1980's, but this has been disputed by

Omran et al, reporting an ongoing increase from their Scottish data collected in 1994[55].

It has been suggested that some of the observed increase in prevalence in respiratory symptoms may be due to increased reporting of mild symptoms.[307] A substantial proportion of this group only reported mild symptoms (table 3). A third reported no sleep disturbance. Two thirds of the children with wheeze reported 3 or less episodes a year and only one in six (5% of the total population) had had an episode of wheeze limiting their speech. However this theory is not supported when comparing these figures with the Shamssain's North-East England 6-7 year olds, the likelihood of more severe, more frequent symptoms in both groups appears similar.[91]

Symptoms of rhinitis, perhaps surprisingly, also proved to be common in this pre-school group. Twenty-seven per cent of the three-year-olds were reported to have current symptoms of rhinitis, and 9% reported hayfever. They were not perceived by the parents as particularly significant symptoms; less than 4% of the whole group's daily activities were moderately or greatly affected. This may go some way to explain why rhinitis has not been particularly well researched or reported in the pre-school age group.[313] Cohort studies are limited in number but suggest that the prevalence of symptoms of rhinitis and a diagnosis of hayfever increase with age,[313] making one expect increased prevalence in older groups assessed using the ISAAC questionnaire. In the 6-7 year old group from the North East of UK a lower prevalence of rhinitis symptoms was reported and a similar prevalence of hayfever, possibly the increase may occur later in childhood.[91] Results from the 12-13 years UK group supports this, 18.2% reported rhinoconjunctivitis, and 34.9% hayfever.[44]

Eczema was also a significant problem, just less than half of this population reported lifetime chronic itchy rash or eczema. A fifth (19%) reported symptoms of chronic itchy rash within the last 12 months, with slightly less (16% of the whole group of children) reported a typically distributed chronic rash. Studies differ in their exact diagnostic criteria for eczema, despite this the prevalence figures in the UK over the last 10 years have remained remarkably stable. A prevalence of 15.9% was reported in the 1994 study on the Isle of Wight in four year olds[45], 14% in 1-4 year olds in Leicester[314] and 20.5% in 6-7 year olds in the North East of England[91]. Sixteen per cent of 12 year olds in South Wales in 1988 reported current eczema[43] and 16.4% of

13-14 year olds in the 1996 UK ISAAC study[44]. Of note are the differing ages of these populations, after the age of 3 there seems little evidence of resolution throughout childhood, presuming few new cases of eczema. Other longitudinal studies have also reported a lower rate of resolution[315] than previously estimated by others[316].

This population's parents seemed very ready to label their child as having had eczema as a baby or in infancy. This may relate to changing diagnostic practices. There is some evidence of resolution of infantile eczema in this population as described clinically[317], only 42% of those who reported 'ever eczema' also reported symptoms within the last 12 months. Despite this tendency to resolution eczema remains a significant problem in this age group. Su has attempted to quantify the costs of eczema to family and society.[318] He estimated at least in children with moderate or severe atopic eczema that the impact on the family was greater than having a child with diabetes, and the personal cost was greater than having a child with asthma. Examining the more severe cases in this data; one in three of the symptomatic children reported that their rash never resolved. Just less than half of them reported some sleep disturbance, nearly 8% of the whole group.

5.4.2 Infant or school age patterns

The Tucson study team have described three clinical phenotypes; early transient wheezers, persistent wheezers and late onset wheezers each with distinct risk factors.[61] Silverman had suggested in 1993 that wheezing in the first *two* years of life did not necessarily lead to school age symptoms. He concluded that infantile wheeze was clinically distinct and unrelated to bronchial hyperresponsiveness or atopy, but associated with maternal smoking during pregnancy (but not current exposure to smoke) low birth weight and prematurity.[305] Some authors report that by the age of 3 years wheezing is associated with atopy[319], while others report that atopy is not the main cause of wheeze until about the age of seven[320]. In FAB 3-year-olds atopy did confer a significant risk for current wheeze (OR; 1.93 (95% CI; 1.43 to 2.60)). However there was also evidence of association with risk factors more typically associated with the transient or infantile wheeze clinical phenotype; current wheeze was independently associated with perinatal adversity, namely antenatal smoke exposure and lower gestation. This study lacked the power to

examine the effect of extreme prematurity upon respiratory symptoms. If we examine the risk factors for wheeze in this group of three-year-olds, the children appear to fit, as one might expect, between infancy and school age children. Thus they were in transition, a 'mixed bag of wheezers'.

5.4.3 Common risk factors for respiratory symptoms and rhinitis

It is accepted that across all age groups allergic rhinitis and asthma commonly co-exist. This has led some groups to suggest the concept 'united airway, one disease'. Others have also suggested a link between non-allergic asthma and rhinitis, although this is less well understood.[321] The diseases may share some common end organ pathophysiology. Genetic determinants of primary abnormalities of airway and nasal epithelium[322] and dermis[71] have been suggested. This group of children illustrates that the coexistence of non-atopic rhinitis and wheeze may be important in infancy.

Just under a quarter of the children in this group with current wheeze also had symptoms of rhinitis. Although atopy was one of the explanations for the observed comorbidity, only 28% of the 3-year-olds with current rhinitis were atopic, as compared to half of the school age children in a comparable Swiss study.[323] There proved to be a persisting association between current rhinitis and wheeze, independent of atopy and independent of environmental factors. It is accepted that in this young age group perennial rhinitis is more common and atopy is less important than in older age groups.[313] Many of the children did not have a pattern of symptoms typical of grass pollen allergy (hayfever). More than half of the three-year-olds with symptoms had perennial symptoms and only 1 in ten children had a diagnosis of hayfever. Atopy was associated with current rhinitis, with adjusted odds ratios of between 2 and 3. There were other important risk factors including socioeconomic deprivation exposure to antenatal tobacco smoke.

As discussed previously a large proportion of children that wheeze before the age of 3 years do not go on to wheeze into school age, so called 'transient wheezers', a clinical picture more typical of children who are not atopic and have been exposed to antenatal tobacco smoke.[60]. Some of the Isle of Wight's three-year-olds were in this group, as revealed by the persisting association of wheeze with antenatal smoke

exposure and socioeconomic deprivation. There appear to be parallel environmental risk factors for current wheeze and rhinitis. I would speculate that there might be three parallel groups of children with rhinitis – transient, persistent and late onset 'sniffers' similar to the groups of wheezers. The similar patterns of epidemiological associations may predict parallel pathophysiological changes in the upper and lower airways. This theory is not entirely supported by the Tucson work, rhinitis at age one was associated with late-onset and persistent wheezing, rather than transient wheezing.[61]

5.4.4 Smoke exposure or material deprivation

Children whose mothers reported smoking during pregnancy were more likely to have current and lifetime wheeze. A fifth of the children had been exposed to smoke antenatally, and just less than half of them were also currently regularly exposed to tobacco smoke. This left 55% of children with no exposure. The ALSPAC study reported less of their mothers who smoked during pregnancy (16% vs 22%) but antenatal smoke exposure was only recorded during the 3rd trimester. Less children were reported as having no exposure to smoke in the ALSPAC study (39%).[324] 'Wheeze' in the FAB 3 year olds was not associated with current smoke exposure, after controlling for antenatal smoke exposure concurring with others' reports.[304;325;326] These results are a long way from proving a causal link between smoking mothers and children with wheeze. Pathophysiological mechanisms have been proposed that link smoking, poor foetal lung growth and subsequent childhood respiratory symptoms.[327] It is accepted however that smoking is a factor which is highly confounded, being a marker of many other sociodemographic factors, many associated with extremes and length of deprivation. One in three children within the lower income bracket were exposed to smoke antenatally, in the top two income brackets only one in eight children were reported to have been exposed to smoke. This smoking data was further weakened by its retrospective nature and lack of objective corroboration of smoking habit; eg urinary cotinine levels, or more detailed assessment of patterns of smoke exposure.[328] Nevertheless the discrimination between the effects of antenatal and post natal smoke exposure is likely to be important.

Children living in rented housing were not only more likely to have reported lifetime and current wheeze, but also to have a diagnosis of asthma. Rented housing has been shown to be an accurate marker of economic deprivation[329] but there may also be some specific factors associated with the poor quality of rented housing that increase the risk of childhood respiratory symptoms, such as dampness[330] and overcrowding.[1]

5.4.5 Nocturnal cough

Nocturnal cough was not associated with atopy but material deprivation was associated with both wheeze and nocturnal cough. Ninan et al concluded that nocturnal cough in isolation was unlikely to be asthma.[331] They showed that children with cough were more similar to the asymptomatic population than children with other respiratory symptoms. This FAB 3 year olds had a differentiating pattern of risk factors; shorter gestation, exposure to antenatal smoke and longer breast feeding predicted lifetime wheeze but had no effect on the risk of nocturnal cough (in fact longer gestation and admission to SCBU was associated with nocturnal cough). This is further evidence that nocturnal cough in isolation has a different pattern of environmental risk factors, is likely to belong to a different group of non-atopic diseases, and is unlikely to be asthma.

5.4.6 Eczema as atopic disease

Eczema however was closely associated with atopy. Atopic children were three times as likely to report current itchy rash than non-atopic children (OR (95% CI)=3.62 (2.63-4.99)). This relationship remained robustly significant in the multivariate analysis. We were unable to show that affluence or any other environmental factors had any association, independent of atopy with symptoms of eczema. The only other significant association further refuted any independent effect of affluence on eczema, *less* educated mothers were *more* likely to report a current flexural itchy rash in their child. The linear relationship shown by Williams et al between social class and presence of eczema in 7 year olds born in 1958 was based upon examination evidence of eczema, rather than parental report, including the more chronic, severe cases of eczema who may be a separate subgroup.[93] Studies of 7 year olds in Northern Europe[332] and UK[91] have reported that girls are at higher

risk of lifetime and current eczema, but there was no gender effect in this population of 3-year-olds. Eczema did appear to be a 'purely' atopic disease.

5.4.7 Atopy

One in five (19%) of this group of children were atopic. This is almost identical to the rates reported by Arshad in the group of 4 years olds born 5 years previously on the Isle of Wight.[45] Other studies with older age groups have reported higher rates of atopy[333;334], at least partly explained by the observed cumulative incidence of new sensitisations later in childhood[100].

There are two pieces of evidence from the risk factors associated with atopy in support of the hygiene hypothesis.[65] The first is the association demonstrated with affluence[102], and the second that with birth order. There was an increased prevalence of atopy shown with higher income in the univariate analysis. Atopy was also shown to be associated with lower birth order. Similar findings have been reported elsewhere.[103;335] The postulated mechanism is the protective effect of exposure to early infections introduced by older siblings. We were not able to examine the protective effect of day care reported by others as 95% of this group spent some part of their week in nursery or playgroup.

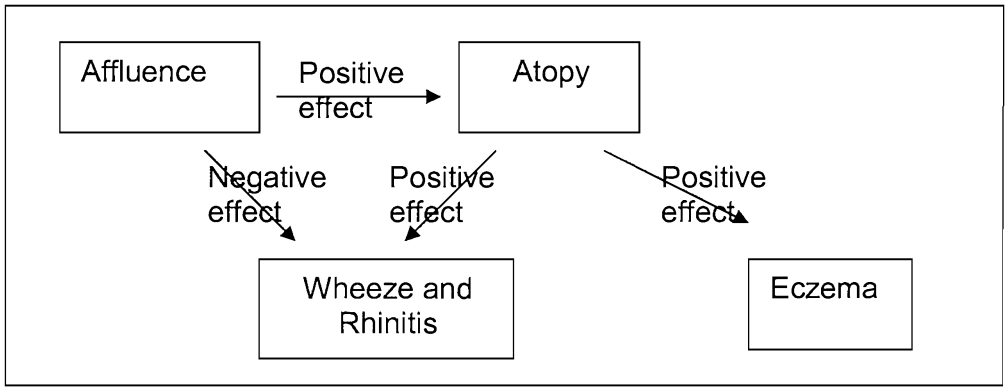


Figure 10 Differential effect of material environment on allergic symptoms

The symptoms of eczema appeared to be more 'purely' atopic in this group, with no other significant environmental or biological associations. Rhinitis and wheeze were clearly more complicated, with associations with socioeconomic deprivation and antenatal smoke exposure. Longitudinal studies have given us increasing insight into

the different trajectories of children with infantile wheeze. Examining the prevalence of wheeze within this population by both socioeconomic and atopic status further illustrates the heterogeneity of infantile wheeze. Although wheeze is more common in the more deprived group, atopic wheeze is more prevalent in the more affluent group of children. Figure 10 illustrates how affluence may be working in opposing directions to increase the risk of wheeze and rhinitis. Lifetime wheeze is less prevalent in the more affluent group of children (those living in owner occupied accommodation), but non-atopic wheeze is more important in the less affluent group of children (those living in rented accommodation), and atopy is more important as a cause of wheeze within the affluent group.

5.4.8 Food allergy and intolerance

The symptoms of food allergy and intolerance proved very difficult to assess. Diagnosis in this sample was limited by its dependence upon retrospective recall of information, solely gathered by questionnaire without objective confirmation.[46] A large number of parents (15.8%) said that their child had suffered gastrointestinal symptoms associated with food, but less than half of these reported more persisting problems. Although a cross sectional study is not best placed to illustrate natural resolution of conditions, this provides support for Bock's finding of the natural history of food related problems.[46] Bock's children presented at a mean of 6 months and most had successfully reintroduced the food after 12 months (median 9 months, range 2-37 months).[46] There were still 7% of the FAB group with a possibly unnecessarily restricted diet, potentially associated with nutritional deficiencies.[98] A concerning finding was the persistent association between short stature and current gastrointestinal symptoms. This may have been secondary to necessary or unnecessary dietary restrictions. It may have been due to a degree of malabsoption associated with the disease. Unfortunately I had no detailed information on the ongoing dietary restrictions of children. It may also have been a result of confounding.

Despite the wide range of foods implicated by parents, many of which were unlikely to be involved in the precipitation of an IgE mediated reaction, there was only weak evidence from our population that atopic children were more likely to have reported a lifetime gastrointestinal problem with food. Bock similarly reported that 'there was

little firm evidence that most adverse reactions to foods in children younger than 3 years of age were due to immunologic mechanisms'.[46]

Urticaria in isolation was commonly reported in this group (one in eight children), more than half of these parents reported no known precipitant and few parents identified foods as putative. Interestingly urticaria as an isolated symptom was significantly associated with atopy, but the only other significant association with young maternal age was sufficiently small as to be dismissed.

The difficulties within the epidemiological setting of defining anaphylactic symptoms are well described. Unfortunately I did not record whether any reactions had resulted in intervention with epinephrine, medical assistance or hospital admission. The FAB study's definition of 'life threatening' was more inclusive than the BPSU study, whose criteria for severe reactions included significant medical intervention.[48] 8 (6/1000) FAB children were reported as having had symptoms that resulted in upper or lower airway problems or symptoms of hypotension, representing the lifetime *prevalence* of these symptoms (in these 3 year old children). This is difficult to compare with, although clearly higher than, the quoted *incidence* from the BPSU study of 0.21/100 000 children 0-15 years per year[48]. Seven out of eight of these children had an identified precipitant. Even at this young age, each child in this group had experienced 3 or more episodes, presumably caused by a delay in identifying the food(s) to which an individual is sensitised, or the subsequent difficulty a family may have in avoiding them.

Excluding children who reported isolated urticaria, 65 children (5.2%) reported significant symptoms, 43 (3.4%) with a food precipitant. Of the 8 children who reported more severe reactions,1 child had no precipitant identified, 2 were secondary to peanuts, 1 to milk, 3 to egg, 1 to kiwi fruit and one after contact with a guinea pig. This compares similarly with the precipitants of 55 severe and near fatal reactions from 1998 to 2000 in UK children, where only 10 were thought to be secondary to peanut, in contrast with other populations where peanuts are more frequently eaten.[337] Seven of the eight children who reported life-threatening symptoms were atopic. Children with serious allergic symptoms, (including urticaria in isolation) were more likely to have reported other current allergic symptoms. All 8 children had one or more other allergic symptoms. Two thirds of the children who

had had life threatening symptoms, also had experienced wheeze within the last 12 months, asthma is a recognised risk factor for death in association with food allergy.[48]

5.4.9 Breast Feeding

Whether there is a protective effect of breast feeding on the development of allergic disease is controversial. Some authors have claimed a reduction in eczema[338], food allergy[338] and respiratory symptoms[338] with prolonged breast feeding. The findings of this study are again limited by their retrospective nature. There appeared to be a protective effect of breast-feeding upon lifetime symptoms of wheeze, but with no effect on atopy and current or lifetime symptoms of eczema or rhinitis.

5.4.10 Gender

Most studies suggest that at least in this young age group there is likely to be a preponderance of atopy and allergic symptoms in boys. This sex ratio has been shown to reverse during childhood.[339] In the earlier Isle of Wight study boys were more likely to be atopic than girls (22.5% vs 16.5%) (OR = 1.47 (1.07-2.02) p=0.02).[45] The ISAAC study from the North East of England concluded that boys were significantly more likely than girls to report respiratory symptoms and a diagnosis of asthma, lifetime and current symptoms of rhinitis and hayfever, but with no significantly sex differences for eczema.[91] In the 12-13 year old ISAAC data, girls were more likely to report itchy flexural rash and rhinoconjunctivitis than boys.[44] The boys in this study were not more likely to have respiratory symptoms, but were more likely to have a diagnosis of asthma. This did not appear to be explained by more severe symptoms. They were more likely to have symptoms of rhinitis, but not a diagnosis of hayfever. The prevalence of current and lifetime symptoms of eczema showed no effect of gender. The boys were more likely to be atopic, but even after controlling for atopy, the gender differences in diagnosis of asthma and symptoms of rhinitis remained. Anderson also reported that the increased risk of respiratory illness in boys was independent of atopy.[339]

5.5 Conclusion

In this group of pre-school children atopy and symptoms associated with asthma, eczema, rhinitis and food intolerance and allergy are very common problems. Parents reported that 33% of their children had current problems with wheeze, 27% had rhinitis and 19% had symptoms of eczema. 7% of the parents felt that their child had gastrointestinal symptoms associated with foods. 5% of the group had had skin, mucous membrane or more severe systemic symptoms, and 0.6% had had life-threatening symptoms. 19% of the children showed signs of skin sensitisation to 6 common allergens. We may have overestimated the prevalence of these symptoms within this population as the response rate lay just below 50%, but these are still common conditions.

The causal role of atopy in this age group has been questioned with regard to rhinitis and wheeze.[320] There was no doubting the strong association in these 3-year-olds, with adjusted odds ratios if atopic of 1.9 (95% CI 1.4-2.5) for wheeze and 2.4 (95% CI 1.7-3.3) for rhinitis. Although there was no association with atopy and current food related gastrointestinal symptoms, children who were atopic had adjusted odds ratios of 4.5 (2.7-7.5) associated with serious allergic symptoms.

Children born into more materially affluent households were more likely to be atopic. There were three indirect measures of affluence, namely higher birthweight, older mothers and non-exposure to smoke antenatally, all of these were associated with a higher risk of atopy. There was also some more direct support for the hygiene hypothesis;[65] children of lower birth order were more likely to be atopic.

There was evidence of other pathophysiological processes increasing the risk of respiratory symptoms. There was no increased risk of respiratory symptoms in boys, although there was some evidence that they were more likely to have more severe symptoms, possibly explaining the increased likelihood of their having asthma reported. There was some evidence of perinatal and later adversity increasing the risk of respiratory symptoms, evident in children of lower gestation but not lighter birth weight; children in rented housing; and children exposed to smoke antenatally. There was no association between respiratory symptoms and current smoke

exposure after careful control for other environmental factors, in particular antenatal exposure to tobacco smoke.

Allergic conditions were associated independent of atopy. 13% of the children had two or three current symptoms of wheeze, rhinitis or eczema. Having symptoms of eczema and rhinitis both increased the risk of wheeze; and of note was all the allergic symptoms independently predicted the risk of significant anaphylactic symptoms, independent of atopy, implying that other pathophysiological mechanisms apart from the propensity to produce specific IgE are important. The children with rhinitis had similar, although not identical adverse socioeconomic associations, after controlling for atopy to those associated with respiratory symptoms, including antenatal smoke exposure. One can speculate about whether 'transient sniff' shares some pathophysiology with 'transient wheeze'.

Eczema was in this group a purely atopic disease. There was no confirmation of previously reported associations with birthweight[71;108] or gestation,[71;109] affluence[93] or female gender[332].

The association of gastrointestinal symptoms with foods appeared to be aetiologically distinct from the symptoms of wheeze, rhinitis and eczema and also from cutaneous and mucous membrane symptoms. The fact that this does not appear to be an IgE mediated disease may be added to Bock's evidence of the high rate of resolution of these symptoms[46] in order to urge clinicians to support parents in their re-challenging of children with foodstuffs, to avoid unnecessary restrictions. Parents who reported significant cutaneous and mucous membrane symptoms in their child were generally able to identify a food precipitant although occasionally it was a furred animal that had triggered these significant symptoms. These symptoms were clearly strongly associated with atopy, but there were no other striking clues as to the aetiology of this potentially lethal problem, and the worryingly high frequency of incidents and reported association with wheeze.

Of interest finally is Butland's comment that despite the ongoing search for clues within cohorts of Western children, changes in sex, birth weight, birth order, maternal age, breast feeding, maternal smoking, social class have not explained any of the

observed rise in the prevalence of hayfever and eczema.[340] The increase in wheeze and rhinitis, at least in this age group, may be due to factors other than atopy.

5.6 Appendix Tables

n (% of those with/without symptoms with asthma)		ever asthma yes	no
ever wheezed or whistled	yes n=626	233 (37%)	393 (63%)
	no n=636	9 (1%)	627 (99%)
wheeze or whistle last 12 months (+/- nocturnal cough)	yes n=415	188 (45%)	227 (55%)
	no n=845	54 (6%)	791 (94%)
nocturnal cough only last 12 months (no wheeze)	yes n=120	20 (17%)	100 (83%)
	no n=1137	221 (19%)	916 (81%)

Table A1 Respiratory symptoms and diagnosis of asthma

n (% of those atopic/not atopic with/without symptoms)	lifetime wheeze	current wheeze	current nocturnal cough only	lifetime asthma
Aeroallergen sensitised – 2mm				
Yes n=222	134 (60.4)	99 (45.6)	22 (9.9)	70 (31.5)
No n=1012	482 (47.6)	314 (31.0)	95 (9.4)	170 (16.8)
Odds Ratio (95% CI)	1.67 (1.25 to 2.25)	1.79 (1.33 to 2.40)	1.06 (0.65 to 1.72)	2.28 (1.64 to 3.16)
X^2 (sig. – Pearson's 2 tailed)	11.81 (p=0.001)	14.97 (p<0.0001)	0.046 (ns)	25.07 (p<0.0001)
Aeroallergen sensitised – 3mm				
Yes n=163	102 (62.6)	81 (49.7)	14 (8.6)	56 (34.4)
No n=1071	514 (48.0)	332 (31.0)	103 (9.6)	184 (17.2)
Odds Ratio (95% CI)	1.81 (1.29 to 2.54)	2.20 (1.57 to 3.06)	0.89 (0.49 to 1.57)	2.52 (1.76 to 3.61)
X^2 (sig. – Pearson's 2 tailed)	12.04 (p=0.001)	22.12 (p<0.0001)	0.19 (ns)	26.50 (p<0.0001)
Atopic – 2mm				
Yes n=233	138 (59.2)	101 (43.3)	23 (9.9)	70 (30)
No n=1000	478 (47.8)	312 (31.2)	94 (9.4)	170 (17)
Odds Ratio (95% CI)	1.59 (1.19 to 2.12)	1.69 (1.26 to 2.26)	1.05 (0.65 to 1.70)	2.09 (1.51 to 2.90)
X^2 (sig. – Pearson's 2 tailed)	9.87 (p=0.002)	12.45 (p<0.0001)	0.038 (ns)	20.37 (P<0.0001)
Atopic – 3mm				
Yes n=171	105 (61.4)	83 (48.5)	14 (8.2)	56 (32.7)
No n=1061	510 (48.1)	329 (31.0)	103 (9.7)	183 (17.3)
Odds Ratio (95% CI)	1.72 (1.24 to 2.39)	2.10 (1.51 to 2.91)	0.82 (0.46 to 1.48)	2.33 (1.63 to 3.33)
X^2 (sig. – Pearson's 2 tailed)	10.48 (p=0.001)	20.25 (p<0.0001)	0.42 (ns)	22.50 (p<0.0001)

Table A2 Respiratory symptoms and skin prick sensitisation

	lifetime wheeze	current wheeze	current nocturnal cough only	lifetime asthma
Income (£)				
<12,0000 (n=347)	180 (51.9)	132 (38.0)	36 (10.4)	74 (21.3)
12-17,999 (n=338)	180 (53.3)	117 (34.8)	38 (11.3)	69 (25.5)
18-29,999 (n=383)	183 (47.8)	107 (27.9)	28 (7.3)	72 (18.8)
30-41,999 (n=133)	60 (45.1)	43 (32.3)	12 (9.1)	15 (11.3)
>42,000 (n=60)	22 (36.7)	15 (25.0)	6 (10.0)	10 (16.7)
Mann-Whitney U (sig. - 2 tailed)	184349.00 (p=0.021)	158163.00 (p=0.004)	63888.000 (ns)	111886.00 (p=0.033)
Housing tenure				
owned (n=935)	442 (47.3)	285 (30.5)	74 (7.9)	157 (16.8)
rented/other (n=328)	185 (56.4)	131 (39.9)	46 (14.1)	84 (25.7)
Odds Ratio (95% CI)	1.44 (1.12 to 1.86)	1.51 (1.16 to 1.96)	1.90 (1.29 to 2.82)	1.71 (1.27 to 2.31)
X^2 (sig. – Pearson's 2 tailed)	8.10 (p=0.004)	9.68 (p=0.002)	10.62 (p=0.001)	12.35 (p<0.0001)
Vehicle ownership				
vehicle (n=1134)	563 (49.6)	367 (32.4)	103 (9.1)	210 (18.6)
no vehicle (n=126)	63 (50.0)	49 (38.9)	17 (13.6)	31 (24.6)
Odds Ratio (95% CI)	1.01 (0.70 to 1.47)	1.33 (0.91 to 1.94)	1.57 (0.91 to 2.72)	1.43 (0.93 to 2.21)
X^2 (sig. – Pearson's 2 tailed)	0.01 (ns)	2.14 (ns)	2.61 (ns)	2.68 (ns)
Maternal age at leaving education				
<=16 n=549	284 (51.7)	196 (35.8)	58 (10.6)	115 (20.9)
17-20 n=545	265 (48.6)	171 (31.4)	52 (9.6)	99 (18.2)
>=21 n=170	79 (46)	50 (29.4)	10 (5.9)	28 (16.6)
Mann-Whitney U (sig - 2 tailed)	191604.5 (ns)	165829.5 (ns)	62989.000 (ns)	116534.5 (ns)
Single parent household				
one parent n=156	541 (48.9)	59 (37.8)	16 (10.3)	31 (19.9)
two parents n=1107 (mother&father/partner)	86 (55.1)	357 (32.3)	104 (9.4)	210 (19.0)
Odds Ratio (95% CI)	1.29 (0.92 to 1.80)	1.27 (0.90 to 1.80)	1.10 (0.63 to 1.91)	1.06 (0.69 to 1.61)
X^2 (sig. – Pearson's 2 tailed)	2.14 (ns)	1.88 (ns)	0.10 (ns)	0.068 (ns)

Symptoms	**yes**	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**
Maternal age mean (sd)	32.07 (5.46)	32.81 (5.20)	32.01 (5.54)	32.66 (5.23)	31.98 (5.81)	32.49 (5.28)	31.41 (5.41)	32.69 (5.29)
t	-2.45		-2.04		-0.99		-3.37	
df	1260		1258		1254		1258	
sig (2-tailed)	p=0.014		p=0.042		ns		p=0.001	
mean difference (95% CI)	-0.73 (-1.32 to -0.15)		-0.65 (-1.28 to -0.02)		-0.51 (-1.51 to 0.50		-1.28 (-2.03 to -0.54)	
Birth order								
no 1 n=519	257 (49.5)		172 (33.1)		50 (9.7)		96 (18.5)	
no 2 n=462	228 (49.4)		151 (32.8)		45 (9.8)		86 (18.6)	
no 3 n=194	99 (51.0)		61 (31.4)		22 (11.4)		40 (20.6)	
no >3 n=87	43 (49.4)		32 (37.2)		3 (3.5)		19 (22.1)	
X^2 (sig. – Pearson's 2 tailed)	0.17		0.80		4.51		0.90	
p	ns		ns		ns		ns	

Table A3 **Respiratory symptoms and material/family environment**

Biological influences		lifetime wheeze		current wheeze		current nocturnal cough only		lifetime asthma	
		no	yes	no	yes	no	yes	no	yes
Birth weight (kgs) mean (sd)		3.40 (0.54)	3.39 (0.58)	3.40 (0.56)	3.38 (0.56)	3.39 (0.56)	3.36 (0.53)	3.40 (0.55)	3.35 (0.62)
t		0.30		0.67		0.59		1.23	
df		1248		1246		1242		1246	
sig (2-tailed)		ns		ns		ns		ns	
mean difference		0.01		0.02		0.03		0.05	
(95% CI)		(-0.05 to 0.07)		(-0.04 to 0.09)		(-0.07 to 0.14)		(-0.03 to 0.13)	
Gestation (weeks) mean (sd)		39.59 (1.86)	39.46 (2.12)	39.62 (1.96)	39.34 (2.04)	39.50 (2.01)	39.77 (1.84)	39.59 (1.90)	39.24 (2.34)
t(sig (2-tailed))		1.16 (ns)		2.37 (p=0.018)		-1.39 (ns)		2.16 (p=0.032)	
df		1236.920		1259		1255		319.996	
mean difference		0.13		0.28		-0.27		0.35	
(95% CI)		(-0.09 to 0.35)		(0.05 to 0.52)		(-0.64 to 0.11)		(0.03 to 0.67)	
Admission to SCBU	Yes n=230	128 (55.7)		85 (37.0)		11 (4.8)		55 (23.9)	
	No n=1030	499 (48.4)		332 (32.2)		109 (10.6)		186 (18.1)	
Odds Ratio (95% CI)		1.34 (1.01 to 1.79)		1.23 (0.92 to 1.66)		0.42 (0.22 to 0.80)		1.43 (1.01 to 2.01)	
X^2 (sig. – Pearson's 2 tailed)		4.01 (p=0.045)		1.90 (ns)		7.42 (p=0.006)		4.17 (p=0.041)	
Antenatal smoke	Yes n=279	165 (59.1)		123 (44.1)		34 (12.2)		67 (24.0)	
	No n=977	461 (47.8)		293 (30.0)		86 (8.8)		174 (17.8)	
Odds Ratio		1.62		1.85		1.44		1.46	
(95% CI)		(1.24 to 2.12)		(1.41 to 2.43)		(0.94 to 2.19)		(1.06 to 2.00)	
X^2 (sig. – Pearson's 2 tailed)		12.41 (p<0.0001)		19.75 (p<0.0001)		2.85 (ns)		5.32 (p=0.021)	
Current smoke	Yes n=536	292 (54.5)		203 (37.9)		62 (11.6)		116 (21.7)	
	No n=724	333 (46.0)		211 (29.2)		58 (8.1)		125 (17.3)	
Odds Ratio (95% CI)		1.41 (1.12 to 1.76)		1.48 (1.17 to 1.88)		1.50 (1.03 to 2.19)		1.32 (1.00 to 1.76)	
X^2 (sig. – Pearson's 2 tailed)		8.87 (p=0.003)		10.69 (p=0.001)		4.48 (p=0.034)		3.83 (p=0.050)	
Current height (cms) mean (sd)		98.24 (3.92)	97.81 (4.09)	98.13 (3.98)	97.82 (4.07)	98.03 (3.98)	98.01 (4.25)	98.06 (4.01)	97.90 (4.02)
t		1.86		1.26		0.05		0.54	
df (sig. - 2 tailed)		1209 (ns)		1207 (ns)		1203 (ns)		1207 (ns)	
mean difference		0.43		0.31		0.02		0.16	
(95% CI)		(-0.02 to 0.88)		(-0.17 to 0.79)		(-0.75 to 0.79)		(-0.42 to 0.73)	
Gender	Girls n=609	290 (47.6)		187 (30.8)		56 (9.2)		98 (16.1)	
	Boys n=655	338 (51.6)		230 (35.2)		64 (9.8)		144 (22.0)	
Odds Ratio (95% CI)		0.85 (0.68 to 1.06)		0.82 (0.65 to 1.04)		0.94 (0.64 to 1.36)		0.68 (0.51 to 0.91)	
X^2 (sig. – Pearson's 2 tailed)		2.00 (ns)		2.77 (ns)		0.12 (ns)		7.08 (p=0.008)	

Table A4 **Respiratory symptoms and biological influences**

	Exp(B) (odds ratio) (95% C.I.) significance			
	lifetime wheeze	current wheeze	current nocturnal cough only	lifetime asthma
Atopy (2mm)	1.66 (1.24 to 2.22) p=0.001	1.78 (1.32 to 2.39) p<0.0001	1.09 (0.67 to 1.76) ns	2.21 (1.58 to 3.07) p<0.0001
household income	1.11 (0.99 to 1.24) p=0.062	1.13 (1.32 to 2.39) p=0.052		1.09 (0.94 to 1.25) ns
housing tenure	1.35 (1.01 to 1.79) p=0.041	1.41 (1.05 to 1.89) p=0.023	1.83 (1.23 to 2.73) p=0.003	1.67 (1.19 to 2.36) p=0.003
constant	0.57	0.26	0.06	0.13

Table A5 **Multiple regression analysis of all respiratory symptoms as a function of significant environmental measures**

	Exp(B) (odds ratio) (95% C.I.) significance			
	lifetime wheeze	current wheeze	current nocturnal cough only	lifetime asthma
Atopy (2mm)	1.71 (1.27 to 2.30) p<0.0001	1.93 (1.43 to 2.60) p<0.0001		2.21 (1.58 to 3.08) p<0.0001
housing tenure	1.35 (1.03 to 1.76) p=0.028	1.37 (1.04 to 1.81) p=0.025	1.74 (1.15 to 2.64) p=0.009	1.60 (1.15 to 2.21) p=0.005
gestation		0.91 (0.86 to 0.97) p=0.004		
admission to SCBU			0.43 (0.22 to 0.81) p=0.009	
sex				0.68 (0.51 to 0.91) p=0.01
maternal age				0.96 (0.94 to 0.99) p=0.009
antenatal smoke exposure	1.65 (1.24 to 2.19) p=0.001	1.87 (1.40 to 2.51) p<0.0001		
constant	0.75	12.03	0.10	0.71

Table A6 **Multiple regression analysis of all respiratory symptoms as a function of significant environmental measures, gender and perinatal measures**

n (% of those atopic/not atopic with/without symptoms)	lifetime rhinitis	current rhinitis	current rhino-conjunctivitis	lifetime hayfever
Aeroallergen sensitised – 2mm				
Yes n=222	100 (45.0)	95 (42.8)	57 (25.7)	48 (21.6)
No n=1012	256 (25.3)	237 (23.4)	103 (10.2)	69 (6.8)
Odds Ratio (95% CI)	2.42 (1.79 to 3.27)	2.45 (1.81 to 3.31)	3.05 (2.12 to 4.37)	3.76 (2.51 to 5.62)
X^2 (sig. – Pearson's 2 tailed)	34.59 (p<0.0001)	34.75 (p<0.0001)	38.75 (p<0.0001)	46.23 (p<0.0001)
Aeroallergen sensitised – 3mm				
Yes n=163	79 (48.5)	75 (46.0)	49 (30.1)	41 (25.2)
No n=1068	277 (25.9)	257 (24.0)	111 (10.4)	76 (7.1)
Odds Ratio (95% CI)	2.70 (1.93 to 3.77)	2.70 (1.92 to 3.79)	3.72 (2.52 to 5.48)	4.34 (2.87 to 6.70)
X^2 (sig. – Pearson's 2 tailed)	35.20 (p<0.0001)	34.87 (p<0.0001)	48.64 (p<0.0001)	53.49 (p<0.0001)
Atopic – 2mm				
Yes n=233	101 (43.3)	96 (41.2)	58 (24.9)	48 (20.6)
No n=997	254 (25.4)	236 (23.6)	102 (10.2)	69 (6.9)
Odds Ratio (95% CI)	2.25 (1.67 to 3.02)	2.27 (1.68 to 3.06)	2.92 (2.03 to 4.18)	3.49 (2.34 to 5.21)
X^2 (sig. – Pearson's 2 tailed)	29.69 (p<0.0001)	29.75 (p<0.0001)	36.12 (p<0.0001)	41.06 (p<0.0001)
Atopic – 3mm				
Yes n=171	80 (46.8)	76 (44.4)	50 (29.2)	41 (24.0)
No n=1061	274 (25.8)	255 (24.0)	109 (10.3)	75 (7.1)
Odds Ratio (95% CI)	2.52 (1.81 to 3.51)	2.53 (1.81 to 3.53)	3.61 (2.46 to 5.30)	4.13 (2.71 to 6.31)
X^2 (sig. – Pearson's 2 tailed)	31.59 (p<0.0001)	31.22 (p<0.0001)	47.33 (p<0.0001)	49.12 (p<0.0001)

Table A7 **Skin prick sensitisation and nose and eye symptoms**

	lifetime rhinitis	current rhinitis	current rhino-conjunctivitis	lifetime hayfever
Income (£)				
<12,0000 (n=347)	111 (32.0)	102 (29.4)	47 (13.5)	38 (11.0)
12-17,999 (n=338)	99 (29.3)	91 (26.9)	42 (12.4)	30 (8.9)
18-29,999 (n=383)	109 (28.5)	106 (27.7)	50 (13.1)	31 (8.1)
30-41,999 (n=133)	26 (19.5)	24 (18.0)	16 (12.0)	13 (9.8)
>42,000 (n=60)	16 (26.7)	13 (21.7)	7 (11.7)	7 (11.7)
Mann-Whitney U (sig. - 2 tailed)	149913.50 (p=0.026)	144345.00 (p=0.045)	87298.500 (ns)	65263.500 (ns)
Housing tenure				
owned (n=935)	248 (26.5)	231 (24.7)	111 (11.9)	91 (9.7)
rented/other (n=328)	113 (34.5)	105 (32.0)	51 (15.5)	28 (8.6)
Odds Ratio (95% CI)	1.46 (1.11 to 1.91)	1.43 (1.09 to 1.89)	1.37 (0.96 to 1.96)	0.87 (0.56 to 1.36)
X^2 (sig. – Pearson's 2 tailed)	7.48 (p=0.006)	6.64 (p=0.01)	2.94 (ns)	0.38 (ns)
Vehicle ownership				
vehicle (n=1134)	319 (28.1)	297 (26.2)	143 (12.6)	109 (9.6)
no vehicle (n=126)	42 (33.3)	39 (31)	19 (15.1)	10 (8.1)
Odds Ratio (95% CI)	1.28 (0.86 to 1.89)	1.26 (0.85 to 1.89)	1.23 (0.73 to 2.07)	0.82 (0.42 to 1.62)
X^2 (sig. – Pearson's 2 tailed)	1.5 (ns)	1.32 (ns)	0.62 (ns)	0.32 (ns)
Maternal age at leaving educ				
<=16 n=549	160 (29.1)	152 (27.7)	77 (14.0)	48 (8.7)
17-20 n=545	158 (29.0)	144 (26.4)	67 (12.3)	56 (10.3)
>=21 n=170	44 (25.9)	41 (24.1)	19 (11.2)	15 (8.9)
Mann-Whitney U (sig- 2 tailed)	160071.0 (ns)	151574.5 (ns)	85293.500 (ns)	66207.000 (ns)
Single parent household				
one parent n=156	49 (31.4)	48 (30.8)	23 (14.7)	17 (11.0)
two parents (moth&fath/ptner) n=1107	312 (28.2)	288 (26)	139 (12.6)	102 (9.2)
Odds Ratio (95% CI)	1.17 (0.81 to 1.67)	1.26 (0.88 to 1.82)	1.20 (0.75 to 1.94)	1.21 (0.70 to 2.09)
X^2 (sig. – Pearson's 2 tailed)	0.70 (ns)	1.58 (ns)	0.59 (ns)	0.48 (ns)

	lifetime rhinitis		current rhinitis		current rhino-conjunctivitis		lifetime hayfever	
	yes	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**
Maternal age (yrs) mean (sd)	31.90 (5.21)	32.66 (5.37)	31.84 (5.23)	32.66 (5.36)	32.13 (5.01)	32.49 (5.38)	32.17 (5.25)	32.47 (5.34)
t	-2.30		-2.44		-0.80		-0.59	
df	1260		1260		1260		1257	
sig (2-tailed)	p=0.022		p=0.015		ns		ns	
mean difference (95% CI)	-0.76 (-1.42 to -0.11)		-0.83 (-1.49 to -0.16)		-0.36 (-1.24 to 0.52)		-0.30 (-1.31 to 0.70)	
Paternal age (yrs) mean (sd)	34.87 (6.57)	35.71 (6.64)	34.61 (6.39)	35.77 (6.69)	34.95 (6.78)	35.54 (6.61)	35.38 (6.44)	35.49 (6.64)
t	-2.01		-2.73		-1.06		-0.17	
df	1241		1241		1241		1238	
sig (2-tailed)	p=0.044		p=0.006		ns		ns	
mean difference (95% CI)	-0.84 (-1.66 to -0.02)		-1.16 (-2.00 to -0.33)		-0.59 (-1.70 to 0.51)		-0.11 (-1.37 to 1.15)	
Birth order								
no 1 n=519	140 (27.0)		128 (24.7)		64 (12.3)		58 (11.2)	
no 2 n=462	144 (31.2)		138 (29.9)		69 (14.9)		44 (9.5)	
no 3 n=194	56 (28.9)		50 (25.8)		17 (8.8)		8 (4.1)	
no >3 n=87	20 (23.0)		19 (21.8)		12 (13.8)		8 (9.2)	
X^2 (sig. – Pearson's 2 tailed)	3.51 (ns)		4.61 (ns)		4.89 (ns)		8.31 (p=0.04)	
Maternal employment								
Out of home F/T n=174	56 (32.2)		47 (27.0)		27 (15.5)		51 (10.2)	
Out of home P/T n=588	154 (26.2)		146 (24.8)		69 (11.7)		49 (8.3)	
In home F/T n=500	150 (30.0)		142 (28.4)		66 (13.2)		19 (10.9)	
one way ANOVA F (sig)	0.008 (ns)		0.622 (ns)		0.123 (ns)		0.038 (ns)	

Table A8 Nose and eye symptoms and material/family environment

Biological influences	lifetime rhinitis		current rhinitis		current rhinoconjun		lifetime hayfever	
	no	yes	no	yes	no	yes	no	yes
Birth weight (kgs) mean (sd)	3.41 (0.55)	3.35 (0.59)	3.41 (0.55)	3.34 (0.58)	3.40 (0.56)	3.35 (0.59)	3.39 (0.55)	3.35 (0.65)
t	1.63		2.06		1.08		0.81	
df	1248		1248		1248		1245	
sig (2-tailed)	ns		p=0.040		ns		ns	
mean difference (95% CI)	0.06 (-0.01 to 0.13)		0.07 (0.00 to 0.14)		0.05 (-0.04 to 0.14)		0.04 (-0.06 to 0.15)	
Gestation (weeks) mean (sd)	39.60 (1.92)	39.35 (2.17)	39.61 (1.91)	39.30 (2.21)	39.56 (1.97	39.31 (2.14)	39.54 (1.95)	39.36 (2.39)
t	1.97		2.26		1.51		0.81	
df	1261		529.067		1261		134.902	
sig (2-tailed)	p=0.05		p=0.024		ns		ns	
mean difference (95% CI)	0.24 (0.0004 to 0.49)		0.31 (0.04 to 0.57)		0.25 (-0.07 to 0.58)		0.18 (-0.26 to 0.63)	
Antenatal smoke exposure								
Yes n=279	95 (34.1)		89 (31.9)		47 (16.8)		31 (11.2)	
No n=977	266 (27.2)		247 (25.3)		115 (11.8)		87 (8.9)	
Odds Ratio (95% CI)	1.38 (1.04 to 1.84)		1.38 (1.04 to 1.85)		1.52 (1.05 to 2.20)		1.28 (0.83 to 1.98)	
X^2 (sig. – Pearson's 2 tailed)	4.93 (p=0.026)		4.85 (p=0.028)		4.98 (p=0.026)		1.26 (ns)	
Current smoke exposure								
Yes n=536	161 (30.0)		187 (25.8)		76 (14.2)		71 (9.8)	
No n=724	199 (27.5)		148 (27.6)		85 (11.7)		48 (9.0)	
Odds Ratio (95% CI)	1.13 (0.89 to 1.45)		1.10 (0.85 to 1.41)		1.24 (0.89 to 1.73)		0.91 (0.62 to 1.34)	
X^2 (sig. – Pearson's 2 tailed)	0.98 (ns)		0.50 (ns)		1.64 (ns)		0.23 (ns)	
Admission to SCBU								
Yes n=230	68 (29.6)		64 (27.8)		30 (13.0)		20 (8.7)	
No n=1032	294 (28.5)		273 (26.5)		133 (12.9)		99 (9.6)	
Odds Ratio (95% CI)	1.05 (0.77 to 1.44)		1.07 (0.78 to 1.48)		1.01 (0.66 to 1.55)		0.90 (0.54 to 1.48)	
X^2 (sig. – Pearson's 2 tailed)	0.11 (ns)		0.67 (ns)		0.004 (ns)		0.19 (ns)	
Current height (cms) mean (sd)	98.15 (4.02)	97.71 (3.97)	98.18 (4.04)	97.59 (3.90)	98.15 (4.01)	97.16 (3.93)	98.05 (4.02)	97.72 (3.90)
t	1.73		2.28		2.89		0.83	
df	1209		1209		1209		1207	
sig (2-tailed)	ns		p=0.023		p=0.004		ns	
mean difference (95% CI)	0.44 (-0.06 to 0.94)		0.59 (0.08 to 1.10)		0.99 (0.32 to 1.66)		0.33 (-0.44 to 1.10)	
Gender								
Girls n=609	151 (24.8)		141 (23.2)		61 (10.0)		54 (8.9)	
Boys n=655	211 (32.2)		196 (29.9)		102 (15.6)		65 (10.0)	
Odds Ratio (95% CI)	0.69 (0.54 to 0.89)		0.71 (0.55 to 0.91)		0.60 (0.43 to 0.85)		0.88 (0.60 to 1.28)	
X^2 (sig. – Pearson's 2 tailed)	8.50 (p=0.004)		7.40 (p=0.007)		8.67 (p=0.003)		0.45 (ns)	

Table A9 Nose and eye symptoms and biological influences

	Exp(B) (odds ratio) (95% C.I.) significance			
	lifetime rhinitis	current rhinitis	current rhinoconjunctivitis	hayfever
Atopy (2mm)	2.41 (1.78 to 3.27) p<0.0001	2.39 (1.74 to 3.28) p<0.0001	2.87 (1.96 to 4.22) p<0.0001	3.63 (2.41 to 5.47) p<0.0001
household income	1.13 (1.01 to 1.27) p=0.035	1.12 (0.99 to 1.23) ns		
sex	0.71 (0.55 to 0.91) p=0.008	0.69 (0.53 to 0.91) p=0.008	0.56 (0.39 to 0.80) p=0.002	
birthweight		0.83 (0.65 to 1.07) ns		
antenatal smoke	1.41 (1.04 to 1.91) p=0.025	1.28 (0.93 to 1.77) ns	1.56 (1.04 to 2.33) p=0.031	
current height		0.97 (0.93 to 1.00) p=0.049	0.93 (0.89 to 0.97) p=0.001	
constant	0.23	12.67	229.06	0.07

Table A10 Multiple regression analysis of all allergic nose and eye symptoms as a function of significant environmental and biological measures

n (% of those with/without symptoms with eczema)		ever eczema yes	ever eczema no
lifetime itchy rash coming and going for 6 months	yes n=297	255 (86%)	42 (14%)
	no n=967	319 (33%)	648 (67%)
current itchy rash	yes n=242	210 (87%)	32 (13%)
	no n=1019	361 (35%)	658 (65%)
current itchy rash - site specific	yes n=204	183 (90%)	21 (10%)
	no n=1057	388 (37%)	669 (63%)

Table A11 All skin symptoms and diagnosis of eczema

n (% of sensitised/nonsensitised)	lifetime itchy rash	current itchy rash	current flexure itchy rash	lifetime eczema
Aeroallergen sensitised – 2mm				
Yes n=222	101 (45.5)	86 (38.8)	78 (35.1)	161 (72.5)
No n=1012	190 (18.8)	150 (14.9)	120 (11.9)	399 (39.4)
Odds Ratio (95% CI)	3.61 (2.65 to 4.91)	3.62 (2.63 to 4.99)	4.01 (2.87 to 5.61)	4.05 (2.94 to 5.59)
X^2 (sig. – Pearson's 2 tailed)	72.13 (p<0.0001)	66.92 (p<0.0001)	72.83 (p<0.0001)	80.45 (p<0.0001)
Aeroallergen sensitised – 3mm				
Yes n=163	84 (51.5)	71 (43.6)	65 (39.9)	131 (80.4)
No n=1071	207 (19.3)	165 (15.4)	133 (12.5)	429 (40.1)
Odds Ratio (95% CI)	4.44 (3.15 to 6.25)	4.22 (2.97 to 6.00)	4.66 (3.25 to 6.70)	6.13 (4.09 to 9.19)
X^2 (sig. – Pearson's 2 tailed)	81.42 (p<0.0001)	72.11 (p<0.0001)	78.80 (p<0.0001)	92.75 (p<0.0001)
Atopic – 2mm				
Yes n=233	107 (45.9)	90 (38.6)	80 (34.3)	**167 (71.7)**
No n=1000	183 (18.3)	145 (14.5)	117 (11.7)	**392 (39.2)**
Odds Ratio (95% CI)	3.79 (2.80 to 5.14)	3.70 (2.69 to 5.08)	3.93 (2.82 to 5.48)	3.93 (2.87 to 5.36)
X^2 (sig. – Pearson's 2 tailed)	80.16 (p<0.0001)	70.87 (p<0.0001)	71.71 (p<0.0001)	80.41 (p<0.0001)
Atopic – 3mm				
Yes n=171	89 (52.0)	74 (43.3)	67 (39.2)	**138 (80.7)**
No n=1061	201 (18.9)	161 (15.2)	130 (12.3)	421 (39.7)
Odds Ratio (95% CI)	4.64 (3.31 to 6.51)	4.25 (3.01 to 6.01)	4.60 (3.22 to 6.58)	6.36 (**4.26 to** 9.48)
X^2 (sig. – Pearson's 2 tailed)	89.66 (p<0.0001)	74.93 (p<0.0001)	79.10 (p<**0.0001**)	99.99 (**p<0.**0001)

Table A12 All symptoms of eczema and skin prick sensitisation

		lifetime itchy rash		current itchy rash		current flexure itchy rash		lifetime eczema	
Income (£)									
<12,0000 (n=347)		84 (24.2)		71 (20.6)		62 (18.0)		155 (44.7)	
12-17,999 (338)		83 (24.6)		71 (21.0)		58 (17.2)		154 (45.6)	
18-29,999 (n=383		82 (21.4)		60 (15.7)		48 (12.6)		174 (45.4)	
30-41,999 (n=133		29 (21.8)		24 (18.0)		23 (17.3)		57 (42.9)	
>42,000 (n=60)		18 (30.0)		12 (25)		12 (20.0)		33 (55.0)	
Mann-Whitney U sig. (2 tailed)		140525.50 (ns)		117717.00 (ns)		102615.00 (ns)		194231.50 (ns)	
Housing tenure									
owned (n=935)		217 (23.2)		174 (18.6)		147 (15.8)		422 (45.1)	
rented/other (n=328)		80 (24.4)		68 (20.8)		57 (17.4)		152 (46.6)	
Odds Ratio (95% CI)		1.07 (0.80 to 1.43)		1.15 (0.84 to 1.57)		1.13 (0.81 to 1.58)		1.05 (0.82 to 1.35)	
X^2 (sig. – Pearson's 2 tailed)		0.19 (ns)		0.72 (ns)		0.50 (ns)		0.14 (ns)	
Vehicle ownership									
vehicle (n=1134)		271 (23.9)		218 (19.3)		182 (16.1)		521 (45.9)	
no vehicle (n=126)		26 (20.6)		24 (19.0)		22 (17.5)		53 (42.1)	
Odds Ratio (95% CI)		0.83 (0.53 to 1.30)		0.99 (0.62 to 1.57)		1.10 (0.68 to 1.79)		0.85 (0.59 to 1.24)	
X^2 (sig. – Pearson's 2 tailed)		0.67 (ns)		0.01 (ns)		0.16 (ns)		0.69 (ns)	
Maternal age at leaving educ									
<=16	n=549	135 (24.6)		115 (21.0)		98 (17.9)		251 (45.7)	
17-20	n=545	119 (21.8)		97 (17.8)		83 (15.3)		239 (43.9)	
>=21	n=170	43 (25.3)		30 (17.6)		23 (13.5)		84 (49.4)	
Mann-Whitney U (sig - 2 tailed)		141408.5 (ns)		116893.5 (ns)		101020.0 (ns)		196524.0 (ns)	
Single parent household									
one parent n=156		40 (25.6)		33 (21.2)		31 (19.9)		71 (45.5)	
two parents n=1107		257 (23.2)		209 (18.9)		173 (15.7)		503 (45.4)	
Odds Ratio (95% CI)		1.14 (0.78 to 1.68)		1.15 (0.76 to 1.74)		1.34 (0.87 to 2.04)		1.00 (0.72 to 1.40)	
X^2 (sig. – Pearson's 2 tailed)		0.45 (ns)		0.44 (ns)		1.78 (ns)		0 (ns)	
		yes	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**
Maternal age (yrs) mean (sd)		32.66 (5.45)	32.38 (5.31)	32.72 (5.48)	32.39 (5.30)	32.59 (5.40)	32.43 (5.32)	32.41 (5.28)	32.47 (5.39)
t (df)		0.81 (1260)		0.87 (1257)		0.40 (1257)		-0.18 (1260)	
sig (2-tailed)		ns		ns		ns		ns	
mean difference (95% CI)		0.29 (-0.41 to 0.98)		0.33 (-0.42 to 1.08)		0.16 (-0.64 to 0.96)		0.05 (-0.65 to 0.54)	
Paternal age (yrs) mean (sd)		35.7 (6.80)	35.4 (6.58)	35.8 (6.97)	35.4 (6.55)	35.4(6.75)	35.5 (6.62)	35.4 (6.31)	35.6 (6.89)
t (df)		0.80 (1241)		0.83 (1238)		-0.11 (1238)		-0.51 (1241)	
sig (2-tailed)		ns		ns		ns		ns	
mean difference (95% CI)		0.35 (-0.52 to 1.23)		0.40 (-0.54 to 1.33)		0.05 (-1.06 to 0.95)		-0.19 (-0.93 to 0.55)	
Birth order									
no 1 n=519		123 (23.7)		97 (18.8)		81 (15.7)		261 (50.3)	
no 2 n=462		101 (21.9)		83 (18.0)		71 (15.4)		191 (41.3)	
no 3 n=194		55 (28.4)		47 (24.2)		44 (22.7)		93 (47.9)	
no >3 n=87		18 (20.7)		15 (17.2)		8 (9.2)		29 (33.3)	
X^2 (sig. – Pearson's 2 tailed)		3.62 (ns)		3.92 (ns)		9.53 (p=0.02)		13.68 (p=0.003)	
Maternal employment									
Out of home F/T	n=174	51 (29.3)		39 (22.5)		77 (15.5)		239 (47.8)	
Out of home P/T	n=588	128 (21.8)		103 (17.5)		93 (15.8)		252 (42.9)	
In home F/T n=118		118 (23.6)		100 (20.1)		34 (19.7)		83 (47.7)	
one way ANOVA	F (signific)	0.890 (ns)		0.024 (ns)		1.170 (ns)		0.407 (ns)	

Table A13 All symptoms of eczema and material/family environment

Biological influences	lifetime itchy rash		current itchy rash		current flexure itchy rash		lifetime eczema	
	No	Yes	No	Yes	No	Yes	No	Yes
Birth weight (kgs) mean (sd)	3.38 (0.57)	3.43 (0.54)	3.38 (0.57)	3.42 (0.52)	3.39 (0.57)	3.39 (0.51)	3.40 (0.54)	3.39 (0.58)
t (df)	-1.26 (1248)		-0.97 (1245)		-0.06 (1245)		0.30 (1248)	
sig (2-tailed)	ns		ns		ns		ns	
mean difference (95% CI)	-0.05 (-0.13 to 0.03)		-0.04 (-0.12 to 0.04)		0.00 (-0.09 to 0.08)		0.01 (-0.05 to 0.07)	
Gestation (weeks) mean (sd)	39.49 (2.04)	39.66 (1.84)	39.50 (2.03)	39.65 (1.83)	39.52 (2.02)	39.58 (1.85)	39.59 (1.93)	39.45 (2.06)
t (df)	-1.31 (1261)		-1.11 (1258)		-0.41 (1258)		1.20 (1261)	
sig (2-tailed)	ns		ns		ns		ns	
mean difference (95% CI)	-0.17 (-0.43 to 0.09)		-0.16 (-0.44 to 0.12)		-0.06 (-0.36 to 0.24)		0.13 (-0.09 to 0.36)	
Antenatal smoke exposure								
Yes n=279	59 (21.1)		46 (16.5)		38 (13.7)		120 (43.0)	
No n=977	237 (24.3)		195 (20.0)		165 (16.9)		451 (46.2)	
Odds Ratio (95% CI)	0.84 (0.61 to 1.16)		0.79 (0.56 to 1.13)		0.78 (0.53 to 1.14)		0.88 (0.67 to 1.15)	
X^2 (sig. – Pearson's 2 tailed)	1.17 (ns)		1.66 (ns)		1.69 (ns)		0.87 (ns)	
Current smoke exposure								
Yes n=536	121 (22.6)		99 (18.5)		84 (15.7)		241 (45.0)	
No=724	176 (24.3)		143 (19.8)		120 (16.6)		333 (46.0)	
Odds Ratio (95% CI)	0.91 (0.70 to 1.18)		0.92 (0.69 to 1.23)		0.94 (0.69 to 1.27)		0.96 (0.77 to 1.20)	
X^2 (sig. – Pearson's 2 tailed)	0.51 (ns)		0.30 (ns)		0.17 (ns)		0.13 (ns)	
Admission to SCBU								
Yes n=230	51 (22.2)		36 (15.7)		30 (13.0)		109 (47.4)	
No n=1032	245 (23.7)		206 (20.0)		174 (16.9)		463 (44.9)	
Odds Ratio (95% CI)	0.92 (0.65 to 1.29)		0.74 (0.50 to 1.09)		0.74 (0.49 to 1.12)		1.11 (0.83 to 1.47)	
X^2 (sig. – Pearson's 2 tailed)	0.26 (ns)		2.31 (ns)		2.07 (ns)		0.49 (ns)	
Current height (cms) mean (sd)	98.03 (3.99)	98.02 (4.09)	98.05 (3.99)	97.96 (4.09)	98.03 (4.01)	98.03 (4.04)	98.05 (4.05)	97.99 (3.96)
t (df)	0.02 (1209)		0.30 (1207)		-0.01 (1207)		0.24 (1209)	
sig (2-tailed)	ns		ns		ns		ns	
mean difference (95% CI)	0.00 (-0.53 to 0.54)		0.09 (-0.49 to 0.66)		0.00 (-0.62 to 0.61)		-0.06 (-0.40 to 0.51)	
Gender								
Girls n=609	138 (22.7)		113 (18.6)		91 (15.0)		262 (43.0)	
Boys n=655	159 (24.3)		129 (19.7)		113 (17.3)		312 (47.6)	
Odds Ratio (95% CI)	0.91 (0.70 to 1.19)		0.93 (0.70 to 1.23)		0.84 (0.63 to 1.14)		0.83 (0.67 to 1.04)	
X^2 (sig. – Pearson's 2 tailed)	0.46 (ns)		0.25 (ns)		1.21 (ns)		2.71 (ns)	

Table A14 All symptoms of eczema and biological influences

	Exp(B) (odds ratio) (95% C.I.) significance			
	lifetime itchy rash	current itchy rash	current flexure itchy rash	lifetime eczema
atopy (2mm)	3.79 (2.80 to 5.13) p<0.0001	3.70 (2.69 to 5.08) p<0.0001	4.03 (2.88 to 5.62) p<0.0001	3.93 (2.87 to 5.36) p<0.0001
maternal education			1.30 (1.03 to 1.64) p=0.029	
constant	0.22	0.17	0.07	0.65

Table A15 Multiple regression analysis of all symptoms of eczema as a function of significant measures

	Atopic (2mm)		Atopic (3mm)	
Income (£)				
<12,0000 (n=337)	50 (14.8)		36 (10.7)	
12-17,999 (n=329)	66 (20.0)		48 (14.6)	
18-29,999 (n=374)	69 (18.4)		50 (13.4)	
30-41,999 (n=131)	24 (18.3)		18 (13.7)	
>42,000 (n=58)	23 (39.7)		19 (32.8)	
Mann-Whitney U sig. (2 tailed)	1.3786.00 (p=0.011)		80051.500 (p=0.012)	
Housing tenure				
owned (n=910)	183 (20.1)		139 (15.3)	
rented/other (n=321)	50 (15.6)		32 (10.0)	
Odds Ratio (95% CI)	0.73 (0.52 to 1.03)		0.61 (0.41 to 0.92)	
X^2 (sig. – Pearson's 2 tailed)	3.15 (ns)		5.59 (p=0.018)	
Vehicle ownership				
vehicle (n=1106)	210 (19.0)		156 (14.1)	
no vehicle (n=122)	22 (18.0)		15 (12.3)	
Odds Ratio (95% CI)	0.94 (0.58 to 1.53)		0.85 (0.49 to 1.50)	
X^2 (sig. – Pearson's 2 tailed)	0.06 (ns)		0.30 (ns)	
Maternal age at leaving education (yrs)				
<=16 n=539	98 (18.1)		73 (13.5)	
17-20 n=534	98 (18.4)		69 (12.9)	
>=21 n=167	40 (24.0)		32 (19.2)	
Mann-Whitney U sig. (2 tailed)	113182.0 (ns)		88326.500 (ns)	
Single parent household				
one parent n=148	22 (14.9)		17 (11.5)	
two parents n=1083 (mother&father/partner)	211 (19.5)		154 (14.2)	
Odds Ratio (95% CI)	0.72 (0.45 to 1.16)		0.78 (0.46 to 1.33)	
X^2 (sig. – Pearson's 2 tailed)	1.80 (ns)		0.81 (ns)	
	yes	**no**	**yes**	**no**
Maternal age (yrs) mean (sd)	33.21 (5.18)	32.26 (5.37)	33.33 (5.38)	32.29 (5.38)
t	-2.44		-2.35	
df	1229		1228	
sig (2-tailed)	p=0.015		p=0.019	
mean difference (95% CI)	-0.95 (-1.71 to -0.19)		-1.03 (-1.90 to –0.17)	
Paternal age (yrs) mean (sd)	36.18 (6.24)	35.35 (6.73)	35.97 (6.26)	35.44 (6.71)
t	-1.71		-2.35	
df	1210		1228	
sig (2-tailed)	ns		ns	
mean difference (95% CI)	-0.83 (-1.79 to 0.12)		-0.53 (-1.62 to 0.55)	
Birth order				
no 1 n=504	113 (22.4)		90 (17.9)	
no 2 n=450	77 (17.1)		52 (11.6)	
no 3 n=192	36 (18.8)		25 (13.0)	
no >3 n=85	7(8.2)		4 (4.7)	
X^2 (sig. – Pearson's 2 tailed)	11.31 (p=0.010)		14.51 (p=0.002)	
Maternal employment mean (sd)				
Out of home F/T n=169	36 (21.2)		27 (16.0)	
Out of home P/T n=573	113 (19.7)		83 (14.5)	
In home F/T n=488	84 (17.2)		61 (12.5)	
one way ANOVA F (significance)	1.681 (ns)		1.557 (ns)	

Table A16 Sensitisation and material/family environment

Biological influences	Atopic (2mm)		Atopic (3mm)	
	No	Yes	No	Yes
Birth weight (kgs) mean (sd)	3.37 (0.55)	3.46 (0.59)	3.38 (0.56)	3.45 (5.77)
t	-2.05		-1.55	
df	1218		1217	
sig (2-tailed)	p=0.041		ns	
mean difference (95% CI)	-0.08 (-0.16 to 0.00)		-0.07 (-0.16 to 0.02)	
Gestation (weeks) mean (sd)	39.51 (1.95)	39.61 (2.15)	39.52 (1.96)	39.55 (2.16)
t	-0.73		-0.16	
df	1230		1229	
sig (2-tailed)	ns		ns	
mean difference (95% CI)	-0.11 (-0.39 to 0.18)		-0.03 (-0.35 to 0.30)	
Antenatal smoke exposure				
Yes n=272	31 (11.4)		23 (8.5)	
No n=953	198 (20.8)		145 (15.2)	
Odds Ratio (95% CI)	0.49 (0.33 to 0.74)		0.51 (0.32 to 0.82)	
X^2 (sig. – Pearson's 2 tailed)	12.25 (p<0.0001)		8.20 (p=0.004)	
Current smoke exposure				
Yes n=523	85 (16.3)		59 (11.3)	
No n=706	148 (21.0)		112 (15.9)	
Odds Ratio (95% CI)	0.73 (0.55 to 0.98)		0.68 (0.48 to 0.95)	
X^2 (sig. – Pearson's 2 tailed)	4.34 (p=0.037)		5.21 (p=0.022)	
Admission to SCBU				
Yes n=223	47 (21.1)		34 (15.2)	
No n=1008	186 (18.5)		137 (13.6)	
Odds Ratio (95% CI)	0.85 (0.59 to 1.21)		0.88 (0.58 to 1.32)	
X^2 (sig. – Pearson's 2 tailed)	0.82 (ns)		0.41 (ns)	
Current height (cms) mean (sd)	97.98 (4.02)	98.04 (3.90)	97.99 (4.01)	97.98 (3.92)
t	-0.22		0.041	
df	1194		1193	
sig (2-tailed)	ns		ns	
mean difference (95% CI)	-0.06 (-0.65 to 0.52)		0.01 (-0.65 to 0.67)	
Gender				
Girls n=601	97 (16.1)		65 (10.8)	
Boys n=640	139 (21.7)		109 (17.0)	
Odds Ratio (95% CI)	0.69 (0.52 to 0.93)		0.59 (0.43 to 0.82)	
X^2 (sig. – Pearson's 2 tailed)	6.26 (p=0.012)		9.86 (p=0.002)	

Table A17 Sensitisation and biological influences

	Exp(B) (odds ratio) (95% C.I.) significance
	Atopy (2mm)
household income	0.96 (0.83 to 1.10) ns
birth order	0.69 (0.57 to 0.84) p<0.0001
gender	0.75 (0.55 to 1.01) ns
birth weight	1.44 (1.08 to 1.93) p=0.013
antenatal smoke exposure	0.53 (0.34 to 0.82) p=0.005
maternal age	1.04 (1.01 to 1.08) p=0.013
constant	0.05

Table A18 Multiple regression analysis of atopy as a function of all significant measures

n (%) N=1261	Lifetime symptoms of allergic reaction including urticaria	Lifetime urticaria (only)	Lifetime significant symptoms (incl life threatening) (face/throat/collapse)	Lifetime serious symptoms (throat/collapse)
Total	230 (18.2%)	165 (13.1%)	65 (5.2%)	8 (0.6%)

Table A19 Lifetime prevalence of urticaria and other allergic symptoms

Lifetime significant symptoms (face/throat/ collapse) n (%) n=230	Age at first episode n=225			Number of episodes ever n=223				Provoking factors identified			
	<1 yr	1-2 yrs	3-4 yrs	1	2	3	>3	None	Food only*	Non-food$ only	Both food* and non-food
	62 (27)	135 (59)	28 (12)	110 (49)	36 (16)	21 (9)	56 (25)	108 (47)	67 (29)	51 (22)	4 (2)

Table A20 Lifetime allergic symptoms (including urticaria)

	Lifetime urticaria (only) N=1262	Age at first episode n=160			Number of episodes ever n=158				Provoking factors identified n=165			
		<1 yr	1-2 yrs	3-4 yrs	1	2	3	>3	None	Food only*	Non-food$ only	Both food* and non-food
Total n (%)	165 (13.1)	38 (23)	103 (62)	19 (12)	84 (51)	27 (16)	12 (7)	35 (21)	99 (60)	26 (16)	38 (23)	2 (1)

* nuts 3, milk 2,egg 2, sauces 4,fish 1,crisps 1,additives 2, ice cream 1,fruit/veg 7,choc 2,desserts 3,wheat 1, drinks 1
$infection 8,animals 3,plants 6,temperature 7,topical 7,drugs 7,dust 1,insect bite 1(2 children had 2 provoking factors)

Table A21 Urticaria as isolated symptom

Ever sig. symp n (%) n=65	Age at first episode			Number of episodes ever				Provoking factors identified			
	<1 yr	1-2 yrs	2-4 yrs	1	2	3	>3	None	Food only*	Non-food$ only	Both food* and non-food
	24 (37)	32 (49)	9 (14)	26 (40)	9 (14)	9 (14)	21 (32)	8 (12)	41(63)	13 (20)	2 (3)

*snacks 2, sauces 5, fish 2, fruit/veg 5, icecream 2, soya 1, sugar 1, margarine 1, desserts 1
$infection 2, furred animal 4, plant 2, topical 1, drugs 6

Table A22 Significant allergic symptoms (face or throat swelling or collapse)

Ever life threatening symptoms n (%) n=8	Age at first episode			Number of episodes ever				Provoking factors identified			
	<1 yr	1-2 yrs	2-4 yrs	1	2	3	>3	None	Food only*	Non-food$ only	Both food* and non-food
	6 (75)	2 (25)	0 (0)	0 (0)	0 (0)	4 (50)	4 (50)	1 (12)	6 (75)	0 (0)	1 (12)

*peanut 2,milk 1,egg 3,fruit/veg 1
$furred animal 1

Table A23 Life threatening allergic symptoms (throat swelling or collapse)

n (%)	Ever any symptoms of allergic reaction including urticaria	Ever urticaria (only)	Ever significant symptoms (face/throat/collapse)	Ever serious symptoms (throat/collapse)
	N=230	N=165	N=65	N=8
Current wheeze	109 (47%)	73 (44%)	36 (55%)	5 (63%)
X^2 (sig)	26.41 (p<0.0001)	10.82 (p=0.001)	15.55 (p<0.0001)	3.16 (ns)
OR (95% CI)	2.13 (1.59 – 2.84)	1.74 (1.25 – 2.43)	2.67 (1.61 – 4.41)	3.41 (0.81 – 14.32)
Current itchy rash	69 (30%)	40 (24%)	29 (45%)	5 (63%)
X^2 (sig)	21.70 (p<0.0001)	3.19 (ns)	29.73 (p<0.0001)	9.77 (p=0.022)
OR (95% CI)	2.15 (1.55 – 2.97)	1.42 (0.97 – 2.10)	3.83 (2.29 – 6.41)	7.16 (1.70 – 30.17)
Current rhinitis	95 (41%)	57 (35%)	38 (58%)	5 (63%)
X^2 (sig)	30.83 (p<0.0001)	6.10 (p=0.014)	35.43 (p<0.0001)	5.26 (p=0.022)
OR (95% CI)	2.30 (1.71 – 3.11)	1.55 (1.09 – 2.19)	4.24 (2.54 – 7.06)	4.62 (1.10 – 19.45)

Table A24 Prevalence of other allergic symptoms in those children with allergic symptoms

n (%)	Ever any symptoms of allergic reactions including urticaria	Ever urticaria (only)	Ever significant symptoms (face/throat/collapse)	Ever life serious (throat/collapse)	Whole population
	N=230	N=165	N=65	N=8	N=1264
Adrenaline	9 (3.9%)	0 (0%)	9 (13.8%)	2 (25%)	9 (0.7%)
Antihistamines	57 (24.8%)	28 (17.0%)	29 (44.6%)	6 (75%)	123 (9.7%)
Inhaled bronchodilator	55 (23.9%)	35 (21.2%)	20 (30.8%)	3 (37.5%)	187 (14.8%)

Table A25 Treatment in those children with allergic symptoms

n (%)	Ever GI symptoms N=191	Current GI symptoms N=79	Ever any serious allergic symptoms (incl urticaria) N=230	Ever urticaria (only) N=165	Ever significant symptoms N=65	Ever life serious symptoms N=8
Milk						
+ve n=20	7 (35%)	2 (10%)	14 (70%)	5 (25%)	9 (45%)	3 (15%)
-ve n=1213	184 (15.2%)	77 (6.3%)	210 (17.3%)	157 (12.9%)	53 (4.4%)	4 (0.3%)
X^2	5.91	0.44	36.61	2.50	67.82	74.88
significance	p=0.025	ns	p<0.0001	ns	p<0.0001	p<0.0001
OR	3.01	1.64	11.11	2.24	17.86	53.25
95% CI	1.19 – 7.65	0.37 – 7.19	4.22 – 29.25	0.80 – 6.25	7.10 - 44.95	11.06 – 256.37
Egg						
+ve n=28	8 (28.6%)	4 (14.3%)	20 (71.4%)	5 (17.9%)	15 (53.6%)	4 (14.3%)
-ve n=1205	184 (15.3%)	76 (3.6%)	205 (17.0%)	157 (13.0%)	48 (4.0%)	3 (0.2%)
X^2	3.68	2.87	54.12	0.56	138.40	95.35
significance	ns	ns	p<0.0001	ns	p<0.0001	p<0.0001
OR	2.22	2.47	12.16	1.45	27.74	66.67
95% CI	0.96 – 5.12	0.84 – 7.31	5.28 – 27.98	0.54 – 3.87	12.50 – 61.54	14.14 – 314.26
Peanut						
+ve n=43	7 (16.3%)	2 (4.7%)	24 (55.8%)	8 (18.6%)	16 (37.2%)	4 (9.3%)
-ve n=1186	185 (15.6%)	78 (6.6%)	201 (16.9%)	153 (12.9%)	48 (4.0%)	4 (0.3%)
X^2	0.02	0.25	41.85	1.19	92.35	57.57
significance	ns	ns	p<0.0001	ns	p<0.0001	p<0.0001
OR	1.05	0.69	6.18	1.55	14.04	30.31
95% CI	0.46 – 2.41	0.16 – 2.92	3.32 – 11.50	0.70 – 3.39	7.09 – 27.78	7.31 – 125.

Table A26 Prevalence of symptoms in those children with positive SPT (2mm)

n (%)	lifetime GI symptoms	current GI symptoms
food allergen sensitised – 2mm		
Yes n=63	14 (22.2)	6 (9.5)
No n=1169	178 (15.2)	74 (6.3)
Odds Ratio (95% CI)	1.59 (0.86 to 2.94)	1.56 (0.63 to 3.73)
X^2 (sig. – Pearson's 2 tailed)	2.24 (ns)	1.00 (ns)
food allergen sensitised – 3mm		
Yes n=46	13 (28.3)	6 (13.0)
No n=1186	179 (15.1)	74 (6.3)
Odds Ratio (95% CI)	2.21 (1.14 to 4.29)	2.25 (0.92 to 5.48)
X^2 (sig. – Pearson's 2 tailed)	5.82 (p=0.016)	3.36 (ns)
Atopic – 2mm		
Yes n=232	45 (19.4)	15 (6.52)
No n=1000	148 (14.8)	66 (6.6)
Odds Ratio (95% CI)	1.38 (0.96 to 2.00)	0.98 (0.55 to 1.75)
X^2 (sig. – Pearson's 2 tailed)	3.01 (ns)	0.006 (ns)
Atopic – 3mm		
Yes n=170	30 (17.6)	14 (8.2)
No n=1061	162 (15.3)	66 (6.2)
Odds Ratio (95% CI)	1.19 (0.78 to 1.83)	1.35 (0.74 to 2.47)
X^2 (sig. – Pearson's 2 tailed)	0.63 (ns)	0.97 (ns)

Table A27 Skin prick sensitisation and GI symptoms

n (%)	lifetime any allergic (probable IgE mediated) symptoms	lifetime urticaria (only)	lifetime significant allergic symptoms	lifetime serious allergic symptoms (including anaphylaxis)
Aeroallergen sensitised – 2mm				
Yes n=221	68 (30.8)	39 (17.6)	29 (13.1)	7 (3.2)
No n=1009	158 (15.7)	123 (12.2)	35 (3.5)	1 (0.1)
Odds Ratio (95% CI)	2.39 (1.72 to 3.34)	1.55 (1.04 to 2.29)	4.20 (2.51 to 7.04)	33.0 (4.04 to 269.65)
X^2 (sig. – Pearson's 2 tailed)	27.60 (p<0.0001)	4.77 (p=0.03)	34.25 (p<0.0001)	26.44 (p<0.0001)
Aeroallergen sensitised – 3mm				
Yes n=162	56 (34.6)	30 (18.5)	26 (16.0)	7 (4.3%)
No n=1068	170 (15.9)	132 (12.3)	38 (3.6)	1 (0.1%)
Odds Ratio (95% CI)	2.79 (1.94 to 4.01)	1.61 (1.04 to 2.50)	5.18 (3.05 to 8.80)	48.23 (5.89 to 394.68)
X^2 (sig. – Pearson's 2 tailed)	32.62 (p<0.0001)	4.71 (p=0.03)	44.50 (p<0.0001)	38.94 (p<0.0001)
Food allergen sensitised – 2mm				
Yes n=63	35 (55.6)	13 (20.6)	22 (34.9)	6 (9.5)
No n=1166	191 (16.4)	149 (12.8)	42 (3.6)	2 (0.2)
Odds Ratio (95% CI)	6.38 (3.79 to 10.74)	1.78 (0.94 to 3.35)	14.6 (7.86 to 26.24)	61.32 (12.12 to 310.53)
X^2 (sig. – Pearson's 2 tailed)	61.12 (p<0.0001)	3.25 (ns)	118.77 (p<0.0001)	80.91 (p<0.0001)
Food allergen sensitised – 3mm				
Yes n=45	30 (66.7)	9 (20.0)	21 (46.7)	6 (13.3)
No n=1183	195 (16.5)	152 (12.8)	43 (3.6)	2 (0.2)
Odds Ratio (95% CI)	10.13 (5.35 to 19.20)	1.70 (0.80 to 3.60)	23.20 (11.99 to 44.89)	90.92 (17.78 to 464.89)
X^2 (sig. – Pearson's 2 tailed)	72.95 (p<0.0001)	1.96 (ns)	162.50 (p<0.0001)	116.18 (p<0.0001)
Atopic – 2mm				
Yes n=232	71 (30.6)	40 (17.2)	31 (13.4)	7 (3.0)
No n=997	155 (15.5)	122 (12.2)	33 (3.3)	1 (0.1)
Odds Ratio (95% CI)	2.40 (1.73 to 3.24)	1.50 (1.01 to 2.21)	4.51 (2.70 to 7.53)	31.02 (3.80 to 253.37)
X^2 (sig. – Pearson's 2 tailed)	28.43 (p<0.0001)	4.17 (p=0.04)	38.52 (p<0.0001)	24.79 (p<0.0001)
Atopic – 3mm				
Yes n=170	59 (34.7)	31 (18.2)	28 (16.5)	7 (4.1)
No n=1058	167 (15.8)	131 (12.4)	36 (3.4)	1 (0.1)
Odds Ratio (95% CI)	2.84 (1.99 to 4.05)	1.58 (1.03 to 2.43)	5.60 (3.31 to 9.46)	45.44 (5.55 to 371.69)
X^2 (sig. – Pearson's 2 tailed)	34.92 (p<0.0001)	4.42 (p=0.04)	50.63 (p<0.0001)	36.66 (p<0.0001)

Table A28 Skin prick sensitisation and serious allergic reactions

			lifetime GI symptoms		current GI symptoms	
Income						
<12,0000 (n=346)			64 (18.5)		26 (7.5)	
12-17,999 (n=338)			49 (14.5)		21 (6.2)	
18-29,999 (n=383)			65 (17.0)		26 (6.8)	
30-41,999 (n=133)			13 (9.8)		6 (4.5)	
>42,000 (n=60)			6 (10.0)		4 (6.7)	
Mann-Whitney U sig. (2 tailed)			95925.500 (ns)		46350.500 (ns)	
Housing tenure						
owned (n=934)			138 (14.8)		63 (6.8)	
rented/other (n=328)			59 (18.0)		20 (6.1)	
Odds Ratio (95% CI)			1.26 (0.91 to 1.77)		0.90 (0.53 to 1.51)	
X^2 (sig. – Pearson's 2 tailed)			1.90 (ns)		0.17 (ns)	
Vehicle ownership						
vehicle (n=1133)			168 (14.8)		72 (6.4)	
no vehicle (n=126)			29 (23.0)		11 (8.7)	
Odds Ratio (95% CI)			1.72 (1.10 to 2.68)		1.41 (0.73 to 2.73)	
X^2 (sig. – Pearson's 2 tailed)			5.76 (p=0.016)		1.03 (ns)	
Maternal age at leaving education						
<=16	n=548		77 (14.1)		33 (6.0)	
17-20	n=545		94 (17.2)		36 (6.6)	
>=21	n=170		27 (15.9)		15 (8.9)	
Mann-Whitney U (sig - 2 tailed)			100441.0 (ns)		46237.5000 (ns)	
Single parent household mean (sd)						
one parent n=156			34 (21.8)		15 (9.6)	
two parents n=1105 (mother&father/partner)			163 (14.7)		68 (6.2)	
Odds Ratio (95% CI)			1.61 (1.07 to 2.44)		1.62 (0.90 to 2.92)	
X^2 (sig. – Pearson's 2 tailed)			5.17 (p=0.023)		2.66 (ns)	
			yes	**no**	**yes**	**no**
Maternal age mean (sd)			32.03 (5.12)	32.52 (5.38)	32.40 (4.94)	32.44 (5.37)
t			-1.20		-0.08	
df			1259		1258	
sig (2-tailed)			ns		ns	
mean difference (95% CI)			-0.50 (-1.31 to 0.32)		-0.05 (-1.24 to 1.14)	
Paternal age mean (sd)			35.72 (6.76)	35.43 (6.61)	36.18 (6.89)	35.42 (6.62)
t			0.56		1.00	
df			1240		1239	
sig (2-tailed)			ns		ns	
mean difference (95% CI)			0.29 (-0.73 to 1.31)		0.76 (-0.73 to 2.25)	
Birth order						
no 1 n=518			79 (15.3)		33 (6.4)	
no 2 n=462			74 (16.0)		31 (6.7)	
no 3 n=194			36 (18.6)		16 (8.2)	
no >3 n=87			8 (9.2)		3 (3.4)	
X^2 (sig. – Pearson's 2 tailed)			4.10		2.31	
		p	ns		ns	
Maternal employment						
Out of home F/T	n=174		25 (14.4)		9 (5.2)	
Out of home P/T	n=588		93 (15.8)		43 (7.3)	
In home F/T n=499			79 (15.8)		31 (6.2)	
one way ANOVA		F	0.134		0.008	
		p	ns		ns	

Table A29 GI symptoms and material/family environment

Biological influences	lifetime GI symptoms		current GI symptoms	
	no	yes	no	yes
Birth weight (kgs) mean (sd)	3.40 (0.56)	3.38 (0.54)	3.39 (0.56)	3.41 (0.53)
t	0.43		-0.29	
df	1247		1246	
sig (2-tailed)	ns		ns	
mean difference (95% CI)	0.02 (-0.07 to 0.10)		-0.02 (-0.14 to 0.11)	
Gestation (weeks) mean (sd)	39.52 (2.02)	39.58 (1.80)	39.52 (2.01)	39.68 (1.69)
t	-0.37		-0.70	
df	1260		1259	
sig (2-tailed)	ns		ns	
mean difference (95% CI)	-0.06 (-0.36 to 0.24)		-0.16 (-0.60 to 0.28)	
Antenatal smoke exposure				
Yes n=279	39 (14.0)		12 (5.4)	
Non=977	158 (16.2)		69 (7.1)	
Odds Ratio (95% CI)	0.84 (0.58 to 1.23)		0.75 (0.42 to 1.33)	
X^2 (sig. – Pearson's 2 tailed)	0.80 (ns)		1.00 (ns)	
Current smoke exposure				
Yes n=535	115 (15.9)		34 (6.4)	
No n=724	81 (15.1)		48 (6.6)	
Odds Ratio (95% CI)	0.95 (0.69 to 1.29)		0.95 (0.61 to 1.50)	
X^2 (sig. – Pearson's 2 tailed)	0.13 (ns)		0.04 (ns)	
Admission to SCBU				
Yes n=230	38 (16.6)		13 (5.7)	
No n=1032	160 (15.5)		71 (6.9)	
Odds Ratio (95% CI)	1.08 (0.74 to 1.60)		0.81 (0.44 to 1.50)	
X^2 (sig. – Pearson's 2 tailed)	0.17 (ns)		0.44 (ns)	
Current height (cms) mean (sd)	98.15 (3.91)	97.36 (4.49)	98.11 (3.97)	96.76 (4.35)
t	2.26		2.95	
df	243.502		1207	
sig (2-tailed)	p=0.025		p=0.003	
mean difference (95% CI)	0.79 (0.10 to 1.48)		1.36 (0.45 to 2.26)	
Gender				
Girls n=609	98 (16.1)		40 (6.6)	
Boys n=654	100 (15.3)		44 (6.7)	
Odds Ratio (95% CI)	1.06 (0.78 to 1.44)		0.98 (0.63 to 1.52)	
X^2 (sig. – Pearson's 2 tailed)	0.15 (ns)		0.01 (ns)	

Table A30 GI symptoms and biological influences

			lifetime any allergic (probable IgE mediated) symptoms		lifetime urticaria (only)		lifetime significant allergic symptoms		lifetime serious allergic symptoms (including anaphylaxis)	
Income	<12,0000 (n=346)		72 (20.8)		57 (16.5)		15 (4.3)		0 (0)	
	12-17,999 (n=338)		56 (16.6)		41 (12.1)		15 (4.4)		3 (0.9)	
	18-29,999 (n=381)		64 (16.8)		43 (11.3)		21 (5.5)		2 (0.5)	
	30-41,999 (n=132)		25 (18.9)		14 (10.5)		11 (8.3)		2 (1.5)	
	>42,000 (n=60)		13 (21.7)		10 (16.7)		3 (5.0)		1 (1.7)	
Mann-Whitney U sig. (2 tailed)			115040.00 (ns)		83133.5000 (ns)		34786.000 (ns)		3245.000 (ns)	
Housing	owned (n=932)		161 (17.3)		111 (11.9)		50 (5.4)		7 (0.8)	
	rented/other (n=327)		69 (21.1)		54 (16.5)		15 (4.6)		1 (0.3)	
	Odds Ratio (95% CI)		1.28 (0.93 to 1.76)		1.47 (1.03 to 2.09)		0.85 (0.47 to 1.53)		0.41 (0.05 to 3.31)	
	X^2 (sig. – Pearson's 2 tailed)		2.37 (ns)		4.56 (p=0.03)		0.30 (ns)		0.76 (ns)	
Vehicle	vehicle (n=1131)		198 (17.5)		140 (12.4)		58 (5.1)		8 (0.7)	
	no vehicle (n=125)		32 (25.6)		25 (20.0)		7 (5.6)		0 (0)	
	Odds Ratio (95% CI)		1.62 (1.06 to 2.49)		1.77 (1.11 to 2.85)		1.10 (0.49 to 2.46)		0.99 (0.99-1.0)	
	X^2 (sig. – Pearson's 2 tailed)		4.93 (p=0.026)		5.77 (p=0.016)		0.05 (ns)		0.89 (ns)	
Maternal age at leaving education										
	<=16	n=170	100 (18.3)		74 (13.5)		26 (4.8)		2 (0.4)	
	17-20	n=543	101 (18.6)		74 (13.6)		27 (5.0)		2 (0.4)	
	>=21	n=547	29 (17.1)		17 (10.0)		12 (7.1)		4 (2.4)	
Mann-Whitney U (sig - 2 tailed)			117643.5 (ns)		87352.500 (ns)		36477.000 (ns)		3167.000 (p=0.049)	
Single parent household mean (sd)										
	one parent n=155		35 (22.6)		27 (17.4)		57 (5.2)		0 (0)	
	two parents n=1105) (mother&father/partner)		195 (17.7)		138 (12.5)		8 (5.2)		8 (0.7)	
	Odds Ratio (95% CI)		1.36 (0.91 to 2.04)		1.48 (0.94 to 2.33)		1.00 (0.47 to 2.14)		0.99 (0.99 to 1.00)	
	X^2 (sig. – Pearson's 2 tailed)		2.20 (ns)		2.92 (ns)		0 (ns)		1.13 (ns)	
			yes	**no**	**yes**	**no**	**yes**	**no**	**yes**	**no**
Maternal age mean (sd)			31.87 (4.96)	32.57 (5.40)	31.59 (5.06)	32.57 (5.36)	32.55 (4.68)	32.43 (5.37)	34.13 (3.87)	32.44 (5.35)
t			-1.81		-2.19		0.18		0.89	
df			1256		1258		1256		1257	
sig (2-tailed)			ns		0.029		ns		ns	
mean difference (95% CI)			-0.70 (-1.46 to 0.06)		-0.97 (-1.84 to – 0.10)		0.12 (-1.21 to 1.45)		1.69 (-2.03 to 5.40)	
Paternal age mean (sd)			35.48 (6.32)	35.45 (6.69)	35.23 (6.40)	35.49 (6.65)	36.11 (6.12)	35.42 (6.65)	36.38 (2.07)	35.47 (6.65)
t			0.05		-0.47		0.81		1.21	
df			1238		1240		1238		7.974	
sig (2-tailed)			ns		ns		ns		ns	
mean difference (95% CI)			0.02 (-0.93 to 0.98)		-0.26 (-1.35 to 0.83)		0.42 (-0.98 to 2.35)		0.91 (-3.71 to 5.53)	
Birth order	no 1	n=518	101 (19.5)		69 (13.3)		32 (6.2)		3 (0.6)	
	no 2	n=459	73 (15.9)		58 (12.6)		15 (3.3)		2 (0.4)	
	no 3	n=194	38 (19.6)		24 (12.4)		14 (7.2)		3 (1.5)	
	no >3	n=87	18 (20.7)		14 (16.1)		4 (4.6)		0 (0)	
X^2 (sig. – Pearson's 2 tailed)			2.81 (ns)		0.88 (ns)		6.18 (ns)		3.42 (ns)	
Maternal employment										
	Out of home F/T	n=173	34 (19.7)		18 (10.4)		16 (9.2)		3 (1.7)	
	Out of home P/T	n=586	105 (17.9)		76 (12.9)		29 (4.9)		4 (0.7)	
	In home F/T n=499		91 (18.2)		71 (14.2)		20 (4.0)		1 (0.2)	
	one way ANOVA	F (significance)	0.077 (ns)		1.589 (ns)		5.748 (ns)		4.451 (ns)	

Table A31 Allergic symptoms (probably IgE mediated) and material/family environment

* face/throat/collapse **throat/collapse

Biological influences		Prevalence lifetime any allergic (probable IgE mediated) symptoms		lifetime urticaria (only)		lifetime significant allergic symptoms		lifetime serious allergic symptoms (including anaphylaxis)	
		No	Yes	No	Yes	No	Yes	No	Yes
Birth weight (kgs) mean (sd)		3.39 (0.58)	3.39 (0.50)	3.39 (0.57)	3.37 (0.48)	3.39 (0.56)	3.42 (0.55)	3.39 (0.56)	3.57 (0.26)
t		0.15		0.52		-0.44		-0.89	
df		1244		239.655		1244		1245	
sig (2-tailed)		ns		ns		ns		ns	
mean difference (95% CI)		0.01 (-0.07 to 0.08)		0.02 (-0.06 to 0.10)		-0.03 (-0.17 to 0.11)		-0.18 (-0.57 to 0.21)	
Gestation (weeks) mean (sd)		39.52 (2.00)	39.56 (1.97)	39.51 (2.02)	39.68 (1.79)	39.54 (1.97)	39.26 (2.35)	39.53 (2.00)	39.88 (0.64)
t		-0.28		-1.04		1.10		-1.50	
df		1257		1259		1257		7.898	
sig (2-tailed)		ns		ns		ns		ns	
mean difference (95% CI)		-0.05 (-0.33 to 0.24)		-0.17 (-0.50 to 0.15)		0.28 (-0.22 to 0.78)		-0.35 (-0.89 to 0.19)	
Antenatal smoke exposure									
	Yes n=279	57 (20.5)		44 (15.8)		13 (4.7)		0 (0)	
	No n=975	172 (17.7)		121 (12.4)		51 (5.2)		8 (0.8)	
Odds Ratio (95% CI)		1.20 (0.86 to 1.68)		1.32 (0.91 to 1.92)		0.89 (0.48 to 1.66)		0.99 (0.99 to 1.00)	
X^2 (sig. – Pearson's 2 tailed)		1.17 (ns)		2.14 (ns)		0.14 (ns)		2.30 (ns)	
Current smoke	Yes n=533	102 (19.1)		77 (14.4)		25 (4.7)		2 (0.4)	
	No n=723	127 (17.6)		87 (12.0)		40 (5.5)		6 (0.8)	
Odds Ratio (95% CI)		1.11 (0.83 to 1.48)		1.23 (0.88 to 1.71)		0.84 (0.50 to 1.40)		0.45 (0.09 to 2.24)	
X^2 (sig. – Pearson's 2 tailed)		0.51 (ns)		1.51 (ns)		0.44 (ns)		1.01 (ns)	
Admission to SCBU	Yes n=230	45 (19.6)		32 (13.9)		13 (5.7)		0 (0)	
	No n=1029	185 (18.0)		133 (12.9)		52 (5.1)		8 (0.8)	
Odds Ratio (95% CI)		1.12 (0.77 to 1.59)		1.09 (0.72 to 1.65)		1.12 (0.60 to 2.10)		0.99 (0.99 to 1.00)	
X^2 (sig. – Pearson's 2 tailed)		0.31 (ns)		0.17 (ns)		0.14 (ns)		1.80 (ns)	
Current height (cms) mean (sd)		98.08 (3.95)	97.78 (4.29)	98.11 (3.97)	97.48 (4.24)	98.00 (3.99)	98.60 (4.36)	98.02 (4.01)	98.29 (4.16)
t		1.00		1.84		-1.11		-0.19	
df		1205		1207		1205		1206	
sig (2-tailed)		ns		ns		ns		ns	
mean difference (95% CI)		0.30 (-0.29 to 0.89)		0.63 (-0.04 to 1.29)		-0.60 (-1.65 to 0.45)		-0.26 (-3.06 to 2.53)	
Gender	Girls n=606	108 (17.8)		82 (13.5)		26 (4.3)		6 (1.0)	
	Boys n=654	122 (18.7)		83 (12.7)		39 (6.0)		2 (0.3)	
	Odds Ratio (95% CI)	0.95 (0.71 to 1.26)		1.07 (0.77 to 1.49)		0.71 (0.43 to 1.18)		3.26 (0.65 to 16.19)	
	X^2 (sig.Pearson's 2 tailed)	0.15 (ns)		0.18 (ns)		1.80 (ns)		2.33 (ns)	

Table A32 Allergic symptoms (probable IgE mediated) and biological influences

	Exp(B) (odds ratio) (95% C.I.) significance	
	lifetime GI symptoms	current GI symptoms
atopy (2mm)	1.47 (1.01 to 2.13) p=0.044	0.99 (0.55 to 1.78) ns
household income	1.20 (1.04 to 1.38) p=0.012	
length of beast feeding		1.03 (1.00 to 1.06) ns
timing of weaning		1.11 (0.97 to 1.27) ns
current height		0.93 (0.88 to 0.99) p=0.018
constant	0.09	47.73

Table A33 **Sequential logistic regression of gastrointestinal symptoms of food intolerance as a function of significant measures**

	Exp(B) (odds ratio) (95% C.I.) significance			
	lifetime any allergic (probable IgE mediated) symptoms	lifetime urticaria (only)	lifetime significant allergic symptoms	lifetime serious allergic symptoms (including anaphylaxis)
atopy (2mm)	2.47 (1.78 to 3.44) p<0.0001	1.55 (1.05 to 2.30) p=0.029	4.51 (2.70 to 7.53) p<0.0001	30.97 (3.80 to 252.67) p=0.001
maternal age	0.97 (0.94 to 1.00) p=0.035	0.97 (0.94 to 1.00) p=0.034		
constant	0.48	0.41	0.03	0.00

Table A34 **Sequential logistic regression of all serious allergic reactions as a function of significant measures**

	Exp(B) (odds ratio) (95% C.I.) significance				
	current wheeze	current rhinitis	current itchy rash	lifetime significant allergic symptoms	current GI food intolerance
atopy(2mm)	1.31 (0.95 – 1.82) ns	1.83 (1.31 – 2.56) p<0.0001	3.11 (2.24 – 4.32) p<0.0001	2.97 (1.72 – 5.14) p<0.0001	0.67 (0.35 – 1.28) ns
household income	1.11 (0.98 – 1.26) ns	1.11 (0.98 – 1.26) ns			
gender		0.72 (0.55 – 0.95) p=0.021			
housing tenure	1.32 (0.97 – 1.81) ns				
gestation	0.94 (0.88 – 1.00) p=0.048				
current height		0.96 (0.93 – 1.00) p=0.036			0.93 (0.87 – 0.98) p=0.011
current wheeze		3.02 (2.29 – 3.99) p<0.0001	1.42 (1.04 – 1.95) p=0.03	1.71 (0.98 – 2.98) ns	1.45 (0.88 – 2.39) ns
current rhinitis	3.12 (2.38 – 4.10) p<0.0001		1.28 (0.91 – 1.79) ns	3.03 (1.72 – 5.32) p<0.0001	1.52 (0.91 – 2.55) ns
current itchy rash	1.40 (1.01 – 1.92) p=0.041	1.25 (0.89 – 1.76) ns		2.42 (1.39 – 4.19) p=0.002	1.02 (0.56 – 1.86) ns
l/t sig allergic symptoms	1.75 (1.00 – 3.06) ns	3.08 (1.73 – 5.49) p<0.0001	2.31 (1.32 – 4.03) p=0.003		5.99 (3.01 – 11.93) p<0.0001
constant	2.23	5.79	0.137	0.02	88.47

Table A35 **Multiple regression analysis of all current allergic symptoms as a function of significant measures.**

Chapter 6

Atopy, allergic symptoms and behaviour

6.1 Background

Allergic symptoms and emotional and behavioural problems in childhood are common and have been shown to occur together more often than expected by chance.[143] There has been little exploration of the outside-family common environmental factors that may explain some of the co-occurrence of allergic symptoms and behaviour problems. Few studies have controlled for the co-existence of allergic symptoms, many concentrating upon asthma. Many studies have employed confused definitions of atopy and allergic disease, with selected study populations.

6.2 Hypothesis and Aims

Hypothesis

Children with symptomatic allergic disease have increased parentally reported behaviour problems (internalising and externalising behaviours), and observable evidence of externalising behaviour problems (impulsivity, attention and activity).

Aims

1. To estimate the association between atopy and current allergic symptoms (wheeze, rhinitis or itchy flexural rash), and both general behaviour problems measured by parental questionnaire (PQ), and behaviour problems associated with hyperactivity (PQ), having controlled for significant environmental factors.

2. To estimate the association between atopy and current allergic symptoms (wheeze, rhinitis or itchy flexural rash) and behaviour problems associated with hyperactivity, measured by direct observation (DO), having controlled for significant environmental factors.

6.3 Methodology

This analysis is based upon the larger group of children from Phase II (n=1273). Information from direct observation of the children's impulsivity, activity and attention is based upon the subgroup of children from Phase III (n=277).

The socio-demographic and biological independent variables have been described previously in Chapters 4 and 5. The child was defined as atopic if they had a reaction to at least one of the six allergens, which was at least 2mm mean wheal diameter, in the presence of a positive histamine and negative saline control (Appendix D). This was the same definition as used in Chapter 5. Parents completed the ISAAC questions and identified whether their child experienced current allergic symptoms – wheeze, rhinitis or flexural itchy rash (Appendix E).

Behavioural outcomes included those derived from the parent questionnaire (PQ) in Phase I, a continuous measure of general behaviour problems (GBP) and a categorical variable, using the same 'cut off' as used previously for extreme general behaviour problems.

Sleep problems are also specifically explored, problems with settling and night waking derived from the BCL.[1] The children who were reported to have problems 'some of the time' or 'all the time' were defined as having a problem, and compared with those children with no problem.

Hyperactivity was reported from the parental questionnaire producing a continuous variable (HB), and a categorical variable, using the same 'cut off' as used previously for extreme behaviour problems associated with hyperactivity. Hyperactivity was also measured by direct observation of the children's impulsivity, activity and attention, producing 3 aggregate variables (see chapter 3 for details); 1) impulsivity 2) attention and activity and 3) hyperactivity.

6.4 Results

6.4.1 Atopy, allergic symptoms and general behaviour problems (GBP - PQ)

n (% of those with current wheeze/without HA or GBP)		Extreme GBP Behaviour problem (BCL>11)	Extreme HB Hyperactive (EAS>4 &WWP≥20)	GBP Behaviour problem BCL SCORE	HB Hyperactive WWP SCORE
Atopy – 2mm	Yes=236	33 (14.0%)	27 (11.4%)		
	No=1005	117 (11.6%)	118 (11.7%)		
Odds Ratio (95% CI)		1.23 (0.81 to 1.87)	0.97 (0.62 to 1.52)		
X^2 (sig. – Pearson's 2 tld)		0.99 (ns)	0.017 (ns)		
Mean (sd)	Yes			7.79 (3.12)	14.69 (9.24)
	No			7.48 (3.35)	14.52 (9.92)
T				1.28	0.24
Df				1239	1239
sig (2-tailed)				ns	ns
mean diffnce (95% CI)				0.31 (-0.16 to 0.78)	0.17 (-1.22 to 1.56)
Current wheeze	Yes=417	60 (14.4%)	58 (13.9%)		
	No=845	94 (11.1%)	88 (10.4%)		
Odds Ratio (95% CI)		1.34 (0.95 to 1.90)	1.39 (0.97 to 1.98)		
X^2 (sig. – Pearson's 2 tld)		2.78 (ns)	3.33 (ns)		
Mean (sd)	Yes			7.99 (3.30)	15.80 (9.90)
	No			7.35 (3.31)	13.99 (9.68)
t				3.24	3.09
df				1260	1260
sig (2-tailed)				p=0.001	p=0.002
mean diffnce (95% CI)				0.64 (0.25 to 1.03)	1.80 (0.66 to 2.95)
Current rhinitis	Yes=337	64 (19.0%)	59 (17.5%)		
	No=927	90 (9.7%)	87 (9.4%)		
Odds Ratio (95% CI)		2.18 (1.54 to 3.09)	2.05 (1.43 to 2.93)		
X^2 (sig. – Pearson's 2 tld)		19.90 (p<0.0001)	15.96 (p<0.0001)		
Mean (sd)	Yes			8.46	17.16
	No			7.24	13.65
t				5.86	5.39
df				1262	535.887
sig (2-tailed)				p<0.0001	p<0.0001
mean diffnce (95% CI)				1.22 (0.81 to 1.63)	3.52 (2.23 to 4.80)
Curr itchy rash	Yes=204	39 (19.1%)	28 (13.7%)		
	No=1057	114 (10.8%)	117 (11.1%)		
Odds Ratio (95% CI)		1.96 (1.31 to 2.92)	1.28 (0.82 to 1.99)		
X^2 (sig. – Pearson's 2 tld)		11.14 (p=0.001)	1.19 (ns)		
Mean (sd)	Yes			8.53 (3.36)	16.55 (10.52)
	No			7.38 (3.28)	14.21 (9.59)
t				4.60	3.15
df				1259	1259
sig (2-tailed)				P<0.0001	p=0.002
mean diffnce (95% CI)				1.16 (0.66 to 1.65)	2.35 (0.88 to 3.81)

Table 1 **Univariate analysis of all parental questionnaire behavioural outcomes as a function of allergic symptoms**

Atopic children were no more likely to have general behaviour problems nor more extreme GBP in a univariate analysis. Children with current wheeze did have a statistically significantly higher GBP score, but were not more likely to have extreme GBP. Children with rhinitis and current flexural itchy rash were significantly more likely to have both a higher GBP score, and to have more extreme GBP (table 1).

The significant environmental (material and family) and biological factors predicting the continuous measure of GBP had been previously identified (rented housing, low household income, young maternal age at leaving full time education, low birthweight, antenatal exposure to smoke and male gender) (ANOVA, F=19.39, p=0.004, R^2 = 0.086) (see chapter 4) and they were first put into the model to control for this potential confounding. The effect of adding atopy and current allergic symptoms to this model was then examined with sequential multiple regression. Atopy and current wheeze did not significantly improve the model fit. Current rhinitis improved the model fit (ANOVA, F=20.176, p<0.0001, R^2 = 0.098) as did current flexural itchy rash (ANOVA, F=19.703, p<0.0001, R^2 = 0.108) (table 2).

Variable	β	P value
housing tenure	0.103	0.001
household income	0.098	0.002
maternal education	0.070	0.017
birthweight	-0.062	0.017
antenatal smoke	0.108	<0.0001
gender	-0.062	0.025
atopy	0.022	ns
current wheeze	0.014	ns
current rhinitis	0.122	<0.0001
current flexural itchy rash	0.097	0.001

Table 2 **Multiple regression analysis of continuous GBP as a function of atopy and allergic symptoms (& significant environmental measures)**

Variable	Exp (B) (OR) (95% CI)	P value
housing tenure	2.17 (1.48 to 3.17)	<0.0001
maternal age	0.94 (0.91 to 0.98)	0.001
atopy	1.09 (0.69 to 1.71)	ns
current wheeze	0.94 (0.64 to 1.38)	ns
current rhinitis	1.72 (1.11 to 2.67)	0.016
current flexural itchy rash	1.96 (1.34 to 2.88)	0.001

Table 3 **Logistic regression analysis of extreme GBP as a function of atopy and allergic symptoms (& significant environmental measures)**

The significant environmental (material and family) and biological factors predicting extreme GBP had been previously identified (rented housing, young mothers) (see chapter 4) and these were first put into the model in order to control for this potential confounding. Casting extreme GBP as the dependent variable sequential logistic regression was used to examine the additional effect of atopy and current allergic symptoms (wheeze, rhinitis and itchy flexural rash). Atopy and current wheeze did not significantly improve the model. Current rhinitis significantly contributed to the model (X^2 = 59.76, df 3, log-likelihood ratio 876.510 (X^2 change = 14.33, df 1, p<0.0001)) as did current flexural itchy rash (X^2 = 53.58, df 3, log-likelihood ratio 877.955 (X^2 change = 9.89, df 1, p=0.002)) (table 3).

The combined effect of the allergic symptoms on extreme GBP was examined with sequential logistic regression. There was a trend from the univariate analysis that children with symptoms from more systems had an increasing tendency to extreme

behaviour problems, 27.1% of the children with all the three symptoms had extreme behaviour problems, as compared with 9.1% of those children with no symptoms (figure one). The trend persisted in the multivariate analysis (table 4), but it was only children with no symptoms or with wheeze alone when compared to those children with all three symptoms that had a statistically significant lower risk of extreme GBP (X^2 = 68.254, df 9, log-likelihood ratio 862.767, p<0.0001 (X^2 change =24.669, df7, P=0.001)).

	Total no of children	No (%) of children with extreme GBP	Exp B (Adjusted OR)* (95% CI)	P value
Allergic symptoms				
All symptoms	48	13 (27.1)	1	
Wheeze only	192	15 (7.8)	0.3 (0.1 to 0.6)	0.001
Rhinitis	127	18 (14.2)	0.5 (0.2 to 1.2)	ns
Flex itchy rash	88	14 (15.9)	0.7 (0.3 to 1.6)	ns
Wheeze & rhinitis	135	26 (19.3)	0.7 (0.3 to 1.6)	ns
Wheeze & rash	41	5 (12.2)	0.5 (0.1 to 1.4)	ns
Rhinitis & rash	26	7 (26.9)	1.1 (0.4 to 3.3)	ns
No symptoms	602	55 (9.1)	0.3 (0.2 to 0.7)	0.003

* all allergic symptoms controlled for housing tenure and maternal age

Table 4 Overlap of allergic symptoms and extreme general behaviour problems

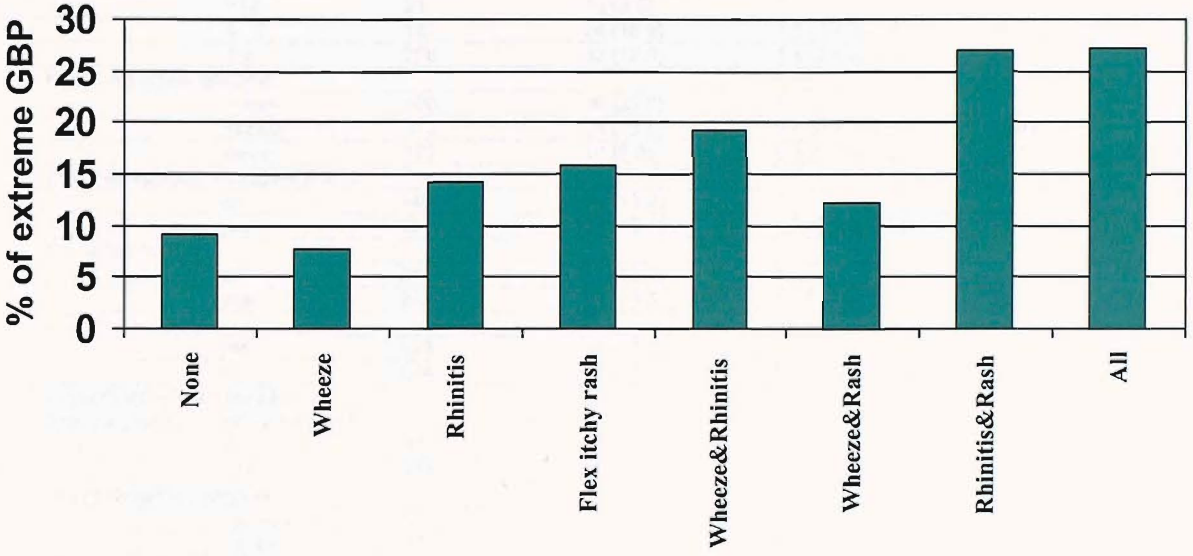
In summary atopic children were no more likely to have GBP or extreme GBP. Children who had current symptoms of wheeze were no more likely to have GBP or more extreme GBP. Children with current rhinitis however were more at risk from GBP and more extreme GBP, this was confirmed in the multivariate analysis. Children with current flexural itchy rash were also found to be more at risk of GBP and extreme GBP, this relationship was also maintained in the multivariate analysis.

Severity of allergic symptoms and general behaviour problems (GBP - PQ)

Children with more severe allergic symptoms may be at increased risk of behaviour problems. The three groups of children with current allergic symptoms (current wheeze, current itchy rash and current rhinitis) were examined separately with sequential logistic regression, casting extreme GBP as the dependent variable. The significant environmental variables (housing tenure and maternal age) were first added to the model.

The group of children with current wheeze was examined, most of the measures of symptom severity failed to predict extreme GBP. Children whose parents reported sleep disturbance secondary to the wheeze were more likely to report extreme GBP (X^2 = 36.23, df 4, log-likelihood ratio 298.924 (X^2 change = 12.57, df 2, p=0.002)).

Fig 1 Allergic symptoms and extreme GBP



The group of children with current itchy rash were next examined. The chronicity of the rash (whether it had ever resolved in the previous 12 months) did not significantly predict extreme GBP, nor did treatment. Children whose parents reported sleep disturbance secondary to their symptoms of eczema however were again increasingly likely to report an extreme GBP (X^2 = 15.78, df 4, log-likelihood ratio 224.86 (X^2 change = 8.12, df 2, p=0.017)). When examining the children with rhinitis by sequential logistic regression there was no relationship between the severity of the child's rhinitis or if they were receiving treatment and the likelihood of extreme GBP.

In summary there no evidence that children with more severe or frequent allergic symptoms were more likely to have behaviour problems. The exception was those children whose parents specifically reported sleep disturbance secondary to wheeze or eczema, who were more likely to have extreme GBP. The severity of rhinitis did not appear to increase the risk of extreme GBP, however the ISAAC questions did not ask about whether rhinitis affected sleep.

	Total no of children	No (%) of children with behaviour problem	Exp B (Adjusted OR)* (95% CI)	P value
Current wheeze (n=417)				
Episodes of wheeze/year:				
>12	21	4 (19.0)	1	
4-12	127	24 (18.9)	1.5 (0.4 to 5.4)	ns
1-3	266	32 (12.0)	1.4 (0.4 to 5.1)	ns
Nights disturbed sleep/wk:				
>once	120	30 (25.0)	1	
<once	172	18 (10.5)	0.4 (0.2 to 0.7)	0.005
never	122	10 (8.2)	0.3 (0.1 to 0.8)	0.011
Ever had episode with speech limit:				
no	349	46 (13.2)	1	
yes	66	13 (19.7)	1.2 (0.5 to 2.7)	ns
Nocturnal cough:				
no	211	21 (10.0)	1	
yes	202	38 (18.8)	1.75 (0.93 to 3.28)	ns
Current treatment:				
yes	193	34 (17.6)	1	
no	224	26 (11.6)	0.8 (0.4 to 1.5)	ns
Current itchy rash (n=241)				
Ever cleared up in last 12 months?				
no	87	18 (20.7)	1	
yes	154	30 (19.5)	1.2 (0.6 to 2.3)	ns
Nights disturbed sleep/wk:				
>once	51	18 (35.3)	1	
<once	47	10 (21.3)	0.4 (0.2 to 1.2)	ns
never	143	21 (14.4)	0.3 (0.1 to 0.6)	0.001
Current treatment:				
yes	183	33 (18.0)	1	
no	58	16 (27.6)	1.9 (0.9 to 4.1)	ns
Current rhinitis (n=337)				
Interfere with daily activities:				
a lot	10	4 (40.0)	1	
a mod amnt	36	8 (22.2)	0.4 (0.1 to 1.8)	ns
a little	105	26 (24.8)	0.5 (0.1 to 2.1)	ns
not at all	185	26 (14.1)	0.3 (0.1 to 1.1)	ns
Current treatment:				
yes	84	16 (19.0)	1	
no	253	48 (19.0)	1.2 (0.6 to 2.4)	ns

* all allergic symptoms controlled for housing tenure and maternal age

Table 5 Severity of allergic symptoms and behaviour problems

6.4.2 Allergic symptoms, atopy and sleep problems (PQ)

Generating models for sleep problems

Specific sleep problems from the BCL[1] have not been examined previously in this thesis. Children's allergic symptoms may affect their ability to settle to sleep or cause them to wake at night. Casting settling problems as the dependent variable sequential logistic regression was used to examine the effect of environmental and biological independent variables first, to be able to control in later models for these potentially confounding effects. Housing tenure, maternal employment and birth order were the only variables to significantly improve the model (X^2 = 32.60, df 6, log-likelihood ratio 1655.69, p<0.0001) (table 8).

	Total no of chldn	No (%) with settling problems	Exp B (Adjusted OR) (95% CI)	P value
Housing tenure				
rented	328	152 (46.3)	1	
owned	933	345 (37.0)	0.7 (0.5 to 0.9)	0.004
Maternal employment				
full time	174	89 (51.1)	1	
part time	586	202 (34.5)	0.5 (0.4 to 0.7)	<0.0001
in home	500	206 (41.2)	0.6 (0.4 to 0.9)	0.006
Birth order				
>3	87	43 (49.4)	1	
3	195	82 (42.1)	0.7 (0.4 to 1.2)	ns
2	460	160 (34.8)	0.6 (0.3 to 0.9)	0.012
1	519	212 (40.8)	0.7 (0.4 to 1.1)	ns

Table 6 **Settling problems and significant environmental variables – logistic regression analysis**

Similarly casting waking problems as the dependent variable sequential logistic regression was used to examine the effect of environmental and biological independent variables. Current smoke exposure, paternal and maternal age and gender significantly predicted night time waking problems (X^2 = 21.717, df 4, log-likelihood ratio 1618.019, p<0.0001) (table 7).

Sequential logistic regression was then used to examine the effect of atopy and allergic symptoms, casting settling problems as the dependent variable. Atopy, current rhinitis and current wheeze had no effect upon settling. Current flexural itchy rash did significantly improve the model (X^2=46.676, df 7, log-likelihood ratio 1640.883 (X^2 change=9.75, df=1, p=0.002)) (table 8).

	Total no of chldn	No (%) with waking problem	Exp B (Adjusted OR) (95% CI)	P value
Current smoke				
yes	536	355 (66.2)	1	
no	723	431 (59.6)	0.7 (0.6 to 0.9)	0.01
Paternal age			1.0 (1.0 to 1.1)	0.004
Maternal age			1.0 (0.9 to 1.0)	0.033
Gender				
female	612	404 (66.0)	1	
male	659	387 (58.7)	0.7 (0.6 to 0.9)	0.015

Table 7 **Waking problems and significant environmental and biological variables - logistic regression analysis**

Casting waking problems as the dependent variable sequential logistic regression was used to examine the additional effect of atopy and allergic symptoms. Atopy, current wheeze and current flexural itchy rash did not predict night-time waking. Current rhinitis did (X^2 = 30.876, df 5, log-likelihood ratio 1608.861 (X^2 change = 9.158, df = 1, p=0.002)) (table 8).

	Total no of children	No (%) with settling problems	Exp B (Adj OR)[1] (95% CI)	P value	No (%) with waking problem	Exp B (Adj OR)[2] (95% CI)	P value
Atopy							
no	1003	386 (38.5)	0.9 (0.7 to 1.2)	ns	610 (60.8)	0.8 (0.6 to 1.1)	ns
yes	236	102 (43.2)	1		160 (67.8)	1	
Current wheeze							
no	843	311 (36.9)	0.8 (0.6 to 1.0)	ns	504 (59.7)	0.8 (0.6 to 1.0)	ns
yes	417	185 (44.4)	1		282 (67.6)	1	
Current rhinitis							
no	927	358 (38.7)	1.0 (0.8 to 1.3)	ns	556 (60.0)	0.7 (0.6 to 1.0)	0.036
yes	337	139 (41.4)	1		231 (68.5)	1	
Current itchy flexural rash							
no	1055	394 (37.3)	0.6 (0.5 to 0.9)	0.005	647 (61.3)	0.8 (0.6 to 1.1)	ns
yes	204	101 (49.4)	1		139 (68.1)	1	

1 Adjusted for housing tenure, maternal employment and birth order
2 Adjusted for current smoke, maternal age, paternal age and gender

Table 8 Atopy and current allergic symptoms and sleep problems

In summary, in the multivariate analysis current flexural itchy rash was the only symptom significantly associated with settling problems. Atopy, current rhinitis and current wheeze had no effect upon settling. Current rhinitis was associated with night-time waking. Atopy, current wheeze and current flexural itchy rash had no effect upon waking.

6.4.3 Atopy, allergic symptoms and behaviour problems associated with hyperactivity (HB - PQ)

The significant environmental (material and family) and biological factors predicting the continuous measure of behaviour problems associated with hyperactivity (HB) had been previously identified (rented housing, low household income, young maternal age at leaving full time education, young mothers) (ANOVA, $F=24.275$, $p=0.008$, $R^2 = 0.072$) (see chapter 4). These were first put into the model to control for these potentially confounding factors. The effects of adding atopy and allergic symptoms (wheeze, rhinitis, and itchy flexural rash) to this model predicting HB was examined with sequential multiple regression. Adding atopy and current wheeze did not significantly improve the model fit. Current rhinitis (ANOVA, $F=25.179$, $p<0.0001$, $R^2 = 0.0.091$), and current flexural itchy rash did improve the model (ANOVA, $F=22.209$, $p=0.009$, $R^2 = 0.096$) (table 9).

Variable	β	P value
housing tenure	0.115	<0.0001
household income	0.095	0.003
maternal education	0.089	0.002
maternal age	-0.073	0.012
current rhinitis	0.134	<0.0001
current flexural itchy rash	0.070	0.009

Table 9 **Multiple regression analysis of the impact of significant environment and biological variables and significant allergic symptoms upon HB**

Variable	Exp (B) (OR) (95% C I)	P value
household income	1.35 (1.14 to 1.60)	<0.0001
gender	1.57 (1.10 to 2.25)	0.014
current rhinitis	0.52 (0.36 to 0.75)	<0.0001

Table 10 **Logistic regression analysis of extreme HB as a function of significant environmental measures and significant allergic symptoms**

The significant environmental (material and family) and biological factors predicting extreme HB had been previously identified (low household income, male gender) (see chapter 4). In order to control for these potentially confounding factors these were first put into the model. Casting extreme HB as the dependent variable sequential logistic regression was used to examine the additional effect of atopy and allergic symptoms upon the previous model. Neither atopy nor current wheeze nor flexural itchy rash significantly improved the model. Current rhinitis did significantly contribute to the model (X^2 = 34.075, df 3, log-likelihood ratio 869.895 (X^2 change = 11.73, df 1, p=0.001)) (table 10).

In summary, current rhinitis and current symptoms of eczema were significantly associated with an increased risk of hyperactive behaviours reported by parental questionnaire.

6.4.4 Atopy and current allergic symptoms and behaviour problems associated with hyperactivity (DO).

Impulsivity

The continuous score from the clinic measures of impulsivity was examined with sequential multiple regression. The environmental and biological variables were first tested in the model. None of the environmental variables associated with material conditions (household income, housing tenure and vehicle ownership) improved the model and most family factors, most of them (maternal education, single parent household, parental age, birth order and maternal employment) did not improve the model. Current exposure to smoke was the only variable that significantly improved the model fit (table 12) (ANOVA, F=1.34, p=0.015, R^2 = 0.034). Of the biological

variables gestation, birth weight, admission to SCBU, antenatal exposure to smoke and current height did not improve the model fit. Gender did improve the model fit (ANOVA, F=1.88, p=0.037, R^2 = 0.050) (table 13).

		Impulsivity Score	Activity and Attention Score	Hyperactivity Score
Atopy – 2mm				
Mean (sd)	Yes n=115	-0.019 (0.650)	0.005 (0.718)	0.016 (0.521)
	No n=162	-0.063 (0.704)	0.005 (0.784)	-0.010 (0.550)
t		0.536	-0.001	0.382
df		275	275	275
sig (2-tailed)		ns	ns	ns
mean diffnce (95% CI)		0.046 (-0.119 to 0.208)	0.000 (-0.182 to 0.182)	0.025 (-0.104 to 0.154)
Current wheeze				
Mean (sd)	Yes n=101	-0.094 (0.779)	-0.057 (0.729)	-0.043 (0.552)
	No n=176	-0.017 (0.619)	0.040 (0.770)	-0.026 (0.528)
t		-0.906	-1.032	-1.039
df		275	275	275
sig (2-tailed)		ns	ns	ns
mean diffnce (95% CI)		-0.078 (-0.245 to 0.0904)	-0.097 (-0.283 to 0.088)	-0.070 (-0.202 to 0.062)
Current rhinitis				
Mean (sd)	Yes n=94	-0.150 (0.667)	-0.098 (0.813)	-0.099 (0.566)
	No n=183	0.009 (0.684)	0.058 (0.721)	0.052 (0.516)
t		-1.85	-1.623	-2.238
df		275	275	275
sig (2-tailed)		ns	ns	p=0.026
mean diffnce (95% CI)		-0.159 (-0.329 to 0.010)	-0.155 (-0.343 to 0.030)	-0.151 (-0.285 to -0.018)
Current flexural itchy rash				
Mean (sd)	Yes n=60	0.021 (0.664)	0.017 (0.769)	0.120 (0.520)
	No n=216	-0.062 (0.688)	-0.038 (0.748)	-0.030 (0.539)
t		0.831	1.909	1.926
df		274	274	274
sig (2-tailed)		ns	ns	ns
mean diffnce (95% CI)		0.083 (-0.113 to 0.279)	0.210 (-0.007 to 0.426)	0.150 (-0.003 to 0.304)

Table 11 Univariate analysis of all clinic tests behavioural outcomes as a function of allergic symptoms

	β	P value
housing tenure	-0.044	ns
household income	-0.038	ns
vehicle	0.023	ns
maternal education	0.007	ns
lone parent family	0.089	ns
maternal age	-0.027	ns
paternal age	0.063	ns
birth order	-0.034	ns
maternal employment	-0.007	ns
current exposure to smoke	-0.140	p=0.037

Table 12 Multiple regression analysis of continuous clinic impulsivity score as a function of all environmental measures

	β	P value
current exposure to smoke	-0.120	ns
gestation	-0.065	ns
birth weight	0.079	ns
admission to SCBU	-0.011	ns
antenatal smoke	0.001	ns
current height	0.112	ns
gender	0.131	p=0.037

Table 13 Multiple regression analysis of continuous clinic impulsivity score as a function of current exposure to smoke and all biological measures

Activity and Attention

The continuous scores from the clinic measures of activity and attention were examined with sequential multiple regression. Most of the environmental variables

associated with material conditions (household income, housing tenure) did not improve the model. Vehicle ownership did significantly improve the model fit (table 15) (ANOVA, F=2.037, p=0.016, R^2 = 0.022), although lost significance when all environmental variables were added to the model. Of the variables associated with family environment, most of them (maternal education, single parent household, parental age, maternal employment and current exposure to smoke) did not improve the model. Birth order was the only variable that significantly improved the model fit (table 15) (ANOVA, F=3.016, p=0.015, R^2 = 0.004). The biological variables were then added to the model, containing only vehicle ownership and birth order. Gestation, birth weight, admission to SCBU, antenatal exposure to smoke and current height did not improve the model fit. Gender did improve the model fit (ANOVA, F=2.76, p=0.014, R^2 = 0.081).

	β	significance
housing tenure	0.028	ns
household income	0.054	ns
vehicle	-0.098	ns
maternal education	0.058	ns
lone parent family	-0.087	ns
maternal age	0.016	ns
paternal age	-0.007	ns
birth order	0.182	p=0.004
maternal employment	0.078	ns
current exposure to smoke	-0.078	ns

Table 14 **Multiple regression analysis of continuous clinic activity and attention score as a function of all environmental measures**

	β	significance
vehicle	-0.124	p=0.045
birth order	0.145	p=0.021
gestation	-0.044	ns
birth weight	0.157	ns
admission to SCBU	0.038	ns
antenatal smoke	0.027	ns
current height	-0.044	ns
gender	0.153	p=0.014

Table 15 **Multiple regression analysis of continuous clinic activity and attention score as a function of current exposure to smoke and all biological measures**

Hyperactivity

The continuous score from the aggregate clinic measure of hyperactivity was examined with sequential multiple regression. None of the environmental variables associated with material conditions (household income, housing tenure and vehicle ownership) improved the model. Of the variables associated with family environment, most of them (maternal education, single parent household, parental age, maternal employment and birth order) did not improve the model. Current exposure to smoke was the only variable that significantly improved the model fit (table 16) (ANOVA, F=7.33, p=0.007, R^2 = 0.026).

The biological variables were then added to the model, containing only current exposure to smoke. Gestation, admission to SCBU, antenatal exposure to smoke and current height did not improve the model fit. Birth weight (ANOVA, F=5.46, p=0.038, R^2 = 0.039) and gender (ANOVA, F=6.66, p=0.016, R^2 = 0.046) did improve the model fit.

	β	Significance
current exposure to smoke	-0.145	P=0.015
gender	0.152	P=0.011
birth weight	0.136	P =0.022

Table 16 **Multiple regression analysis of continuous clinic hyperactivity score as a function of significant environmental and biological measures**

Having generated models containing the environmental confounding factors (current exposure to smoke, birth weight and gender). I now examine whether children with atopy or allergic symptoms are more likely to have hyperactive behaviours on direct observation.

Impulsivity

The continuous score from the clinic measures of impulsivity was examined with sequential multiple regression. The effect of adding atopy and allergic symptoms to the model generated previously with the significant environmental and biological variables (current exposure to smoke and gender) was examined. Atopy, and the allergic symptoms did not improve the model predicting impulsivity (table 17).

	β	significance
current exposure to smoke	-0.151	p=0.014
gender	0.088	ns
atopy	0.025	ns
current wheeze	-0.002	ns
current rhinitis	-0.101	ns
current flexural itchy rash	0.062	ns

Table 17 **Multiple regression analysis of continuous clinic impulsivity score as a function of significant environmental measures, atopy and allergic symptoms**

Attention and activity

The continuous score from the clinic measures of attention and activity was examined with sequential multiple regression. The effect of adding atopy and allergic symptoms to the model generated previously with the significant environmental and biological variables (vehicle ownership, birth order and gender) was examined. Atopy, current rhinitis, and current wheeze did not improve the model predicting attention and activity (table 18). Current flexural itchy rash did improve the model fit

(ANOVA, F=6.86, p=0.021, R^2 = 0.093), with children *with* symptoms of eczema having less inattentive and active behaviour.

	β	significance (p)
vehicle	-0.138	p=0.019
birth order	0.203	p=0.001
gender	0.117	p=0.049
atopy	-0.002	ns
current wheeze	-0.014	ns
current rhinitis	-0.117	ns
current flexural itchy rash	0.151	p=0.013

Table 18 **Multiple regression analysis of continuous clinic attention and activity score as a function of significant environmental measures, atopy and allergic symptoms**

Hyperactivity

The continuous aggregate score of hyperactivity was examined with sequential multiple regression. The effect of adding atopy and allergic symptoms to the model generated previously with the significant environmental and biological variables (current exposure to smoke, birth weight and gender) was examined. Atopy, current rhinitis, and current wheeze did not improve the model predicting hyperactivity (table 19). Current flexural itchy rash did improve the model fit (ANOVA, F=5.63 p=0.032, R^2 = 0.077), with children *with* symptoms of eczema having less hyperactive behaviour (table 19).

	β	significance (p)
current exposure to smoke	-0.135	p=0.026
birth weight	0.135	p=0.026
gender	0.144	p=0.017
atopy	-0.005	ns
current wheeze	-0.023	ns
current rhinitis	-0.103	ns
current flexural itchy rash	0.142	p=0.021

Table 19 **Multiple regression analysis of continuous clinic hyperactivity score as a function of significant environmental measures, atopy and allergic symptoms**

In summary this section has examined whether atopy or current symptoms of the three allergic conditions increase the risk of behaviours associated with hyperactivity, measured on clinic tests. Neither atopy, nor the three allergic symptoms were associated with impulsivity. Atopy, current rhinitis, and current wheeze were not associated with attention and activity or hyperactivity but children *without* current flexural itchy rash appeared to be more likely to have problems with attention and activity, and to have a worse aggregate hyperactivity score. I speculate that this is due to inadequate control for affluence, or a type 2 error and have occurred by chance.

1) Atopy alone did not increase the risk of GBP or behaviour associated with hyperactivity (PQ or CT) – after controlling for allergic symptoms.
2) Children with current wheeze were not more at risk of any of the measures of behaviour problems.
3) Children with current rhinitis were more likely to have a higher GBP score and higher HB score, and were more likely to be represented in both extreme groups.
4) Children with current itchy rash were more likely to have a higher GBP score and higher HB score, and were more likely to be represented in the extreme general behaviour problem group but not the extreme HB group.
5) Children with current itchy rash had an increased risk of settling, but not waking problems. Children with rhinitis were more likely to have problems with waking, but not settling. Children with wheeze were not more likely to have either sleep problem.
6) The only measure of severity of symptoms that increased the risk of behaviour problems was symptoms that affected sleep, both for wheeze and symptoms of eczema. Children with more severe rhinitis were not more at risk of behaviour problems
7) The direct observations provided by the clinic tests did not confirm the findings from the parental questionnaires. The children with atopy, or any of the allergic symptoms were not more likely to be impulsive on clinic testing. Atopy, wheeze and rhinitis had no effect upon attention and activity.

Table 20 **Summary of Main findings**

	GBP	HB	extreme GBP	extreme HB
	Change in R^2		Adjusted OR (95%CI)	
atopy	ns	ns	ns	ns
wheeze	ns	ns	ns	ns
rhinitis	1.7%	2.0%	2(1.4-2.9)	1.9(1.3-2.7)
eczema	1.1%	0.5%	2(1.3-3)	ns

Figure 2 Strength of association allergic symptoms and behaviour (PQ)

6.5 Discussion

This study examined whether 3 year olds with signs of atopy (as measured by skin prick tests) or symptoms of allergic disease were more at risk of behaviour problems. The presence of behaviour problems was measured by parental questionnaire and externalising behaviour problems associated with hyperactivity were measured both by parental questionnaire and systematic observation.

On first examination there did seem to be an excess of general behaviour problems by parental report in atopic children. There was no excess of hyperactive behaviours reported by parents or by direct observation. However once the symptoms of rhinitis and eczema were controlled for, the relationship with atopy disappeared. Gaitens et al found no link between atopy and behaviour problems.[341] Few other studies have looked at atopy independently from symptoms. Two groups have reported higher rates of emotional problems in children with non-atopic asthma.[138;139] The lack of association makes a common genetic predisposition for *atopy* and behaviour unlikely, although does not rule out a genetic link with symptomatic phenotypes. Studies that have suggested a common genetic predisposition such as Wamboldt's twin study,[143] are problematic to compare directly as they often have failed to identify atopy alone but instead have examined a symptomatic allergic phenotype. These findings also makes Marshall's [342;343] theory of a common atopic and ADHD neuro-endocrine environment less likely, although it could be argued that the environment may be only produced by symptomatic atopic disease, not simply the presence of specific IgE.

There was no suggestion that children with symptoms of wheeze were at increased risk of behaviour problems. This has been reported by others.[131;112;132;133] We were not only examining asthma. Wheeze is a common symptom in pre-school children, a third of these 3-year-olds reported symptoms within the previous 12 months, only a subgroup continuing to wheeze, and prove to have asthma.[344] Other authors examining older children have reported an increased risk of behaviour problems only in those children with more severe symptoms.[112;129;132;137] There was no evidence in this group that that children with more severe or more frequent wheeze were more vulnerable to behaviour problems, suggesting that any effect of asthma symptoms on behaviour occurs later on in childhood, and may be mediated by other factors such as school absence.

It is possible that the children with behaviour problems were less concordant with treatment, resulting in worse symptoms. This is less likely in this group given that most of these children probably had episodic viral wheeze with less robust evidence of the efficacy of prophylactic medication.[345] Other groups have suggested that some anti-asthma medications may themselves be associated with behaviour problems.[346] This study was not designed to specifically examine the behavioural effects of asthma medications. We did not measure how frequently or effectively they were given medication. Despite these limitations there was no evidence that children on any form of anti-asthma medication were more or less likely to have behaviour problems.

There was no association between wheeze and general sleep problems. The children with wheeze were not more difficult to settle and not more prone to night-time waking. This finding is unexpected given the potential effect of nocturnal respiratory symptoms on disturbed sleep. Others have also shown no effect of asthma upon sleep.[179;349] Stores concluded that the effect of asthma on sleep is to fragment it by brief arousals and not to have any effect on the conventional sleep stages. This type of sleep disturbance is more difficult to observe, and less likely to be reported by parents. He postulated that, though not normally observable it is still sufficient to affect day time functioning.[164] In this population the children whose parents reported sleep disturbance secondary to their wheeze were more likely to have extreme behaviour problems. Their behaviour also may have made them less concordant with treatment and thus more prone to nighttime symptoms. There may

have been a common factor not controlled for in the statistical analysis, such as parenting style that may have affected both respiratory symptoms and behaviour. Finally this may be a group of parents that were more likely to score their child's behaviour and allergic symptoms highly.

Parental report suggested that the symptoms of rhinitis and eczema were associated with a greater risk of general behaviour problems. This was an increase in both internalising and externalising behaviours. Although statistically significant it should be noted that the effects on general behaviour problems were small, adding at most 1.7% (rhinitis) to explaining the variance in behaviour problems. However the effect on the more extreme behaviours were larger with odds ratios around 2 (95% confidence intervals 1.3 to 2.9).

The evidence that the increased risk of behaviour problems in this group is mediated by sleep problems is mixed. The children with symptoms of eczema were more likely to have settling problems but not waking problems (although this group as well may have had subtle interruptions of sleep not detected by parents[350]). Although the chronicity of the children's skin symptoms did not increase their risk of behaviour problems, disturbed sleep secondary to itching was associated with increased extreme behaviour problems. Children with rhinitis were more likely to have waking problems, but not settling problems, plausibly explained by obstructive sleep apnoea.[177] The parents were not directly asked whether their child's rhinitis affected sleep or whether there were symptoms of obstructive sleep apnoea.

Unlike other groups[120] the direct observations provided by the clinic tests were not able to confirm the findings of an excess of externalising behaviours. The children with atopy, or with any of the three groups of allergic symptoms were no more likely to have any of the symptoms of hyperactivity on clinic testing than asymptomatic children. In fact the children *without* current flexural itchy rash were more likely to have problems with attention and activity, and to have more generally hyperactive behaviour (the absence of symptoms of eczema only increased the explanation of variance from 7.1% to 7.7%). It is hard to explain why having eczema may be protective against hyperactive behaviours, and may be due to confounding.

The observed association between some of the allergic symptoms and behaviour problems could be explained by correlated error variance. This is more likely when the same person rates both disorders, as parents here were rating both allergic symptoms and behaviour.[122] Unfortunately there is no further way to explore this in the data set. My measure of atopy (not dependent upon parents) showed no independent association with behaviour ratings. The behaviour ratings observed by the research team also showed no relationship with the parental reporting of allergic symptoms.

Independent measures of allergic symptoms in the preschool age group are difficult. The allergic symptoms were more common than 'diagnosis' of asthma, eczema or hayfever (see chapter 3) and only 46% of the children with current wheeze, 25% with current rhinitis and 76% with symptoms of eczema were receiving treatment for their allergic symptoms. The parental behavioural descriptions were simply that. It is important to note that few of the children in this study would have met the criteria for clinical psychiatric disorder.

This study has two main strengths. The first is that the children were a non-clinical sample. Children's behaviour and allergies were both described by reference to their symptoms, and independent of access to clinicians. Symptoms of all three common allergic diseases were sought, and atopy was measured by direct evidence of specific IgE on skin prick tests. Many other studies have relied upon physician diagnosis. They have looked for an excess of behaviour problems in selected groups of children with allergic symptoms, or examined adults with psychiatric diagnoses for allergic symptoms. The second strength of this study is that parental report was not the sole source of information regarding children's behaviour, the externalising behaviours of the children were also assessed through systematic observation. I have already discussed the possible problems with some parents over reporting both behavioural problems in children with asthma.[148] Unfortunately, the children in this study group were too young to describe their own emotions and behaviour.

6.6 Conclusion

Unselected 3-year-old children with symptoms of rhinitis and eczema on parental report can be shown to have a small but significant increase in behaviour problems. General and hyperactive behaviours were both increased.

There was no evidence that children with wheeze (even more severe or frequent) were more at risk of behaviour problems. Children whose rhinitis or symptoms of eczema were reported to disturb their sleep were more at risk of behaviour problems, and all three symptoms were associated with specific sleep problems. We were not able to confirm the increased risk of behaviour problems on clinic testing. There was no evidence of impaired attention, increased impulsivity or activity.

This study used an objective measure of atopy. By controlling for allergic symptoms it enabled the conclusion that there was no increased risk of behaviour problems from atopy alone. This makes any genetic link with atopy and behaviour unlikely.

Many of these children may suffer from two or even three allergic symptoms. There appears to be a differential impact upon sleep and behaviour of symptoms of wheeze, rhinitis or eczema. It is clearly important that when researching their behavioural impact that these symptoms should not be addressed in isolation, as many teams have done, both for children and adult. This also has important clinical implications, that Lack emphasises when discussing rhinitis in childhood.[351]

Chapter 7

The effects of artificial food colourings and benzoate on hyperactivity and allergic symptoms

7.1 Background

The search to explain behaviour problems in children extended further following Feingold's claim of the detrimental effect of artificial additives.[192] The 1980s and 90s produced many studies examining the behavioural effects of artificial colours and preservatives. These studies, with improved methodology, failed to substantiate Feingold's claim[236;352-356] or only showed a small effect.[210;231;233;235;237;238;354;357-360]

A double blind placebo controlled high dose azo dye challenge in a highly selected group of children with behaviour disturbance suggested a small adverse effect on the children's behaviour based on ratings on the Conners' scale.[238] There was no association between response and atopy, leading the authors to conclude any effect was pharmacological rather than IgE mediated. There is further clinical evidence from research on urticaria linking artificial food additive responses to IgE independent histamine (and other mediator) release.[361] An in vitro study demonstrated that circulating basophils released histamine in a non-IgE dependent response on exposure to azo dyes[362] and in an in vivo study in which high doses of tartrazine were administered to normal subjects induced significant histamine release.[363] Despite this suggested non-IgE dependent mechanism of action there persists particularly in the public mind links between "allergy" to artificial food additives and behaviour disturbance.

The generalisability of findings from previous studies is limited by samples which are small, depend on an ADHD diagnosis[357] are in patients already thought to show adverse behaviour triggered by artificial additives[238] or are recruited from specialist clinics.[354] It has also been suggested by some that younger children may be more susceptible.[216;226] Kaplan's team looked at 3-6 year olds[220] but no study has focused solely on pre-school children. Some studies have identified a higher than expected proportion of atopic children within those whose behaviour appeared to be affected,[231] but this has never been systematically examined.

There is a further evidence of non-IgE mediated exacerbation of allergic symptoms by additives. Sulphite additives[204] and to a lesser extent tartrazine[205] have been associated with asthmatic reactions.[204] Other dyes and preservatives (including sodium benzoate and sodium metabisulphite) have also been associated with urticaria and asthma.[206] Evidence that azo and non-azo dyes and benzoates provoke reactions however continues to be disputed.[208] There are methodological criticisms of some of the work, but also the estimated low prevalence (0.15 to 2%[209]) of possible reactions to food additives may explain some of the discrepancies between different groups' findings. Fuglsang et al[207] estimated the prevalence in a paediatric population of true exacerbation of allergic symptoms by artificial food additives at between 1-2%. Even at this higher estimated prevalence a population-derived challenge study, such as ours, would be likely to be under-powered for investigating the effect upon allergic symptoms.

7.2 Aims and hypothesis

Hypothesis

Food additives have a pharmacological effect on behaviour irrespective of baseline behavioural and atopic status.[200]

Aims

1. To examine the effect of artificial colours and sodium benzoate on the behaviour of 3-year-olds supported by parental questionnaire and direct observation.
2. To examine the effect of artificial colours and sodium benzoate on the symptoms of asthma, eczema and rhinitis of 3-year-olds by parental questionnaire.
3. To examine whether pre-existing hyperactivity makes the child's behaviour more vulnerable to the effects of artificial additives.
4. To examine whether atopic status makes the child's behaviour more vulnerable to the effects of artificial additives.

7.3 Methods

These are detailed in Chapter 3.

	Completed Phase II				Completed Phase III				Failed to complete Phase III			
	H A	H nA	nH A	nH nA	H A	H nA	nH A	nH nA	H A	H nA	nH A	nH nA
N	47	183	201	806	36	75	79	87	7	26	18	9
Males n, (%)	28 (60)	106 (58)	118 (59)	386 (48)	22 (61)	39 (52)	44 (56)	46 (53)	4 (57)	15 (58)	8 (44)	7 (78)
Mean age at baseline testing in years (range)					3.64 (3.17 - 3.99)	3.70 (3.22 – 3.95)	3.72 (3.18 – 4.01)	3.76 (3.19 – 4.14)				
Children with behaviour problems (BCL) n, (%)	33 (70)	114 (62)	31 (15)	130 (16)	24 (67)	40 (53)	11 (14)	9 (10)	5 (71)	21 (81)	3 (17)	0 (0)
Mean maternal age leaving FT education (range)	17.8 (15-26)	16.9 (13-25)	17.8 (15-34)	17.7 (13-35)	17.9 (15-26)	17.0 (15-25)	17.9 (15-34)	17.7 (15-30)	16.4 (16-17)	17.0 (15-21)	17.8 (16-23)	17.4 (16-22)
Parents perceived food affect behaviour	19 (40)	97 (53)	58 (29)	232 (29)	13 (36)	40 (53)	25 (32)	19 (22)	3 (43)	19 (73)	4 (22)	4 (44)
Parents perceived drink affect behaviour	16 (34)	83 (45)	52 (26)	236 (29)	10 (28)	36 (48)	23 (29)	17 (20)	3 (43)	14 (54)	4 (22)	2 (22)

Table 1 **Characteristics of children from Phases II and III**

	Baseline			Pre-placebo			Post-placebo			Pre-active			Post-active		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Testing															
Aggregated hyperactivity	277	.00	.53	277	-.03	.57	277	-.03	.56	277	.01	.54	277	-.03	.55
Impulsivity	277	-.04	.68	276	-.01	.76	277	-.02	.78	277	.03	.78	277	.00	.80
Activity & inattention	277	.00	.76	277	.05	.77	277	-.07	.74	277	.06	.75	277	.04	.70

Table 2 **Mean scores at the five time points on test ratings of hyperactivity**

	Baseline			Pre-placebo			Post-placebo			Pre-active			Post-active		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Parental rating															
Aggregated hyperactivity	275	.00	.76	277	.52	1.15	277	.14	1.80	276	.71	1.25	277	-.06	1.61
Activity	275	.00	1.00	277	.61	1.39	277	.16	2.11	276	.85	1.49	277	-.11	1.99
Impulsivity	275	.00	1.00	275	.47	1.30	276	.08	1.68	273	.58	1.23	274	-.02	1.53
Inattention	274	.00	1.00	277	.48	1.46	276	.19	2.30	276	.69	1.78	274	-.03	2.05
Aggregated general behaviour	No baseline score from diaries			277	.00	1.00	277	-0.36	1.65	277	-.37	1.57	275	-.22	1.93
Settling	274	.00	1.00	276	.30	1.12	274	.15	1.39	276	.43	1.17	276	.08	1.37

Table 3 **Mean scores at the five time points on parental ratings of hyperactivity**

Placebo-Active	Baseline			Pre-placebo			Post-placebo			Pre-active			Post-active		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
eczema	149	8.72	1.12	150	8.87	1.04	150	9.03	1.26	148	9.17	1.29	150	8.88	1.13
rhinitis	148	5.72	0.73	150	5.84	0.83	150	5.84	0.74	148	5.95	0.74	149	5.83	0.71
asthma	148	8.50	1.47	150	8.88	1.51	149	8.79	1.51	148	8.86	1.30	149	8.85	1.21
Active-Placebo	Baseline			Pre-active			Post-active			Pre-placebo			Post-placebo		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
eczema	126	8.90	0.91	127	9.10	0.83	126	8.85	1.23	127	9.12	1.09	127	8.80	1.35
rhinitis	127	5.78	0.69	127	5.93	0.70	126	5.84	0.72	127	5.94	0.74	127	5.87	0.68
asthma	126	8.61	1.35	127	8.70	1.36	127	8.87	1.38	127	9.00	1.50	127	8.67	1.40
Symptomatic	Baseline			Pre-placebo			Post-placebo			Pre-active			Post-active		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
eczema	60	8.50	1.85	60	9.30	1.98	60	9.17	2.35	59	9.46	2.06	60	8.70	2.06
rhinitis	93	5.56	0.93	94	5.84	1.11	94	5.89	0.96	93	6.04	0.91	93	5.69	0.87
asthma	99	8.33	1.87	101	8.96	1.91	101	8.62	1.67	100	8.79	1.73	101	8.66	1.58
Whole group	Baseline			Pre-placebo			Post-placebo			Pre-active			Post-active		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
eczema	275	8.80	1.03	277	8.99	1.07	277	8.93	1.30	275	9.14	1.10	276	8.88	1.77
rhinitis	275	5.75	0.71	277	5.88	0.79	277	5.86	0.71	275	5.94	0.72	275	5.83	0.72
asthma	274	8.55	1.42	277	8.93	1.50	276	8.73	1.33	275	8.78	1.33	276	8.86	1.29

Table 4 **Mean scores at the five time points on parental ratings of allergic symptoms**

7.4 Results

Study population

The characteristics of the children entering the crossover challenge phase of the study are presented in table 1. There were no significant differences between the four groups in terms of gender and mothers' age at leaving full time education. As would be expected the children in the HA/AT and HA/not-AT groups had a significantly higher rate of behaviour problems than the other two groups (X^2 (3,N= 277) = 67.79, p <.001).

From the group that had responded to the behaviour questionnaire (Phase I) 31% of the parents believed that food and 30% that drink affected their child's behaviour. The group that finished the randomised controlled trial were almost identical, 35% believed that food and 31% that drink affected their child's behaviour.

Validation of the tests

To establish that the tests administered to the children were sensitive to cognitive and behavioural differences between hyperactive and non-hyperactive pre-schoolers a preliminary analysis was conducted to compare the scores at baseline for these two groups. It was found that on the test measures of Impulsivity (t (275) = 2.97, p <.004) and Attention and Activity (t (275) = 2.95, p<.004) as well as the ATH measure (t (275)= 3.91, p <.001), the hyperactive children had significantly worse scores (table 5).

Mean scores on testing and parent ratings from baseline to time 4

The pattern of mean scores for children in the active-then-placebo and placebo-then-active groups are shown in figures 2 and 3. There was no evidence for any changes across time for the ATH score. For the parent ratings by contrast there was a pattern indicating a reduction in hyperactivity (an increase in APHR) between baseline and time 1; a period over which food additives were removed from the diet. In the active-then-placebo and the placebo-then-active groups there were increases in hyperactivity for both the placebo and active challenge periods. However in both groups the slope of the lines indicates a greater increase in hyperactivity during the active periods.

Behaviour - effects of withdrawal of artificial colours and sodium benzoate

There was a similar APHR increase for both groups between time 2 and time 3 i.e. the wash out period between challenges. This indicates that the removal of food additives and colourings from the diet may have a beneficial effect detected by parental ratings (figure 3) but not by formal clinic testing (figure 2). These changes in APHR between baseline and time 1 (t (274)= 5.97, p<.001) and time 2 and time 3 were significant (t (275)= 7.38, p <.001). There were no significant interactions of order with the effects of active and placebo on the mean scores for either ATH scores (F(1,275) = 1.28,ns) or APHR (F(1,274) = 1.42,ns) and subsequent analyses were based on the pooled scores for the active and placebo periods ignoring the order. The means for the five time points are presented in table 3.

Behaviour - effects of challenges

A repeated measures analysis of variance showed that there were no significant changes in the test scores in either the active or placebo periods for the Impulsivity (F(1,276) = 1.13 , ns), Activity and Inattention (F(1,275) = 0.33 , ns) or ATH (F(1,276) = 1.13, ns) measures. There were however significant changes in parental ratings that were shown to interact with type of dietary supplement indicating a significantly greater increase in hyperactive behaviour during the active period. These significant interactions were found for Activity (F(1,275) = 7.72 , p<.007) as well as for the APHR (F(1,275) = 6.21 , p<.02) but not for Impulsivity (F(1,266) = 0.2.77 , ns (p<.10)) or Inattention (F(1,271) = 3.52 , ns (p<.07)). To reduce the risk of Type I errors, the remaining analyses were conducted only on the ATH scores and the APHR.

Adherence to diet and challenges

The children were given 14 drinks over the two challenge weeks. Parents were asked to record in their 'snack' diary the quantity of drink that the child had consumed each day. Parental reports were that 224 (81%) of children drank all or nearly all of the active and placebo drinks, 39 (14%) drank more than two thirds. Only 14 (5%) children drank less than two thirds all of the active and placebo drinks.

Dietary infractions were estimated from the 'snack diary'. This was essentially a qualitative estimate. Each time a portion of drink or food was recorded containing sodium benzoate or an artificial colour this was counted as one 'mistake'. The dietitian reviewed the child's 'snack' diary each week and provided feed back to the parent, adherence to the diet was very good, and appeared to improve over the 4 weeks. The percentage of children with one or no mistakes increased from 221 (80%) in the first week, to 255 (92%) in the fourth week. Over the study month 34% of children recorded no 'mistakes', 58% recorded 1-6, and 8% more than 6 total 'mistakes'. There was no difference in infractions during active or during placebo weeks.

Attrition

120 children of 397 failed to complete all four weeks (277 completed, 61 failed to ever attend, 59 attended at least 1 but not all 5 visits). Children were no more likely to drop out when taking active than placebo. Gender, hyperactivity and atopy were unrelated to failure to complete (Figure 2 Chapter 3 Methodology and table 1).

	Hyperactive			Not hyperactive			t test
	N	mean	sd	n	mean	sd	t (df) p value
Testing Aggregated hyperactivity (ATH)	111	-0.15	0.53	166	0.10	0.52	3.87 (275) <0.001
Impulsivity	111	-0.19	0.69	166	0.05	0.66	2.97 (275) 0.003
Activity and inattention	111	-0.16	0.80	166	0.11	0.71	2.95 (275) 0.003
Inattention 1 (Free play - toy change)	111	-0.17	0.92	166	0.11	0.92	2.36 (275) 0.019
Inattention 2 (Free play – quality)	109	-0.15	1.03	164	0.10	0.97	1.98 (271) 0.049
Inattention 3 (Stickers – off task)	111	-0.03	1.01	166	0.02	1.00	0.38 (275) 0.708
Activity 1 (Free play – quality of activity)	111	-0.12	1.01	166	0.08	0.99	1.69 (275) 0.093
Activity 2 (Stickers – out of seat)	111	-0.21	1.16	166	0.15	0.82	2.80 (181.953) 0.006
Activity 3 (Actometer)	87	-0.08	1.11	139	0.05	0.93	0.960 (224) 0.338
Impulsivity 1 (Puppet – tasks inhibited)	41	0.09	0.93	79	-0.05	1.03	-0.708 (118) 0.480
Impulsivity 2 (Puppet – levels of inhibition)	41	-0.05	0.98	79	0.03	1.00	0.406 (118) 0.685
Impulsivity 3 (Stickers – Time waited)	111	-0.09	1.08	166	0.05	0.96	1.15 (217.763) 0.253
Impulsivity 4 (Draw-a-line-slowly- line)	109	-0.015	0.95	163	0.10	1.02	2.05 (270) 0.042
Impulsivity 5 (Draw-a-line-slowly-circles)	108	-0.21	0.95	163	0.14	1.01	2.81 (269) 0.005
Impulsivity 6 (Walk-a-line-slowly)	101	-0.24	0.97	163	0.15	0.99	3.17 (262) 0.002

Table 5 **Hyperactive and non-hyperactive children - mean scores from visit 1 (preintervention) clinic tasks**
NB - Lower scores – more impulsive/more inattentive/more active behaviour

To test whether the child's initial hyperactivity level or atopy status influenced these changes in hyperactivity under dietary challenge, a set of 2x2 analyses of variance were conducted to detect interactions between the between subject factors and the interaction between time and challenge type. With the ATH score as the dependent variable there was no significant effect of challenge ($F(1,273) = 0.16$,ns) nor any evidence of interactions between challenge type and atopy or initial hyperactivity.

With the APHR there was a significant effect of challenge type ($F(1,272) = 6.48$, $p<.02$) but this effect did not interact with either initial hyperactivity status ($F(1,272) = 0.01$,ns) or atopy ($F(1,272) = 0.52$,ns) nor was there a joint interaction between these two factors and challenge type ($F(1,272) = 0.46$,ns). The effects of the challenges were analysed for the subset of 140 subjects who were in complete quartet sets; there were 35 such quartets. Using the balanced matched design on this sub-set of children, the results remain the same. There was no significant change in ATH scores over time ($F(1,139) = 0.01$,ns) nor a significant intervention between time and type of challenge ($F(1,139) = 0.15$,ns). For APHR there was a significant effect of time ($F(1,138 = 26.71$, $p<.001$) and a significant interaction between time and diet challenge type ($F(1,138) = 7.48$, $p<.01$).

It can be seen in table 3 that by chance the mean scores on the APHR pre-placebo were lower than pre-active ($t(275) = 2.46$, $p<.02$). It is necessary to establish whether the significant differences under the placebo and active challenges remain when the initial behaviour scores differences are controlled. An analysis of covariance was conducted on the post-period scores with placebo/active as a between group factor and the pre-period scores as covariates. There was a significant effect of the covariate ($F(1,550) = 43.12$, $p<.001$) and the effect of type of challenge remained significant ($F(1,550) = 3.94$, $p<.05$).

Sub-groups differentially affected by food additives

The study was designed to test whether children who showed high levels of hyperactivity were more likely to respond adversely to the presence of additives in their food. Similarly there was reason to believe that children with atopy may be more susceptible to the effects of additives. Neither the presence or absence of hyperactivity nor atopy moderated the impact of additives on the mean

Aggregated Parental Hyperactivity Rating scores. In that sense the main sub-groups that were postulated to be possibly differentially susceptible to the effects of additives were not shown to be more affected than other children.

To examine this issue further a number of additional analyses were undertaken on the APHR scores. The first examined the distribution of change scores under the active and placebo conditions to determine whether the increased scores in the active period were being produced by a group of children making major changes whilst the moiety remained unaffected. Inevitably there would be individual differences in the extent to which the hyperactivity scores were altered by the presence of additives. The consequence of removing food additives in the diet of pre-school children would be to shift the distribution of hyperactivity scores downward. This would leave individual differences in hyperactivity relatively unaffected since the remaining genetic and social influences would still be operating. This prediction was tested by examining the correlation between individual differences in hyperactivity before and after the removal of additives from the diet. The third analysis established whether the children showing the most marked worsening of hyperactivity scores were the same under the active and placebo conditions. The final analysis examined the characteristics of those children who showed the most marked effects of additives – did they differ from other children on the measures we had available?

Distribution of change scores: the distribution of change scores for the placebo and active periods are shown in figure 4, these two sets of change scores are significantly different (paired test $t = 2.49$, $df = 275$, $p<.02$). There is evidence that both these distributions deviate from normal (one sample Kolmolgorov-Smirnov test: placebo $z = 2.90$, $p<.001$ and active $z = 2.95$, $p<.001$). The curves were very similar to each other in having a small number of children who had substantial changes. Accordingly those children showing increases in hyperactivity of more than 3 SD units were excluded from both the placebo and active scores and the t-test re-run. Although the mean difference in change on active and placebo was reduced from 0.39 to 0.28, the increase in hyperactivity was still significantly greater during the active period ($t = 2.59$, $df = 226$, $p<.02$). The distribution of scores with the children who increase in hyperactivity by more than 3 SD units excluded is shown in figure 5.

One salient feature of the distributions in figure 5 are the large number of children who were rated by their parents as showing no change in both the placebo and active periods. The shift towards greater hyperactivity scores during the active period can be clearly seen in figure 5 (more children with negative than with positive change scores). This shift was not accounted for by a small number of children making an extreme change as these were excluded from figure 5.

Relationship between hyperactivity scores before and after the removal of additives from the diet: the correlations between these two sets of APHR scores was -0.093 (ns). This suggests that rather than simply shifting the mean scores the exposure to the food additives changed the relative hyperactivity scores for individuals. Some children changed more than others and thereby reduced this correlation to zero. This raises the question of whether these responders were systemically different from other children and this is addressed below.

Relationship between change during placebo and active periods: the correlation between change in APHR during the placebo and active periods was calculated and was not significant ($r = -0.044$). It remained not significant when the children making extreme 3 SD gains in hyperactivity scores were excluded ($r = 0.038$). These findings support the notion that parental ratings reflect real changes in the children's behaviour. The increased ratings of hyperactivity were not produced by parents who always reported a worsening of their children's behaviour, which happened to be more accentuated during the active period.

The children were grouped into those getting worse, the same and better during the placebo and the active periods. The cross-tabulation of these groups is shown in table 6.

The proportion of children whose hyperactivity was rated as worsening during the active period was significantly higher (51%) than during the placebo period (43%) (McNemar - χ^2 (1,n = 277) = 4.06, $p<0.05$).

		Active change Worse	Same	Better	%
Placebo Change	Worse	65	23	30	43%
	Same	22	47	8	28%
	Better	55	8	19	30%
	%	51%	28%	21%	

Table 6 The relationship between change during the placebo and active periods

Characteristics of children whose hyperactivity became worse during the active period: from the results presented in table 6, the clearest comparison that would identify the characteristics of children responsive to the food additives would be as follows. The 77 children who became worse during the active challenge but were not worse during the placebo challenge should be compared to the 135 who did not become worse during the active period. The 65 children who became worse during both the active and the placebo challenge periods will be treated as a separate group.

The results of these comparisons for the main variables used in the study are presented in table 7. There are no significant differences between the Only Active Responders and the Non-responders. The Active and Placebo Responders were significantly more like to be boys (χ^2 (1, N= 277)= 6.66, p <.01) than those in the other groups. However the Active Only Responders were not significantly different from the Non-Responders in terms of gender. There was a wider range of measures available from Phase I and II of the study that were examined in an exploratory analysis to identify differences between the Only Active Responders and Non-responders. For this analysis logistic regression was used to detect possible differences. The results are presented in Table 8 and were uniformly negative. There were no significant differences that could be detected in either the social background of the children or in terms of biological status at birth or subsequent growth.

	Only Active Responders	Non-responders	Active and Placebo Responders	1 vs 2 χ^2, df = 1	p
N	77	135	65		
% Boys	57%	46%	69%	2.04	ns
% Hyperactive	43%	36%	45%	0.64	ns
% Atopic	43%	42%	40%	.01	ns
Mean Baseline APHR	-0.146	0.061	0.045	t,df = 209 1.90	ns

Table 7 Comparison of the responders and non-responders to food additives

Social and biological factors	Odds Ratio	$CI_{.95}$	p
Mother's age	1.05	0.99 - 1.01	ns
Father's age	1.03	0.98 - 1.08	ns
Family income	1.06	0.83 - 1.36	ns
Housing tenure (home owner vs. other)	0.85	0.44 - 1.63	ns
Playgroup attendance (half days per week)	0.91	0.77 - 1.06	ns
Gestational age	0.96	0.83 - 1.12	ns
Birth weight	0.99	0.98 - 1.01	ns
Height	1.00	0.92 - 1.07	ns
Weight	0.97	0.84 - 1.12	ns

Table 8 Comparison of the Active Only Responders and Non-responders social and biological factors

Allergic symptoms - removal of artificial colours and sodium benzoate

The distribution of wheeze, rhinitis and eczema scores for the whole group and the 3 symptomatic subgroups are shown in table 4 and figures 7,8 and 9. There was some but inconsistent evidence of an improvement in allergic symptoms on removal of artificial additives. When examining the whole group all three symptoms improved between baseline and time 1; wheeze t (273) –2.13, p=0.034; rhinitis t (274) –2.22, p=0.027; eczema t (274) –2.17, p=0.031. These results were not all replicated between time 2 and time 3, during the washout period. Neither wheeze nor rhinitis showed a significant change in parental ratings of symptoms. Eczema however did t (273) –2.60, p=0.010.

There were mixed findings when examining the 3 symptomatic sub-groups. Between baseline and time 1 there was no significant change in symptoms of

wheeze, although between time 2 and time 3 there was t (92) –2.40, p=0.018. Eczema however showed a significant improvement in symptoms between baseline and time 1 t (67) –2.36, p=0.021 but no significant change during the washout period. Rhinitis similarly showed an improvement on initial withdrawal of artificial colours and benzoate t (92) -2.40, p=0.018, but no significant change during the time 2 and 3.

Time period 2 to 3 was only truly a withdrawal period for those children who had been randomised to receive active during the first challenge week (time 1 to time 2). If we examine that group only, there were no significant improvement in symptoms of asthma, rhinitis, but there was an improvement in symptoms of eczema t (125) –2.53, p=0.013.

Allergic symptoms - effects of challenges

Children with symptoms of rhinitis within the last 12 months had a deterioration of their symptoms of rhinitis during the active period as compared to the placebo period (t (272) -1.74,p=0.037) (table 7, figure 12). The group of children with wheeze (figure 13) and the group of children with flexural itchy rash (figure 12) had no similar deterioration in symptoms when exposed to the artificial additives. There was no significant effect on symptoms of rhinitis, eczema or wheeze for the whole group (figures 10 and 11).

Relationship between the changes in rhinitis and APHR

It had been postulated that behavioural changes may have been directly or indirectly (e.g. by disturbed sleep) mediated by deterioration or improvement in allergic symptoms. In an attempt to examine this hypothesis the correlation between the reported changes in symptoms of rhinitis and parental ratings of behaviour (APHR) were examined. Children with more marked changes in rhinitis also ought to have had the most marked changes in behaviour. To facilitate comparison the 'rhinitis score' was standardised similarly to the behaviour scores, by expressing it as change from the baseline mean in standard deviation units (table 8 and figure 14). There was evidence of weak but significant correlation between the two scores at baseline and time 1, 2 and 3, but not a time 4. As time 4 was the post active change, this makes it unlikely that the worsening in symptoms of rhinitis were secondary to the behaviour changes, or vice versa.

7.5 Discussion

The observed effect of food additives and colourings on hyperactivity in this community sample is substantial, at least for parental ratings. The change in aggregated hyperactivity as rated by parents whilst the child was on placebo was 0.38 and for the active supplement was 0.77. The difference between these changes is 0.39 and represents an effect size of 0.51 in relation to the baseline standard deviation of 0.76. The standard deviation at baseline was chosen for this comparison since it represents the extent of variance in hyperactive behaviour in this general population sample before any intervention or dietary manipulations. The change effect size of removing additives and colourings is shown in the increase from baseline to the Time 1 scores and was approximately 0.5; a value slightly higher that the 0.39 estimate above. This would be expected given that the parents were not blind to the removal of additives/colourings from their children's diets and expectancy effects would therefore inflate this change estimate. Nevertheless these two estimates of the impact of food additives/colourings on three-year-old children's hyperactive behaviour both indicate a statistically substantial effect detectable by parents. Reanalysing Pollock and Warner's[238] data their effect size is slightly less, (0.34). The effect size is less than that obtained for methylphenidate (0.82)[366] but similar to that for clonidine (0.58)[367] in the treatment of children with ADHD.

It was not possible in the present study to obtain parallel evidence for changes in hyperactivity on the basis of psychologist administered tests. This has proved difficult to obtain in previous studies of dietary changes in selected hyperactive samples.[238 368] Parents' reports have also been found to show the largest effects in drug trials of treatment for ADHD.[367] One possible explanation of this is that the tests are not sensitive to hyperactivity in this age group. However the hyperactive children did show significantly worse scores on the psychologist administered tests at baseline.

Parental ratings might be more sensitive to changes in behaviour in that parents experience their child's behaviour over a longer period of time, in more varied settings and under less optimal conditions. The tests conducted in clinic are liked

by the majority of children who see them as an entertaining game and are administered when they are optimally alert and engaged. In contrast, parents will observe their child's behaviour when they are competing with siblings for attention; when the child is hungry or tired; with less devoted attention from one adult; when interacting with other children; or in a constraining setting such as on public transport or in a supermarket queue. In this range of disparate settings the child's hyperactive behaviour is more likely to be aggravated.

An additional possibility is that the test-re-test reliability of the tests being used was simply insufficient to detect systematic effects of dietary supplements. The reliabilities of the test scores were only modest (0.24 – 0.72) but comparable with a number of physiological measures at this age (0.25 – 0.50)[244;245].

These findings therefore suggest that significant changes in children's hyperactive behaviour could be produced by the removal of artificial colourings and sodium benzoate from their diet. The results were obtained in a general population sample with only a modest degree of self selection i.e. 1269 families were invited to enter the double blind food challenge phase and 92% initially agreed to take part. Although approximately one sixth of families did not complete the challenge phase, the completers were no different from the non-completers on any of our baseline measures. Such losses from the study would be expected given the heavy demands placed upon the families to modify their children's diet over a five-week period, however the attrition rate is smaller than that reported by other similarly demanding studies[238].

The reduction in hyperactive behaviour that arose from the removal of artificial colours and sodium benzoate from the diet of pre-school children were not related to initial levels of hyperactivity. The child with more extreme hyperactivity showed changes no greater but also no less than other children. The potential long term public health benefit that might arise is indicated by the follow-up studies that have shown that the young hyperactive child is at risk of continuing behavioural difficulties including the transition to conduct disorder and educational difficulties.[280;369]

This study has shown that the effect of food additives on behaviour occurs

independently of pre-existing hyperactive behaviour or indeed atopic status. This is consistent with other findings suggesting that any effect of food additives is likely to be pharmacological, best exemplified by non-IgE dependent histamine release.[202;370]

The withdrawal of additives showed an improvement in allergic symptoms, but with little corroborative evidence of deterioration in symptoms on challenge. The children with pre-existing rhinitis did however show a deterioration of their symptoms on re-challenge. Histamine is certainly important in mediating the cardinal symptoms of the immediate allergic reaction, associated with symptoms of rhino-conjunctivitis, it is probably less important in mediating the symptoms of asthma and eczema.[371] This adds clinical support to other work that has demonstrated histamine release following tartrazine challenge.[201;202] There was little evidence of correlation however between the changes in symptoms of rhinitis, and those in behaviour, making it less likely that deterioration in rhinitis was causing behaviour changes, but requires further investigation with more detailed evaluations of upper respiratory symptoms and signs. It also does no rule out a common mechanism, with different between-child end-organ sensitivities. It is well accepted that genetic and environmental factors determine whether different individuals have asthma, eczema or rhinitis. Genetic determinants of primary abnormalities of airway and nasal epithelium[322] and dermis[71] have been suggested. It is possible to conceive that there may be a group of children with a phenotype that predisposes them to the central nervous effects of mediators such as histamine.

Some children seemed to be responding to food additives more markedly than are others, but we were unable to identify any characteristics that were related to a greater sensitivity to food additives. It may be that these were chance variations in the extent of the response to the presence of additives. However there may be additional social or family factors that relate to differential intolerance. It is perhaps more likely that other biological markers, such as genetic polymorphisms, [372;373] would identify the most susceptible children.

The effect of shifting the mean of the hyperactivity scores for the population down by 0.5 standard deviation is shown in figure 15. This is the estimated effect size

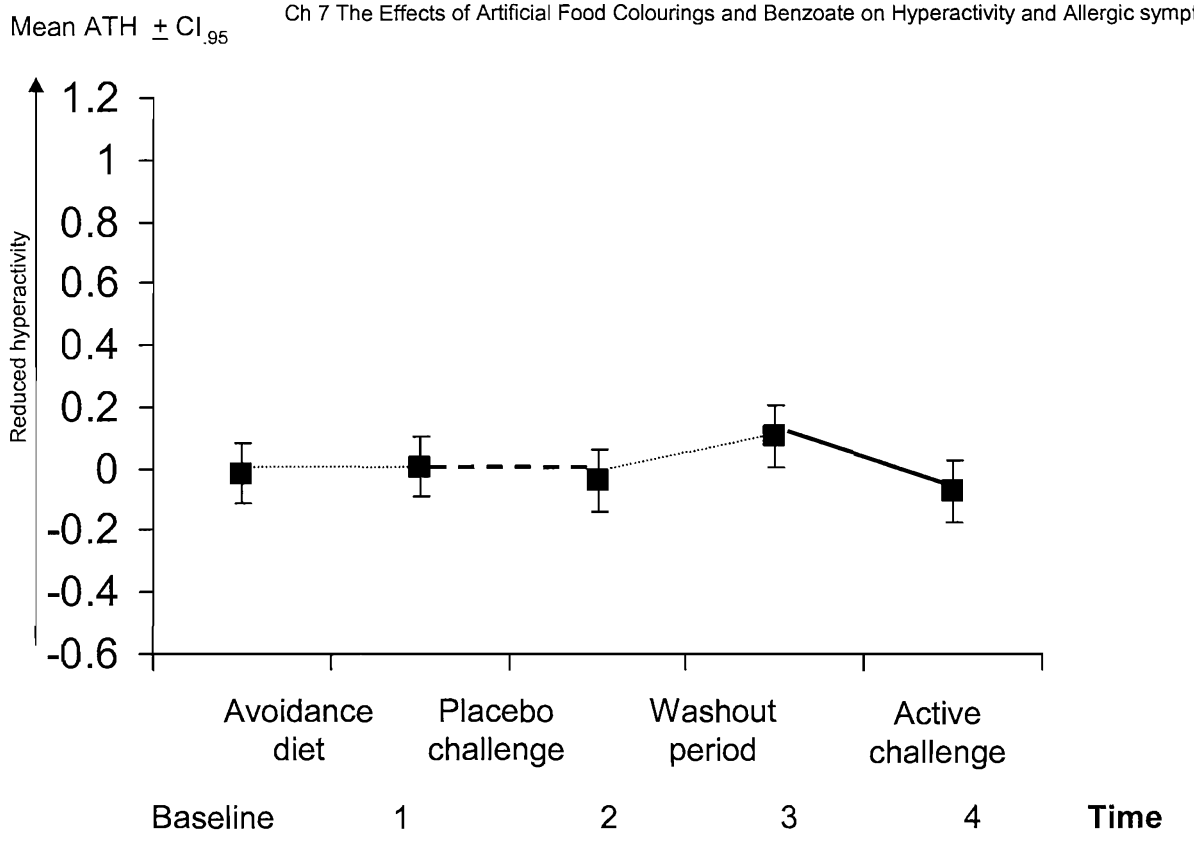
for removing additives on the basis of the findings from the present study. The impact on the proportion of children with elevated hyperactivity score (above the 85 percentile) would be to reduce the prevalence from 15% to 6%. We believe that the behavioural findings suggest that benefit would accrue for all children if artificial food colours and benzoate preservatives were removed from their diet. These findings are sufficiently strong to warrant attempts at replication in other general population samples and to examine whether similar benefits of the removal of artificial colourings and sodium benzoate from the diet could be identified in community samples at older ages, and whether there is any impact on more long term outcomes such as educational attainment.

7.6 Conclusion

This study showed a significant effect of artificial colourings on the behaviour of 3-year-old children, by parental report. This effect was not corroborated with clinic tests.

Atopic children were no more likely to have behaviour changes with the artificial additive challenge. There was no deterioration in wheeze or eczema during the challenges, but children with rhinitis did have a deterioration in their physical symptoms, but these were not related to behaviour changes. This supports other authors' suggestions[238] that behaviour change with artificial additives is unlikely to have any relationship with atopy or allergic symptoms.

There were no identifying characteristics of children who had a significant behaviour change with artificial colours and sodium benzoate. It is likely that biological rather than clinical markers may be more likely to identify susceptible children. Future studies should aim to use general population samples of children.



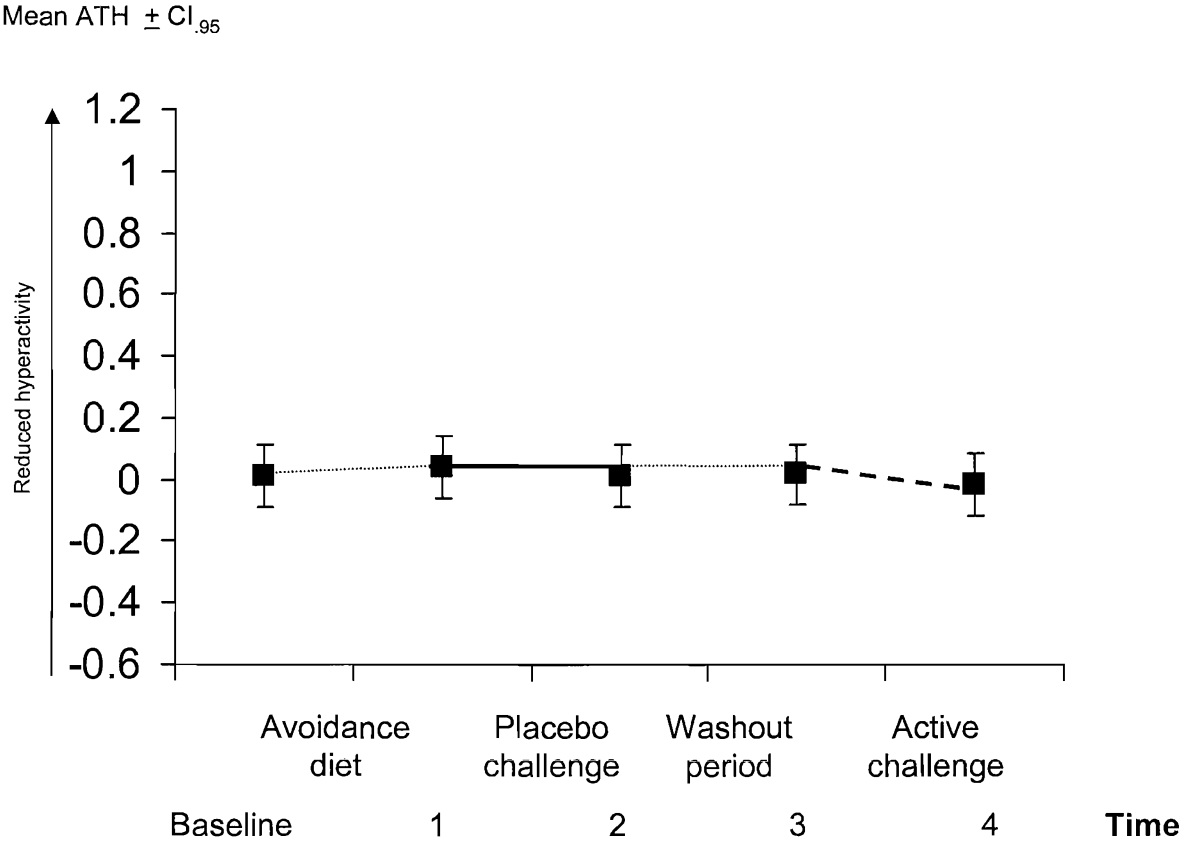
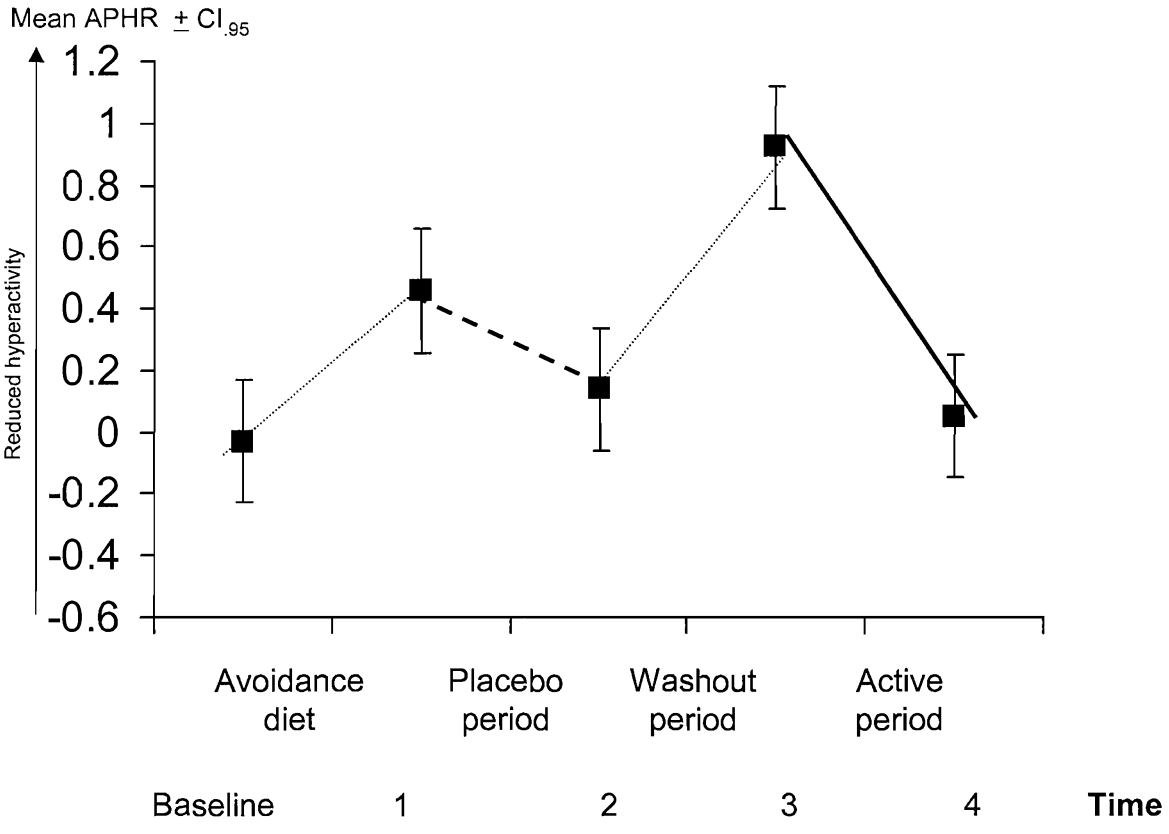


Figure 2 Mean standardised Aggregated Test Hyperactivity (ATH) scores at 5 time points for active-then-placebo and placebo-then-active groups



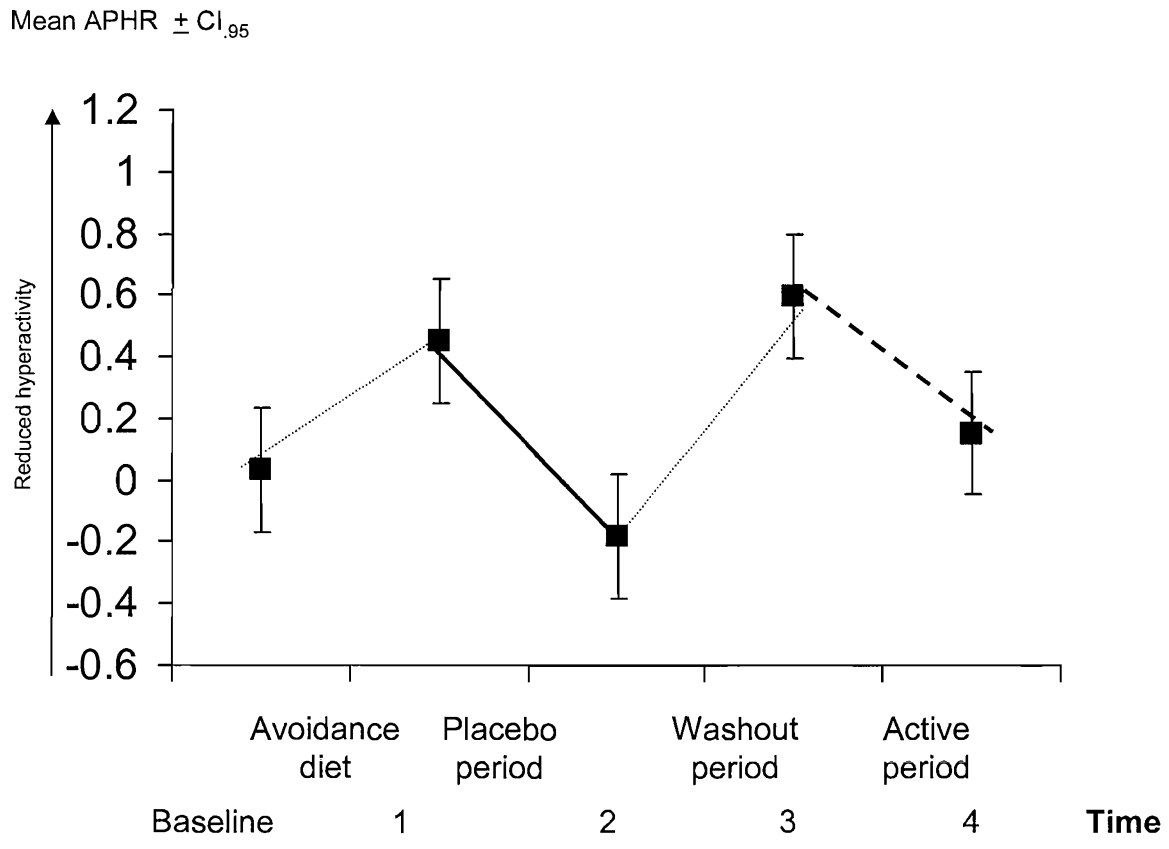


Figure 3 Mean standardised Aggregated Parental Hyperactivity Rating (APHR) scores

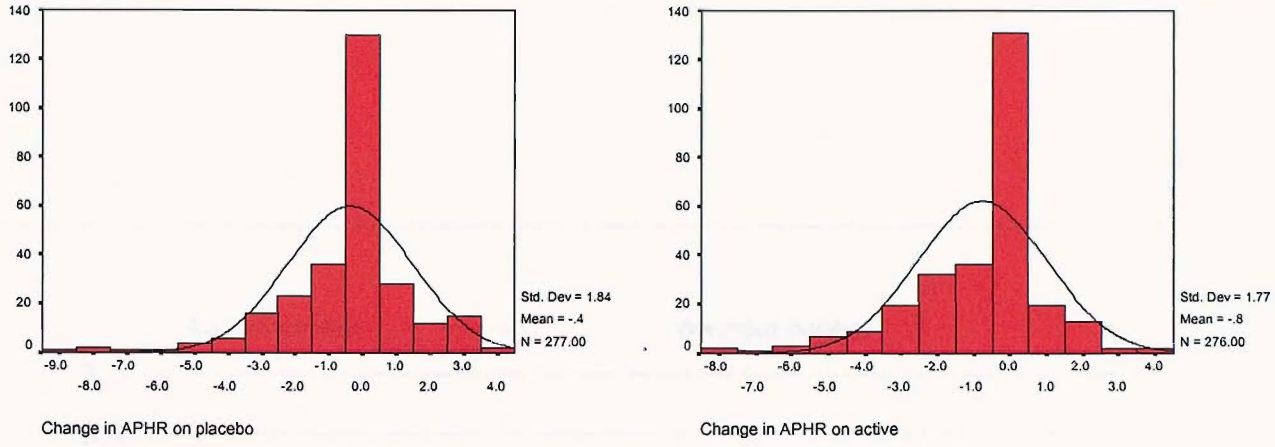


Figure 4 Range of changes in Aggregated Parental Hyperactivity Rating score during the placebo and active periods

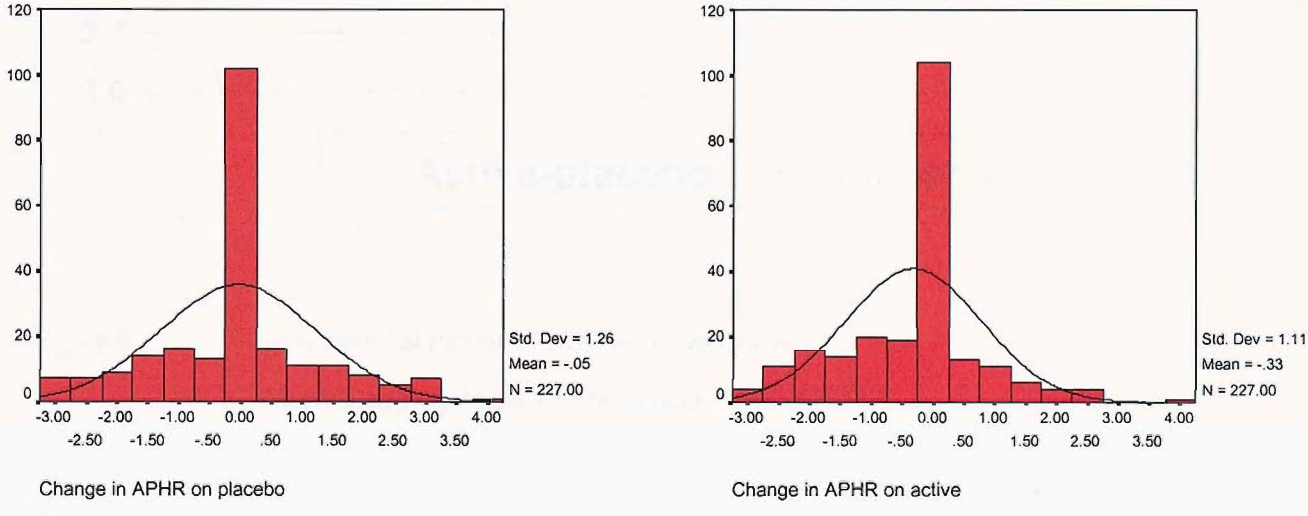


Figure 5 Range of changes in Aggregated Parental Hyperactivity Rating score during the placebo and active periods (extreme changes excluded)

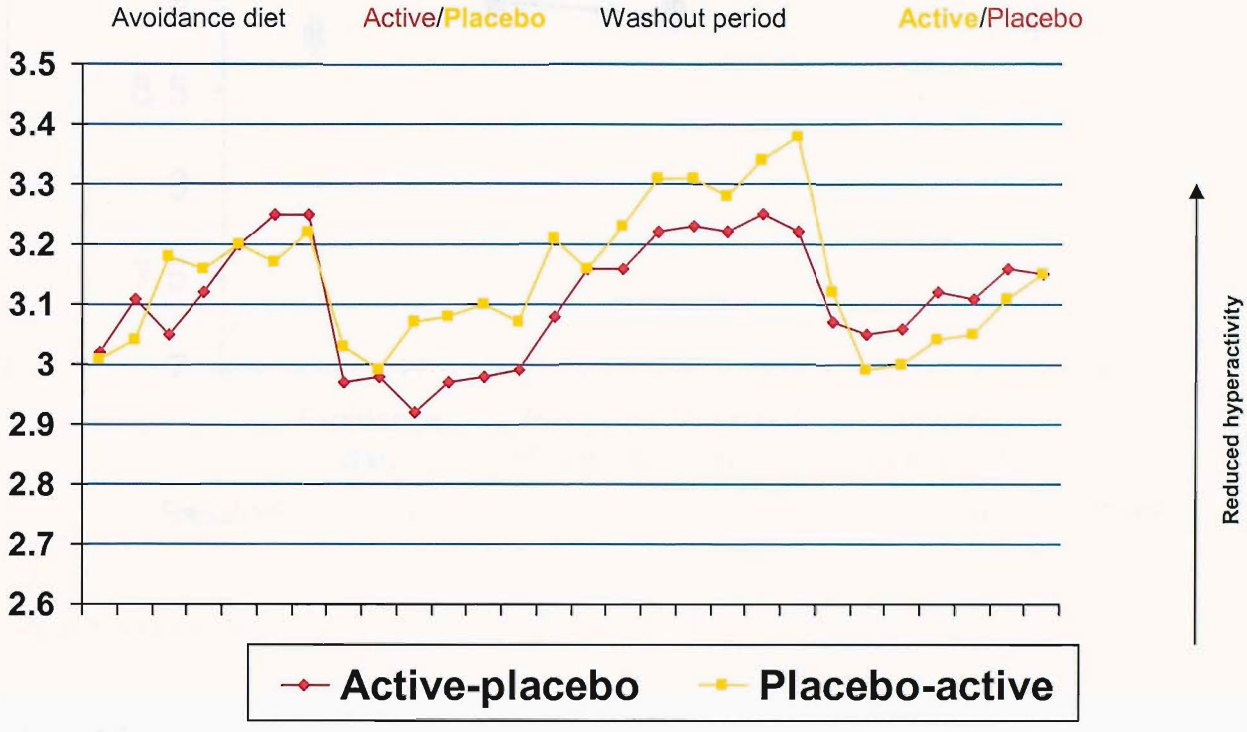
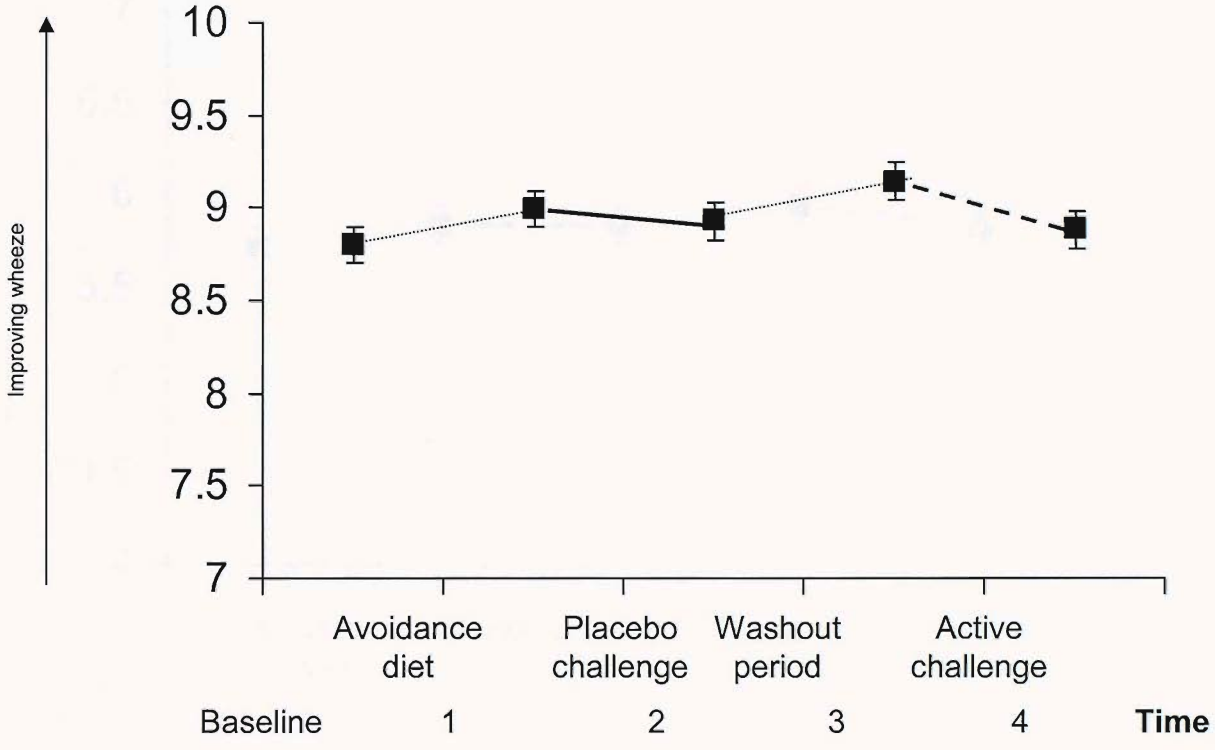


Figure 6 Daily parental ratings of behaviour over 4 weeks

Parental aggregate general behaviour rating (APGBR)

PA

Mean wheeze ± $CI_{.95}$



AP

Mean wheeze ± $CI_{.95}$

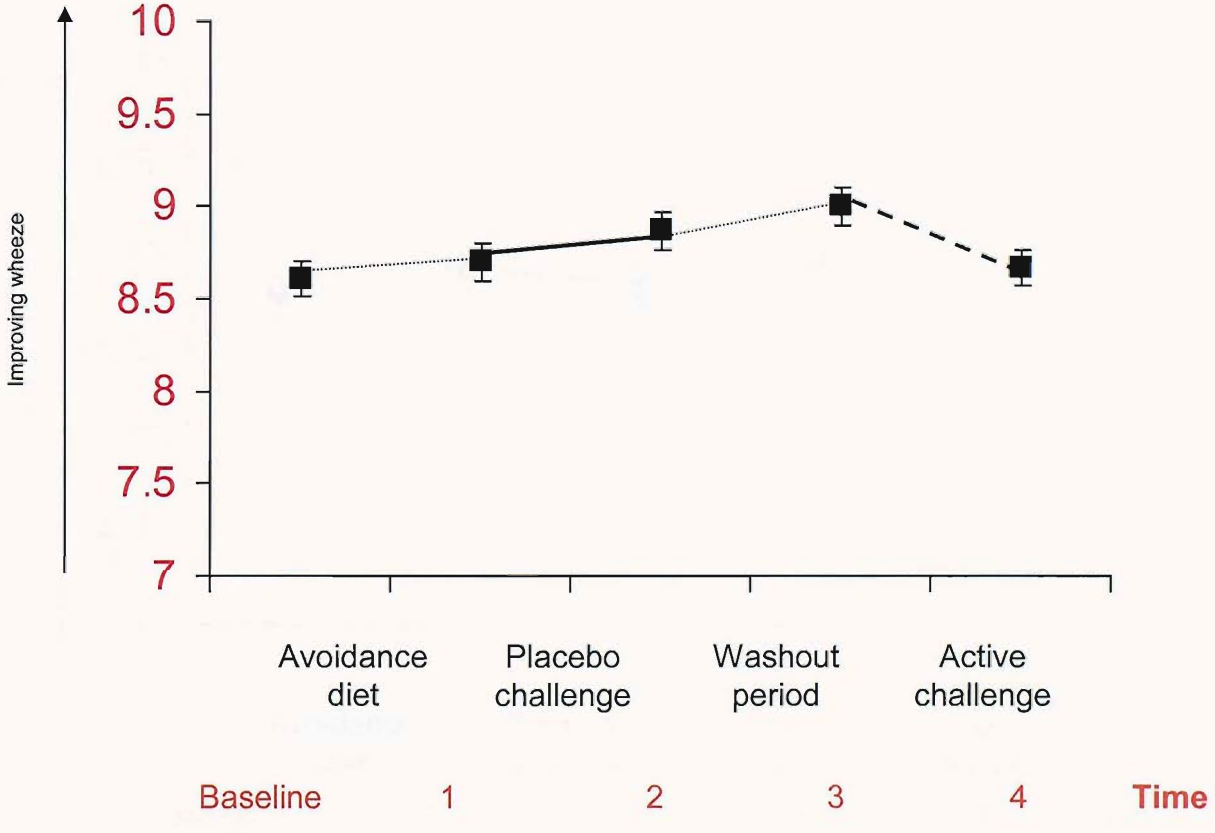
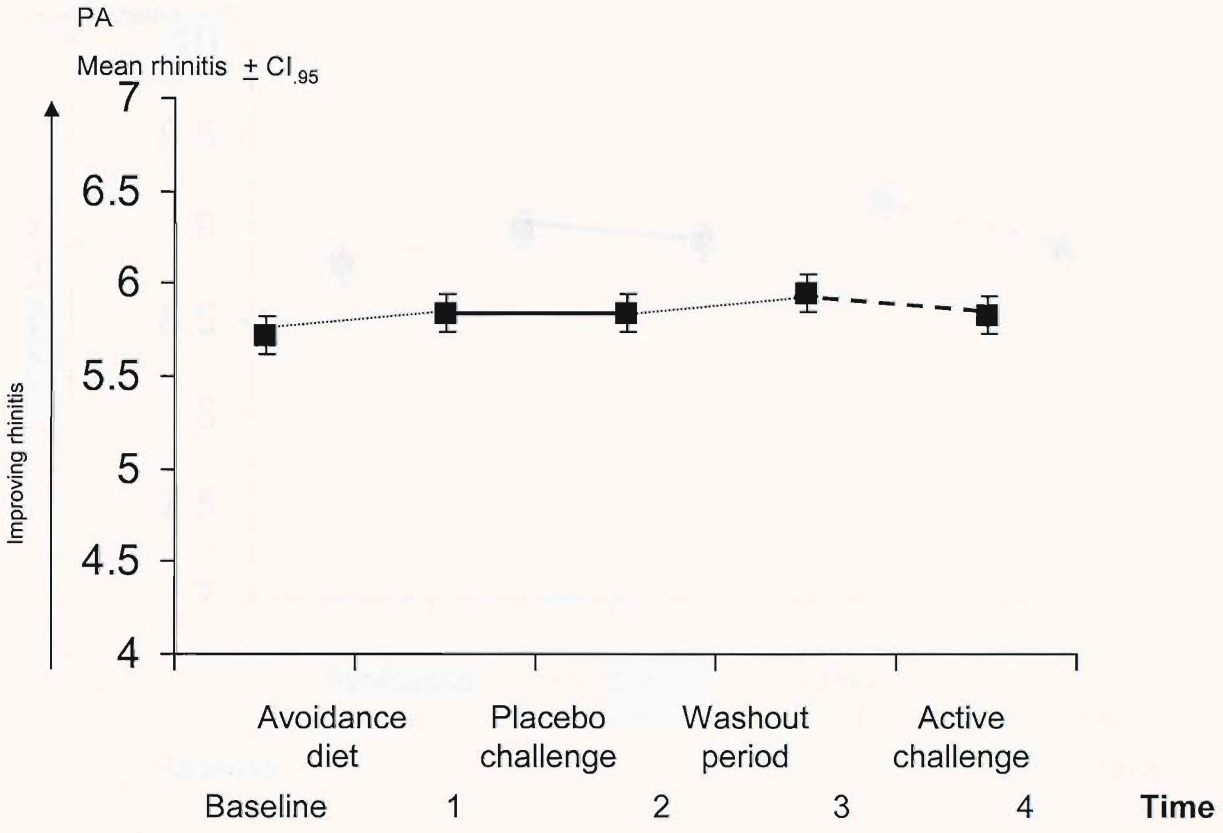


Figure 7 Mean wheeze scores at 5 time points for the AP and PA groups



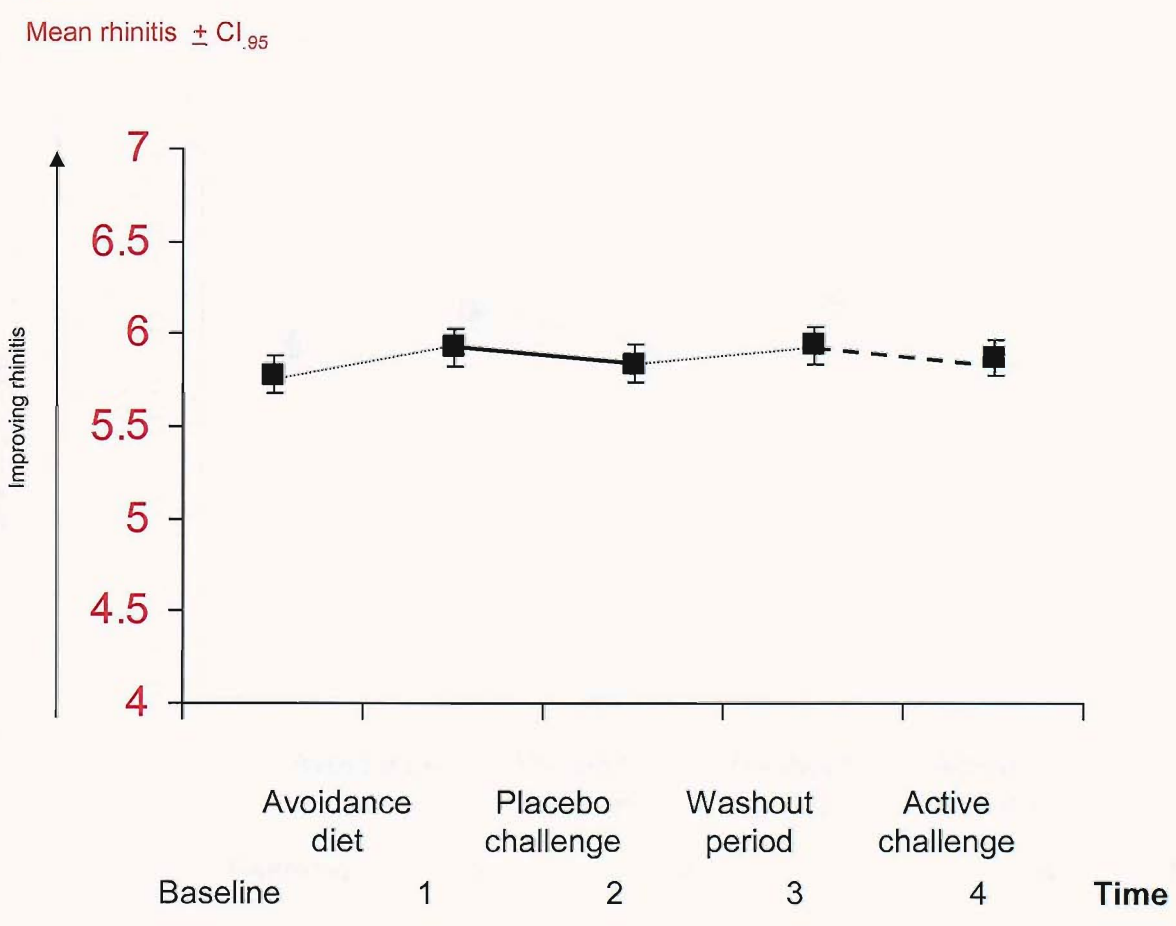
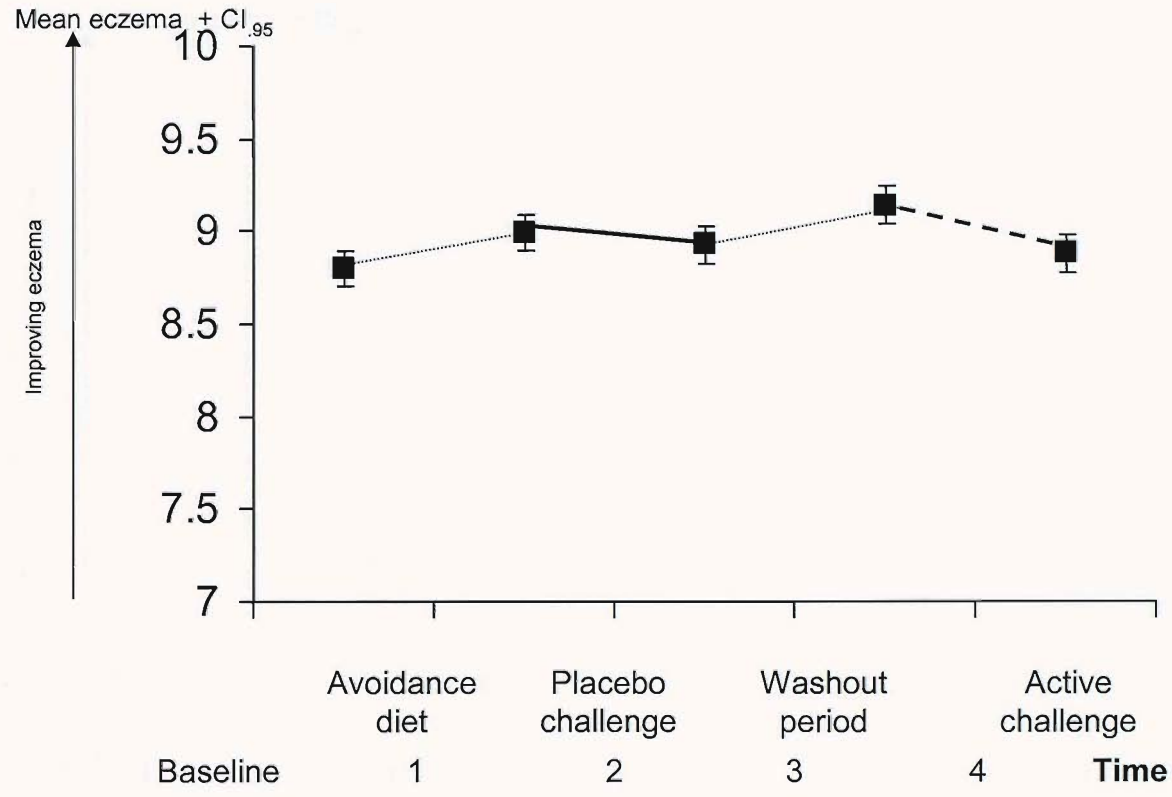


Figure 8 Mean rhinitis scores at 5 time points for the AP and PA groups



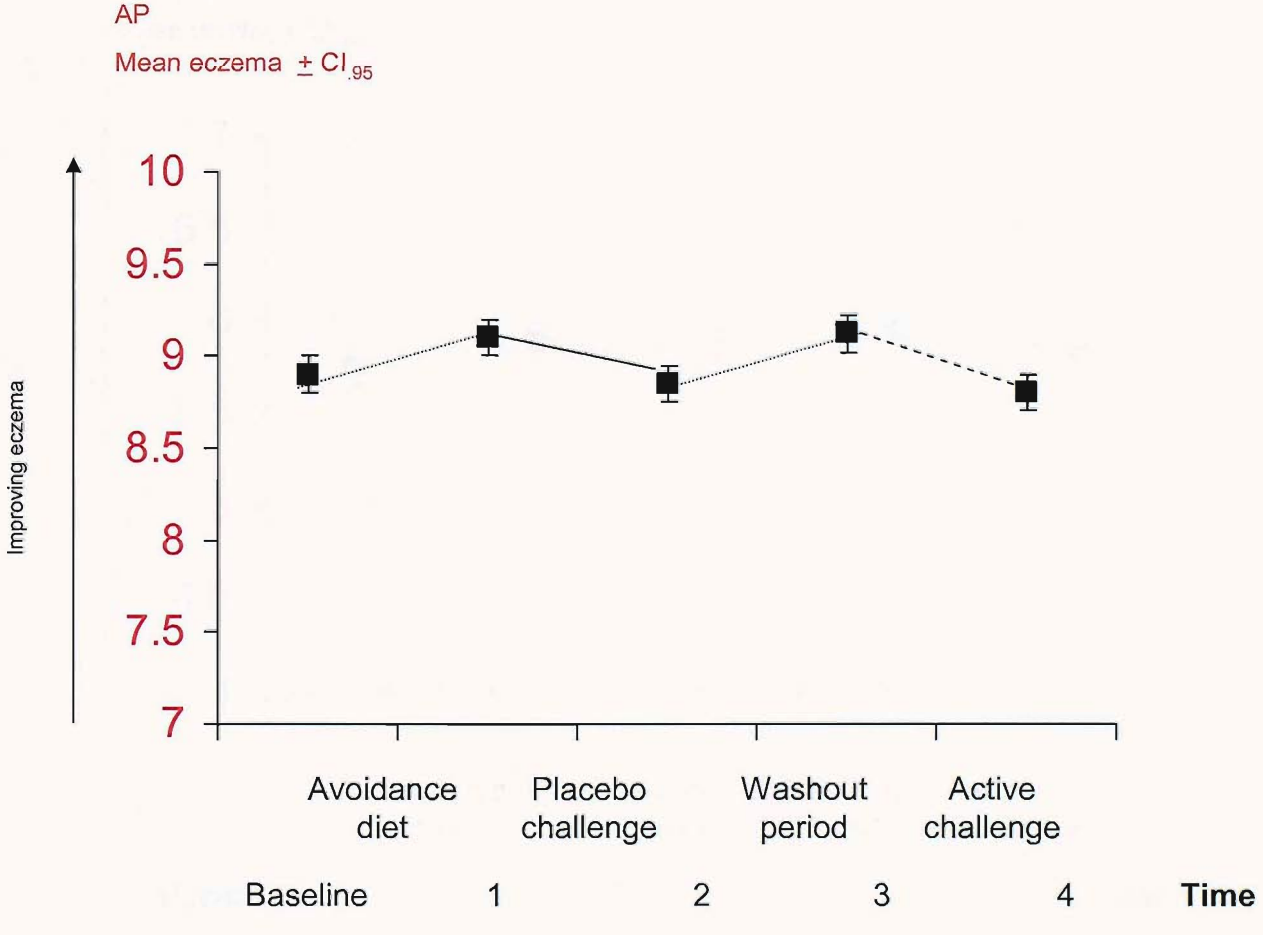
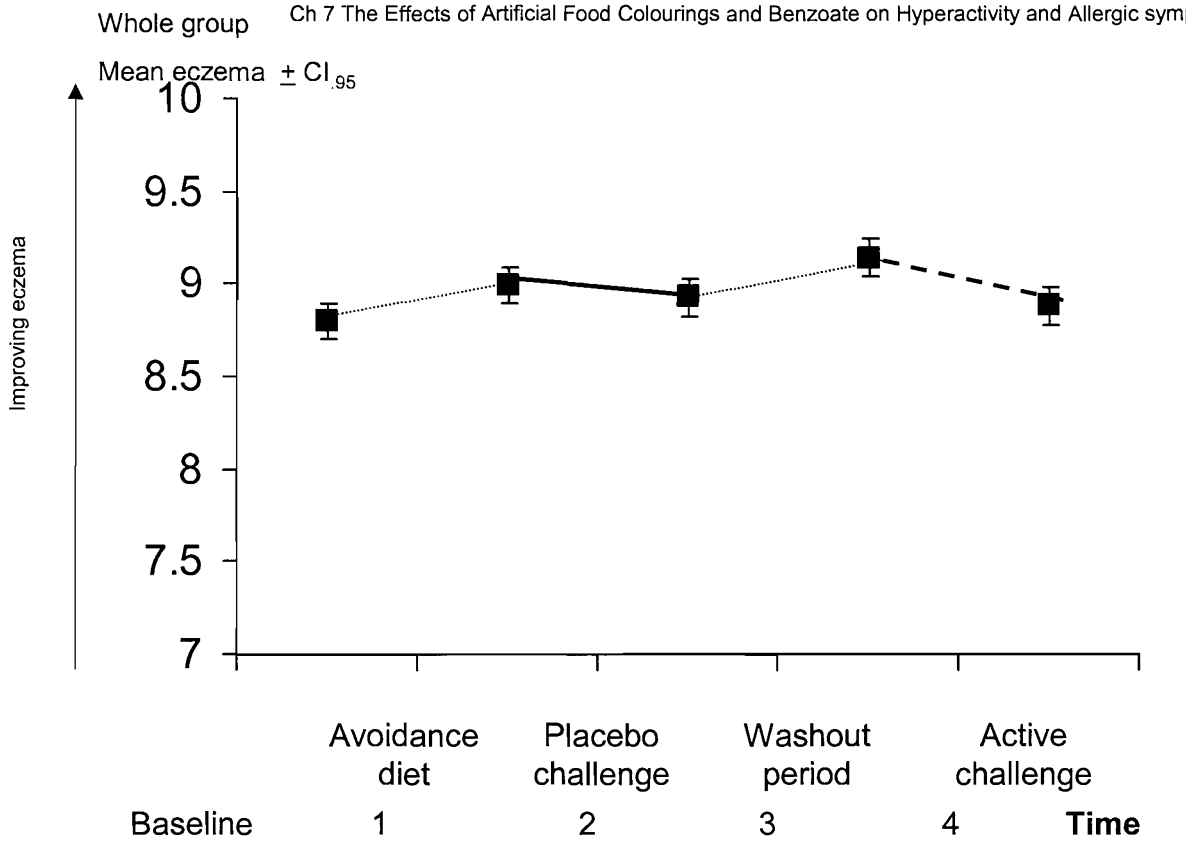


Figure 9 Mean eczema scores at 5 time points for the AP and PA groups



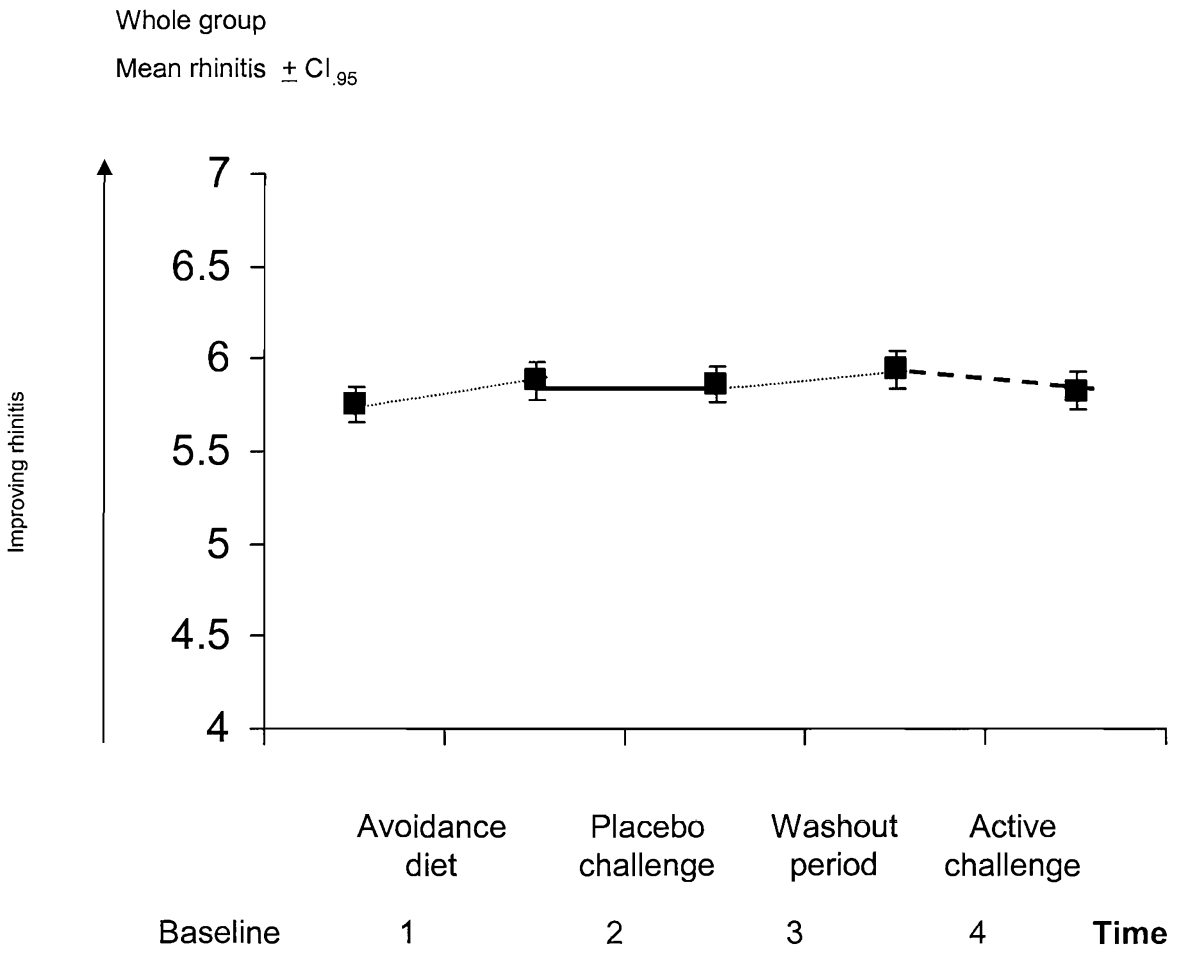


Figure 10 Mean eczema and rhinitis scores for the whole group

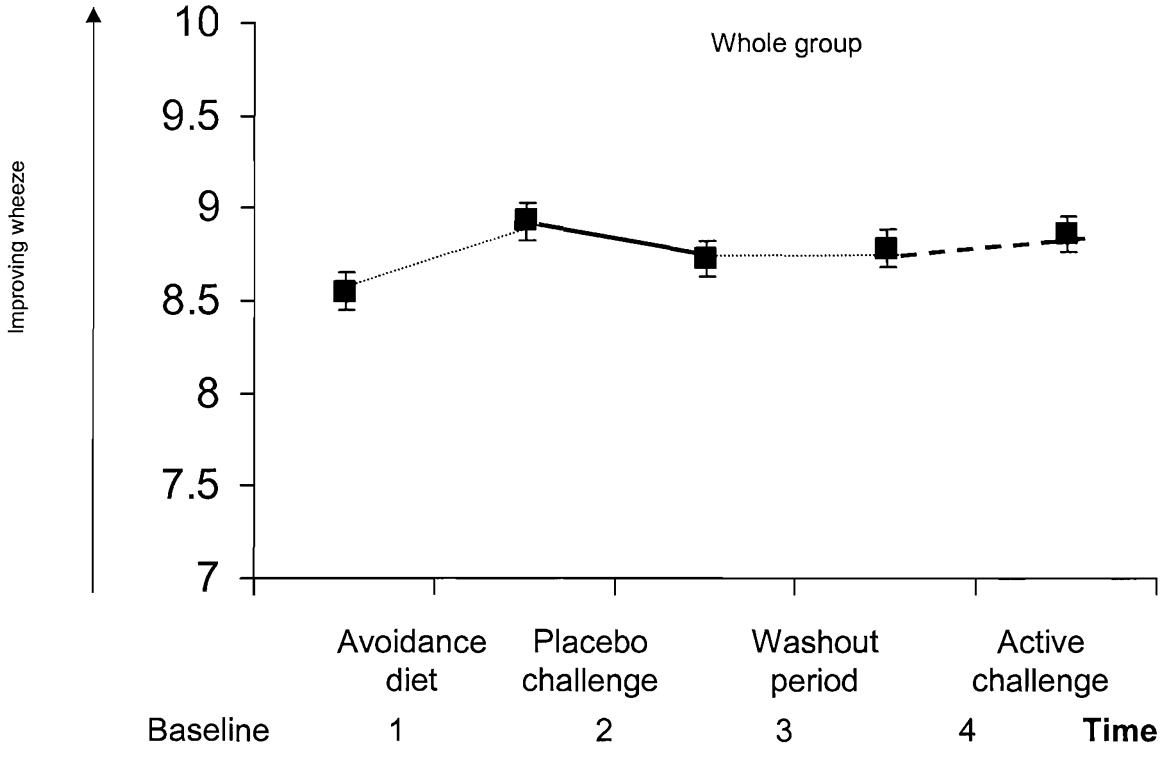
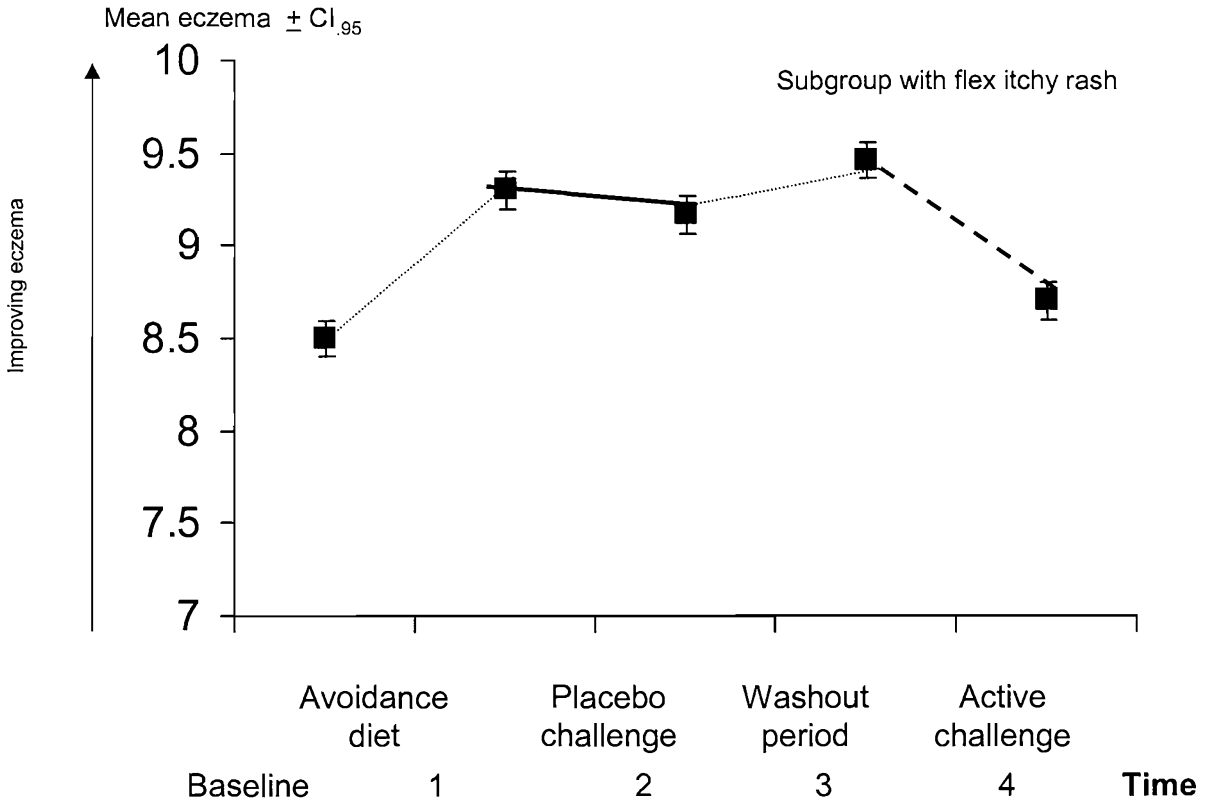


Figure 11 Mean wheeze scores for the whole group



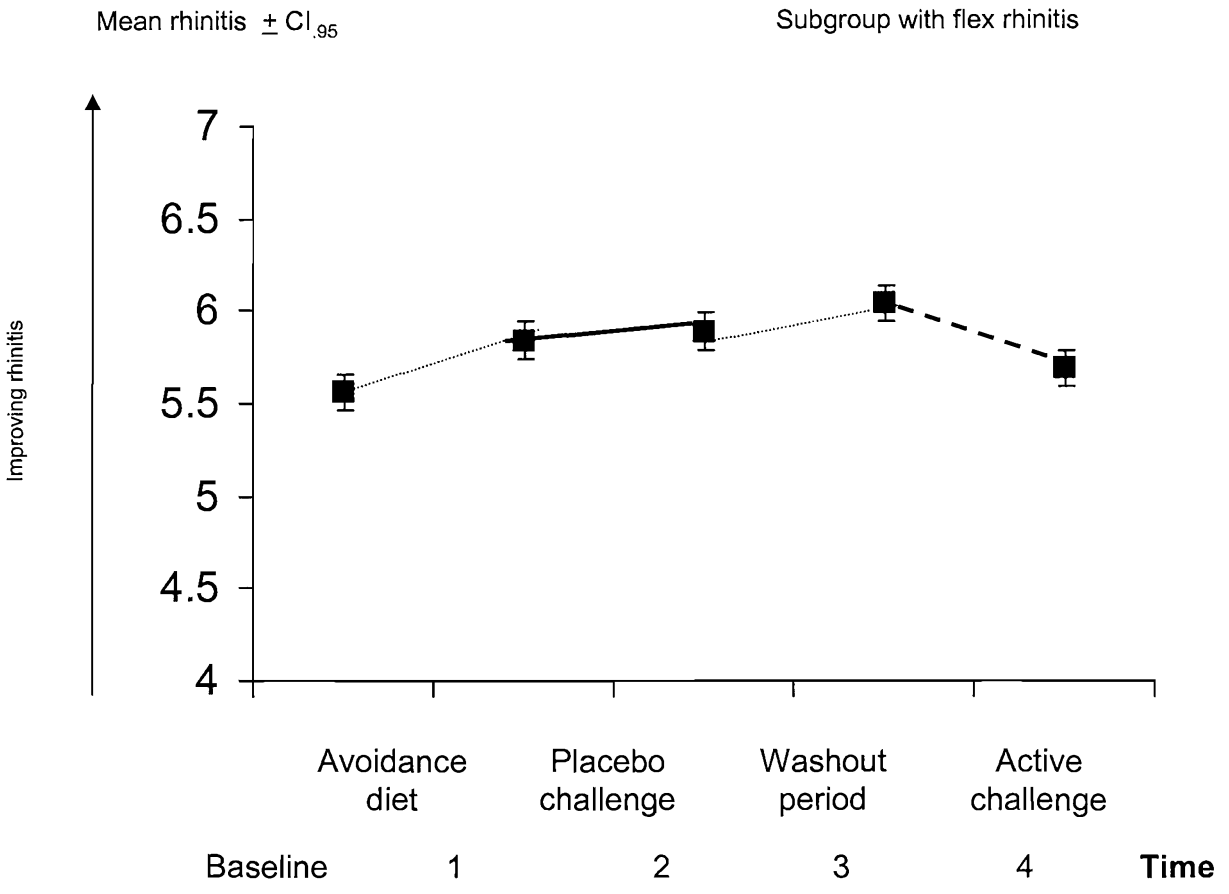


Figure 12 Mean eczema and rhinitis scores for the respective symptomatic sub-groups

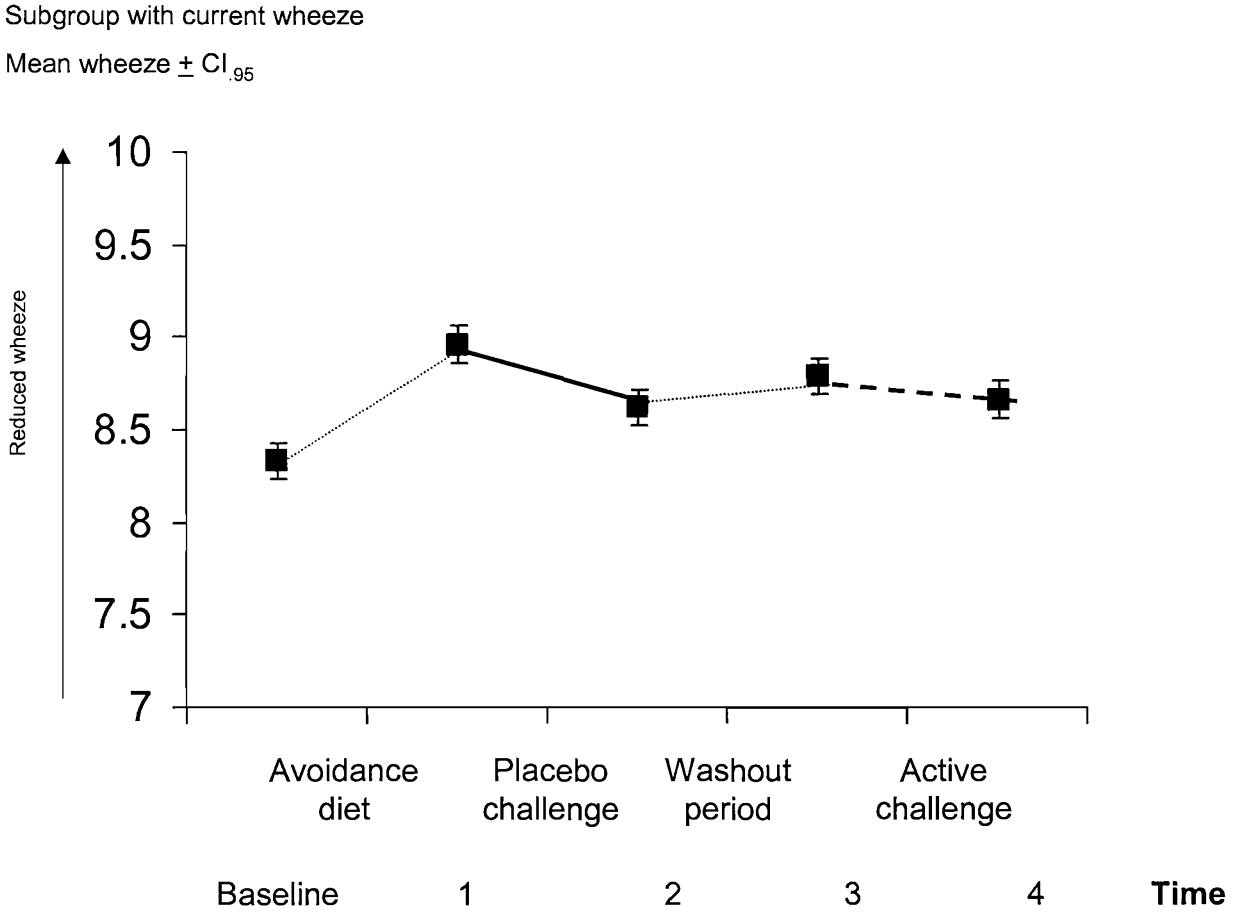


Figure 13 Mean wheeze scores for the symptomatic sub-group

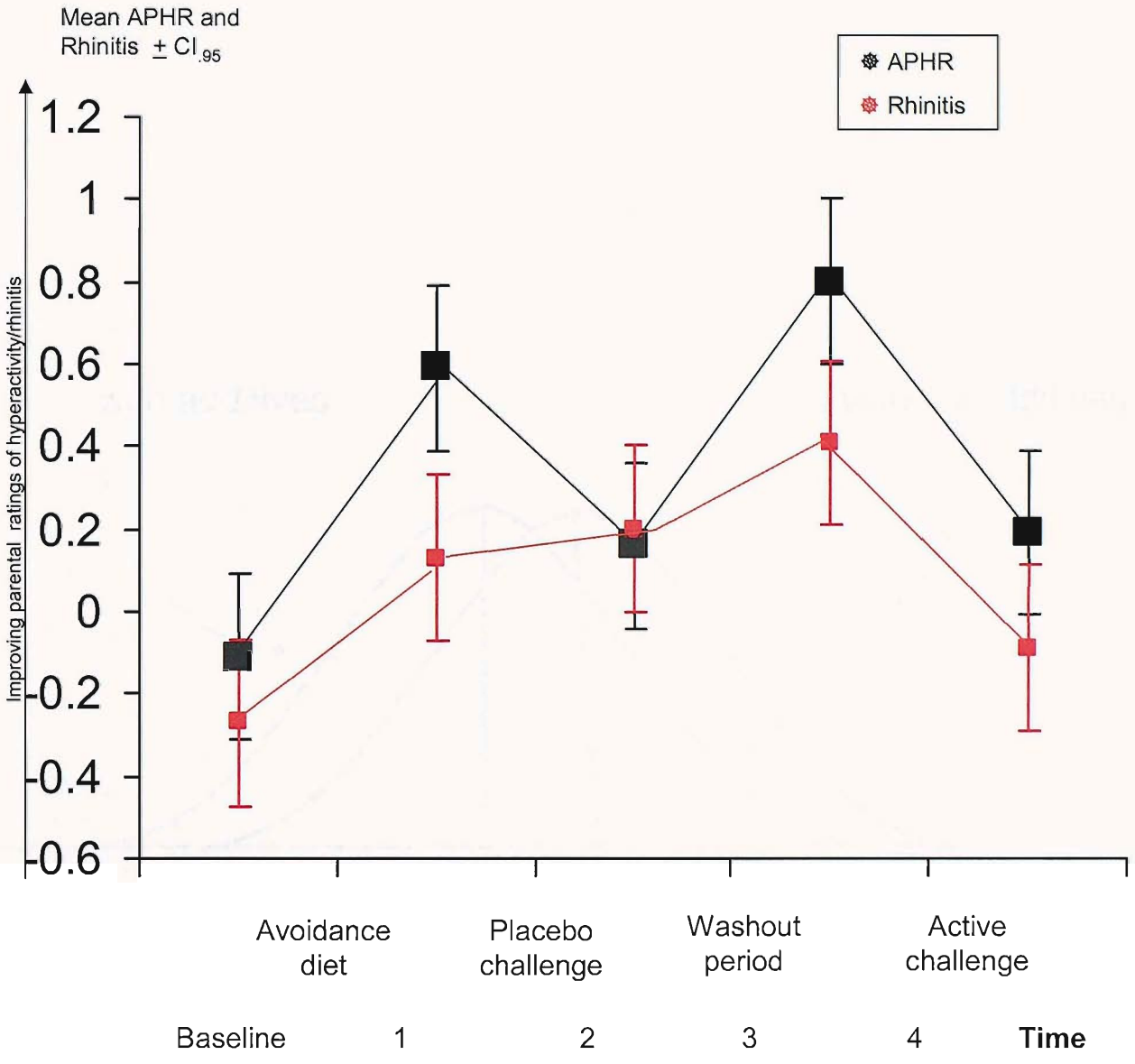


Figure 14 Changes in rhinitis and parental ratings of hyperactivity

Symptomatic rhinitis sub-group APHR and rhinitis (standardised)

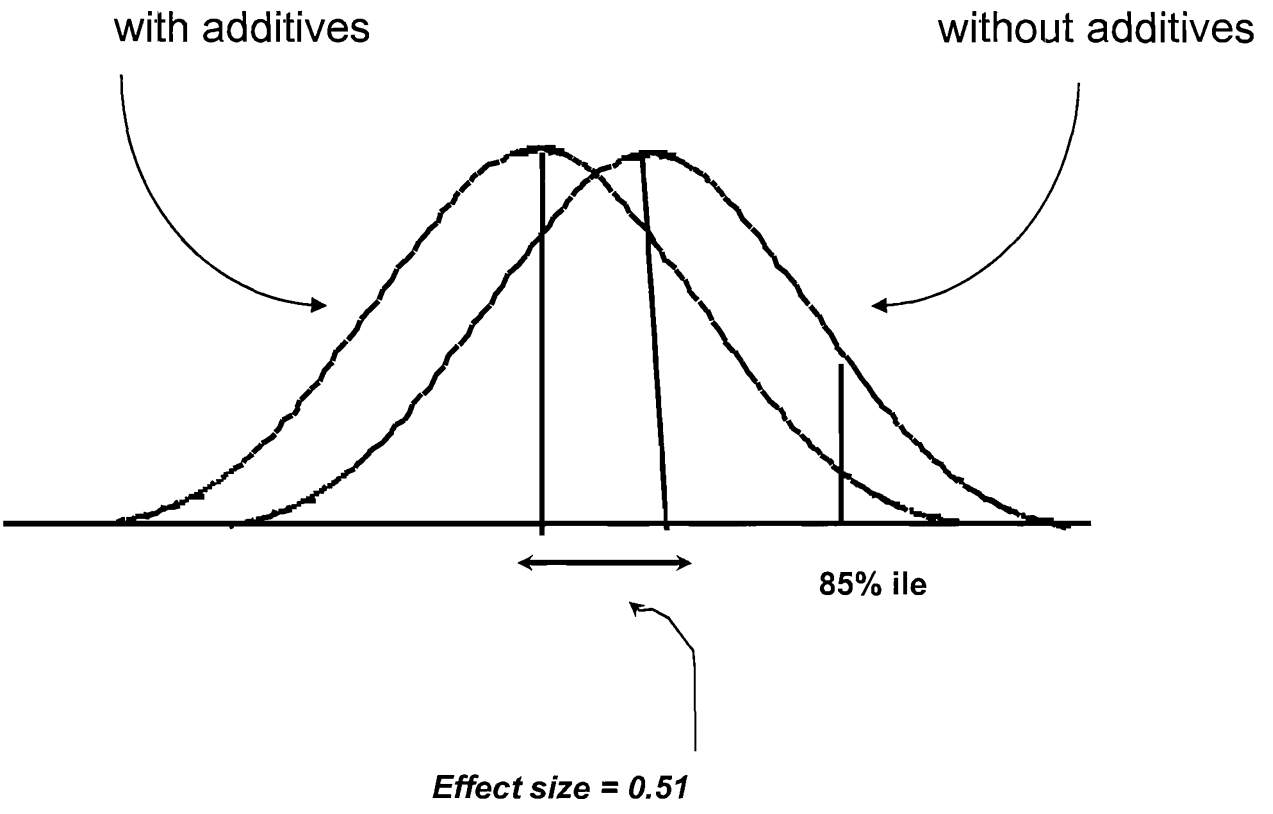


Figure 15 The hypothesised effect of removing food additives on the prevalence of hyperactivity

Chapter 8

Conclusions

8.1 General Conclusions

There are four main conclusions from my study. The first is that socio-economic deprivation and family adversity frustrate good parenting and increase the risk of general behaviour problems in childhood. Poorer families and younger, less educated mothers were more likely to have a child with more behaviour problems. These environmental factors explained 10% of the variance in total behaviour problems. I did not try to measure other factors which might explain the remainder of the variance but genetic factors are likely to be important. In respect of more extreme hyperactive behaviours, there was an association with socio-economic adversity but there was little association with any other environmental factors leading me to conclude that non-environmental factors play an even more important role in determining these more extreme behaviours.

My second conclusion is that there are complex associations between socio-economic adversity and allergic diseases for which it has not been possible to develop a satisfactory explanatory model. Children born into materially *affluent* households were more likely to be atopic. Three indirect measures of affluence also increased the risk of atopy; higher birthweight, older mothers and non-exposure to smoke antenatally. Atopy was strongly associated with allergic symptoms; wheeze, rhinitis and eczema. However socio-economic *adversity* increased the risk of wheeze and rhinitis. Children living in rented housing, of lower gestation and those exposed to smoke antenatally (but interestingly not current smoke exposure) were at increased risk. Wheeze and rhinitis are due to at least two conditions in this age group. The children with wheeze (and rhinitis) associated with atopy are likely to have ongoing asthma. The children with non-atopic wheeze associated with socio-economic deprivation are more likely to be the group of children with small airways, whose symptoms will resolve. Eczema was different, it was evenly distributed throughout the population of 3-year-olds, and, apart from atopy, had few environmental associations. The association of atopy with affluence and lower birth order both give direct support for the hygiene hypothesis.[65]

My third conclusion is that in the population of three year olds, after I had controlled for socio-economic factors, atopy did not increase the likelihood behaviour problems making a genetic link with atopy and behaviour very unlikely. There was no evidence that children with symptoms of mild or frequent or severe asthma were more at risk of behaviour problems. Children with other allergic symptoms were different. The 3-year-olds with symptoms of rhinitis and eczema on parental report had a small but significant increase in both general and hyperactive behaviour problems. This was not corroborated by clinic observations of increased impulsivity, activity and attention.

My final conclusion, generated from the randomised controlled trial, is that artificial colourings and the preservative sodium benzoate have a significant detrimental effect on children's behaviour as reported by parents but not as observed in clinic testing. These results are generalisable to the whole population of pre-school children. 10% (277) of the whole population of 3-year-olds completed four weeks of this randomised placebo controlled trial. Most previous studies had used children only with behaviour problems, limiting the generalisability of the findings. Other researchers, using other selected populations had suggested that atopic children[374] might have been particularly vulnerable. There were no particular characteristics of children who had a significant behaviour change with artificial colours and sodium benzoate. Children who were atopic and children who had hyperactive baseline behaviours were no more likely to have behavioural deterioration.

A number of further observations contribute to understanding of this complex field. They are of secondary importance to my principal conclusions and are set out in earlier chapters.

8.2 Strengths and Limitations

The initial response rate was over 70% of the population, making selection bias less likely. However some of the epidemiological results are based upon 49% of the population. It was likely that overestimates of atopy and allergy were made, given that the recruitment took place from the local 'Asthma and Allergy Centre'. There were no systematic differences between the children who completed each phase of the study, making the reported relationships between allergy and behaviour likely to

be robust. 10% of the population completed the randomised controlled trial. The nested case controlled design meant that the children were selected for this phase by the research group, after consent by their parents. There was no difference between those who completed the randomised controlled trial and those who did not. Parents who stated that they thought food and drink affected their child's behaviour were not more likely to complete any of the phases. For 10% of any population to complete a trial makes these results robust and generalisable.

It was not possible to link records back to birth data and therefore some historical data will be affected by recall bias. However most of the study's main conclusions are based upon current physical and behavioural symptoms, and sociodemographic variables and are thus reliable.

A strength of my study was the direct reporting of household income; as this is rarely undertaken in socio-medical research in UK studies.[29] Even so these data were limited, as there was no attempt to record state benefits collected by the families, or to estimate their amount of debt. Housing tenure was recorded, but without details of overcrowding or method of heating. Car ownership was recorded but it showed little correlation with the other two measures of material environment, and was not particularly predictive of measures of behaviour or respiratory symptoms. Parental occupation was rejected as a proxy measure of material situation, 12% of these children lived with only their mother, 27% of the children lived in households with an annual income of less than £12,000, most of these households had no adult in paid employment. These two groups of children are potentially the most deprived and would have been 'unclassifiable'. There are specific child-centred subjective measures of deprivation[378] that could have been used, but involve fairly lengthy questionnaires. Compounds measures such as the Townsend Deprivation Index[379] are based on several indicators of material deprivation based upon a geographical unit, these work less well in rural areas such as the Isle of Wight as the sub-units are more heterogeneous.

Most of the measures were parent reported. Parents' reports of their child's behaviour have been shown to correlate well with those of other observers.[1] The parental reported measures of allergic disease that were symptom based were probably over-inclusive particularly in this pre-school group, but would have been

difficult to corroborate. Objective measures of lung function are difficult in this age group. The diagnosis of eczema could have been partly corroborated by examination, by using a validated examination tool such as SCORAD.[87] Despite these limitations this was a very full data set of information on this population-derived cohort. This included information about behaviour, allergic symptoms, with a more objective measure of atopic status and wide sociodemographic data.

8.3 Further Research

The association of psychological and physical problems with deprivation is not a new finding. Many authors have reported the many problems associated with determining the putative aspects of deprivation.[29;379] More sophisticated measures of neighbourhood and family are needed to understand how they affect children's health. These include measures of parenting styles and mental health and the effect of social and extended family networks. The association of rented housing with behavioural and allergic symptoms may make one assume that an effective intervention would be to further home-ownership. This research gives little insight into the mechanisms of this association; further measures of overcrowding, and the quality of housing and neighbourhood would have been valuable.

The problems with measuring the effect of tobacco smoke exposure on children's health have been discussed[255] and are well illustrated here. Despite attempts to gather several measures of material situation, the reported relationship with antenatal smoke exposure and behaviour problems persisted. There remain several possible mechanisms for this relationship; a toxic neurological effect of antenatal tobacco smoke exposure, antenatal smoking may be a marker for maternal behaviour, possibly depression, or the reported relationship may have been due to inadequately controlled socioeconomic deprivation. These different mechanisms all need further evaluation.

More detailed work to understand the interrelationship between sleep problems, behaviour problems and allergic symptoms would be fruitful in this young age group. It is interesting that rhinitis was particularly associated with behaviour problems in the epidemiological phase and, although symptoms of rhinitis did not appear to be the mediating factor in the worsening of behaviour in the randomised controlled trial,

they were affected by the challenge. Repeat studies need to examine more fully the relationship between rhinitis and behaviour. They should make some attempt to gather biological inflammatory markers to elucidate this further.

Children with rhinitis were reported as having exacerbation of their symptoms during the challenges. Biological markers able to confirm inflammation would give information as to the pharmacological mechanisms.

I selected children to enter my study, in order to ensure that I had adequate power to say whether or not the additives had any specific effect on children with baseline hyperactive behaviour or atopy. In open meetings I have been criticised that my selecting children makes the results less generalisable. A larger randomised controlled trial is needed using a random sample of a general population of children to answer this criticism. My study did not identify any characteristics of children more likely to have behavioural deterioration with the additives. Genetic studies may identify any subgroups of children whose behaviour was vulnerable.

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