
# Multi-level modelling of international variations and time trends in asthma and allergic diseases in children

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# Declaration

I, Charlotte Emma Rutter, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

There are papers included in this thesis that I have co-authored. I have only included papers for which I contributed a large amount of the work involved, both analyses and writing. Other papers, for which I contributed a lesser amount are included in the list in Appendix A.

# Abstract

***Introduction***

Asthma is the most common chronic disease in children, but little is understood about its underlying causes and reasons for global differences and time trends in prevalence. This thesis uses data from the International Study of Asthma and Allergies in Childhood (ISAAC) and Global Asthma Network (GAN) to explore these issues. These are multi-centre, multi-country, standardised cross-sectional symptom and risk factor surveys, at three time points over a 27-year period, in adolescents aged 13-14 and children aged 6-7.

***Methods***

The ISAAC and GAN data form a complex hierarchy including individuals within schools, within centres, within countries, with centre-level data available at multiple time points. Mixed-effects logistic regression models were used to estimate associations between individual-level risk factors and asthma symptoms, and also between school-level risk factors and individual-level asthma symptoms, at one time-point. Mixed-effects linear regression models were used to estimate ecological associations at the centre level, between the same risk factors and both current symptom prevalence and time trends in prevalence.

***Findings***

Prevalence of asthma symptoms is generally highest in high income countries and has remained stable, while it has been increasing in lower-middle income countries, and decreasing or remaining stable in low-income countries. Risk factors including paracetamol use, frequent truck traffic, and antibiotics in the first year of life have strong associations with asthma symptoms at the individual level, and generally also at the school level. However, these factors do not explain geographical differences in prevalence or global time trends.

***Conclusion***

Risk factors with strong evidence of an association with asthma symptoms at the individual level do not explain global patterns and time trends. This could be due to either ecological bias, unmeasured confounding or because the determinants of asthma at a population level are actually different to the determinants at an individual level.

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# Abbreviations

| | |
|---|---|
| AD | Atopic dermatitis |
| AE | Atopic eczema |
| BLUP | Best linear unbiased predictor |
| BMI | Body mass index (kg/m$^2$) |
| CI | Confidence interval |
| CIA | Central Intelligence Agency |
| COVID-19 | 2019 Novel Coronavirus |
| CrI | Credible interval |
| DALY | Disability-adjusted life year |
| ECRHS | European Community Respiratory Health Survey |
| ERC | European Research Council |
| GAN | Global Asthma Network |
| GAR | Global Asthma Report |
| GBD | Global Burden of Disease Study |
| GNI | Gross National Income |
| GWAS | Genome-wide association study |
| IgE | Immunoglobulin E (antibody) |
| IQR | Inter-quartile range |
| IUATLD | International Union Against Tuberculosis and Lung Disease |
| ISAAC | International Study of Asthma and Allergies in Childhood |
| MAR | Missing at random |
| MCAR | Missing completely at random |
| MCMC | Markov chain Monte Carlo |
| MeDALL | Mechanisms of the Development of Allergy Study |

| | |
|---|---|
| MNAR | Missing not at random |
| MRC | Medical Research Council |
| N | Number in sample |
| NSAID | Non-steroidal anti-inflammatory drug |
| OR | Odds ratio |
| PAF | Population attributable fraction |
| PCA | Principal components analysis |
| PIPPA Tamariki | Paracetamol and Ibuprofen in Primary Prevention of Asthma in Tamariki |
| RC | Rhinoconjunctivitis |
| SD | Standard deviation |
| SE | Standard Error |
| SES | Socio-economic status |
| Th1 | T helper cell 1 |
| Th2 | T helper cell 2 |
| TV | Television |
| UK | United Kingdom |
| UN | United Nations |
| WHO | World Health Organization |

# 1 Introduction

## Summary

Asthma, eczema and rhinoconjunctivitis are common diseases that affect both children and adults. However, there is still a great deal that is unknown about their causes, and factors that affect their population distribution. This has in part been due to a lack of globally comparable data on geographic patterns and time trends, and their determinants.

This thesis aims to explore this gap by using data from the International Study of Asthma and Allergies in Childhood (ISAAC) and the Global Asthma Network (GAN). Methods are compared and developed for complex multi-level modelling of international data on symptoms and risk factors, to explore global patterns and time trends in prevalence. The focus is on asthma, but some analyses also include data on eczema and rhinoconjunctivitis.

## 1.1 Introduction

Asthma is a chronic disease involving inflammation of the airways. Although it is often considered to be primarily a disease of high income countries, there is now a large burden of asthma in many low- and middle-income countries where health care resources for this chronic disease may not be readily available.[1] The prevalence of asthma varies dramatically throughout the world and the reasons for this are not fully understood.

This thesis uses data from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase I and III surveys,[2,3] and the Global Asthma Network (GAN) Phase I survey[4]. These are large cross-sectional studies involving more than 100 countries. The aim is to model the international patterns and time trends, and also to assess which risk factors may explain these patterns. The focus is on asthma, but these studies have also collected data on eczema and rhinoconjunctivitis, and these will also be considered in some analyses.

These studies involve hundreds of thousands of individual participants, but these are nested within schools, within centres and within countries as well as at different time points for each phase. The unique structure makes it possible to analyse associations at each of these different levels, each with its own interpretation. Similar results at multiple levels could provide more evidence for a causal effect as each level is susceptible to different forms of bias and confounding. Existing and novel methods are compared, to analyse such multi-level data, in order to investigate the role of different risk factors in the three diseases and how this varies around the world and over time. This starts with cross-sectional analyses of the ISAAC Phase III data, which is the largest individual phase, and in further analyses, incorporates the ISAAC Phase I and GAN Phase I survey data in order to analyse the time trends. Chapter 2 describes these studies in detail.

## 1.2 Asthma, rhinoconjunctivitis and eczema

Asthma is a non-communicable chronic disease involving inflammation of the airways.[1] The most common symptom of asthma is wheeze, but other symptoms include breathlessness, chest tightening and coughing.[1] An estimated global prevalence of asthma across all ages from the 2017 GBD (Global Burden of Disease) study is 3.6%, varying from 2.4% in South Asia to 5.3% in High-income countries.[5] Asthma affects both adults and children, but prevalence peaks at about age 5-9 years[5]. Asthma is often considered to be a "Western" disease, i.e. a problem of the developed world, but there is now a large burden of asthma in many low- and middle-income countries.[6] However, much of the existing research into the causes of asthma is based on patients from English speaking countries, that are not representative of the situation globally.[6] Thus, conducting global studies to compare countries with different exposure patterns and prevalence rates, not only provides a picture of how the burden differs around the world, but also provides an opportunity to learn more about the aetiology of and risk factors for asthma.

Eczema, also known as atopic dermatitis, is a chronic inflammatory skin disease that often "runs in families" with other allergies.[7] It can start in infancy, often on the face and limbs, but later presentations are more often in flexural regions such as the backs of knees, armpits, elbows and neck. Typically, a dry red itchy rash which comes and goes, more severe cases can be over large areas and can include weeping, crusting and bleeding.[7] First line treatments include emollients for prevention of flare ups and corticosteroids.[7] It is estimated that up to

20% of children in high income countries have eczema at some point during their life and there is evidence that rates are increasing in low and middle income countries.[8]

Rhinoconjunctivitis is a common chronic condition involving inflammation of the nasal membranes and eyes. It often affects children and adolescents and can interfere with school performance and sleep.[9] Symptoms include nasal congestion, runny nose, post-nasal drip, sneezing, red eyes, and itchy nose or eyes, that are not viral or infectious in origin.[9]

## 1.3 Risk factors

Asthma is a complex disease and its epidemiology and aetiology are not fully understood. The situation is further complicated because some factors may be risk factors for developing asthma, whereas others may cause asthma exacerbations once someone has the condition. Risk factors could be genetic, environmental or lifestyle-related. Here the focus is on existing evidence for possible risk factors in children and adolescents. This is not a comprehensive review, but rather introduces some of the key risk factors that will feature in later analyses.

It is well known that family history of asthma is indicative of higher risk of asthma in an individual, but it is not yet known how much of this is genetic or environmental, as family members tend to have similar lifestyles and exposure to allergens, as well as having similar genes. GWAS (Genome-wide association studies) and candidate gene studies have identified some loci that are associated with asthma, but few that are consistently replicated or that account for a substantial proportion of disease. This is probably due to the complexity of asthma, with multiple genes and environmental exposures playing a role, and with the sensitivity and specificity of many measures of asthma being relatively low.[10]

Demographic factors associated with childhood asthma include age, sex and ethnicity, of which age is the strongest. Symptoms of asthma may emerge in pre-school years, becoming more common in pre-adolescent children and then often wane.

Diet has been investigated in many asthma studies. Breastfeeding has been shown to be both protective and a risk factor in different studies. Some observational studies have shown a protective effect of eating fruits and vegetables, whole grains and fish.[10] However, studies on dietary supplements with similar nutrients have not shown convincing evidence of an effect, so it is possible that many of the associations with dietary factors may be due to confounding by other aspects of lifestyle.[10] There is some evidence that obesity is associated with asthma but

again this is not consistent across all studies. It is possible that obesity may also be an exacerbating factor due to the extra strain put on the pulmonary system.[10]

There is some evidence that ozone, PM2.5, soot and $NO_2$ are associated with increased asthma symptoms, but lesser evidence that outdoor air pollution is a risk factor for the onset of asthma. Indoor air pollution may also play a role. In particular, there may be an impact on asthma from $NO_2$ or $SO_2$ from burning fossil fuels or particulates from burning wood, as well as fungal exposure from damp housing.[10] Tobacco smoke exposure, both active and passive, has been considered in many studies, and the evidence to date indicates that passive tobacco smoke exposure is very likely to exacerbate symptoms of asthma in children but the evidence for causing the onset of asthma is less clear. Similar results have been shown for personal smoking, although this is not usually an issue for younger children.[10]

Respiratory viral infections are known to exacerbate asthma symptoms, but the evidence is less clear as to whether viral infections can affect the initial incidence of asthma. The potential mechanisms are not understood but are thought to involve an impaired immune response.[10]

Antibiotics have been hypothesised to affect the onset of asthma via the “hygiene hypothesis”. This states that lower microbial exposure at a young age can increase the risk of both allergies and asthma. Many studies have shown evidence that early use of antibiotics is associated with a higher risk of asthma, including a dose response relationship, but other large studies have shown conflicting results so as of yet there is no consensus.[10]

Paracetamol (also known as acetaminophen) is another medication with considerable evidence that early use can increase the risk of both asthma onset and worsening of symptoms. The mechanism is not understood, and there has been concern that associations may be due to unmeasured confounding or reverse causation. Comparison of studies has been complicated by the cessation of aspirin use in children since the 1970s, due to the association of aspirin use with Reye’s syndrome. The alternative has generally been paracetamol, but ibuprofen is becoming more popular as a first line treatment in young children.[10]

Indoor allergens such as house dust mites have been extensively studied. It is well known that for asthmatics sensitive to these allergens, acute exposure can trigger an asthma attack and prolonged exposure can lead to worsening of symptoms. However, most studies only show weak associations between exposure to dust mites and current asthma, indicating that a

causal effect on the onset of asthma is unlikely. For other indoor allergens such as dog, cat or cockroach, the evidence of an association with onset of asthma is even weaker.[10]

For childhood eczema, many environmental risk factors are similar to those of asthma. These include obesity and tobacco smoke, and the possible protective effects of breastfeeding and a diet including fresh fruits and fish.[11] Other factors that exacerbate symptoms of eczema are skin irritants, cold temperature, hard water and low humidity, whereas UV light is thought to be protective.[11] For underlying causes there is considerable evidence that genetic polymorphisms in genes affecting filaggrin (a skin barrier protein) are associated with higher risk of eczema, though it is considered that environmental factors are also required to cause disease onset.[11,12]

Risk factors for rhinitis differ by type. The main trigger for seasonal rhinoconjunctivitis (or hay fever) in susceptible people is pollen, although in tropical regions this can manifest as a perennial problem.[13] Mould, animal dander, dust mites and air pollution have been shown to be associated with increased risk of perennial rhinitis and rhinoconjunctivitis, but it is not clear if they affect initial sensitisation or just exacerbate symptoms in susceptible individuals. Genetics may also play a part, as family history is strongly associated with risk of disease. However, similar to asthma, no specific mutations have consistently been shown to have a significant effect and it is possible some of the association is due to similar environment and lifestyles within families. Early-life infections (bacterial or viral) could be protective, as part of the hygiene hypothesis for allergy.[14] Allergic rhinitis has been linked to asthma as part of the united allergic airway theory given its similar risk factors and links to atopy.[15]

Thus, despite the thousands of studies completed, it is still not clearly understood which risk factors actually affect the onset of these diseases, or whether the observed associations are causal, or arise from confounding or reverse causation. Analyses of international patterns and time trends can play a key role in increasing our understanding of these issues. These analyses not only provide key descriptive information as to the global and regional burdens but they can also contribute to our understanding of asthma aetiology and causes. For example, studies at the individual level may be biased due to inaccurate recall, or reverse causation (e.g. if parents get rid of the family cat if a child becomes sensitised). Population level studies can in part remove these biases, but in turn they may suffer from population-level confounding (the ecological fallacy), and lack of individual exposure data.

## 1.4 Time trends

Over recent decades, affluent countries have had the highest levels of asthma symptom prevalence, and it has been suggested that prevalence is increasing over time. Because of this high burden, along with available resources, most studies were conducted in these affluent countries. It was believed that asthma was also increasing in less affluent countries, but this was hard to determine without standardised studies repeated at different time points. In addition, there are major problems with studies that involve diagnosed asthma, for which differences in prevalence could be partly explained by international differences in access to health care and in diagnostic practice.[10]

The time trends in the ISAAC Phase I and Phase III studies, conducted during 1992-2005, are described in more detail in the next chapter. These show that asthma prevalence peaked in affluent countries but continued to rise in non-affluent countries during this period.[16] Though this was the largest study of its type to look at childhood asthma, this was over 15 years ago and updated estimates are needed.

There are very few more recent studies and all in single areas. A Netherlands study, using medical records between 2000-2012 showed prevalence of asthma in school-aged children increased up to 2008 followed by weak evidence of a decrease from 2008-2012.[17] In Brazil, using data from a nationally representative survey, the prevalence of asthma between 1998-2008 increased from 7.7% to 8.5% in children and 4.4% to 5.5% in adolescents, with the highest increases in boys within rural areas.[18] In Sweden, a study between 1996-2008 showed that a previous increasing prevalence of current wheeze in 7-8-year-olds had plateaued overall, though sub-analysis showed an increase for boys and a decrease for girls.[19] A study in Norway of children aged 7-14 showed that the prevalence of current asthma and current eczema symptoms more than doubled between 1995 and 2008, and the prevalence of rhinoconjunctivitis symptoms tripled in the same time period.[20]

It is only recently, that the work of ISAAC has been continued under the Global Asthma Network (GAN). Phase I of this study, though smaller in scale than ISAAC, included data from over 50 centres across 20 countries[21] using the same methodologies as ISAAC[2-4] to allow for analysis of further time trends.

## 1.5 Aims and objectives

This is a biostatistical PhD, but with a focus on applying appropriate methods to the analysis of data from ISAAC and GAN. The overall aim is to compare and develop methods for complex multi-level modelling of data containing multiple exposures, ages, clusters, regions and time points. The specific objectives are as follows:

**Objective 1: Investigate the role of bias due to reverse causation within cross-sectional data for risk factors of asthma, eczema and rhinoconjunctivitis, by utilising cluster information.**
Questions have arisen about the potential role of reverse causation in some previously identified risk factors for the three diseases being considered. An example is regular paracetamol use. Does paracetamol have a direct effect on future symptoms or could it be due to NSAID avoidance in families with asthma sufferers, or pain relief for symptoms in eczema (confounding by indication)? This is investigated using school-level exposure prevalence. The assumption is that if individuals who have asthma change their behaviour regarding the risk factor then their individual exposure values will change, but there would be little change expected at the school (cluster) level as the proportion of people with asthma symptoms is quite small. Thus, if the association is still evident using school-level exposures then this is less likely to be due to reverse causation.

**Objective 2: Incorporate newly available data to estimate time trends in global symptom prevalence and differences around the world.**
Prepare data from GAN Phase I to incorporate with existing ISAAC data on asthma symptoms. Assess time trends at the centre level and identify patterns globally. This involves collapsing the data to centre level within each study phase to assess changes over time.

**Objective 3: Estimate the effects of risk factors on time trends in symptom prevalence, even when some clusters have missing time points.**
Use appropriate methods to model the partial data available, to utilise the maximum available information, in order to assess the effects of risk factors and centre-level data on time trends in asthma symptom prevalence.

**Objective 4: Use modelled time trends to estimate an up to date prevalence of symptoms for all studies that have taken part in multiple ISAAC/GAN studies, even those that did not complete the most recent phase.**

Fit the most appropriate models of the time trends in prevalence, including identified risk factor covariates, and use model predictions to form up-to-date prevalence estimates of asthma symptoms around the world.

## 1.6 Outline of thesis

This thesis is a single document, but incorporates four published papers, two together as part of Chapter 3, one in Chapter 4 and one in Chapter 5. Each paper is prefaced with a cover sheet and has been reformatted to fit the style of the thesis. The appendices include two further papers, one published (Appendix D) and one submitted (Appendix E), along with a list of all relevant papers written or co-written by the author during the work of the PhD (Appendix A). Evidence of copyright retention for all 5 published papers is listed in Appendix B.

References are included in Vancouver style with one bibliography at the end, for the main document and appendices together.

This first chapter has covered the rationale for the thesis and the aims and objectives along with brief outlines of the diseases and their risk factors.

Chapter 2 describes the study data used, including the author's role in the GAN study, and summarises previously published findings.

Chapter 3 investigates the role of reverse causation in risk factors identified in ISAAC, as per Objective 1. It includes two published papers on asthma and eczema plus additional unpublished findings on rhinoconjunctivitis.

Chapter 4 brings together the different results from Chapter 3 with a published paper synthesising the findings from the three diseases.

Chapter 5 addresses Objective 2, adding the ISAAC Phase I data along with new data from GAN Phase I to assess the global time trends in asthma prevalence. This chapter consists of a published paper with similar published and submitted papers for rhinoconjunctivitis and eczema in Appendices D and E.

Chapter 6 incorporates centre-level risk factor prevalence data to identify which risk factors are associated with centre-level asthma symptom prevalence and with trends in prevalence over time, to address Objective 3.

Chapter 7 takes the modelling from Chapters 5 and 6 a step further to identify the best method to predict estimates of up-to-date asthma symptom prevalence, including centres with only partial time trends data, to meet Objective 4.

Chapter 8 brings together the results from previous chapters to draw more general conclusions, discuss the strengths and weaknesses of the data, highlight statistical issues in the work and discuss opportunities for future research.

# 2 Study Data from ISAAC (International Study of Asthma and Allergies in Childhood) and GAN (Global Asthma Network)

## Summary

This chapter describes the methods and main results from ISAAC and GAN so far. Firstly, there are summaries of each of the three ISAAC phases, their study designs, and study findings.

Secondly, the methods for GAN are described along with the author's contribution to the study. The initial results from GAN are summarised from recently published co-authored papers.

Finally, findings from previous analyses of time trends across ISAAC Phases I and III are summarised.

## 2.1 Introduction

The International Study of Asthma and Allergies in Children (ISAAC) was established in 1991 in response to concerns about increasing asthma, eczema and rhinitis around the world. Its main aims were to compare prevalence and severity of the three diseases between countries, monitor trends over time and investigate other factors affecting these diseases[2]. The main outcomes were based on symptoms rather than diagnoses to avoid bias from differing levels and priorities of healthcare around the world.

ISAAC was a large worldwide collaborative research project into asthma involving over 100 countries and nearly 2 million children.[22] The study included multiple phases over more than a decade. Phase I involved a global cross-sectional survey on symptoms of asthma, eczema and rhinoconjunctivitis. Phase II was a more in depth study in fewer centres, involving objective clinical and laboratory tests for allergy alongside questions on symptoms, treatments and risk factors. Phase III was a repeat of Phase I but expanded to include a questionnaire on potential risk factors.

The Global Asthma Network (GAN), established in 2015, followed on from where ISAAC finished, using the same methodology and some of the same personnel. GAN Phase I involved similar surveys to ISAAC Phase III but with further expansion to an adult age group using parents/guardians of participating children and adolescents.[4] Fieldwork recently completed in 2020.

The key is that all centres used a standardised methodology, and double translated questionnaires, to administer the surveys across all phases of both studies so that results were comparable across geography and time.

## 2.2 ISAAC Phase I

### 2.2.1 Methods

Individual centres registered to be included in ISAAC Phase I, which took place during 1992-1995. There was no selection process other than the ability to comply with the study rules. Each centre completed surveys on symptoms and treatments of disease for adolescents aged 13-14 years and optionally for children aged 6-7 years. Schools were randomly selected from all schools within a defined geographical area. Within each school, all students within the age group (or appropriate class/grade) were invited to participate.

Adolescents were asked to complete the questionnaire themselves at school, and for the younger age group, questionnaires were sent home for parents/guardians to complete on the child's behalf. More details on the methods are available.[2]

The most common outcomes used were symptom prevalence of the three conditions of asthma, eczema and rhinoconjunctivitis, defined as follows:

1. Current asthma symptoms, defined as wheeze in the last 12 months, required a positive response to the question "Have you (has your child) had wheezing or whistling in the chest in the past 12 months?"

2. Current eczema symptoms, defined as flexural rash in the last 12 months, required positive responses to the two questions "Have you (has this child) had this itchy rash at any time in the past 12 months?" [itchy rash defined in previous questions as an itchy rash which was coming and going for at least six months] and "Has this itchy rash at

any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?".

3. Current rhinoconjunctivitis symptoms, defined as symptoms in the last 12 months, required positive responses to the two questions "In the past 12 months, have you (has this child) had a problem with sneezing, or a runny or blocked nose when you (he/she) did not have a cold or the flu?" and "In the past 12 months, has this (child's) nose problem been accompanied by itchy-watery eyes?".

### 2.2.2 Results overview

There were 463,801 participating adolescents, in 156 centres within 56 countries. In the younger age group there were 257,800 participants, in 91 centres within 38 countries.[23]

There were 24 papers published on worldwide ISAAC Phase I analyses, with over 200 additional papers at a regional or country level. Generally, the prevalence of the three disease symptoms varied significantly across the world.

Prevalence of asthma symptoms in adolescents varied by centre from 1.9% in Jima, Ethiopia to 36.7% in Scotland, UK with an average of 13.8%.[16] The highest rates (>20%) were seen in English speaking countries (Australia, Canada, New Zealand, United Kingdom, United States of America) and lower rates (<10%) in Asia, Northern Africa and Eastern Europe.[16] For children, the average was 11.8%, varying by centre (and country) from 4.1% in Bandung, Indonesia to 32.1% in Costa Rica (whole country study).[16] Regions with the lowest rates (from 5-10%) were Asia, Eastern Mediterranean and Europe and the highest rate (25%) was Oceania.[16]

For eczema, prevalence of symptoms in adolescents varied by centre from 0.8% in Tiranë, Albania to 19.9% in Addis Ababa, Ethiopia[24] with an average of 7.4%. The most prevalent regions were >10% in Africa and Oceania and the least prevalent were <5% in Asia.[24] In children, eczema symptom prevalence varied from 0.8% in Tehran, Iran to 18.4% in Stockholm and Uppsala, Sweden[24] with an average of 7.1%. The region with highest prevalence of >10% was Oceania and the lowest prevalence of <5% were South-East Asia and the Eastern Mediterranean.[24]

Mean prevalence of rhinoconjunctivitis symptoms in adolescents was 13.4% ranging from 1.4% in Akola, India to 39.7% in Ibadan, Nigeria.[25] The most prevalent regions were North America and Oceania at just under 20%; the least prevalent region was South Asia at 6%. For children,

rhinoconjunctivitis symptom prevalence averaged 6.8% ranging from 0.8% in Akola, India to 14.9% in Perth, Australia.[25] The most prevalent regions were North America and Oceania at just over 10%; the least prevalent regions were Eastern Mediterranean and South Asia at <5%.[25]

With additional country level data on environmental factors the ISAAC Phase I study group were able to identify population level associations between asthma symptom prevalence and Gross National Product, smoking, trans-fatty acids and immunisations, among other things.[26-29]

## 2.3 ISAAC Phase II

### 2.3.1 Methods

ISAAC Phase II commenced in 1998, took place in 30 selected centres in 22 countries and aimed for at least 1,000 participants per centre.[30] This was a smaller but more detailed study which compared the use of objective markers of allergy to reported symptoms and looked for genetic factors that may influence these. In addition, following hypotheses of interest from the ISAAC Phase I ecological analyses, there were investigations into using symptom data along with that of risk factors at an individual level.

One age group of 8-12 years was chosen, in between the two previous age groups from Phase I. Objective measures taken included a hypertonic saline aerosol challenge, skin prick tests for atopy (common seasonal and perennial allergens plus optional allergens of local relevance), serum IgE, blood samples for genetic analysis, and a physical skin exam for flexural dermatitis. A questionnaire on symptoms and treatment of asthma, eczema and rhinitis, similar to that in ISAAC Phase I, and a further detailed questionnaire on environmental risk factors were also completed by a parent/guardian.[30]

### 2.3.2 Results overview

There were 54,439 participants across the 30 centres, though in some centres the objective tests were only available for a random sub-sample; 31,759 for skin prick tests and 8,951 for serum antibodies. Prevalence of atopy, defined by positive reaction to at least one allergen in the skin prick test, ranged from 1.7% in Kintampo, Ghana to 45.3% in Hong Kong, China. Raised IgE levels varied from 16.7% in Tallinn, Estonia to 48.5% in Almeria, Spain.[31]

The prevalence of current asthma symptoms based on questionnaire response ranged from 0.8% in Pichincha, Ecuador to 25.6% in Uruguaiana, Brazil. There was evidence of a positive

association between skin test positivity and asthma symptoms in nearly all centres. This was strongest in affluent countries with a combined OR of 4.0 (95% CI = 3.5, 4.6) compared to 2.2 (1.5, 3.3) in non-affluent countries.[31]

Current rhinoconjunctivitis symptoms (questionnaire-based) ranged from 1.5% in Pichincha, Ecuador to 24.5% in Almeria, Spain. Skin sensitivity to perennial airborne allergens varied from 1.4% in Kintampo, Ghana to 45.2% in Hong Kong, China, and to seasonal allergens from 9.1% in Kintampo, Ghana to 25.8% in Tromsø, Norway.[32]

The prevalence of current eczema symptoms (flexural rash identified in the skin exam) ranged from 0.4% in Kintampo, Ghana to 14.2% in Östersund, Sweden. The OR for current eczema symptoms in atopic individuals compared to non-atopic ranged from 0.74 (95% CI 0.31, 1.81) in Pichincha, Ecuador to 4.53 (1.72,11.93) in Madrid, Spain, after adjustment for age and sex. In general, affluent countries showed a stronger association than non-affluent; the combined OR (adjusted for age and sex) for centres in affluent countries was 2.69 (2.31, 3.13) and non-affluent was 1.17 (0.81, 1.70). Similar analysis using the questionnaire-derived definition of current eczema symptoms (which takes into account any flexural rash over the past 12 months) showed consistent results: affluent countries 2.03 (1.84, 2.23) and non-affluent 1.36 (1.07, 1.74).[33]

Overall, atopy explains some of the patterns in symptoms of asthma, eczema and rhinoconjunctivitis, but there is a large amount that remains unexplained at a global level.

Environmental factors were considered at an individual level for their effect on between centre differences in the prevalence of current asthma symptoms. When considered singly the amount of between centre variation that was explained by each risk factor was up to 8.4% (for current use of a synthetic quilt). In total there were 15 factors that could each explain more than 2% of the variation, although some others increased the amount of unexplained variation. However, when all influential risk factors were included together in the model, the total amount of unexplained variation actually increased by 2.4%. After including a measure of atopy as well, this resulted in an overall small decrease in unexplained variation of 0.4%.[34]

There was little evidence of genetic factors influencing both asthma symptoms and atopy.[35]

The data from Phase II are not directly comparable to the other phases, as the age group was different along with many of the measurements, and will not be analysed in this thesis.

## 2.4 ISAAC Phase III

### 2.4.1 Methods

Phase III took place between 2001 to 2003 and was expanded to include an optional environmental questionnaire with questions on home environment, lifestyle and diet. Centres that completed Phase I were invited to complete Phase III and additionally other new centres were able to register for Phase III. Each centre completed a new randomisation of schools to include, but otherwise followed the same procedures as for Phase I.[3]

Similar to Phase I, the younger age group of 6-7-year-olds was optional for centres, and the questionnaire was completed by their parents/carers. The environmental questionnaire for this age group additionally included questions on early life. These were not included for the older age group as the 13-14-year-olds were unlikely to know the answers themselves.[3]

### 2.4.2 Results overview

In total, 798,685 adolescents aged 13-14 years from 233 centres in 97 countries and 388,811 children aged 6-7 years from 144 centres in 61 countries took part in the study.

The prevalence of asthma symptoms in adolescents ranged from 0.8% in Tibet, China to 32.6% in Wellington, New Zealand, averaging 14.1%. In children, the prevalence was 11.5% on average and ranged from 2.4% in Jodhpur, India to 37.6% in Costa Rica (whole country study).[36] Overall, there was higher prevalence of asthma symptoms in higher income countries but the proportion of those with severe asthma symptoms was higher in lower income countries.[36]

The prevalence of eczema symptoms in adolescents ranged from 0.2% in Tibet, China to 24.6% in Barranquilla, Colombia with an average of 7.3%. In children, eczema symptom prevalence ranged from 0.9% in Jodhpur, India to 22.3% in Quito, Ecuador with an average of 7.9%.[7] Prevalence of rhinoconjunctivitis symptoms in adolescents was 14.6% on average, ranging from 1.0% in Davangere, India to 45% in Asunción, Paraguay. In children rhinoconjunctivitis symptom prevalence ranged from 1.8% in Davangere and Pune, in India to 24.2% in Taipei, Taiwan with an average of 8.5%.[37]

The environmental questionnaire was completed by 337,226 adolescents (from 116 centres in 52 countries) and 210,200 children (from 74 centres in 31 countries). Separate analyses were produced for a number of different individual level risk factors from the environmental

questionnaire and their association with the main outcomes.[38-51] Although analysis methods used in these papers were similar to each other, there were differences in covariates/confounders included in the models, which makes it harder to compare results directly, though all analyses did adjust for region, sex, language and gross national income (GNI). Tables 2.1 and 2.2 show the summarised findings of the most adjusted available model for each age group from the relevant risk factor paper, but without details of the amount of adjustment. More detailed summaries of the main risk factor findings from ISAAC Phase III papers (including adjustment information) are in Appendix C.

**Age 6-7 findings**

Details are in Table 2.1. Paracetamol given in the 1st year of life showed associations with symptoms of asthma (OR 1.46; 95% CI 1.36, 1.56), eczema (1.48; 1.38, 1.60) and rhinoconjunctivitis (1.35; 1.26, 1.45) even after adjustment for a number of other risk factors.[38]

Current paracetamol use (at least once a month over the past 12 months) was positively associated with asthma (3.23; 2.91, 3.60), eczema (2.81; 2.52, 3.14) and rhinoconjunctivitis (1.87; 1.68, 2.08) symptoms.[38]

Both frequent and all-day truck traffic, compared to none, showed positive associations with the three outcomes even after adjusting for some other confounders.[39]

The use of antibiotics in the first year of life showed strong evidence of associations with asthma symptoms (1.70; 1.60, 1.80), eczema symptoms (1.56; 1.46, 1.66) and rhinoconjunctivitis symptoms (1.42; 1.33, 1.51) after adjusting for other risk factors.[40]

Breastfeeding showed a weak association with asthma symptoms which disappeared with further adjustment of confounders and no evidence of association with the other two outcomes.[41]

Contact with farm animals, both in the first year of life or maternal contact while pregnant, showed a weak association with asthma symptoms and stronger associations with eczema and rhinoconjunctivitis after adjusting for lots of confounders.[42]

There was no evidence that currently owning a cat or dog or having contact with dogs in the first year of life were associated with any of the outcomes. However, contact with cats in the

first year of life showed an association with asthma symptoms (1.17; 1.09, 1.26) after adjustment for many other factors.[43]

There were many different analyses based on parental tobacco use but they all only adjusted for the minimal number of covariates. From this there was strong evidence that asthma symptoms were associated with maternal smoking, both current smoking (1.28; 1.22, 1.34) and smoking in the first year of life (1.36; 1.29, 1.43) and also with paternal current smoking but to a lesser extent (1.17; 1.12, 1.21). There were slightly weaker associations with eczema and rhinoconjunctivitis symptoms.[44]

Looking at BMI there was some evidence that being overweight or obese was associated with asthma but not eczema symptoms. Only being obese, not overweight, was associated with rhinoconjunctivitis symptoms. These analyses did not adjust for many other factors except exercise and TV viewing.[45]

Exercising three or more times a week (compared to less frequently) was protectively associated with asthma symptoms (0.83; 0.76, 0.91) but not with eczema or rhinoconjunctivitis symptoms. Again this only adjusted for the few factors of BMI and TV viewing.[45]

Excessive TV viewing (5 hours or more per day compared to less than 1 hour per day) was associated with asthma symptoms (1.26; 1.07, 1.47) but there was no evidence of associations with symptoms of eczema or rhinoconjunctivitis.[45]

There were many dietary factors considered but the only ones that showed evidence of strong associations were fast food three or more times a week for asthma (1.17; 1.08, 1.27) and eczema symptoms (1.20; 1.11, 1.31) and both eggs and milk at least once a week were protective for all three outcomes.[46]

There was very strong evidence that cooking on an open fire was associated with symptoms of asthma (1.51; 1.25, 1.81) after adjustment for many factors, but no evidence of associations for the other outcomes.[47]

The only association found with birthweight was that low birthweight (<2.5kg) was associated with increased odds of asthma symptoms (1.20; 1.12, 1.30), but this analysis only adjusted for the minimal adjustments plus mother smoking in the first year of life.[48]

*Table 2.1 Reference table of reported main ISAAC Phase III results for 6-7 year-olds*

| Risk Factor | Asthma symptoms | | Eczema symptoms | | Rhinoconjunctivitis symptoms | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Paracetamol in 1st year[38] | 1.46 | 1.36-1.56 | 1.48 | 1.38-1.60 | 1.35 | 1.26-1.45 |
| Paracetamol in last 12 months (once per month vs none)[38] | 3.23 | 2.91-3.60 | 2.81 | 2.52-3.14 | 1.87 | 1.68-2.08 |
| Truck traffic – all day vs never[39] | 1.35 | 1.22-1.48 | 1.33 | 1.20-1.48 | 1.36 | 1.23-1.50 |
| Truck traffic – frequently vs never[39] | 1.27 | 1.17-1.38 | 1.14 | 1.05-1.24 | 1.18 | 1.09-1.28 |
| Antibiotics in 1st year[40] | 1.70 | 1.60-1.80 | 1.56 | 1.46-1.66 | 1.42 | 1.33-1.51 |
| Breastfeeding[41] | 0.99 | 0.92-1.05 | 1.00 | 0.93-1.08 | 1.05 | 0.97-1.12 |
| Farm animals in 1st year[42] | 1.09 | 1.00-1.18 | 1.18 | 1.08-1.30 | 1.16 | 1.07-1.27 |
| Pregnant mother contact with farm animals[42] | 1.13 | 1.03-1.24 | 1.24 | 1.12-1.37 | 1.17 | 1.07-1.29 |
| Cats 1st year of life[43] | 1.17 | 1.09-1.26 | 1.09 | 1.00-1.18 | 1.09 | 1.01-1.17 |
| Cats currently[43] | 1.07 | 1.00-1.14 | 1.07 | 0.99-1.15 | 1.05 | 0.98-1.12 |
| Dogs 1st year of life[43] | 1.03 | 0.97-1.09 | 1.06 | 0.99-1.14 | 1.04 | 0.97-1.10 |
| Dogs currently[43] | 0.98 | 0.92-1.04 | 1.03 | 0.96-1.10 | 1.03 | 0.97-1.09 |
| Father currently smokes[44] | 1.17 | 1.12-1.21 | 1.08 | 1.04-1.13 | 1.09 | 1.04-1.13 |
| Mother currently smokes[44] | 1.28 | 1.22-1.34 | 1.12 | 1.06-1.18 | 1.15 | 1.09-1.21 |
| Mother smoked 1st year of life[44] | 1.36 | 1.29-1.43 | 1.17 | 1.10-1.24 | 1.20 | 1.13-1.27 |
| Overweight (BMI) vs normal[45] | 1.20 | 1.09-1.31 | 0.99 | 0.91-1.09 | 1.08 | 0.98-1.19 |
| Obese (BMI) vs normal[45] | 1.27 | 1.12-1.44 | 0.99 | 0.87-1.12 | 1.20 | 1.05-1.37 |
| Exercise 3+ times a week vs none[45] | 0.83 | 0.76-0.91 | 0.98 | 0.89-1.07 | 0.97 | 0.88-1.06 |
| TV viewing 5hrs+ per day vs less than 1hr[45] | 1.26 | 1.07-1.47 | 1.05 | 0.90-1.23 | 1.02 | 0.86-1.20 |
| Fast food (3+ times a week vs never or occasionally)[46] | 1.17 | 1.08-1.27 | 1.20 | 1.11-1.31 | 1.04 | 0.95-1.14 |
| Eggs (once or twice a week vs never or occasionally[46] | 0.80 | 0.75-0.85 | 0.82 | 0.76-0.88 | 0.78 | 0.73-0.84 |
| Milk (3+ times a week vs occasionally)[46] | 0.83 | 0.76-0.90 | 0.77 | 0.71-0.85 | 0.73 | 0.67-0.79 |
| Any open fire cooking[47] | 1.51 | 1.25-1.81 | 1.06 | 0.86-1.30 | 1.14 | 0.96-1.35 |
| Low birthweight (<2.5kg vs 3-4kg)[48] | 1.20 | 1.12-1.30 | 1.08 | 1.00-1.17 | 0.93 | 0.85-1.01 |
| Migration[49] | 0.87 | 0.77-0.98 | 0.93 | 0.81-1.06 | 0.80 | 0.70-0.91 |
| Siblings, each extra older sibling[50] | 1.01 | 0.99-1.03 | 0.98 | 0.96-1.00 | 0.98 | 0.96-1.00 |
| Siblings, each extra younger sibling[50] | 0.96 | 0.93-0.98 | 1.06 | 1.03-1.09 | 1.03 | 1.00-1.06 |

There was a protective association with being a recent migrant on symptoms of rhinoconjunctivitis (0.80; 0.70, 0.91), with weak evidence of similar for asthma and no evidence of an association with eczema symptoms, after adjustment for other factors.[49]

Each additional younger sibling was associated with a small decrease in risk of asthma symptoms (0.96; 0.93, 0.98) and a small increase in risk of eczema symptoms (1.06; 1.03, 1.09), but no effect on symptoms of rhinoconjunctivitis; there was no evidence that number of older siblings was associated with symptoms of any of the three diseases.[50]

**Age 13-14 findings**

There were fewer risk factors available for the adolescents as the early life questions were not included. Details are in Table 2.2.

Similarly to the younger age group, frequent or all-day truck traffic showed an association with the three outcomes even after adjusting for some other confounders.[39]

Current use of paracetamol showed a strong association with all three outcomes at both the medium and higher level (at least once per year or once per month). The high level compared to none showed around a doubling of odds for symptoms; asthma (2.51; 2.33, 2.70), eczema (2.39; 2.24, 2.55) and rhinoconjunctivitis (1.99; 1.82, 2.16), after adjusting for other factors.[51]

There was some evidence that currently owning a cat was associated with rhinoconjunctivitis symptoms (1.23; 1.15, 1.32) but only weak evidence for the other outcomes after adjustment for many other factors. This was similar for currently owning a dog.[43]

There was strong evidence of associations across the outcomes with mothers and fathers who currently smoke. This increased further when both parents smoked. The highest individual effect was mother smoking on asthma symptoms (1.32; 1.26, 1.37). However, this paper only used minimal adjustment.[44]

Having a high BMI (overweight or obese) was associated with asthma and rhinoconjunctivitis symptoms but not eczema symptoms, when compared to normal BMI.[45]

Perhaps unexpectedly, exercising either once or twice a week, or three times a week was associated with an increased risk of asthma, eczema and rhinoconjunctivitis symptoms (the

ORs varied from 1.18 to 1.27). This analysis did not adjust for many extra variables, only BMI and TV watching, along with the minimal adjustments.[45]

There were associations between high levels of TV viewing (5hrs or more per day) and both eczema symptoms (1.16; 1.06, 1.28) and rhinoconjunctivitis symptoms (1.17; 1.09, 1.26) but only marginally for asthma symptoms (1.08; 1.00, 1.17), but again these didn't adjust for many confounding risk factors.[45]

Looking at a number of dietary factors the only one with strong effects was fast food three or more times a week compared to never or occasionally; asthma (1.25; 1.18, 1.33), eczema (1.21; 1.14, 1.28) and rhinoconjunctivitis (1.20; 1.11, 1.28) symptoms after adjustment for a few factors.[46]

*Table 2.2 Reference table of reported main ISAAC Phase III results for 13-14 year-olds*

| Risk Factor | Asthma symptoms | | Eczema symptoms | | Rhinoconjunctivitis symptoms | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | OR | 95% CI | OR | 95% CI |
| Paracetamol in last 12 months (once per month vs none)[51] | 2.51 | 2.33-2.70 | 2.39 | 2.24-2.55 | 1.99 | 1.82-2.16 |
| Truck traffic – all day vs never[39] | 1.35 | 1.23-1.49 | 1.39 | 1.27-1.52 | 1.54 | 1.37-1.73 |
| Truck traffic – frequently vs never[39] | 1.24 | 1.13-1.35 | 1.21 | 1.12-1.32 | 1.30 | 1.17-1.45 |
| Cats currently[43] | 1.09 | 1.02-1.15 | 1.08 | 1.02-1.15 | 1.23 | 1.15-1.32 |
| Dogs currently[43] | 1.10 | 1.04-1.16 | 1.07 | 1.01-1.13 | 1.16 | 1.08-1.24 |
| Father currently smokes[44] | 1.20 | 1.15-1.24 | 1.15 | 1.11-1.19 | 1.19 | 1.14-1.25 |
| Mother currently smokes[44] | 1.32 | 1.26-1.37 | 1.20 | 1.15-1.25 | 1.22 | 1.16-1.28 |
| Overweight (BMI) vs normal[45] | 1.15 | 1.08-1.22 | 1.03 | 0.97-1.09 | 1.16 | 1.07-1.24 |
| Obese (BMI) vs normal[45] | 1.29 | 1.14-1.46 | 0.97 | 0.86-1.09 | 1.42 | 1.23-1.64 |
| Exercise 3+ times a week vs none[45] | 1.27 | 1.19-1.36 | 1.25 | 1.18-1.32 | 1.24 | 1.15-1.34 |
| TV viewing 5hrs+ per day vs less than 1hr[45] | 1.08 | 1.00-1.17 | 1.16 | 1.06-1.28 | 1.17 | 1.09-1.26 |
| Fast food (3+ times a week vs never or occasionally)[46] | 1.25 | 1.18-1.33 | 1.21 | 1.14-1.28 | 1.20 | 1.11-1.28 |
| Any open fire cooking[47] | 1.19 | 1.05-1.35 | 1.07 | 0.95-1.21 | 1.29 | 1.13-1.49 |
| Migration[49] | 0.88 | 0.79-0.99 | 1.00 | 0.88-1.13 | 0.90 | 0.82-0.99 |
| Siblings, each extra older sibling[50] | 0.99 | 0.97-1.01 | 1.03 | 1.01-1.05 | 1.00 | 0.99-1.02 |
| Siblings, each extra younger sibling[50] | 1.01 | 0.99-1.03 | 1.03 | 1.01-1.06 | 1.03 | 1.01-1.05 |

The use of an open fire for cooking was associated with symptoms of asthma (1.19; 1.05, 1.35) and rhinoconjunctivitis (1.29; 1.13, 1.49) but not eczema, even after adjusting for other factors.[47]

There were only very marginal associations between recent migration and higher asthma and rhinoconjunctivitis symptoms, with no association with eczema symptoms[49]

Each additional sibling was marginally associated with increased risk of eczema symptoms (older sibling 1.03; 1.01, 1.05; younger sibling 1.03; 1.01, 1.06). For symptoms of rhinoconjunctivitis only additional younger siblings were associated with increased risk (1.03; 1.01, 1.05). There was no evidence of associations between number of siblings and asthma symptoms.[50]

Each of these results are useful in their own right but direct comparisons cannot be made due to the different factors that are adjusted for in each of the papers. However, they are more comparable than separate studies because the data collection and exclusions were the same.

## 2.5 GAN Phase I

### 2.5.1 Methods

GAN was founded in 2012, as the ISAAC project ended, to continue the work of tracking and understanding asthma, eczema and rhinoconjunctivitis around the world. The methodology follows on from ISAAC but is expanded to incorporate adults, using parents/guardians of participating children and adolescents. This thesis focuses only on the adolescents and children, the results of which can be incorporated into time trends analyses with the ISAAC Phase I and Phase III data.

The questionnaires were similar to those of ISAAC Phase III but with some minor changes. There were no questions on parental smoking in GAN Phase I although these questions were included in the optional adult questionnaire. There was however a new question for adolescents on their own smoking. There was an additional question in GAN Phase I on itchy nose, as an extra symptom of rhinitis, though this was not added to the standard definition of rhinoconjunctivitis for comparability. There were also a few new questions added to GAN Phase I on asthma management and lifestyle.[4]

Due to the lower number of participating centres and external issues affecting data collection (such as the Covid-19 pandemic and civil wars) centres were accepted if they achieved a response rate of at least 50%, rather than the 70% initially requested. Details of these exceptions to protocol are included in the paper on response rates.[21]

Centres each submitted data to the global data centre in Auckland, of which data from Spanish and Portuguese speaking countries were sent to the Murcia Data Centre for checking and data from all other countries were sent to the London Data Centre for checking in English (though questionnaires may have been originally in other languages).

### 2.5.2 Author's contribution to the study

As an integral part of the London data centre, the author was involved, over 3 years, in the data checking and cleaning of submitted datasets (completing 27 of the study centres, each comprised of between one and four age-group datasets). This involved checking submitted data for coding errors or potential data entry errors using a suite of Stata programs that was created and maintained jointly by the London and Murcia data centres. Data reports along with queries and requests for clarifications were sent back to the centre contacts, ready to then receive updated files and repeat the process, until all data were deemed clean and in the required format. On average each dataset required four iterations of checks. During this time, regular progress updates were provided to the GAN steering committee and the global data centre. Finally, the author created the global analysis datasets, one per age group, collating data from all centres, for use in all future global analyses of GAN Phase I.

### 2.5.3 Results overview

In total, 157,784 adolescents from 63 centres in 25 different countries and 101,777 children from 44 centres in 16 countries took part in the study between 2015 and 2020.[52]

Prevalence of asthma symptoms averaged 11.1% for adolescents, ranging from 0.9% in New Delhi, India to 21.4% in San Francisco, Argentina. For children, the average prevalence was 9.1%, ranging from 0.3% in Bikaner, India to 23.2% in a whole country study in Costa Rica.[52]

Eczema symptoms in adolescents averaged 6.4%, ranging from 1.1% in Anuradhapura, Sri Lanka to 18.5% in South Santiago, Chile. In children the average was 5.9%, ranging from 0.4% in Bikaner, India to 15.7% in Taipei, Taiwan.[52]

Symptoms of rhinoconjunctivitis averaged 13.3% in adolescents, ranging from 0% in Tegucigalpa, Honduras to 30.1% in Lattakia, Syrian Arab Republic. For children, the prevalence averaged 7.7%, ranging from 0.2% in Bikaner, India to 24.0% in Taipei, Taiwan. Prevalence of all three diseases in both age groups was highest in high-income countries and lowest in low- to lower-middle-income countries.[52]

Additional data from 193,912 adult participants from 43 centres in 17 countries showed the overall prevalence of asthma symptoms was 6.6%, ranging from 0.9% in New Delhi, India to 32.7% in Tegucigalpa, Honduras. This also showed a similar relationship between country income and symptom prevalence with high-income countries having the highest prevalence of asthma symptoms.[53] Data were not collected for eczema and rhinoconjunctivitis symptoms in adults.

Prior to this PhD there have been no published analyses of the risk factor associations in GAN Phase I.

## 2.6 Time trends

Following ISAAC Phase III, papers were published describing the directly comparable, within-centre change in prevalence between ISAAC Phase I and ISAAC Phase III for the 106 centres (66 in the younger age group) that took part in both phases (see yellow dots on Figure 2.1).

For asthma symptoms, the mean prevalence increased slightly in both age groups (0.06% per year for adolescents and 0.13% per year for children, in absolute percentage points) but there were geographical differences in trend, with adolescents in Western Europe and the Eastern Mediterranean regions experiencing a slight decrease and Oceania experiencing a more substantial decrease of 0.39% per year for adolescents and 0.29% per year for children. All other regions experienced increases, the most notable being 0.79% per year for children in the Eastern Mediterranean and 0.32% per year for adolescents in Latin America.[54]

For eczema, the mean change in prevalence of symptoms for adolescents was a small increase of 0.06% per year but for children the increase was 0.21% per year. For adolescents, symptoms in high prevalence affluent countries decreased but high prevalence non-affluent countries increased. For children, all regions except the Indian sub-continent increased in prevalence.[55]

Similarly, for rhinitis an increase in symptom prevalence was found overall, 0.18% per year for adolescents and 0.17% per year for children, but this varied greatly between centres with a few centres having substantial decreases, a few with larger increases and many with similar or slight increases. There were no obvious regional patterns.[56]

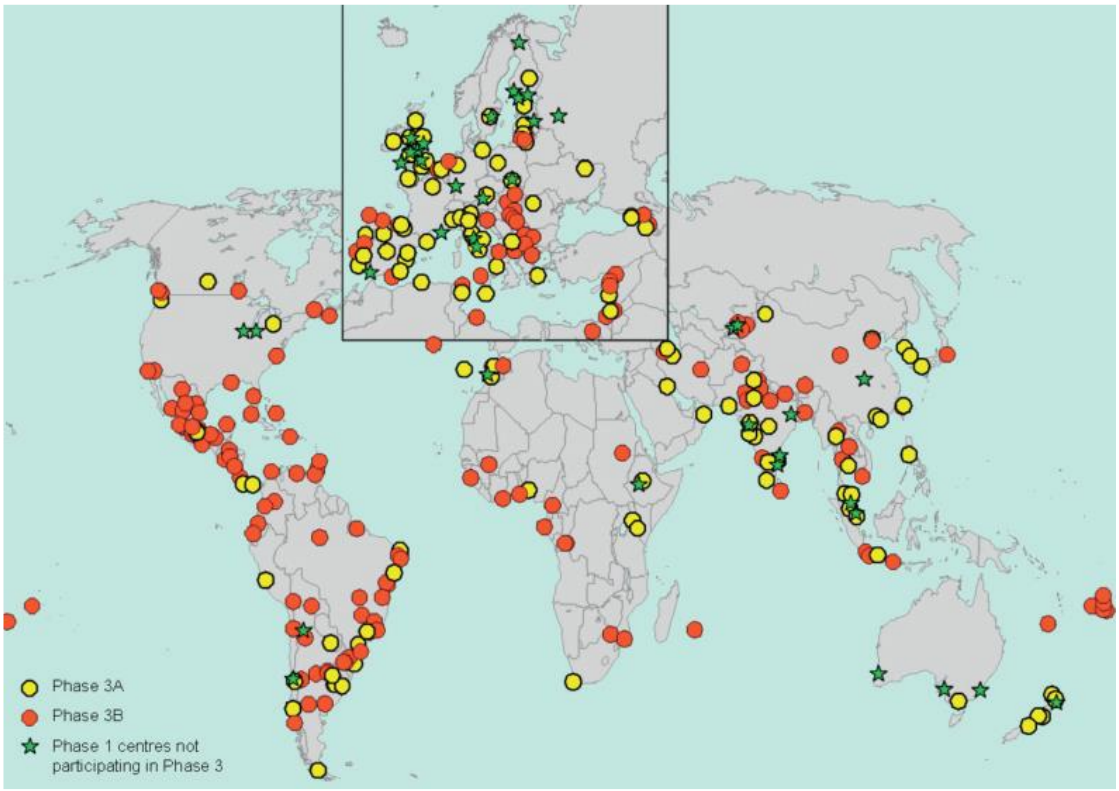


*Figure 2.1 World map of centres for ISAAC Phases I and III*

*source: the ISAAC Phase III rationale and methods paper*[3]

Clarification: Yellow circles are centres that took part in Phase I and Phase III; Red circles are new centres for Phase III only; Green stars are Phase I centres only.

A time trends centre is defined as a centre that provided data for at least two phases out of ISAAC Phase I, ISAAC Phase III and GAN Phase I. With the addition of the latest GAN Phase I data at the end of 2020, there are 121 time trends centres in adolescents, of which only 13 have data available from all three phases. For children, there are 76 time trends centres of which just 9 include data from all three phases. In the Venn diagrams in Figure 2.2 they are represented by the intersections of the circles (by both area and numeric label).

This is the total data available for analyses and the difficulty in using all the information in one analysis is the lack of overlap between data phases as well as the fact that each study uses a new set of individuals (understandably) so time points are not truly longitudinal data except at the centre level (as selection within centre is random at the school level). This is what is addressed in the rest of this thesis.

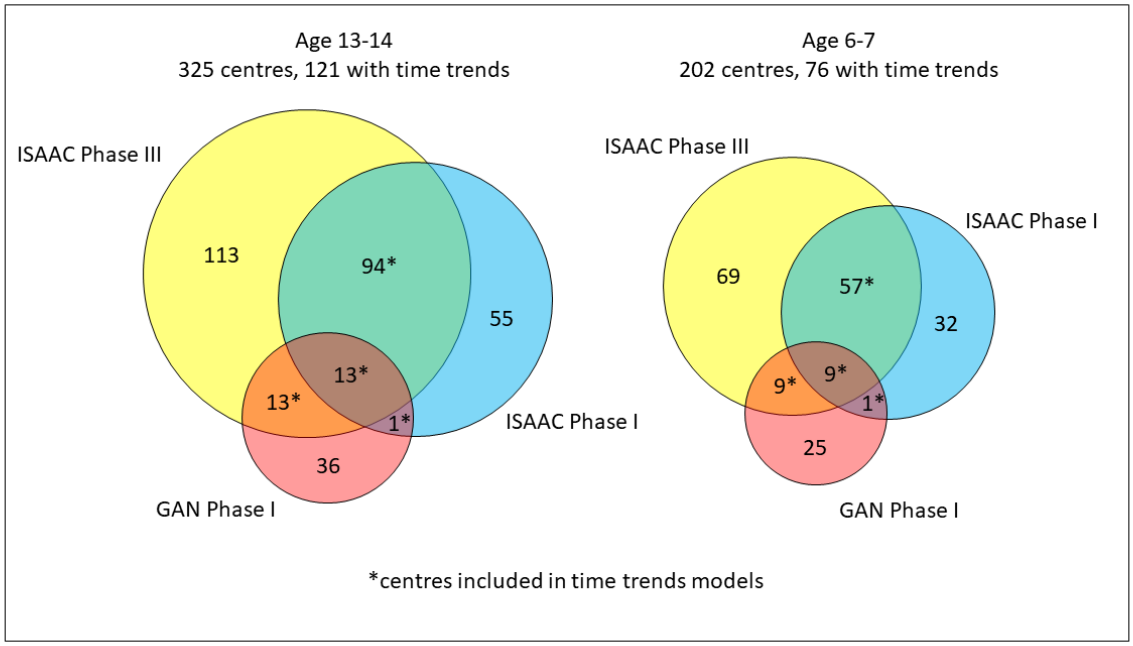


*Figure 2.2 Venn diagrams of ISAAC and GAN centre overlap*

# 3 Investigating risk factors and reverse causation in ISAAC Phase III

## Summary

This chapter investigates the role of reverse causation between potential risk factors and symptoms of disease, and includes two published papers on asthma and eczema, as well as unpublished results on rhinoconjunctivitis.

The methods used are based on the premise that at the school (cluster) level the prevalence of a risk factor will not change markedly if there are individual changes to exposure status due to reverse causation. In contrast, at the individual level such changes are absolute (in a binary variable), and may result in serious bias.

The analyses identified several risk factors that showed strong individual-level and school-level associations, thus supporting causal interpretations. These risk factors were similar for the three diseases under study.

All three analyses come to similar conclusions, i.e. that reverse causation is not a major factor in explaining the associations between the identified risk factors and the prevalence of recent symptoms of these three diseases.

## 3.1 Introduction

In this chapter the ISAAC Phase III data (see Section 2.4 for details) was used to assess whether reverse causation could be biasing the associations seen between various risk factors and symptoms of asthma, eczema and rhinoconjunctivitis. This was achieved by comparing models using individual-level exposures to models with school-level prevalence of exposures.

Individual-level exposures can be susceptible to reverse causation in a cross-sectional study. A change by one or two individuals (due to reverse causation) will not have a large effect on the school-level exposure prevalence and therefore will also not have a large effect on any associations with the outcomes.

Two papers were published using a similar methodology, one on asthma and the other on eczema. They are included here (reformatted) along with the relevant supplementary material. Also include are results from similar analyses for rhinoconjunctivitis that have not been published. An additional paper that includes some rhinoconjunctivitis results but focuses on a synthesis of the findings for the three diseases can be found in Chapter 4.

There is some repetition in the methods sections for the two papers because they were published at similar times rather than sequentially. Note that where Paper I refers to current wheeze, this means the same as current asthma symptoms in the rest of the thesis.

## 3.2 Paper I: Are environmental risk factors for current wheeze in ISAAC Phase III due to reverse causation?

### 3.2.1 Article submitted

**SECTION A – Student Details**

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300807 | **Title** | Mrs |
| **First Name(s)** | Charlotte Emma | | |
| **Surname/Family Name** | Rutter | | |
| **Thesis Title** | Multi-level modelling of international variations and time trends in asthma and allergic diseases in children. | | |
| **Primary Supervisor** | Neil Pearce | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

**SECTION B – Paper already published**

| | | | |
|---|---|---|---|
| Where was the work published? | Clinical and Experimental Allergy | | |
| When was the work published? | 28th March 2019 | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | **Yes** | Was the work subject to academic peer review? | **Yes** |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

**SECTION C – Prepared for publication, but not yet published**

| | |
|---|---|
| Where is the work intended to be published? | |
| Please list the paper's authors in the intended authorship order: | |
| Stage of publication | |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role was running the analyses jointly with Richard Silverwood, creating the tables and reviewing all drafts. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | [redacted] |
| **Date** | 10/07/2019 |

| | |
|---|---|
| **Supervisor Signature** | [redacted] |
| **Date** | 23/03/2022 |

### 3.2.2 Abstract

**Background**

Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC) measured the global prevalence of symptoms of asthma in children. We undertook comprehensive analyses addressing risk factors for asthma symptoms in combination, at both the individual and the school level, to explore the potential role of reverse causation due to selective avoidance or confounding by indication.

**Objective**

To explore the role of reverse causation in risk factors of asthma symptoms.

**Methods**

We compared two sets of multilevel logistic regression analyses, using (i) individual-level exposure data and (ii) school-level average exposure (i.e. prevalence), in two different age groups. In individual-level analyses, reverse causation is a possible concern if individual-level exposure statuses were changed as a result of asthma symptoms or diagnosis. School-level analyses may suffer from ecologic confounding, but reverse causation is less of a concern because individual changes in exposure status as a result of asthma symptoms would only have a small effect on overall school exposure levels.

**Results**

There were 131,924 children age 6-7 years (2,428 schools, 25 countries) with complete exposure, outcome and confounder data. The strongest associations in individual-level analyses (fully-adjusted) were for current paracetamol use (odds ratio = 2.06; 95% confidence interval 1.97-2.16), early life antibiotic use (1.65; 1.58-1.73), and open fire cooking (1.44; 1.26-1.65). In school-level analyses these risk factors again showed increased risks.

There were 238,586 adolescents age 13-14 years (2,072 schools, 42 countries) with complete exposure, outcome and confounder data. The strongest associations in individual-level analyses (fully-adjusted) were for current paracetamol use (1.80; 1.75-1.86), cooking on an open fire (1.32; 1.22-1.43), and maternal tobacco use (1.23; 1.18-1.27). In school-level analyses these risk factors again showed increased risks.

**Conclusions & clinical relevance**

These analyses strengthen the potentially causal interpretation of previously reported individual-level findings, by providing evidence against reverse causation.

### 3.2.3 Introduction

Asthma is becoming increasingly important as a childhood disease on a global basis.[57] The Global Asthma Report 2018 estimated that as many as 339 million people have asthma and that the burden of disability is high.[58]

The International Study of Asthma and Allergies in Childhood (ISAAC), using a simple and inexpensive standardised methodology,[2,3,30] has documented a wide variation of asthma prevalence in different parts of the world,[16,36] and a number of papers have been published addressing the findings for individual risk factors, with a several associations observed (see "Variables" below).[38-51] However, these risk factors have not previously been considered together within the same analysis, so it is possible that some of the observed associations may be at least partially due to confounding by other risk factors.

The current paper represents the first comprehensive analyses to address these risk factors together, in order to fill this gap in the current knowledge. We have done this in two ways. Firstly, we have conducted a 'standard' analysis using the individual level exposure data for each risk factor (e.g. maternal smoking). However, for some risk factors the cross-sectional nature of the study means that such analyses may be subject to 'reverse causation' if individual-level exposure statuses were changed as a result of asthma symptoms or diagnosis. This may occur due to selective avoidance (e.g. if the child's mother stops smoking because the child has developed asthma) or "confounding by indication" (e.g. if exposures such as paracetamol or antibiotics are taken in response to symptoms which are related to the subsequent development of asthma).

As schools were the level of sampling in ISAAC, we have therefore conducted a second set of analyses using the school-level average reported exposure (i.e. the prevalence; rather than the reported individual exposure) to each risk factor to attempt to avoid or minimise such biases. School-level analyses may suffer from ecologic (community-level) confounding, but reverse causation is perhaps less of a concern because individual changes in exposure status as a result of asthma symptoms would only have a small effect on overall school exposure levels. It is therefore of considerable interest to compare the individual-level and school-level analyses.

If reverse causation due to confounding by indication was exerting a major influence on the individual-level associations, we would expect the associations to be much reduced at the school-level. Conversely, if there was reverse causation due to selective avoidance, we would expect a stronger association at the school-level, although this could also be due to contextual

factors operating at the school level. Consistency of findings at the two levels thus provides indirect evidence against reverse causation and against strong contextual factors.

Biases may differ in different parts of the world, for example breast feeding is more strongly associated with socioeconomic status in high-income countries than in low and middle income-countries,[59] hence there is a greater potential for confounding by socioeconomic status in the former. Therefore, we additionally conducted analyses stratified by country-level affluence to examine the extent to which associations and biases differed.

### 3.2.4 Methods

**Study**

ISAAC Phase Three methods have been described in detail elsewhere,[3] and will be summarised briefly here. ISAAC Phase Three is a multi-centre, multi-country, cross-sectional study of two age groups of schoolchildren (6-7-year-old children and 13-14-year-old adolescents) chosen from a random sample of schools in a defined geographical area.[2,3] The Phase Three survey took place in 2000-2003 and included two standardised questionnaires. The first obtained data on symptoms of asthma, rhinoconjunctivitis and eczema, and was identical to that used in Phase One of ISAAC.[16,23] The second, the environmental questionnaire, obtained data on a range of possible risk factors for the development of asthma and allergic disorders.[38] The questionnaires can be found on the ISAAC website (http://isaac.auckland.ac.nz).

**Variables**

We considered the outcome of wheeze in the last 12 months, defined by a positive response to the question "Has your child/have you had wheezing or whistling in the chest in the past 12 months?". In many countries in the world we find that most asthma (based on symptoms) has not been diagnosed, which is why ISAAC is based on symptoms. The ISAAC symptoms questionnaire validates well against doctor-diagnosed asthma.[60]

The environmental questionnaires in the two age groups did not contain identical questions, so it was not possible to examine the same set of potential risk factors in each age group. In addition, we restricted our analyses to the risk factors which had shown associations with wheeze in the last 12 months in previous analyses at the individual level. For the younger age group, we included paracetamol use in the first year of life and in the past 12 months,[38] antibiotic use in the first year of life,[40] breast feeding,[41] cat in the home in the first year of life,[43] regular contact with farm animals in the first year of life,[42] truck traffic,[39] fast food consumption,[46] television viewing,[45] parental smoking,[44] cooking on an open fire,[47] and birth

weight.[48] For the older age group, we included truck traffic,[39] fast food consumption,[46] television viewing,[45] parental smoking,[44] paracetamol use in the past 12 months,[51] and open fire cooking.[47]

Most of the above risk factors were parameterised as binary variables from "yes/no" questions in the environmental questionnaire. The exceptions were: paracetamol use in the past 12 months (at least once per month vs. less than once per month), truck traffic (seldom or more frequently vs. never), fast food consumption (once per week or more vs. less than once per week), television viewing (at least 1 hour per day vs. less than 1 hour per day), and birth weight (less than 2.5 kg vs. at least 2.5 kg). Full definitions are in Table 3.1.

Sex was self-reported as male/female and the highest level of maternal education was recorded as primary, secondary, tertiary or missing/not stated.

Gross National Income (GNI) as of 2002 was obtained from the World Bank website[61] where available, with gaps filled by the CIA World Factbook[62]. Countries were classified as 'affluent' or 'non-affluent' using a 2001 GNI value of US$9,205 per capita as a cut-off, which separates high-income countries from low and middle-income countries.[63]

**Statistical analyses**

To be included in the analysis for a particular age-group, centres had to include at least 1,000 individuals and to have a response rate of >60% for children and >70% for adolescents. Analyses were conducted separately in the two age groups. Within each age group, schools with fewer than 10 individuals were excluded from the analysis.

All analyses were conducted using mixed effect (multilevel) logistic regression models. The four-level hierarchical nature of the data (individuals [level 1], schools [level 2], centres [level 3] and countries [level 4]) was acknowledged by allowing random intercepts at levels 2, 3 and 4 in individual-level models and by including random intercepts at levels 3 and 4 in school-level models. Centres were self-selected, whereas schools were randomly sampled within centres, making school the preferred level of analysis. Sex and maternal education were adjusted for as individual-level confounders in all models.

Three different modelling approaches were used: (i) individual-level, (ii) school-level and (iii) hybrid fixed effects.[64] However, results from the hybrid fixed effect models were very similar to those from the individual-level and school-level models, so they are not discussed further.

*Table 3.1 Definitions of risk factors for asthma*

| Risk Factors for ages 6-7 | Question (asked to parent) | Positive Response |
|---|---|---|
| Low birthweight | What was the weight of your child when he / she was born? | Less than 2.5kg |
| Paracetamol (1st year) | In the first 12 months of your child's life, did you usually give paracetamol for fever? | Yes |
| Antibiotics (1st year) | In the first 12 months of your child's life, did your child have any antibiotics? | Yes |
| Breastfed ever | Was your child breastfed? | Yes |
| Cat (1st year) | Did you have a cat in your home during the first year of your child's life? | Yes |
| Farm animals (1st year) | In your child's first year of life, did he / she have regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry)? | Yes |
| Truck traffic (current) | How often do trucks pass through the street where you live, on weekdays? | Seldom or more frequent |
| Fast food (current) | In the past 12 months, how often, on average did your child eat fast food / burgers? | At least once a week |
| Television (current) | During a normal week, how many hours a day (24 hours) does your child watch television? | At least one hour per day |
| Paternal tobacco (current) | Does your child's father (or male guardian) smoke cigarettes? | Yes |
| Maternal tobacco (current) | Does your child's mother (or female guardian) smoke cigarettes? | Yes |
| Paracetamol (current) | In the past 12 months, how often, on average, have you given your child paracetamol? | At least once per month |
| Open fire cooking (current) | In your house, what fuels are usually used for cooking? Electricity, gas, open fires, other | Any that include open fires |

| Risk Factors for ages 13-14 | Question (asked to child) | Positive Response |
|---|---|---|
| Truck traffic (current) | How often do trucks pass through the street where you live, on weekdays? | Seldom or more frequent |
| Fast food (current) | In the past 12 months, how often, on average did you eat fast food / burgers? | At least once a week |
| Television (current) | During a normal week, how many hours a day (24 hours) do you watch television? | At least one hour per day |
| Paternal tobacco (current) | Does your father (or male guardian) smoke cigarettes? | Yes |
| Maternal tobacco (current) | Does your mother (or female guardian) smoke cigarettes? | Yes |
| Paracetamol (current) | In the past 12 months, how often, on average, have you taken paracetamol? | At least once per month |
| Open fire cooking (current) | In your house, what fuels are usually used for cooking? Electricity, gas, open fires, other | Any that include open fires |

Individual-level models related the individual-level outcome to each individual-level risk factor within schools. School-level models related the individual-level outcome to the school-level average exposure (i.e. prevalence) of each risk factor. In these models the estimated OR corresponding to the school-level prevalence of the risk factor can be interpreted as the effect on the individual outcome of attending a school where all children are exposed compared to attending a school where no-one is exposed.

Within each approach, models were fitted for: (i) each exposure of interest using the sub-sample who had data present for wheeze, sex, maternal education and the given exposure (the "maximum sample"), (ii) each exposure of interest using the sub-sample who had data present for wheeze, sex, maternal education and all exposures of interest (the "common sample"), and (iii) each exposure of interest mutually adjusted using the sub-sample who had data present for wheeze, sex, maternal education and all exposures of interest (the "common sample").

The extent of collinearity in the mutually adjusted models was examined by comparing the standard errors in the mutually adjusted model and the minimally adjusted model fitted to the same sub-sample.[65] There was no evidence of substantial collinearity.

Additionally, we ran the fully adjusted analyses separately for "affluent" and "non-affluent" countries. We then separately tested for effect modification of each risk factor by country-level affluence.

Analyses were conducted using Stata version 14.[66]

### 3.2.5 Results

**6-7 year olds**

The 6-7 year-old participants included 221,280 children from 75 centres which met the initial data quality criteria (at least 1,000 children and a response rate of >60%). Of these, 212,480 children (from 2,903 schools, 75 centres, 32 countries) were from schools with at least 10 children and had data present for wheeze, sex, maternal education and at least one of the exposures of interest so contributed to the analyses for one or more exposures (the "maximum sample"), with 131,924 children (from 2,428 schools, 64 centres, 25 countries) having data present for all analysis variables (the "common sample"). See the data flowchart (Figure 3.1) for further details. Individual- and school-level summary statistics are presented in Table 3.2 for the maximum sample and in Table 3.3 for the common sample.

Minimally adjusted associations in the common sample were broadly similar to those in the maximum sample (Tables 3.4 and 3.5). The strongest associations in the fully-adjusted individual-level analyses were for current paracetamol use (OR=2.06, 95% CI 1.97-2.16), antibiotic use in the first year of life (1.65; 1.58-1.73), and open fire cooking (1.44; 1.26-1.65) (Table 3.4).

In the fully-adjusted school-level analyses the associations for current paracetamol use (1.58; 1.18-2.10), early life antibiotic use (1.38; 1.07-1.78) and open fire cooking (2.02; 1.16-3.50) were maintained (Table 3.4). Stronger associations were observed at the school-level compared with the individual-level for low birthweight (2.13; 1.39-3.25 compared to 1.12; 1.05-1.21), maternal tobacco use (1.83; 1.36-2.47 compared to 1.20; 1.14-1.27), fast food consumption (1.68; 1.37-2.06 compared to 1.07; 1.03-1.12), and early life farm animal exposure (1.36; 1.00-1.85 compared to 1.12; 1.06-1.20). An association was seen at the school-level only for television viewing (1.80; 1.37-2.37 compared to 1.04; 0.99-1.10) (Table 3.4).

In the analyses stratified by country-level affluence (Tables 3.6 and 3.7) there was strong evidence ($p<0.001$) of effect modification at the individual-level for early life exposure to cats (1.36; 1.26-1.48 in non-affluent countries vs. 1.09; 1.00-1.18 in affluent countries), early life exposure to farm animals (1.23; 1.14-1.33 vs. 0.96; 0.87-1.06), and current paracetamol use (1.89; 1.79-2.01 vs. 2.38; 2.21-2.56) (Table 3.7).

When using the school-level prevalence (Table 3.7) there was again some evidence ($p=0.04$) of effect modification of current paracetamol use (1.31; 0. 89-1.92 in non-affluent countries vs. 2.32; 1.52-3.55 in affluent countries). However, there was little evidence of a difference between affluent and non-affluent countries for the associations of wheeze with cat and farm animal exposure in the first year of life. Several risk factors showed greater effect modification in the school-level analysis than in the individual-level analysis: maternal tobacco (3.30; 1.87-5.83 in non-affluent countries vs. 1.49; 1.06-2.10 in affluent countries in the school-level analysis), antibiotics in the first year of life (1.13; 0.80-1.61 vs. 1.77; 1.22-2.55), and paracetamol use in the first year of life (0.90; 0.63-1.29 vs. 1.30; 0.88-1.93).

**13-14 year olds**

The 13-14 year-old participants included 362,048 adolescents from 122 centres which met the initial data quality criteria (at least 1,000 adolescents and a response rate of >70%). Of these 350,915 adolescents (from 2,511 schools, 122 centres, 54 countries) were from schools with at least 10 adolescents and had data present for wheeze, sex, maternal education and at least

one of the exposures of interest so contributed to the analyses for one or more exposures (the "maximum sample"), with 238,586 adolescents (from 2,072 schools, 99 centres, 42 countries) having data present for all analysis variables (the "common sample"). See the data flowchart (Figure 3.2) for further details. Individual- and school-level summary statistics are presented in Table 3.2 for the maximum sample and in Table 3.3 for the common sample.

Minimally adjusted associations in the common sample were broadly similar to those in the maximum sample (Tables 3.4 and 3.5). The strongest associations in the fully-adjusted individual-level analyses were for current paracetamol use (1.80; 1.75-1.86), cooking on an open fire (1.32; 1.22-1.43), and maternal tobacco use (1.23; 1.18-1.27) (Table 3.4).

In the fully-adjusted school-level analyses the association for current paracetamol use (2.31; 1.71-3.12) and maternal tobacco use (2.51; 1.74-3.61) were maintained. Although the evidence for an association with cooking on an open fire was reduced, the point estimate was comparable to that in the individual-level analysis (1.28; 0.85-1.94) (Table 3.4). An association was also observed at the school-level (but not the individual level) for television viewing (2.01; 1.36-2.96). At the individual-level there was an association with paternal tobacco use (1.12; 1.08-1.15), but this was in the other direction at the school-level (0.51; 0.37-0.70).

In the analyses stratified by country-level affluence (Tables 3.6-3.7) there was evidence ($p<0.001$) at the individual-level that paracetamol use in the last 12 months was more strongly associated with wheeze in affluent countries (1.97; 1.85-2.09) than non-affluent (1.75; 1.69-1.82) (Table 3.6). There was no evidence of effect modification at the school-level (Table 3.7).

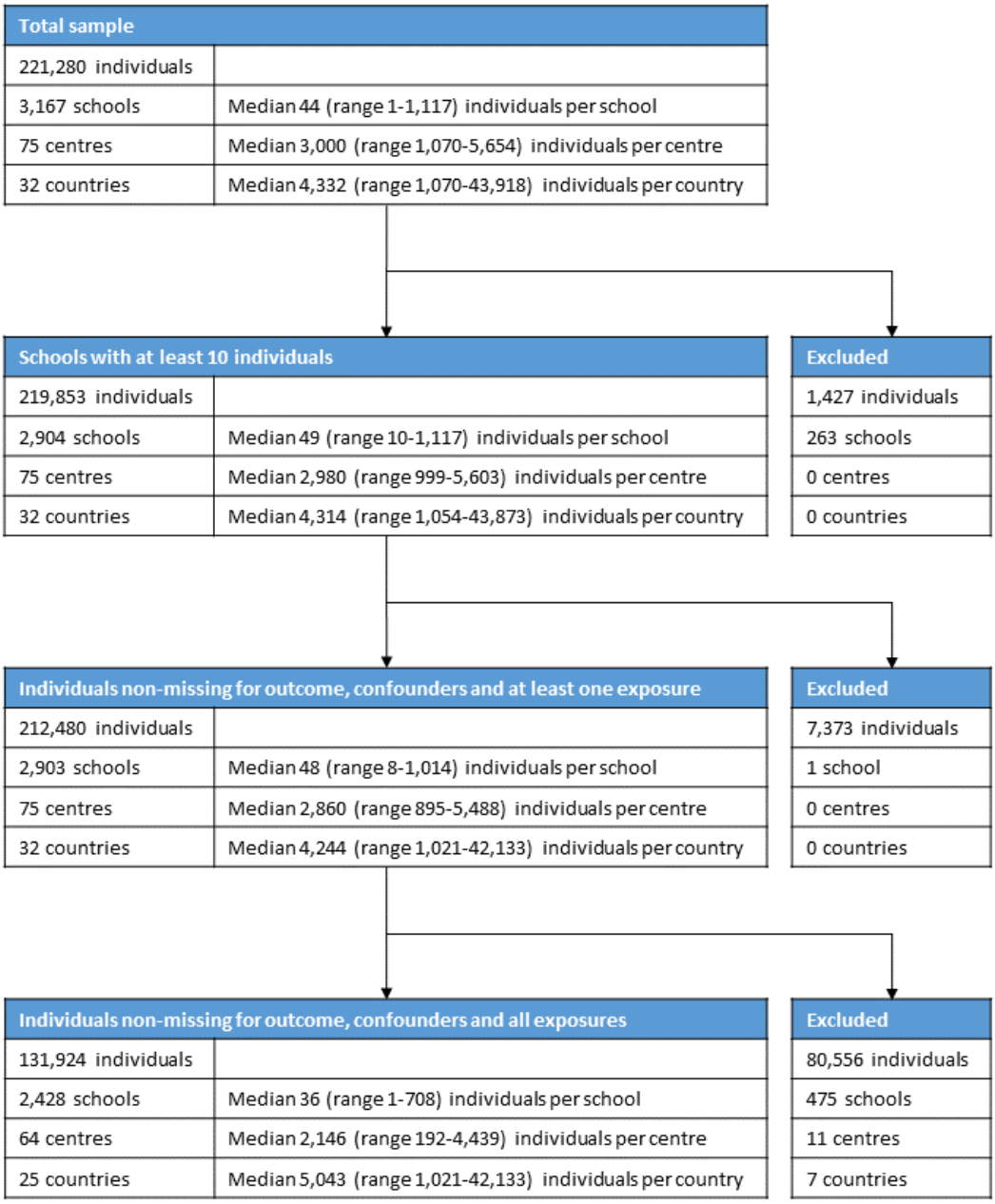


*Figure 3.1 Asthma data flowchart for 6-7 year-old children.*

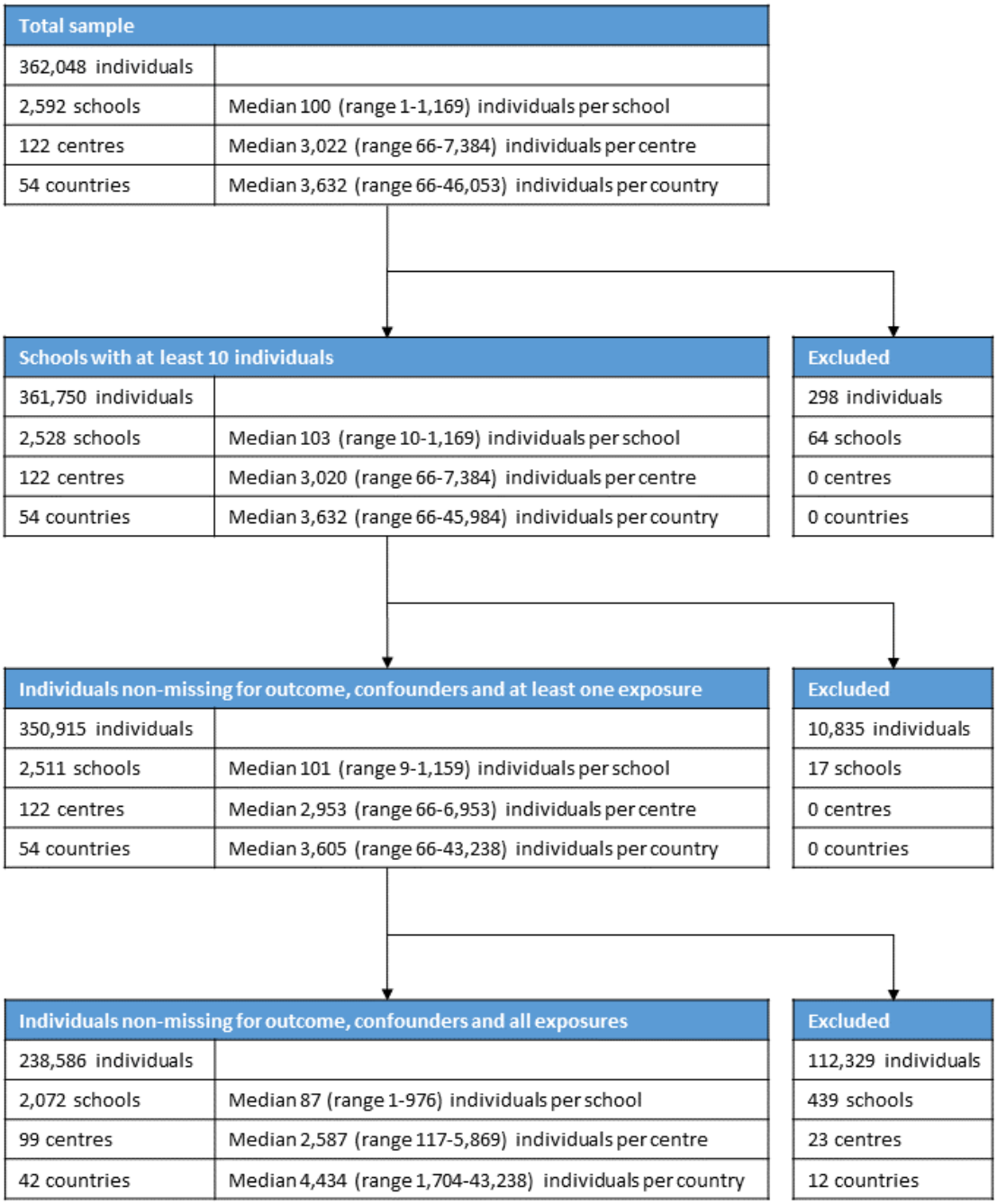


*Figure 3.2 Asthma data flowchart for 13-14 year-old adolescents.*

*Table 3.2 Asthma - Summary statistics in the maximum sample*

Variables and their prevalence in subjects who had data present for wheeze, sex, maternal education and the given exposure.

| Age group | Variable | Individual-level | | School-level | | |
|---|---|---|---|---|---|---|
| | | n | Prevalence (%) | n | Median prevalence (%) | Prevalence IQR (%) |
| 6-7 years | Wheeze in the last 12 months | 212,480 | 10.4 | 2,903 | 10.2 | (5.7, 16.7) |
| | Low birthweight | 177,104 | 8.6 | 2,601 | 6.3 | (3.2, 10.5) |
| | Paracetamol (1st year) | 188,961 | 65.2 | 2,635 | 69.6 | (56.2, 82.1) |
| | Antibiotics (1st year) | 187,633 | 54.2 | 2,715 | 56.0 | (46.3, 64.6) |
| | Breastfed ever | 200,012 | 80.1 | 2,753 | 84.5 | (73.5, 92.9) |
| | Cat (1st year) | 197,501 | 11.8 | 2,753 | 10.3 | (4.7, 19.3) |
| | Farm animals (1st year) | 189,212 | 11.3 | 2,686 | 9.6 | (4.3, 17.7) |
| | Truck traffic (current) | 191,713 | 79.9 | 2,781 | 85.4 | (76.2, 91.7) |
| | Fast food (current) | 188,841 | 41.1 | 2,850 | 33.3 | (18.6, 51.3) |
| | Television (current) | 204,310 | 77.8 | 2,855 | 83.8 | (74.1, 90.9) |
| | Paternal tobacco (current) | 203,914 | 31.5 | 2,800 | 33.3 | (19.2, 46.7) |
| | Maternal tobacco (current) | 207,143 | 13.9 | 2,833 | 13.9 | (2.9, 30.0) |
| | Paracetamol (current) | 199,057 | 19.5 | 2,786 | 16.4 | (7.6, 30.9) |
| | Open fire cooking (current) | 192,631 | 3.1 | 2,776 | 0.0 | (0.0, 2.3) |
| 13-14 years | Wheeze in the last 12 months | 350,915 | 11.4 | 2,511 | 10.0 | (5.6, 15.8) |
| | Truck traffic (current) | 318,661 | 82.5 | 2,382 | 87.0 | (78.9, 92.5) |
| | Fast food (current) | 320,128 | 55.2 | 2,421 | 55.4 | (40.8, 69.5) |
| | Television (current) | 339,823 | 85.3 | 2,483 | 90.0 | (81.2, 94.3) |
| | Paternal tobacco (current) | 310,700 | 37.5 | 2,293 | 36.8 | (23.6, 48.3) |
| | Maternal tobacco (current) | 338,740 | 17.9 | 2,467 | 18.2 | (3.8, 33.3) |
| | Paracetamol (current) | 323,051 | 28.8 | 2,438 | 30.7 | (19.1, 43.7) |
| | Open fire cooking (current) | 312,624 | 7.6 | 2,355 | ,1.2 | (0.0, 4.8) |

IQR = interquartile range.

*Table 3.3 Asthma - Summary statistics in the common sample*

Variables and their prevalence in subjects who had data present for wheeze, sex, maternal education and all exposures of interest.

| Age group | Variable | Individual-level (n = 131,924) | School-level (n = 2,428) | |
|---|---|---|---|---|
| | | Prevalence (%) | Median prevalence (%) | Prevalence IQR (%) |
| 6-7 years | Wheeze in the last 12 months | 9.8 | 9.2 | (4.7, 15.3) |
| | Low birthweight | 8.1 | 6.1 | (2.6, 10.7) |
| | Paracetamol (1st year) | 65.4 | 70.6 | (56.3, 83.9) |
| | Antibiotics (1st year) | 56.2 | 57.6 | (47.1, 66.0) |
| | Breastfed ever | 81.3 | 85.2 | (74.7, 93.7) |
| | Cat (1st year) | 11.5 | 9.1 | (3.8, 19.0) |
| | Farm animals (1st year) | 10.2 | 9.1 | (3.9, 16.7) |
| | Truck traffic (current) | 79.2 | 84.5 | (75.0, 91.3) |
| | Fast food (current) | 39.9 | 31.6 | (16.7, 50.0) |
| | Television (current) | 79.8 | 84.4 | (73.9, 91.6) |
| | Paternal tobacco (current) | 32.3 | 34.4 | (20.2, 48.3) |
| | Maternal tobacco (current) | 15.3 | 14.2 | (2.1, 30.7) |
| | Paracetamol (current) | 18.3 | 14.7 | (6.4, 28.0) |
| | Open fire cooking (current) | 2.0 | 0.0 | (0.0, 1.7) |
| Age group | Variable | Individual-level (n = 238,586) | School-level (n = 2,072) | |
| | | Prevalence (%) | Median prevalence (%) | Prevalence IQR (%) |
| 13-14 years | Wheeze in the last 12 months | 10.6 | 9.8 | (5.0, 15.5) |
| | Truck traffic (current) | 83.2 | 87.3 | (79.5, 92.9) |
| | Fast food (current) | 53.6 | 52.8 | (38.9, 67.9) |
| | Television (current) | 85.6 | 90.5 | (81.7, 94.8) |
| | Paternal tobacco (current) | 38.3 | 37.3 | (23.5, 49.4) |
| | Maternal tobacco (current) | 18.1 | 18.6 | (3.4, 35.6) |
| | Paracetamol (current) | 26.7 | 29.4 | (17.3, 41.3) |
| | Open fire cooking (current) | 5.2 | 0.7 | (0.0, 3.0) |

IQR = interquartile range.

*Table 3.4 Effects of individual- and school-level exposures on wheeze in the last 12 months in the common sample.*

For subjects who had data present for wheeze, sex, maternal education and all exposures of interest. Mixed logistic regression models with random intercepts at the school, centre and country levels.

| Age group | Exposure | Individual-level exposure | | School-level exposure | |
|---|---|---|---|---|---|
| | | Minimally adjusted[a] OR (95% CI) | Fully adjusted[b] OR (95% CI) | Minimally adjusted[a] OR (95% CI) | Fully adjusted[b] OR (95% CI) |
| 6-7 years (n = 131,924) | Low birthweight | 1.20 (1.12, 1.29) | 1.12 (1.05, 1.21) | 2.43 (1.60, 3.69) | 2.13 (1.39, 3.25) |
| | Paracetamol (1st year) | 1.75 (1.67, 1.84) | 1.33 (1.27, 1.40) | 1.42 (1.11, 1.82) | 1.01 (0.78, 1.32) |
| | Antibiotics (1st year) | 1.90 (1.83, 1.98) | 1.65 (1.58, 1.73) | 1.49 (1.17, 1.90) | 1.38 (1.07, 1.78) |
| | Breastfed ever | 0.91 (0.87, 0.96) | 0.96 (0.91, 1.01) | 0.80 (0.60, 1.09) | 1.11 (0.82, 1.50) |
| | Cat (1st year) | 1.29 (1.22, 1.37) | 1.22 (1.15, 1.29) | 1.44 (1.06, 1.94) | 1.20 (0.88, 1.65) |
| | Farm animals (1st year) | 1.24 (1.16, 1.31) | 1.12 (1.06, 1.20) | 1.47 (1.11, 1.94) | 1.36 (1.00, 1.85) |
| | Truck traffic (current) | 1.24 (1.17, 1.30) | 1.17 (1.11, 1.23) | 1.25 (0.97, 1.62) | 1.04 (0.81, 1.33) |
| | Fast food (current) | 1.14 (1.09, 1.19) | 1.07 (1.03, 1.12) | 1.80 (1.47, 2.20) | 1.68 (1.37, 2.06) |
| | Television (current) | 1.11 (1.06, 1.17) | 1.04 (0.99, 1.10) | 2.08 (1.61, 2.69) | 1.80 (1.37, 2.37) |
| | Paternal tobacco (current) | 1.20 (1.15, 1.25) | 1.12 (1.07, 1.17) | 1.51 (1.20, 1.89) | 0.83 (0.63, 1.08) |
| | Maternal tobacco (current) | 1.32 (1.25, 1.38) | 1.20 (1.14, 1.27) | 2.22 (1.72, 2.87) | 1.83 (1.36, 2.47) |
| | Paracetamol (current) | 2.35 (2.24, 2.46) | 2.06 (1.97, 2.16) | 2.05 (1.55, 2.71) | 1.58 (1.18, 2.10) |
| | Open fire cooking (current) | 1.44 (1.26, 1.65) | 1.44 (1.26, 1.65) | 1.95 (1.15, 3.29) | 2.02 (1.16, 3.50) |
| Age group | Exposure | Individual-level exposure | | School-level exposure | |
| | | Minimally adjusted[a] OR (95% CI) | Fully adjusted[b] OR (95% CI) | Minimally adjusted[a] OR (95% CI) | Fully adjusted[b] OR (95% CI) |
| 13-14 years (n = 238,586) | Truck traffic (current) | 1.20 (1.15, 1.25) | 1.16 (1.12, 1.21) | 1.52 (1.09, 2.11) | 1.28 (0.92, 1.79) |
| | Fast food (current) | 1.11 (1.08, 1.15) | 1.07 (1.04, 1.10) | 1.36 (1.09, 1.71) | 1.21 (0.96, 1.51) |
| | Television (current) | 1.06 (1.01, 1.11) | 1.02 (0.97, 1.07) | 2.29 (1.56, 3.37) | 2.01 (1.36, 2.96) |
| | Paternal tobacco (current) | 1.19 (1.16, 1.23) | 1.12 (1.08, 1.15) | 0.85 (0.63, 1.13) | 0.51 (0.37, 0.70) |
| | Maternal tobacco (current) | 1.30 (1.26, 1.35) | 1.23 (1.18, 1.27) | 1.94 (1.39, 2.70) | 2.51 (1.74, 3.61) |
| | Paracetamol (current) | 1.83 (1.78, 1.89) | 1.80 (1.75, 1.86) | 2.43 (1.79, 3.29) | 2.31 (1.71, 3.12) |
| | Open fire cooking (current) | 1.31 (1.21, 1.41) | 1.32 (1.22, 1.43) | 0.98 (0.65, 1.48) | 1.28 (0.85, 1.94) |

[a]Adjusted for sex and mothers level of education. [b]Additionally adjusted for all other variables in the table.

*Table 3.5 Minimally adjusted effects of individual- and school-level exposures on wheeze in the last 12 months in the maximum sample.*

In subjects who had data present for wheeze, sex, maternal education and the given exposure. Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Individual-level exposure | | School-level exposure | |
|---|---|---|---|---|---|
| | | n | OR (95% CI) | n | OR (95% CI) |
| 6-7 years | Low birthweight | 177,104 | 1.21 (1.14, 1.28) | 177,104 | 2.29 (1.56, 3.38) |
| | Paracetamol (1st year) | 188,961 | 1.79 (1.72, 1.86) | 188,961 | 1.35 (1.07, 1.69) |
| | Antibiotics (1st year) | 187,633 | 1.99 (1.92, 2.06) | 187,633 | 1.42 (1.14, 1.77) |
| | Breastfed ever | 200,012 | 0.94 (0.91, 0.98) | 200,012 | 0.77 (0.59, 1.01) |
| | Cat (1st year) | 197,501 | 1.37 (1.31, 1.44) | 197,501 | 1.84 (1.41, 2.40) |
| | Farm animals (1st year) | 189,212 | 1.36 (1.30, 1.42) | 189,212 | 1.77 (1.38, 2.26) |
| | Truck traffic (current) | 191,713 | 1.22 (1.17, 1.27) | 191,713 | 1.13 (0.90, 1.42) |
| | Fast food (current) | 188,841 | 1.12 (1.08, 1.16) | 188,841 | 1.62 (1.36, 1.93) |
| | Television (current) | 204,310 | 1.09 (1.05, 1.14) | 204,310 | 1.64 (1.32, 2.04) |
| | Paternal tobacco (current) | 203,914 | 1.20 (1.16, 1.24) | 203,914 | 1.85 (1.50, 2.27) |
| | Maternal tobacco (current) | 207,143 | 1.28 (1.23, 1.34) | 207,143 | 2.56 (2.03, 3.23) |
| | Paracetamol (current) | 199,057 | 2.36 (2.28, 2.45) | 199,057 | 2.30 (1.81, 2.91) |
| | Open fire cooking (current) | 192,631 | 1.30 (1.19, 1.43) | 192,631 | 3.28 (2.11, 5.07) |
| Age group | Exposure | Individual-level exposure | | School-level exposure | |
| | | n | OR (95% CI) | n | OR (95% CI) |
| 13-14 years | Truck traffic (current) | 318,661 | 1.22 (1.18, 1.26) | 318,661 | 1.64 (1.21, 2.21) |
| | Fast food (current) | 320,128 | 1.12 (1.09, 1.14) | 320,128 | 1.37 (1.12, 1.69) |
| | Television (current) | 339,823 | 1.05 (1.01, 1.08) | 339,823 | 2.09 (1.50, 2.91) |
| | Paternal tobacco (current) | 310,700 | 1.20 (1.17, 1.23) | 310,700 | 0.81 (0.62, 1.05) |
| | Maternal tobacco (current) | 338,740 | 1.33 (1.29, 1.37) | 338,740 | 1.78 (1.34, 2.38) |
| | Paracetamol (current) | 323,051 | 1.84 (1.79, 1.89) | 323,051 | 2.25 (1.72, 2.94) |
| | Open fire cooking (current) | 312,624 | 1.27 (1.19, 1.35) | 312,624 | 0.79 (0.58, 1.07) |

[a]Adjusted for sex and mothers level of education.

*Table 3.6 Fully adjusted effects of individual-level exposures on wheeze in the last 12 months stratified by country affluence.*

In subjects who had data present for wheeze, sex, maternal education and all exposures of interest (the "common sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Affluent Countries (n = 45,164) | | Non-Affluent countries (n = 86,760) | | Effect modification |
|---|---|---|---|---|---|---|
| | | Number exposed (%) | OR (95% CI) | Number exposed (%) | OR (95% CI) | p-value |
| 6-7 years | Low birthweight | 2,623 (5.8) | 1.17 (1.05, 1.31) | 8,051 (9.3) | 1.09 (0.99, 1.19) | 0.37 |
| | Paracetamol (1st year) | 28,106 (62.2) | 1.38 (1.28, 1.49) | 58,210 (67.1) | 1.30 (1.22, 1.39) | 0.03 |
| | Antibiotics (1st year) | 23,923 (53.0) | 1.71 (1.60, 1.82) | 50,193 (57.9) | 1.60 (1.51, 1.70) | 0.04 |
| | Breastfed ever | 30,903 (68.4) | 1.03 (0.97, 1.10) | 76,316 (88.0) | 0.88 (0.82, 0.95) | 0.006 |
| | Cat (1st year) | 6,762 (15.0) | 1.09 (1.00, 1.18) | 8,423 (9.7) | 1.36 (1.26, 1.48) | <0.001 |
| | Farm animals (1st year) | 3,710 (8.2) | 0.96 (0.87, 1.06) | 9,762 (11.3) | 1.23 (1.14, 1.33) | <0.001 |
| | Truck traffic (current) | 36,889 (81.7) | 1.12 (1.04, 1.21) | 67,569 (77.9) | 1.20 (1.12, 1.29) | 0.22 |
| | Fast food (current) | 13,924 (30.8) | 1.08 (1.02, 1.15) | 38,767 (44.7) | 1.06 (1.00, 1.12) | 0.51 |
| | Television (current) | 35,694 (79.0) | 1.05 (0.98, 1.13) | 69,573 (80.2) | 1.04 (0.96, 1.12) | 0.89 |
| | Paternal tobacco (current) | 18,031 (39.9) | 1.10 (1.04, 1.17) | 24,595 (28.3) | 1.13 (1.06, 1.19) | 0.49 |
| | Maternal tobacco (current) | 12,410 (27.5) | 1.19 (1.12, 1.28) | 7,839 (9.0) | 1.23 (1.12, 1.34) | 0.48 |
| | Paracetamol (current) | 5,051 (11.2) | 2.38 (2.21, 2.56) | 19,030 (21.9) | 1.89 (1.79, 2.01) | <0.001 |
| | Open fire cooking (current) | 256 (0.6) | 1.59 (1.17, 2.18) | 2,326 (2.7) | 1.40 (1.20, 1.63) | 0.60 |
| Age group | Exposure | Affluent Countries (n=50,637) | | Non-Affluent Countries (n=187,949) | | Effect modification |
| | | Number exposed (%) | OR (95% CI) | Number exposed (%) | OR (95% CI) | p-value |
| 13-14 years | Truck traffic (current) | 43,519 (85.9) | 1.14 (1.05, 1.24) | 154,914 (82.4) | 1.17 (1.12, 1.23) | 0.11 |
| | Fast food (current) | 25,567 (50.5) | 1.03 (0.97, 1.08) | 102,199 (54.4) | 1.09 (1.05, 1.12) | 0.34 |
| | Television (current) | 46,066 (91.0) | 1.04 (0.94, 1.14) | 158,202 (84.2) | 1.01 (0.96, 1.07) | 0.63 |
| | Paternal tobacco (current) | 20,731 (40.9) | 1.09 (1.03, 1.16) | 70,752 (37.6) | 1.13 (1.09, 1.17) | 0.09 |
| | Maternal tobacco (current) | 15,167 (30.0) | 1.29 (1.21, 1.37) | 28,090 (14.9) | 1.20 (1.14, 1.25) | 0.69 |
| | Paracetamol (current) | 13,453 (26.6) | 1.97 (1.85, 2.09) | 50,368 (26.8) | 1.75 (1.69, 1.82) | <0.001 |
| | Open fire cooking (current) | 535 (1.1) | 1.14 (0.89, 1.45) | 11,930 (6.3) | 1.35 (1.24, 1.47) | 0.86 |

[a]Adjusted for sex, mother's level of education and all other variables in the table.

*Table 3.7 Fully adjusted effects of school-level exposures on prevalence on wheeze in the last 12 month stratified by country affluence.*

In subjects who had data present for wheeze, sex, maternal education and all exposures of interest (the "common sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Affluent countries (n = 45,164) | | Non-affluent countries (n = 86,760) | | Effect modification |
|---|---|---|---|---|---|---|
| | | Median prevalence (%) | OR (95% CI) | Median prevalence (%) | OR (95% CI) | p-value |
| 6-7 years | Low birthweight | 5.2 | 1.51 (0.73, 3.14) | 7.0 | 2.01 (1.16, 3.47) | 0.37 |
| | Paracetamol (1st year) | 75.0 | 1.30 (0.88, 1.93) | 68.7 | 0.90 (0.63, 1.29) | 0.03 |
| | Antibiotics (1st year) | 57.1 | 1.77 (1.22, 2.55) | 57.8 | 1.13 (0.80, 1.61) | 0.02 |
| | Breastfed ever | 74.1 | 1.31 (0.92, 1.86) | 90.8 | 0.89 (0.53, 1.51) | 0.14 |
| | Cat (1st year) | 9.3 | 0.95 (0.65, 1.41) | 9.0 | 1.50 (0.90, 2.51) | 0.08 |
| | Farm animals (1st year) | 7.7 | 1.18 (0.76, 1.84) | 10.0 | 1.53 (0.99, 2.36) | 0.16 |
| | Truck traffic (current) | 84.4 | 1.00 (0.68, 1.47) | 84.5 | 1.14 (0.82, 1.60) | 0.61 |
| | Fast food (current) | 26.9 | 1.14 (0.80, 1.61) | 36.8 | 1.88 (1.45, 2.45) | 0.07 |
| | Television (current) | 83.3 | 1.90 (1.32, 2.73) | 85.7 | 1.82 (1.19, 2.78) | 0.72 |
| | Paternal tobacco (current) | 42.0 | 0.83 (0.59, 1.19) | 28.6 | 0.79 (0.54, 1.15) | 0.23 |
| | Maternal tobacco (current) | 29.0 | 1.49 (1.06, 2.10) | 5.1 | 3.30 (1.87, 5.83) | 0.004 |
| | Paracetamol (current) | 11.1 | 2.32 (1.52, 3.55) | 18.2 | 1.31 (0.89, 1.92) | 0.04 |
| | Open fire cooking (current) | 0.0 | 0.82 (0.15, 4.51) | 0.0 | 2.15 (1.16, 3.97) | 0.20 |
| Age group | Exposure | Affluent countries (n = 50,637) | | Non-affluent countries (n = 187,949) | | Effect modification |
| | | Median prevalence | OR (95% CI) | Median prevalence | OR (95% CI) | p-value |
| 13-14 years | Truck traffic (current) | 87.7 | 1.72 (0.69, 4.28) | 87.1 | 1.25 (0.86, 1.80) | 0.69 |
| | Fast food (current) | 48.3 | 1.48 (0.91, 2.41) | 55.2 | 1.13 (0.87, 1.47) | 0.33 |
| | Television (current) | 92.1 | 1.03 (0.41, 2.57) | 89.6 | 2.17 (1.40, 3.36) | 0.43 |
| | Paternal tobacco (current) | 43.5 | 0.39 (0.21, 0.72) | 33.6 | 0.55 (0.38, 0.80) | 0.72 |
| | Maternal tobacco (current) | 35.5 | 3.56 (1.86, 6.83) | 13.3 | 2.28 (1.47, 3.53) | 0.58 |
| | Paracetamol (current) | 29.9 | 1.85 (1.07, 3.21) | 29.2 | 2.46 (1.73, 3.51) | 0.56 |
| | Open fire cooking (current) | 0.0 | 1.23 (0.09, 16.44) | 0.8 | 1.31 (0.85, 2.04) | 0.84 |

[a]Adjusted for sex, mother's level of education and all other variables in the table.

### 3.2.6 Discussion

A number of papers have been published describing the association of asthma symptoms with individual-level risk factors in ISAAC Phase Three.[38-51] Here, we present the first comprehensive analyses to address these risk factors together in a multilevel framework and compare the individual-level and school-level findings to assess the possibility of various types of bias and confounding.

The associations we present here at the individual-level (Table 3.4) generally confirm the results for recent wheeze in published ISAAC papers. However, the ORs do not correspond exactly with previous publications due to the following differences in analytical approach. Firstly, the ISAAC survey methodology involved cluster sampling (sampling schools, then selecting all children of the appropriate age within each selected school). In previous publications no adjustment was made for within-school clustering of risk factors. In our multilevel models, inclusion of school as a random intercept adjusts more formally for intra-class correlation of both symptoms and exposures. This is a strength of the multilevel modelling approach.

Secondly, previous ISAAC Phase Three publications have adjusted for sex but not for socioeconomic status at the individual-level, whereas we included individual-level maternal education as a socioeconomic indicator in all models. Although maternal education is problematic to interpret as a socioeconomic indicator across diverse study centres from different countries and cultures, it is more likely to be valid for adjustment of socioeconomic confounding within local communities, such as school catchment areas, which is how it is used in our multi-level analyses.

Thirdly, previous ISAAC publications have adjusted for selected confounders (with a different set for each analysis), whereas we took a more comprehensive and harmonised approach in constructing our fully adjusted model. Comparison between the minimally adjusted and fully adjusted results in Table 3.4 confirms that the associations of wheeze with each risk factor are mutually independent, although in general there is some attenuation of the effects when all covariates are included. Some factors (e.g. paracetamol use in the first year of life) reduced markedly after confounder adjustment, indicating the possibility of residual confounding due to unmeasured confounders. Breastfeeding (in the younger children) and television viewing (in each age group) were the only individual-level risk factors which became non-significant after mutual adjustment, though the estimated associations in the minimally adjusted models were limited in magnitude prior to further adjustment.

A potential drawback of including multiple variables in a single model is a reduced sample size due to missing covariate data. About one-third of the 6-7-year-olds and about one-quarter of the 13-14-year-olds were excluded from the fully adjusted model due to incomplete risk factor information. However, comparison of results from the maximum sample with those from the common sample show that findings were generally very similar for the subset of respondents with complete covariate data, suggesting that valid conclusions can be drawn from the "common sample" dataset.

It should also be noted that, whilst early life exposures are less prone to reverse causality than current exposures, recall errors (which may be biased with respect to disease status) are perhaps more likely to have affected early childhood exposures in an interview conducted when the child was 6-7 years old.

An innovative feature of this paper is the presentation of associations of school-level prevalence of risk factors with individual-level wheeze. This type of population-level analysis is potentially vulnerable to the "ecological fallacy",[67,68] but this concept has several components, of which only one (ecological or population-level confounding) applies in our study. We avoid other forms of ecological fallacy because the population-level exposure (school-level prevalence of each risk factor) was derived by aggregating individual-level data, so the exposure measure relates directly to the schools actually participating in the study (not, for instance, a city-wide or national average) and to the children for whom questionnaire data were returned (not, for instance, children of a different age or social group in the same area). We regard these as strengths of the multilevel analytical approach.

The school-level associations shown in Table 3.4 generally maintained their direction on mutual adjustment, but the magnitude of the ORs (comparing the minimally adjusted and fully adjusted results) were less stable than the corresponding individual-level associations (also in Table 3.4). Nevertheless, in the younger age group, significant school-level associations were observed in the fully adjusted model with low birthweight, antibiotics in infancy, farm animal exposure in the first year, frequent fast-food and television exposure, maternal smoking (but not paternal smoking) and current paracetamol use (but not paracetamol use in first year of life). In the older age group, significant school-level associations were also observed with television viewing, maternal smoking and current paracetamol use.

The observed consistency of findings at the two levels provides indirect evidence against reverse causation and against strong contextual factors. Furthermore, since the spectrum of

unmeasured confounders is likely to be different at the individual and population levels, consistency of results between the two levels provides additional reassurance against unmeasured confounding. Therefore, on both counts, cross-level consistency strengthens the evidence for a causal relationship at the individual level.

Such cross-level comparisons (Table 3.4) show a close similarity in ORs at the individual-level and school-level for current paracetamol exposure and wheeze in each age group. This is of particular interest as a causal interpretation of this association has been disputed, due to the possibility of reverse causation (due to confounding by indication for paracetamol use and wheezing in infancy, or due to aspirin avoidance by older children with asthma or their families).

ISAAC Phase Three findings for paracetamol in the first year of life have also been debated.[69] At the individual level in the present study we found an OR of 1.75 for paracetamol use in the first year of life, which reduced to 1.33 after adjusting for other risk factors; this is similar to the findings from the original report,[38] which had ORs of 1.77 and 1.46 respectively. It has been suggested that this finding may be due to either residual confounding (given that more than one-half of the excess risk has disappeared after adjustment for known confounders), or due to confounding by indication.[69] This viewpoint is perhaps supported by the findings from our school-level analyses, where the minimally adjusted association with paracetamol use in the first year of life (OR = 1.42) disappears on adjustment for other risk factors (OR = 1.01).

Another risk factor which might be prone to reverse causation (due to pet avoidance in allergic families) is cat exposure in infancy. Here, the school-level association is somewhat stronger than the individual-level association in the minimally adjusted models, as would be predicted from avoidance bias. However, after full adjustment the estimated associations are very similar.

In the older age group, we found associations with paternal tobacco smoking which differed in direction between the individual- and school-level analyses. This was a surprising finding which we have been unable to satisfactorily explain.

Finally, stratified analyses identified some risk factors whose effects seemed to differ by country-level affluence (Tables 3.6 and 3.7). In the younger age group, current paracetamol use was consistently (i.e. in both individual- and school-level analyses) found to be a stronger risk factor for wheeze in affluent countries relative to non-affluent countries. Cat and farm animal exposure in the first year of life were found to be stronger risk factors in non-affluent

countries (where there is perhaps less avoidance bias) in the individual-level analysis. In the school-level analysis the affluence level-specific associations similarly differed, though there was not statistical evidence for effect modification. In the older age group, current paracetamol use was again found to be a stronger risk factor for wheeze in affluent countries relative to non-affluent countries, though only in the individual-level analysis.

In conclusion, these multilevel analyses generally confirm previously reported child-level findings for wheeze in ISAAC but, importantly, they provide additional evidence in favour of direct (rather than reverse) causation. This is the first comprehensive analysis of school-level associations, which may be particularly relevant to public health policies, which aim to prevent asthma symptoms by modifying environment, lifestyle or medication use among whole communities, rather than individual children or their families.

## 3.3 Paper II: Are environmental factors for atopic eczema in ISAAC Phase III due to reverse causation?

### 3.3.1 Article submitted

**SECTION A – Student Details**

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300807 | **Title** | Mrs |
| **First Name(s)** | Charlotte Emma | | |
| **Surname/Family Name** | Rutter | | |
| **Thesis Title** | Multi-level modelling of international variations and time trends in asthma and allergic diseases in children. | | |
| **Primary Supervisor** | Neil Pearce | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

**SECTION B – Paper already published**

| | | | |
|---|---|---|---|
| Where was the work published? | Journal of Investigative Dermatology | | |
| When was the work published? | December 2018 (online), May 2019 (print) | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | **Yes** | Was the work subject to academic peer review? | **Yes** |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

**SECTION C – Prepared for publication, but not yet published**

| | |
|---|---|
| Where is the work intended to be published? | |
| Please list the paper's authors in the intended authorship order: | |
| Stage of publication | |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role was running the analyses, creating the tables, writing the first draft of the methods and results, reviewing all drafts. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | [redacted] |
| **Date** | 10/07/2019 |

| | |
|---|---|
| **Supervisor Signature** | [redacted] |
| **Date** | 23/03/2022 |

### 3.3.2 Abstract

**Introduction**

Some previously described environmental associations for atopic eczema (AE) may be due to reverse causation. We explored the role of reverse causation by comparing individual- and school-level results for multiple AE risk factors.

**Methods**

ISAAC Phase Three surveyed children within schools (the sampling unit) on AE symptoms and potential risk factors. We assessed the effect of these risk factors on AE symptoms using mixed-effect logistic regression models, first with individual-level exposure data and second with school-level exposure prevalence.

**Results**

546,348 children from 53 countries were included. At age 6-7 the strongest individual-level associations were with current paracetamol use (odds ratio=1.45, 95% confidence interval 1.37-1.54), which persisted at school-level (1.55, 1.10-2.21), antibiotics (1.41, 1.34-1.48) and early life paracetamol use (1.28, 1.21-1.36) with the former persisting at school-level while the latter was no longer observed (1.35, 1.00-1.82 and 0.94, 0.69-1.28 respectively). At age 13-14 the strongest associations at individual-level were with current paracetamol use (1.57, 1.51-1.63) and open-fire cooking (1.46, 1.33-1.62); both were stronger at school-level (2.57, 1.84-3.59 and 2.38, 1.52-3.73 respectively). Association with exposure to heavy traffic (1.31, 1.27-1.36) also persisted at school-level (1.40, 1.07-1.82).

**Conclusion**

Most individual- and school-level effects were consistent tending to exclude reverse causation.

### 3.3.3 Introduction

Atopic eczema (AE) prevalence has increased substantially over the last 30 years; up to 20% of children in affluent westernised countries have AE during their lives and prevalence in low-and-middle income countries is increasing.[7] AE can have a major impact on sufferers and their families.[70,71]

While genetic factors clearly play an important role in AE aetiology, the dramatic increase in prevalence of AE in low- and middle-income countries is not consistent with a major role of genetic factors (since these do not change rapidly over time), and strongly suggests that environmental factors are important.[7,72]

Phase Three of the International Study of Asthma and Allergies in Childhood (ISAAC) has contributed significantly to understanding the associations between single environmental exposures and asthma, AE and rhinitis.[26] However, environmental factors may confound each other's effects in allergic diseases; hence assessing the role of many key environmental factors together is useful. Findings of cross-sectional studies, including ISAAC, may be limited by reverse causation, where the direction of cause-and-effect is contrary to a common presumption. This arises when a child being at risk of or having AE has led to changes in environmental exposures. For example, parents may remove pets following AE onset if they believe pets exacerbate AE symptoms, resulting in a paradoxical association between increased pet exposure and decreased AE when measured at a single time point,[43,73] rather than increased pet exposure increasing AE risk. Cross-sectional studies may also be limited by confounding by indication where the association with the risk factor has an alternative explanation; for example, AE may be complicated by skin infections requiring antibiotic treatment, leading to an observed increased association between AE and antibiotic use, rather than antibiotics being on the causal pathway for AE. Confounding by indication has been considered as an alternative explanation in relation to paracetamol (acetaminophen) use and asthma aetiology (but not AE) in previous ISAAC papers, although paracetamol may be taken for symptoms of severe skin and other infections associated with AE.[38]

In this study, we assessed the effects of the all the key environmental variables previously each singly associated with AE in ISAAC at an individual-level, aiming to find which variables were the most important. The individuals in ISAAC were within schools (the sampling unit). Therefore, at the same time, we also incorporated average school-level exposure estimates (calculated from the individual-level data) to assess whether associations seen for these multiple variables at individual-level could be due to bias from reverse causation.
In standard individual-level exposure models the estimated effect (here an odds ratio [OR]) corresponding to the individual-level risk factor can be interpreted as the OR of the exposed compared to the unexposed child, after adjustment for school-level prevalence (as a random intercept). This means that bias due to reverse causation may be a concern where this is plausible, but the estimated effects will not be confounded by unmeasured ecological factors (other environmental factors affecting the whole population).

In school-level exposure prevalence models, the estimated OR corresponding to the school-level prevalence of the risk factor can be interpreted as the effect on an individual of attending a hypothetical school where all children are exposed compared to a hypothetical school where

no children are exposed. School-level analyses can suffer from ecological bias, but there is less concern about reverse causation as the actions of a few parents will not significantly affect the school-level prevalence of an exposure. Therefore, comparing the results of these models enables exploration of whether single individual-level risk factors, which could plausibly be due to reverse causation, persist or diminish when explored at school-level.

The complementary approach of individual- and school-level analyses used in this paper enables exploration of mutual confounding by environmental factors and different forms of reverse causation, including avoidance bias and confounding by indication

### 3.3.4 Methods

**Study**

A detailed description of the ISAAC Phase Three methods can be found elsewhere,[3] and they will be briefly summarised here. ISAAC Phase Three is a multi-centre, multi-country, cross-sectional study of two age groups of schoolchildren (6-7 year-old children and 13-14 year-old adolescents) chosen from a random sample of schools in a defined geographical area.[2] The Phase Three survey included a standardised symptom questionnaire, which obtained data on symptoms of asthma, rhinoconjunctivitis and AE.[2] It also included a supplementary questionnaire which obtained data on a wide range of possible risk factors for the development of allergic disorders.[38] Parents or guardians completed the questionnaires for 6-7 year-olds and 13-14 year-olds answered the questionnaires themselves (http://isaac.auckland.ac.nz).

Only centres that met ISAAC methodology standards were included in the analysis. Excluded centres were those with fewer than 1,000 participants or response rates below 60% for the 6-7-year-old age group or below 70% for the 13-14 year-olds. Centres were also excluded if they did not return the Centre Report.[3] Schools with fewer than 10 participants for a given age group were excluded from that analysis.

**Variables**

The outcome of interest, AE symptoms in the last 12 months, was defined by positive responses to the questions “Has your child/have you ever had an itchy rash which was coming and going for at least six months?”, “Has your child/have you had this itchy rash at any time in the last 12 months?” and “Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?”.

Analyses in this paper included only the key environmental variables previously each singly associated with AE in ISAAC at an individual-level. For the 6-7 year-olds, risk factors were paracetamol use in the first year of life and in the past 12 months,[38] antibiotic use in the first year of life,[40] breast feeding,[41] cat and dog in the home in the first year of life,[43] regular contact with farm animals in the first year of life,[42] regular maternal contact with farm animals while pregnant,[42] heavy truck traffic,[39] fast food consumption,[46] parental smoking,[44] cooking on an open fire,[47] birthweight[48] and number of siblings.[50] For the 13-14 year olds, risk factors were heavy truck traffic,[39] fast food consumption,[46] parental smoking,[44] paracetamol use in the past 12 months,[51] open fire cooking,[47] and number of siblings.[50]

Most of these items had simple "yes/no" answers. The exceptions have been dichotomised: paracetamol use in the last 12 months (at least once per month vs. less than once per month), heavy truck traffic (frequently or almost the whole day vs. seldom or never), fast food consumption (once per week or more vs. less than once per week), low birthweight (less than 2.5 kg vs. at least 2.5 kg), and number of siblings (2 or more vs. 1 or fewer). Full definitions of the environmental risk factors are in Table 3.8.

Additionally, the analysis considered confounding by sex and highest level of maternal education (primary, secondary, tertiary, missing/not stated).

Finally, stratification by affluence of country was achieved using standard approaches. Gross National Income (GNI) as of 2002 (obtained from the World Bank website[61] where available and filled in by the Central Intelligence Agency (CIA) World Factbook[62]) and a classification of affluent countries (GNI over US$9,205) and non-affluent countries (GNI US$9,205 or lower) taken from the 2001 World Bank definition of high-income countries versus low- to middle-income countries.[63]

**Statistical analyses**

The two age groups were analysed separately. All analyses were conducted using mixed effect logistic regression models. There are four hierarchies of data in the study design: individual, school, centre and country. We accounted for this by including random intercepts at each of the higher 3 levels. Sex and highest level of maternal education were adjusted for as individual-level confounders in all models. The school-level prevalence of each risk factor was calculated as the proportion of children with that risk factor out of all children included in the analysis within that school.

Separate models were used to assess the effects of individual-level exposures and aggregated school-level prevalence of exposures on the individual-level outcome. Using the approach proposed by,[64] these effects were formally compared within a multi-level framework, by fitting "hybrid fixed effect models". Results from these models were consistent with a simpler approach and are not discussed further.

Within each of these approaches, a minimally adjusted model was fitted. This was done on two samples (i) the "maximum sample" which was the sub-sample that had no data missing for AE, the confounders (sex, level of maternal education) and the one exposure of interest (ii) the "common sample" which was the sub-sample that had no data missing for AE, confounders and all exposures of interest. A fully adjusted model was also fitted to the common sample. Fully adjusted models included all risk factors at the individual level for the individual-level models, school-level prevalence of all the risk factors for the school-level models.

The extent of co-linearity in fully adjusted models was examined by comparing the standard errors in the fully adjusted model with the standard errors in the minimally adjusted model (common sample). Fully adjusted analyses were additionally stratified by 'affluent' and 'non-affluent' countries to assess whether avoidance behaviour may have contributed to observed associations (since such behaviour is more likely in more affluent countries). Effect modification by country-level affluence was tested for each risk factor separately.

All analyses were conducted using Stata version 14.[66] Informed consent was obtained from parents of all participating children; the ISAAC Phase Three study was approved by local institutional review boards in all participating centres.

### 3.3.5 Results

**6-7 year olds**

The 6-7-year-old sample contained 221,280 children (from 3,167 schools, 75 centres, 32 countries). There were 120,799 children (from 2,165 schools, 59 centres, 22 countries) with complete data across all analysis variables. See the data flowchart (Figure 3.3) for further details. Individual- and school-level summary statistics are presented in Table 3.9 for the "common sample" and Table 3.10 for the "maximum sample" (see "Statistical analyses" section for definitions).

*Table 3.8 Definitions of risk factors for eczema*

| Risk factors for ages 6-7 | Question (asked to parent) | Positive Response |
|---|---|---|
| Farm animals (in utero) | Has the child's mother had regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry) while being pregnant with this child? | Yes |
| Low birthweight | What was the weight of your child when he / she was born? | Less than 2.5kg |
| Paracetamol (1st year) | In the first 12 months of your child's life, did you usually give paracetamol for fever? | Yes |
| Antibiotics (1st year) | In the first 12 months of your child's life, did your child have any antibiotics? | Yes |
| Breastfed ever | Was your child breastfed? | Yes |
| Cat (1st year) | Did you have a cat in your home during the first year of your child's life? | Yes |
| Dog (1st year) | Did you have a dog in your home during the first year of your child's life? | Yes |
| Farm animals (1st year) | In your child's first year of life, did he / she have regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry)? | Yes |
| 2 or more siblings | How many older and younger brothers and sisters does your child have? | Total of 2 or more |
| Heavy truck traffic (current) | How often do trucks pass through the street where you live, on weekdays? | Frequently or almost the whole day |
| Fast food (current) | In the past 12 months, how often, on average did your child eat fast food / burgers? | At least once a week |
| Paternal tobacco (current) | Does your child's father (or male guardian) smoke cigarettes? | Yes |
| Maternal tobacco (current) | Does your child's mother (or female guardian) smoke cigarettes? | Yes |
| Paracetamol (current) | In the past 12 months, how often, on average, have you given your child paracetamol? | At least once a month |
| Open fire cooking (current) | In your house, what fuels are usually used for cooking? Electricity, Gas, Open fires, Other | Any that include open fires |

| Risk factors for ages 13-14 | Question (asked to child) | Positive Response |
|---|---|---|
| 2 or more siblings | How many older and younger brothers and sisters do you have? | Total of 2 or more |
| Heavy truck traffic (current) | How often do trucks pass through the street where you live, on weekdays? | Frequently or almost the whole day |
| Fast food (current) | In the past 12 months, how often, on average did you eat fast food / burgers? | At least once a week |
| Paternal tobacco (current) | Does your father (or male guardian) smoke cigarettes? | Yes |
| Maternal tobacco (current) | Does your mother (or female guardian) smoke cigarettes? | Yes |
| Paracetamol (current) | In the past 12 months, how often, on average, have you taken paracetamol? | At least once a month |
| Open fire cooking (current) | In your house, what fuels are usually used for cooking? Electricity, Gas, Open fires, Other | Any that include open fires |

Minimally adjusted associations in the common sample were broadly similar to those in the maximum sample (Tables 3.11 and 3.12). The strongest associations in the fully-adjusted individual-level analyses were for current paracetamol use (odds ratio (OR) = 1.45, 95% CI 1.37-1.54), antibiotic use in the first year of life (1.41, 1.34-1.48), and paracetamol use in the first year of life (1.28, 1.21-1.36) (Table 3.11).

In fully-adjusted school-level analyses, the associations for current paracetamol use (1.55, 1.10-2.21) and early life antibiotic use (1.35, 1.00-1.82) were maintained, but the association with early life paracetamol use disappeared (0.94, 0.69-1.28) (Table 3.11). Stronger associations were observed at school-level for open fire cooking (1.84, 0.98-3.45 compared to 1.12, 0.95-1.32 at individual-level), and maternal tobacco use (1.61, 1.14-2.25 compared to 1.06, 0.99-1.13 at individual-level). A weak association with current heavy traffic exposure observed at individual-level was no longer significant at school level. Associations with breastfeeding were similar in individual and school-level analyses (1.11, 1.05-1.18 and 1.06, 0.75-1.48) but with less precision. A potentially harmful association of low birthweight with AE symptoms was seen at school-level (1.78, 1.07-2.95) compared to a small protective association at individual-level (0.89, 0.81-0.97) (Table 3.11).

In analyses stratified by country-level affluence (Tables 3.13 and 3.14), there was strong evidence at individual-level that being exposed to a cat, dog or farm animals in the first year of life, or maternal contact with farm animals while pregnant, was associated with AE symptoms in non-affluent countries at individual level (Tables 3.13 and 3.14), while none of these associations were observed at school-level in either setting. There was also evidence that the association of AE symptoms with current paracetamol was strong at individual and school-level with stronger estimates in affluent countries (1.64; 1.49-1.79) than non-affluent settings (1.35, 1.25-1.45). Weak associations with breastfeeding were only observed at individual-level in affluent countries, but were not observed at school-level, with no association being seen in non-affluent countries.

**13-14 year olds**

The full 13-14-year-old sample contained 362,048 adolescents (from 2,592 schools, 122 centres, 54 countries). There were 233,159 adolescents (from 2,039 schools, 97 centres, 41 countries) with complete data across all analysis variables. See the data flowchart (Figure 3.4) for further details. Individual- and school-level summary statistics are presented in Table 3.9 for the common sample and Table 3.10 for the maximum sample.

Minimally adjusted associations in the common sample were broadly similar to those in the maximum sample (Tables 3.11 and 3.12). The strongest associations in fully-adjusted individual-level analyses were for current paracetamol use (1.57, 1.51-1.63), cooking on an open fire (1.46, 1.33-1.62), and exposure to heavy truck traffic (1.31, 1.27-1.36) (Table 3.11).

In fully-adjusted school-level analyses associations for current paracetamol use (2.57, 1.84-3.59), cooking on an open fire (2.38, 1.52-3.73) and heavy truck traffic (1.40, 1.07-1.82) were maintained (Table 3.11). An association was also observed at school-level for fast food consumption (2.11, 1.66-2.70) with a much weaker association at individual-level (1.05, 1.02-1.10). At individual-level there was an association with paternal tobacco use (1.15, 1.10-1.19), with conflicting findings at school-level (0.64, 0.44-0.94).

In analyses stratified by country-level affluence (Tables 3.13 and 3.14) there was evidence at individual-level that current paracetamol use was slightly more strongly associated with AE symptoms in affluent (1.75, 1.60-1.92) than non-affluent (1.53, 1.47-1.60) countries (Table 3.13), with stronger associations in both settings at school-level (Table 3.14). There was also some evidence that paternal tobacco use was associated with AE symptoms in non-affluent countries (1.17, 1.12-1.23) at individual-level, but not at school-level, and no association was seen in affluent settings (1.05, 0.96-1.14).

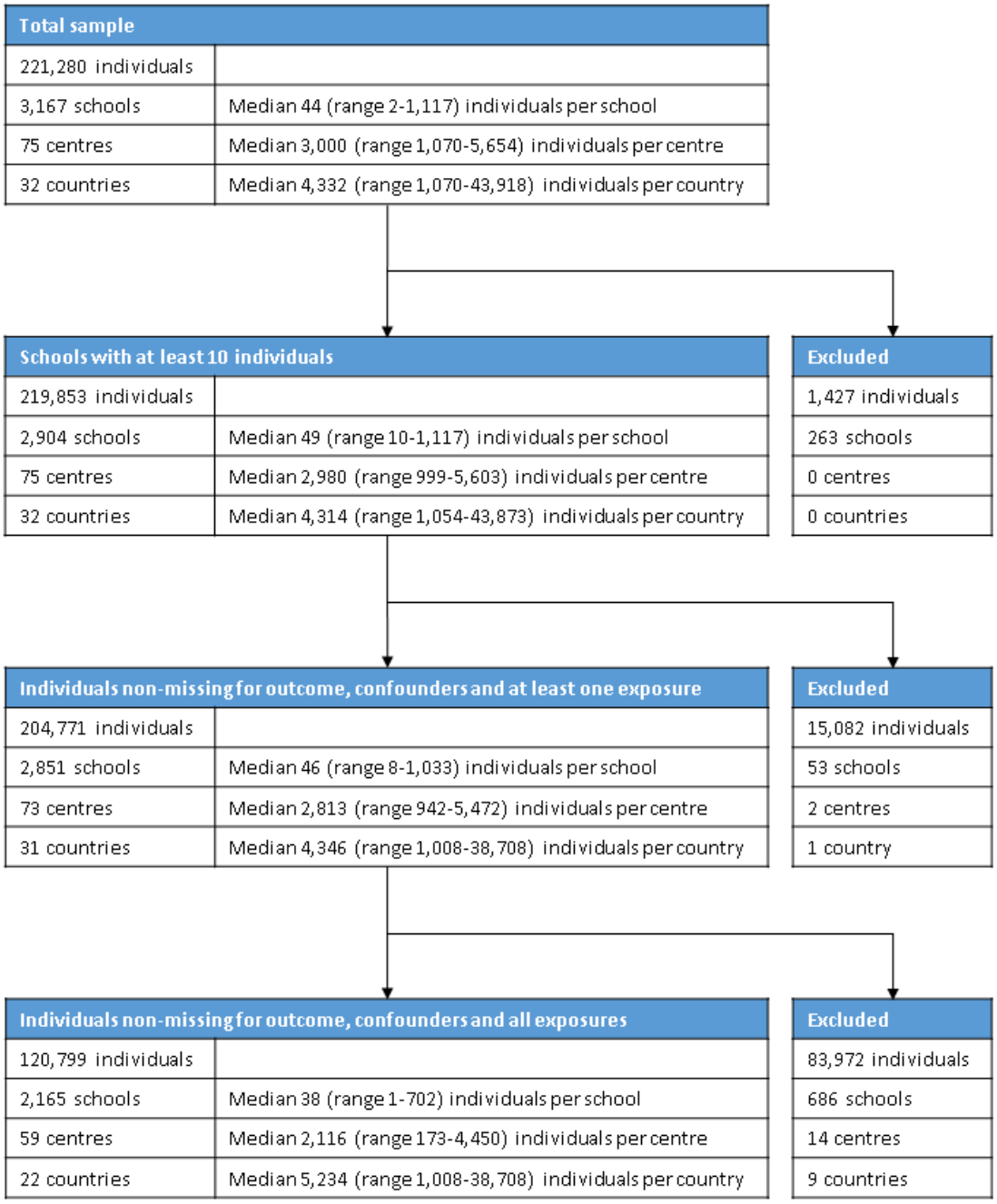


*Figure 3.3 Atopic eczema data flowchart, age 6-7 years*

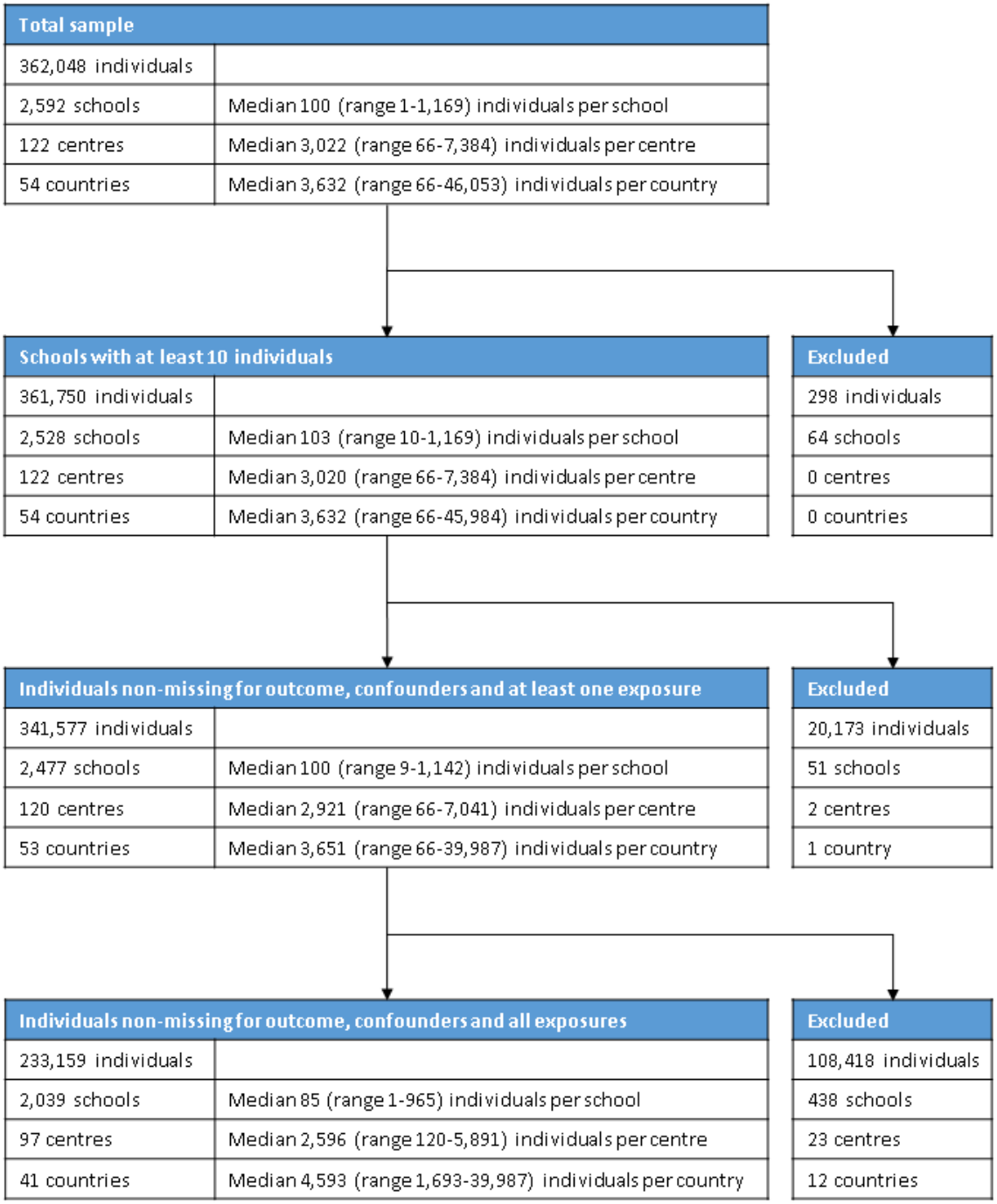


*Figure 3.4 Atopic eczema data flowchart, age 13-14 years*

*Table 3.9 Atopic eczema - Summary statistics in the common sample.*

In subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest.

| Age group | Variable | Individual-level (n = 120,799) | School-level (n = 2,165) | |
|---|---|---|---|---|
| | | Prevalence (%) | Median prevalence (%) | Prevalence IQR (%) |
| 6-7 years | AE in the last 12 months | 7.4 | 6.4 | (2.1, 12.0) |
| | Farm animals (in utero) | 7.7 | 6.6 | (2.3, 12.7) |
| | Low birthweight | 7.7 | 5.6 | (2.2, 9.7) |
| | Paracetamol (1st year) | 6.2 | 70.7 | (57.1, 84.3) |
| | Antibiotics (1st year) | 5.7 | 57.1 | (47.2, 65.4) |
| | Breastfed ever | 80.5 | 83.7 | (73.5, 91.8) |
| | Cat (1st year) | 10.9 | 8.3 | (3.6, 16.7) |
| | Dog (1st year) | 19.8 | 19.7 | (10.0, 30.7) |
| | Farm animals (1st year) | 9.4 | 8.3 | (3.7, 14.8) |
| | 2 or more siblings | 34.7 | 32.8 | (18.5, 48.4) |
| | Heavy Truck traffic (current) | 38.0 | 37.8 | (27.0, 48.7) |
| | Fast food (current) | 39.6 | 31.1 | (16.5, 50.0) |
| | Paternal tobacco (current) | 31.8 | 34.8 | (21.1, 47.8) |
| | Maternal tobacco (current) | 16.3 | 16.7 | (4.4, 32.8) |
| | Paracetamol (current) | 18.0 | 14.2 | (6.1, 25.0) |
| | Open fire cooking (current) | 1.9 | 0.0 | (0.0, 1.6) |
| Age group | Variable | Individual-level (n = 233,159) | School-level (n = 2,039) | |
| | | Prevalence (%) | Median prevalence (%) | Prevalence IQR (%) |
| 13-14 years | AE in the last 12 months | 6.2 | 4.8 | (2.2, 9.1) |
| | 2 or more siblings | 54.1 | 59.3 | (37.7, 80.0) |
| | Heavy Truck traffic (current) | 39.6 | 39.2 | (30.1, 50.0) |
| | Fast food (current) | 53.6 | 52.8 | (39.1, 68.0) |
| | Paternal tobacco (current) | 38.4 | 37.1 | (23.8, 49.0) |
| | Maternal tobacco (current) | 18.3 | 18.5 | (3.6, 35.4) |
| | Paracetamol (current) | 27.0 | 29.8 | (17.7, 41.7) |
| | Open fire cooking (current) | 5.2 | 0.6 | (0.0, 2.9) |

*Table 3.10 Atopic eczema - Summary statistics in the maximum sample.*

In subjects with data for atopic eczema symptoms, sex, level of maternal education and the one exposure of interest.

| Age group | Variable | Individual-level | | School-level | | |
|---|---|---|---|---|---|---|
| | | n | Prevalence (%) | n | Median prevalence (%) | Prevalence IQR (%) |
| 6-7 years | Atopic eczema in the last 12 months | 204,771 | 7.4 | 2,851 | 6.7 | (2.9, 11.6) |
| | Farm animals (in utero) | 181,600 | 10.0 | 2,630 | 7.8 | (3.4, 15.6) |
| | Low birthweight | 169,993 | 8.5 | 2,549 | 6.3 | (3.2, 10.6) |
| | Paracetamol (1st year) | 182,134 | 65.2 | 2,583 | 70.0 | (56.3, 82.6) |
| | Antibiotics (1st year) | 180,799 | 54.0 | 2,663 | 55.9 | (46.2, 64.6) |
| | Breastfed ever | 192,559 | 80.0 | 2,701 | 84.6 | (73.6, 92.9) |
| | Cat (1st year) | 189,922 | 12.0 | 2,701 | 10.5 | (4.8, 20.0) |
| | Dog (1st year) | 174,772 | 20.6 | 2,469 | 22.2 | (12.3, 32.8) |
| | Farm animals (1st year) | 181,744 | 11.6 | 2,634 | 9.8 | (4.6, 17.8) |
| | 2 or more siblings | 203,603 | 38.1 | 2,851 | 37.5 | (22.2, 54.4) |
| | Heavy Truck traffic (current) | 184,503 | 38.6 | 2,729 | 38.2 | (27.8, 49.1) |
| | Fast food (current) | 181,864 | 41.1 | 2,798 | 33.3 | (18.5, 51.1) |
| | Paternal tobacco (current) | 196,353 | 31.3 | 2,748 | 33.3 | (19.3, 46.5) |
| | Maternal tobacco (current) | 199,522 | 14.1 | 2,781 | 14.0 | (3.0, 30.1) |
| | Paracetamol (current) | 191,900 | 19.8 | 2,734 | 16.7 | (7.9, 31.3) |
| | Open fire cooking (current) | 185,718 | 3.0 | 2,724 | 0.0 | (0.0, 2.2) |
| 13-14 years | Atopic eczema in the last 12 months | 341,577 | 6.8 | 2,477 | 5.5 | (2.7, 10.2) |
| | 2 or more siblings | 334,708 | 55.2 | 2,402 | 62.1 | (38.9, 81.0) |
| | Heavy Truck traffic (current) | 309,621 | 39.6 | 2,348 | 39.4 | (30.3, 51.0) |
| | Fast food (current) | 313,066 | 55.2 | 2,388 | 55.2 | (40.7, 69.5) |
| | Paternal tobacco (current) | 301,502 | 37.6 | 2,259 | 36.7 | (23.9, 48.2) |
| | Maternal tobacco (current) | 329,659 | 18.1 | 2,433 | 18.3 | (4.0, 33.3) |
| | Paracetamol (current) | 314,005 | 28.8 | 2,404 | 31.0 | (19.5, 43.5) |
| | Open fire cooking (current) | 303,363 | 7.3 | 2,321 | 1.1 | (0.0, 4.7) |

*Table 3.11 Effects of individual- and school-level exposures on atopic eczema symptoms in the last 12 months in the common sample.*

In subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest. Mixed logistic regression models with random intercepts at the school, centre and country levels.

| Age group | Exposure | Individual-level exposure | | School-level exposure | |
|---|---|---|---|---|---|
| | | Minimally adjusted[a] | Fully adjusted[b] | Minimally adjusted[a] | Fully adjusted[b] |
| 6-7 years (n = 120,799) | Farm animals (in utero) | 1.32 (1.22, 1.43) | 1.11 (1.00, 1.23) | 1.48 (1.04, 2.12) | 1.05 (0.54, 2.04) |
| | Low birthweight | 0.92 (0.84, 1.01) | 0.89 (0.81, 0.97) | 2.32 (1.43, 3.76) | 1.78 (1.07, 2.95) |
| | Paracetamol (1st year) | 1.53 (1.45, 1.61) | 1.28 (1.21, 1.36) | 1.11 (0.85, 1.46) | 0.94 (0.69, 1.28) |
| | Antibiotics (1st year) | 1.56 (1.49, 1.64) | 1.41 (1.34, 1.48) | 1.32 (1.00, 1.75) | 1.35 (1.00, 1.82) |
| | Breastfed ever | 1.09 (1.03, 1.16) | 1.11 (1.05, 1.18) | 0.97 (0.69, 1.35) | 1.06 (0.75, 1.48) |
| | Cat (1st year) | 1.17 (1.10, 1.25) | 1.10 (1.03, 1.17) | 1.40 (0.99, 1.97) | 1.15 (0.78, 1.71) |
| | Dog (1st year) | 1.12 (1.07, 1.18) | 1.05 (1.00, 1.11) | 1.20 (0.90, 1.61) | 0.96 (0.69, 1.32) |
| | Farm animals (1st year) | 1.32 (1.23, 1.42) | 1.16 (1.06, 1.27) | 1.50 (1.07, 2.10) | 1.15 (0.62, 2.15) |
| | 2 or more siblings | 0.96 (0.91, 1.01) | 0.95 (0.90, 0.99) | 1.26 (1.01, 1.56) | 1.11 (0.88, 1.40) |
| | Heavy Truck traffic (current) | 1.16 (1.11, 1.22) | 1.11 (1.06, 1.16) | 0.92 (0.74, 1.14) | 0.81 (0.65, 1.02) |
| | Fast food (current) | 1.03 (0.98, 1.08) | 0.99 (0.94, 1.04) | 0.94 (0.75, 1.18) | 0.96 (0.76, 1.22) |
| | Paternal tobacco (current) | 1.08 (1.03, 1.13) | 1.04 (0.99, 1.10) | 1.18 (0.92, 1.53) | 0.83 (0.61, 1.13) |
| | Maternal tobacco (current) | 1.10 (1.04, 1.17) | 1.06 (0.99, 1.13) | 1.56 (1.18, 2.07) | 1.61 (1.14, 2.25) |
| | Paracetamol (current) | 1.60 (1.51, 1.69) | 1.45 (1.37, 1.54) | 1.63 (1.17, 2.26) | 1.55 (1.10, 2.21) |
| | Open fire cooking (current) | 1.15 (0.97, 1.35) | 1.12 (0.95, 1.32) | 2.30 (1.27, 4.16) | 1.84 (0.98, 3.45) |
| Age group | Exposure | Individual-level exposure | | School-level exposure | |
| | | Minimally adjusted[a] | Fully adjusted[b] | Minimally adjusted[a] | Fully adjusted[b] |
| 13-14 years (n = 233,159) | 2 or more siblings | 1.10 (1.05, 1.14) | 1.08 (1.03, 1.12) | 1.34 (1.04, 1.74) | 1.26 (0.97, 1.65) |
| | Heavy Truck traffic (current) | 1.36 (1.31, 1.41) | 1.31 (1.27, 1.36) | 1.66 (1.28, 2.17) | 1.40 (1.07, 1.82) |
| | Fast food (current) | 1.10 (1.05, 1.14) | 1.05 (1.02, 1.10) | 2.08 (1.63, 2.66) | 2.11 (1.66, 2.70) |
| | Paternal tobacco (current) | 1.21 (1.16, 1.25) | 1.15 (1.10, 1.19) | 0.85 (0.61, 1.17) | 0.64 (0.44, 0.94) |
| | Maternal tobacco (current) | 1.19 (1.14, 1.25) | 1.11 (1.06, 1.16) | 0.72 (0.50, 1.04) | 0.79 (0.52, 1.19) |
| | Paracetamol (current) | 1.61 (1.55, 1.67) | 1.57 (1.51, 1.63) | 2.68 (1.91, 3.75) | 2.57 (1.84, 3.59) |
| | Open fire cooking (current) | 1.47 (1.33, 1.62) | 1.46 (1.33, 1.62) | 2.29 (1.47, 3.57) | 2.38 (1.52, 3.73) |

[a]Adjusted for sex and mothers level of education. [b]Additionally adjusted for all other variables in the table.

*Table 3.12 Minimally adjusted effects of individual- and school-level exposures on atopic eczema symptoms in the last 12 months in the maximum sample.*

In subjects with data for atopic eczema symptoms, sex, level of maternal education and the one exposure of interest. Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Individual-level exposure | | School-level exposure | |
|---|---|---|---|---|---|
| | | n | OR (95% CI) | n | OR (95% CI) |
| 6-7 years | Farm animals (in utero) | 181,600 | 1.37 (1.29, 1.45) | 181,600 | 1.85 (1.39, 2.45) |
| | Low birthweight | 169,993 | 0.93 (0.86, 1.00) | 169,993 | 1.65 (1.07, 2.55) |
| | Paracetamol (1st year) | 182,134 | 1.55 (1.48, 1.62) | 182,134 | 1.12 (0.87, 1.44) |
| | Antibiotics (1st year) | 180,799 | 1.60 (1.53, 1.66) | 180,799 | 1.29 (1.00, 1.66) |
| | Breastfed ever | 192,559 | 1.09 (1.04, 1.14) | 192,559 | 0.94 (0.69, 1.26) |
| | Cat (1st year) | 189,922 | 1.27 (1.21, 1.34) | 189,922 | 1.79 (1.33, 2.41) |
| | Dog (1st year) | 174,772 | 1.16 (1.11, 1.21) | 174,772 | 1.48 (1.14, 1.92) |
| | Farm animals (1st year) | 181,744 | 1.41 (1.34, 1.49) | 181,744 | 2.06 (1.56, 2.72) |
| | 2 or more siblings | 203,603 | 0.98 (0.94, 1.01) | 203,603 | 1.44 (1.20, 1.73) |
| | Heavy Truck traffic (current) | 184,503 | 1.19 (1.14, 1.23) | 184,503 | 1.15 (0.94, 1.39) |
| | Fast food (current) | 181,864 | 1.03 (0.99, 1.07) | 181,864 | 0.84 (0.69, 1.02) |
| | Paternal tobacco (current) | 196,353 | 1.11 (1.07, 1.16) | 196,353 | 1.27 (1.01, 1.60) |
| | Maternal tobacco (current) | 199,522 | 1.17 (1.11, 1.22) | 199,522 | 1.61 (1.24, 2.09) |
| | Paracetamol (current) | 191,900 | 1.60 (1.53, 1.67) | 191,900 | 1.69 (1.28, 2.23) |
| | Open fire cooking (current) | 185,718 | 1.14 (1.02, 1.29) | 185,718 | 2.98 (1.83, 4.85) |
| 13-14 years | 2 or more siblings | 334,708 | 1.06 (1.03, 1.10) | 334,708 | 1.25 (0.99, 1.57) |
| | Heavy Truck traffic (current) | 309,621 | 1.31 (1.27, 1.35) | 309,621 | 1.53 (1.20, 1.96) |
| | Fast food (current) | 313,066 | 1.09 (1.06, 1.13) | 313,066 | 1.85 (1.48, 2.32) |
| | Paternal tobacco (current) | 301,502 | 1.22 (1.18, 1.26) | 301,502 | 0.72 (0.54, 0.96) |
| | Maternal tobacco (current) | 329,659 | 1.23 (1.19, 1.28) | 329,659 | 0.91 (0.66, 1.24) |
| | Paracetamol (current) | 314,005 | 1.57 (1.52, 1.62) | 314,005 | 2.14 (1.59, 2.88) |
| | Open fire cooking (current) | 303,363 | 1.43 (1.34, 1.53) | 303,363 | 1.50 (1.09, 2.06) |

[a]Adjusted for sex and mothers level of education.

*Table 3.13 Fully adjusted effects of individual-level exposures on atopic eczema symptoms in the last 12 months stratified by country affluence.*

In subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest (the "common sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Affluent Countries | | Non-Affluent countries | | Effect modification |
|---|---|---|---|---|---|---|
| | | Number exposed (%) | OR (95% CI) | Number exposed (%) | OR (95% CI) | |
| 6-7 years | Farm animals (in utero) | 2,970 (6.8) | 1.00 (0.84, 1.20) | 6,365 (8.2) | 1.19 (1.06, 1.35) | <0.001 |
| | Low birthweight | 2,508 (5.8) | 0.92 (0.80, 1.06) | 6,763 (8.7) | 0.85 (0.76, 0.96) | 0.51 |
| | Paracetamol (1st year) | 27,222 (62.8) | 1.29 (1.17, 1.41) | 52,751 (68.1) | 1.30 (1.21, 1.40) | 0.93 |
| | Antibiotics (1st year) | 22,736 (52.4) | 1.44 (1.34, 1.55) | 44,504 (57.5) | 1.37 (1.28, 1.47) | 0.33 |
| | Breastfed ever | 29,658 (68.4) | 1.16 (1.07, 1.25) | 67,532 (87.2) | 1.05 (0.97, 1.15) | 0.11 |
| | Cat (1st year) | 6,717 (15.5) | 1.01 (0.92, 1.10) | 6,508 (8.4) | 1.21 (1.09, 1.33) | <0.001 |
| | Dog (1st year) | 8,102 (18.7) | 0.98 (0.90, 1.06) | 15,790 (20.4) | 1.09 (1.02, 1.17) | <0.001 |
| | Farm animals (1st year) | 3,688 (8.5) | 0.96 (0.81, 1.13) | 7,662 (9.9) | 1.29 (1.15, 1.44) | <0.001 |
| | 2 or more siblings | 12,887 (29.7) | 0.95 (0.89, 1.03) | 29,066 (37.5) | 0.93 (0.87, 1.00) | 0.95 |
| | Heavy Truck traffic (current) | 14,353 (33.1) | 1.07 (1.00, 1.15) | 31,515 (40.7) | 1.14 (1.07, 1.21) | 0.14 |
| | Fast food (current) | 13,496 (31.1) | 1.05 (0.97, 1.13) | 34,343 (44.4) | 0.96 (0.89, 1.02) | 0.10 |
| | Paternal tobacco (current) | 16,991 (39.2) | 1.05 (0.98, 1.14) | 21,468 (27.7) | 1.04 (0.97, 1.11) | 0.40 |
| | Maternal tobacco (current) | 12,058 (27.8) | 1.00 (0.92, 1.08) | 7,620 (9.8) | 1.15 (1.05, 1.26) | 0.008 |
| | Paracetamol (current) | 5,011 (11.6) | 1.64 (1.49, 1.79) | 16,724 (21.6) | 1.35 (1.25, 1.45) | 0.003 |
| | Open fire cooking (current) | 255 (0.6) | 1.09 (0.73, 1.63) | 2,000 (2.6) | 1.10 (0.92, 1.33) | 0.60 |
| 13-14 years | 2 or more siblings | 18,086 (37.2) | 1.06 (0.97, 1.16) | 108,122 (58.6) | 1.08 (1.03, 1.13) | 0.51 |
| | Heavy Truck traffic (current) | 17,725 (36.5) | 1.32 (1.21, 1.44) | 74,568 (40.4) | 1.31 (1.26, 1.37) | 0.81 |
| | Fast food (current) | 24,780 (51.0) | 1.06 (0.97, 1.15) | 100,139 (54.3) | 1.06 (1.01, 1.10) | 0.79 |
| | Paternal tobacco (current) | 19,486 (40.1) | 1.05 (0.96, 1.14) | 70,043 (38.0) | 1.17 (1.12, 1.23) | 0.01 |
| | Maternal tobacco (current) | 14,713 (30.3) | 1.09 (0.99, 1.20) | 27,899 (15.1) | 1.12 (1.06, 1.18) | 0.31 |
| | Paracetamol (current) | 13,211 (27.2) | 1.75 (1.60, 1.92) | 49,682 (26.9) | 1.53 (1.47, 1.60) | 0.007 |
| | Open fire cooking (current) | 513 (1.1) | 1.55 (1.10, 2.18) | 11,565 (6.3) | 1.44 (1.30, 1.60) | 0.73 |

[a]Adjusted for sex, mother's level of education and all other variables in the table.

*Table 3.14 Fully adjusted effects of school-level exposures on prevalence on atopic eczema symptoms in the last 12 months stratified by country affluence.*

In subjects with data for atopic eczema symptoms, sex, maternal education and all exposures of interest (the "common sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Affluent countries | | Non-affluent countries | | Effect modification |
|---|---|---|---|---|---|---|
| | | Median | OR (95% CI) | Median | OR (95% CI) | |
| 6-7 years | Farm animals (in utero) | 5.7 | 1.51 (0.56, 4.03) | 7.0 | 0.77 (0.30, 1.97) | 0.13 |
| | Low birthweight | 5.1 | 1.16 (0.49, 2.73) | 6.3 | 1.87 (0.94, 3.70) | 0.19 |
| | Paracetamol (1st year) | 76.0 | 1.29 (0.82, 2.05) | 68.2 | 0.88 (0.58, 1.34) | 0.28 |
| | Antibiotics (1st year) | 56.6 | 1.39 (0.91, 2.12) | 58.3 | 1.23 (0.79, 1.90) | 0.41 |
| | Breastfed ever | 74.1 | 1.15 (0.77, 1.71) | 89.1 | 0.83 (0.45, 1.54) | 0.35 |
| | Cat (1st year) | 10.0 | 1.02 (0.64, 1.64) | 7.7 | 1.45 (0.68, 3.09) | 0.03 |
| | Dog (1st year) | 18.8 | 0.79 (0.51, 1.24) | 20.6 | 1.18 (0.72, 1.92) | 0.03 |
| | Farm animals (1st year) | 7.8 | 0.57 (0.22, 1.47) | 8.6 | 1.86 (0.81, 4.31) | 0.02 |
| | 2 or more siblings | 27.8 | 1.01 (0.72, 1.40) | 36.4 | 1.08 (0.77, 1.51) | 0.44 |
| | Heavy Truck traffic (current) | 33.3 | 0.83 (0.60, 1.14) | 40.4 | 0.83 (0.60, 1.16) | 0.77 |
| | Fast food (current) | 27.3 | 0.79 (0.54, 1.17) | 35.7 | 1.11 (0.81, 1.52) | 0.34 |
| | Paternal tobacco (current) | 41.5 | 1.02 (0.67, 1.55) | 29.4 | 0.61 (0.38, 0.99) | 0.57 |
| | Maternal tobacco (current) | 30.0 | 1.43 (0.96, 2.14) | 7.7 | 1.88 (1.01, 3.51) | 0.54 |
| | Paracetamol (current) | 11.7 | 2.05 (1.23, 3.42) | 16.9 | 1.35 (0.83, 2.22) | 0.38 |
| | Open fire cooking (current) | 0.0 | 2.75 (0.40, 18.79) | 0.0 | 1.62 (0.80, 3.27) | 0.97 |
| 13-14 years | 2 or more siblings | 34.8 | 1.26 (0.76, 2.10) | 67.7 | 1.33 (0.97, 1.82) | 0.16 |
| | Heavy Truck traffic (current) | 37.0 | 0.99 (0.53, 1.84) | 40.0 | 1.47 (1.10, 1.97) | 0.12 |
| | Fast food (current) | 50.0 | 1.40 (0.80, 2.43) | 54.9 | 2.42 (1.84, 3.20) | 0.03 |
| | Paternal tobacco (current) | 42.9 | 0.45 (0.21, 0.95) | 34.0 | 0.73 (0.47, 1.12) | 0.16 |
| | Maternal tobacco (current) | 35.3 | 1.46 (0.68, 3.12) | 13.4 | 0.64 (0.39, 1.04) | 0.48 |
| | Paracetamol (current) | 30.2 | 2.38 (1.26, 4.51) | 29.4 | 2.62 (1.79, 3.85) | 0.58 |
| | Open fire cooking (current) | 0.0 | 1.08 (0.04, 26.81) | 0.7 | 2.26 (1.40, 3.66) | 0.45 |

[a]Adjusted for sex, mother's level of education and all other variables in the table.

### 3.3.6 Discussion

This study is the first comprehensive analysis of key risk factors for childhood AE, analysed together in a multivariable regression analysis, at individual (child) level to find which variables were the most important, and community (school) level to find which ones remained important. The school was the sampling unit, so analyses using school-level prevalence of exposures offer to our knowledge previously unreported insights into the possible extent of bias due selective avoidance or confounding by indication. These forms of reverse causation, which are a particular issue in cross-sectional analyses, are less of an issue using school-level exposures rather than individual-level exposures. When comparing school-level and individual-level findings, if confounding by indication was a major issue, associations would be weaker at school-level, whereas if selective avoidance was the source of reverse causation, associations at the school-level would appear more harmful. Consistent findings between school and individual-level analyses suggest that neither of the two forms of reverse causation explain the findings. In contrast, school-level analyses are prone to ecologic (population level) confounding, which is not an issue when using the individual-level approach. Given that the individual- and school-level analyses will potentially be affected in different ways by reverse causation and confounding by indication, we consider it is sensible to fit regression models at each level (child within school and school within centre) and compare the results to assess robustness to different interpretations, rather than considering one approach more appropriate than the other. The analyses use the data from ISAAC Phase Three, where many individual-level single risk factor analyses found associations, but some of these were not corroborated in the present analyses.

**6-7 year olds**

The 6-7 year-old results from the present study are summarised and compared with previous ISAAC analyses in Table 3.15, along with an assessment of potential bias and an outline of the biological plausibility of the effect.

The strongest associations for 6-7 year-olds in individual-level analyses were for current paracetamol use, and antibiotic and paracetamol use in the first year of life. However, in school-level analyses, only associations with current paracetamol persisted. These school-level findings provide evidence against reverse causation, including confounding by indication, as an explanation, and thus make a causal link more likely. Associations between AE and current paracetamol use are consistent with those from individual-level single risk factor analyses in previous ISAAC Phase Three publications, which reported dose-response relationships between the quantity of paracetamol taken in the previous year and current AE symptoms

*Table 3.15 Associations between eczema symptoms in the last 12 months and risk factors for 6-7-year-old age group comparing results from different analyses*

| Exposure | Current analysis | | | Previous ISAAC analysis | | Assessment of bias | Biological plausibility of effect |
|---|---|---|---|---|---|---|---|
| | Individual level[a] | School level[b] | Comparison | Individual level[c] | Comparison with current | | |
| Farm animals (in utero) | 1.11 (1.00, 1.23) | 1.05 (0.54, 2.04) | No association at school level | 1.17 (1.07,1.29)[42] | Consistent | No evidence of reverse causation bias | Not observed at school level |
| Low birthweight | 0.89 (0.81, 0.97) | 1.78 (1.07, 2.95) | Individual shows a protective effect but school level is harmful | 0.93 (0.85, 1.01)[48] | Consistent with current individual level estimate | There could be SES confounding at community level | Unclear |
| Paracetamol (1st year) | 1.28 (1.21, 1.36) | 0.94 (0.69, 1.28) | The significantly harmful effect seen at the individual level doesn't show at the school-level | 1.35 (1.26, 1.45)[38] | Consistent with current individual level estimate | Possible evidence of reverse causation | Unclear |
| Antibiotics (1st year) | 1.41 (1.34, 1.48) | 1.35 (1.00, 1.82) | Consistent but weaker | 1.42 (1.33,1.51)[40] | Consistent | Confounding by indication may partly contribute to the association. | Confounding by indication may contribute |
| Breastfed ever | 1.11 (1.05, 1.18) | 1.06 (0.75, 1.48) | Consistent but weaker | 1.05 (0.97,1.12)[41] | Consistent | No evidence of reverse causation bias | Weak association; biological basis not clear |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Cat (1st year) | 1.10 (1.03, 1.17) | 1.15 (0.78, 1.71) | Consistent | 1.09 (1.01,1.17)[43] | Consistent | No evidence of reverse causation bias | - |
| Dog (1st year) | 1.05 (1.00, 1.11) | 0.96 (0.69, 1.32) | Consistent | Not available | N/A | No evidence of effect | - |
| Farm animals (1st year) | 1.16 (1.06, 1.27) | 1.15 (0.62, 2.15) | Consistent | 1.16 (1.07,1.27)[42] | Consistent | No evidence of reverse causation bias | Proposed mechanism related to endotoxin exposure, although unclear |
| 2 or more siblings | 0.95 (0.90, 0.99) | 1.11 (0.88, 1.40) | The estimates are in opposing directions but the individual CI is contained within the school level CI | [d]Categorical<br>No siblings 1.00 (ref)<br>One sibling 1.09 (1.03, 1.15)<br>2 siblings 1.01 (0.95, 1.08)<br>3+ siblings 1.04 (0.97, 1.12)[50] | Hard to compare due to different models | If there is an effect, it appears small. There is no dose response relationship (from previous analysis) | - |
| Heavy truck traffic (current) | 1.11 (1.06, 1.16) | 0.81 (0.65, 1.02) | The estimates are in opposing directions with a harmful effect at the individual level | [d]Categorical<br>Never 1.00 (ref)<br>Low 1.07 (0.99, 1.15)<br>Med 1.18 (1.09, 1.28)<br>Heavy 1.36 (1.23, 1.50)[39] | Consistent with the individual level estimate | May relate to bias- parents of children with eczema may move if they are concerned about traffic exposure | Unlikely causal |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fast food (current) | 0.99 (0.94, 1.04) | 0.96 (0.76, 1.22) | Consistent | [d]Categorical<br>Never/Occasional 1.00 (ref)<br>1-2/wk 1.04 (0.99, 1.09)<br>3+/wk 1.04 (0.95, 1.14)[46] | Consistent | No evidence of effect | - |
| Paternal tobacco (current) | 1.04 (0.99, 1.10) | 0.83 (0.61, 1.13) | The estimates are in opposing directions but the confidence intervals overlap substantially | 1.09 (1.04, 1.13)[44] | Consistent with individual level effect | Very weak association only | No dose response relationship, unlikely causal |
| Maternal tobacco (current) | 1.06 (0.99, 1.13) | 1.61 (1.14, 2.25) | The school level harmful effect is much greater | 1.15 (1.09, 1.21)[44] | Shows a stronger effect than the individual level in the current analysis | | No dose response relationship, unlikely causal |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Paracetamol (current) | 1.45 (1.37, 1.54) | 1.55 (1.10, 2.21) | Consistent | [d]Categorical<br>Never/Low 1.00 (ref)<br>Med 1.18 (1.08,1.30)<br>High 1.87 (1.68,2.08)[38] | Consistent, the high level is the equivalent to a positive response in the current analysis | No evidence of reverse causation bias | Depletion of glutathione in antigen presenting cells resulting in a shift from a Th1 to mainly Th2 immune response.[8,40] |
| Open fire cooking (current) | 1.12 (0.95, 1.32) | 1.84 (0.98, 3.45) | Stronger harmful effect seen at school level | 1.10 (0.91-1.33)[47] | Consistent with individual level effect from current analysis | Possible avoidance bias as people with children with AE remove open fires, masking the true magnitude of effect | Persistent AE may be associated with impaired skin barrier and more likely to react to aeroallergens and irritants |

a - fully adjusted for sex, mothers' education level and all other variables in the table

b - fully adjusted for sex, mothers' education level and school level prevalence of all other variables in the table

c - could be adjusted for a variety of different variables

d - no direct comparison possible, so closest results are shown

(medium 1.18 (1.08-1.30) and high 1.87 (1.68-2.08) compared to no paracetamol).[38] Possible biological mechanisms underlying the observed association between paracetamol use and AE may relate to a depletion of glutathione in antigen presenting cells resulting in a shift from a Th1 to a predominantly Th2 immune response.[38,43,74]

Associations with early antibiotic use persisted after adjusting for confounders and were also observed in school-level analyses, although this association was weaker, suggesting that confounding by indication may partly contribute to the association, but does not completely explain it. Findings are consistent with those observed in individual-level single risk factor analyses (1.42 (1.33-1.51)) in previous ISAAC Phase Three publications.[40] In our further analyses, stratifying by affluence, similar associations with early antibiotic use were observed in affluent and non-affluent countries. The reasons for this association with antibiotics and potential causality are unclear, with proposed theories including changes in the gut microbiome.[75]

Breastfeeding was associated with a slightly increased risk of AE at individual-level with similar but weaker results at school-level. The individual-level association was strongest in affluent countries but was not significant at school level (Tables 3.13 and 3.14). These observations reflect previous reports when assessing breastfeeding as an individual-level exposure in ISAAC Phase Three data (1.05, 0.97-1.12).[41] Our findings do not support the reverse causation theory that in affluent countries those children at highest risk of developing AE are more likely to be breastfed.[41,76]

We observed evidence of a weak protective effect of low birthweight in individual-level analyses in contrast to a potentially harmful effect in school-level analyses. Individual-level findings are consistent with the previous ISAAC individual-level single risk factor analyses; although additionally these analyses showed no association between birthweight and AE severity and the importance of the finding from a public health perspective was not clear.[48] It is possible that the opposite school-level association may indicate residual socio-economic confounding at community level as schools with a high proportion of low birthweight children may be in more deprived areas.[77]

We also observed weak evidence in individual-level analyses that current AE was slightly more common in children exposed to cats, dogs and farm animals in the first year of life. There were similar results at school-level. In stratified analyses all of these associations were restricted only to non-affluent settings, where there is likely to be less awareness of these associations

with AE, making bias or differential recall of exposure less likely explanations. Findings for these combined analyses of the ISAAC Phase Three data are consistent with those observed in individual-level single risk factor analyses.[42,43]

Current heavy traffic exposure was associated with a weak increased risk of AE symptoms in individual-level but not school-level analyses. A possible explanation for the differential associations at individual-level and school-level relates to bias; perhaps parents of individuals with current AE symptoms are more concerned about heavy traffic exposure and more likely to report it compared to those without symptoms. These findings may help interpret the similar associations observed in previous individual-level single risk factor analyses.[39]

**13-14 year olds**

The 13-14-year-old results from the present study are summarised and compared with previous ISAAC analyses in Table 3.16, along with an assessment of potential bias and an outline of the biological plausibility of the effect.

The strongest association with current AE in adolescents at individual-level was with current paracetamol use, with even stronger potentially harmful associations observed at school-level. The stronger school-level associations suggest that reverse causation is unlikely to explain these associations, although ecological confounding, whereby confounding arises due to within-area heterogeneity of exposures, is possible. Findings are consistent with previous individual-level single risk factors analyses.[51]

Using open fires for cooking was more strongly associated with current AE symptoms at school-level compared to individual-level, findings which could be partially attributed to avoidance behaviour in parents of children with current AE.[47] The association with AE observed at individual-level at age 13-14 years with no association at age 6-7 years is consistent with previous single exposure ISAAC studies.[47]

Strong potentially harmful associations with AE symptoms were seen for current heavy traffic exposure at individual-level and school-level. This is in contrast to the younger age-group; a possible explanation is that persistent AE may be more severe and more likely to react to aeroallergens and irritants. Individual-level analyses demonstrated similar associations with a dose-response relationship between levels of exposure to traffic and AE symptoms.[39]

*Table 3.16 Associations between eczema symptoms in the last 12 months and risk factors for 13-14-year-old age group comparing results from different analyses*

| Exposure | Current analysis | | | Previous ISAAC analysis | | Assessment of bias | Biological plausibility of effect |
|---|---|---|---|---|---|---|---|
| | Individual level[a] | School level[b] | Comparison | Individual level[c] | Comparison with current | | |
| 2 or more siblings | 1.08 (1.03,1.12) | 1.26 (0.97, 1.65) | The school level shows a stronger harmful effect although the CI includes the full individual level CI | [d]Categorical<br>No siblings 1.00 (ref)<br>One sibling 0.91 (0.85, 0.98)<br>2 siblings 0.96 (0.88, 1.03)<br>3+ siblings 1.05 (0.97, 1.13)[50] | Consistent, although not easy to compare | | May represent a chance association. No dose-response relationship in individual studies. |
| Heavy truck traffic<br>(current) | 1.31 (1.27, 1.36) | 1.40 (1.07, 1.82) | Consistent | [d]Categorical<br>Never 1.00 (ref)<br>Low 1.08 (0.97, 1.19)<br>Med 1.30 (1.17, 1.45)<br>Heavy 1.54 (1.37, 1.73)[39] | Consistent | No evidence of reverse causation bias | Previous studies demonstrated dose-response relationship between levels of exposure to traffic and AE symptoms. No clearly established biological mechanism. Inverse school-level association found in 6-7-year-olds contrasts with the positive school-level association shown here for 13-14-year-olds, suggesting caution in drawing firm conclusions regarding causality. |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fast food (current) | 1.05 (1.02, 1.10) | 2.11 (1.66, 2.70) | The school level shows a stronger harmful effect | [d]Categorical Never/Occasional 1.00 (ref) 1-2/wk 1.04 (0.99, 1.10) 3+/wk 1.20 (1.11, 1.28)[46] | Consistent with individual level effect in current analysis | Possible avoidance bias as people with adolescents with AE avoid fast food, masking the true magnitude of effect | Not fully understood; theories around ingested fatty acids and inflammation. |
| Paternal tobacco (current) | 1.15 (1.10, 1.19) | 0.64 (0.44, 0.94) | The estimates are in opposing directions but the confidence intervals overlap substantially; school-level estimates look protective. | 1.19 (1.14, 1.25)[44] | Consistent with individual level effect in current analysis | The finding might support differential reporting of tobacco exposure in those with current AE symptoms or ecologic bias at school level | - |
| Maternal tobacco (current) | 1.11 (1.06, 1.16) | 0.79 (0.52, 1.19) | The estimates are in opposing directions but the confidence intervals overlap substantially | 1.22 (1.16, 1.28)[44] | Stronger effect than current individual level analysis | As for paternal tobacco. | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Paracetamol (current) | 1.57<br>(1.51, 1.63) | 2.57<br>(1.84, 3.59) | The school level harmful effect is much greater | [d]Categorical<br>Never/Low 1.00 (ref)<br>Med 1.31 (1.21, 1.42)<br>High 1.99 (1.82, 2.16)[51] | Consistent with individual level current analysis (High is the same as the positive value in current analysis) | Some evidence of possible avoidance bias masking the true magnitude of the harmful effect | Possible biological mechanisms underlying the observed association between paracetamol use and AE may relate to a depletion of glutathione in antigen presenting cells resulting in a shift from a Th1 to a predominantly Th2 immune response.[24,40] |
| Open fire cooking (current) | 1.46<br>(1.33, 1.62) | 2.38<br>(1.52, 3.73) | Stronger harmful effect seen at school level. | 1.37 (1.13-1.66)[47] | Consistent with individual level effect in current analysis | Possible avoidance bias as people with asthmatic children remove open fires, masking the true magnitude of effect | Persistent AE may be associated with impaired skin barrier and more likely to react to aeroallergens and irritants. |

a - fully adjusted for sex, mothers' education level and all other variables in the table
b - fully adjusted for sex, mothers' education level and school level prevalence of all other variables in the table
c - could be adjusted for a variety of different variables
d - no direct comparison possible, so closest results are shown

Though weak associations were observed at individual-level with current maternal and paternal tobacco exposure, at school-level the effect was reversed with weak evidence of a protective effect for paternal smoking. This finding might support differential reporting of tobacco exposure in those with current AE symptoms or ecologic bias at school level.[44]

Strong associations were observed at school-level with fast food consumption, with very weak associations being observed at individual-level. Findings are consistent with previous individual-level single risk factor analyses and might plausibly be important for the aetiology of AE, although ecologic bias and residual confounding are alternative possibilities.[28,46]

Weak associations were observed between having two or more siblings and current AE symptoms at an individual-level with slightly stronger associations at school-level (but with weaker precision). Findings are not consistent with those observed at age 6-7 years of age, are in contrast to protective associations reported in individual-level single risk factor analyses, and may represent a chance association.[50]

**Strengths and limitations of the study**

The ISAAC study had worldwide coverage and a very large sample size, including countries from less affluent settings, thus facilitating the study of environmental factors in varied settings.[7] The use of standardised and validated methods of symptoms reporting is a particular strength of the ISAAC study.[78] Although self-reported symptoms may be prone to misclassification, they avoid major diagnostic differences due to access to care in different countries and settings, where relying on doctor diagnosis may be more problematic. Selection bias is an unlikely explanation for the findings as response rates of the children were high (85%).

Assessment of exposures was based on parental or guardian (6-7 year-old children) and study participant (13-14 year-old adolescents) completion of questionnaires about historical exposures rather than objective measures, leading to possible misclassification, which for different exposures may be non-differential or may be prone to recall biases or reverse causation. Schools were the sampling unit, with individual children of the age group responding within the school, and this structure of the cross-sectional survey enabled these analyses.

Both individual-level and school-level analyses may be biased by residual confounding by factors that were either imperfectly measured or not measured at all; however, as the

unmeasured confounders are likely to be different at school and individual level, consistency of findings at both levels is reassuring against associations being due to residual confounding.

**Conclusions**

We have further enhanced the ISAAC analyses by using school-level as well as individual-level exposures, thus allowing us to explore whether specific findings may be due to reverse causation, including confounding by indication. Despite plausible mechanisms, we did not observe findings supportive of selective avoidance in relation to furry pet exposure. The consistent associations between current paracetamol exposure in both age groups and at both individual and school-level argues against reverse causation as the sole explanation. The consistent associations between current paracetamol exposure in both age groups and at both individual and school-level argues against reverse causation as the sole explanation. If paracetamol use in early childhood does have a direct biological role in the development of atopic eczema and related disorders such as asthma, then reducing paracetamol use in infancy could reduce the incidence of such diseases. Indeed, a randomised controlled prevention trial in New Zealand called PIPPA Tamariki (ACTRN12618000303246) that seeks to determine whether ibuprofen instead of paracetamol for fever/pain in infancy reduces the incidence of asthma and eczema, is already underway.

Some individual-level single risk factor associations previously identified in ISAAC Phase Three data were not corroborated in the present analyses, but several were: current paracetamol use at ages 6-7 and 13-14, early life antibiotic exposure and AE at age 6-7, and current heavy road traffic and open fire cooking and AE symptoms at 13-14 years. The approach of using school-level exposure estimates provides insight that some of the previously reported associations in ISAAC Phase Three studies may be due to reverse causation, but that paracetamol use is unlikely to be explained in this way.

## 3.4 Are environmental risk factors for rhinoconjunctivitis in ISAAC Phase III due to reverse causation?

### 3.4.1 Introduction

A similar analysis to the previous two papers has been applied to rhinoconjunctivitis symptoms. This has not been submitted for publication because a different type of analysis has been published and this can be found in Chapter 4. However, these rhinoconjunctivitis analyses are included here, to provide comparability with the findings for asthma and eczema symptoms.

### 3.4.2 Methods

The methods used and the study data are the same as for the published articles in Sections 3.2 and 3.3 except with a different outcome (rhinoconjunctivitis) and some differences in the included risk factors.

The outcome of interest, non-infectious rhinoconjunctivitis symptoms in the last 12 months, hereafter known as rhinoconjunctivitis, was defined using positive responses to all three of the following questions:

1. *Has your child / have you ever had a problem with sneezing, or a runny, or blocked nose when you did not have a cold or the flu?*
2. *In the past 12 months, has your child / have you had a problem with sneezing, or a runny, or blocked nose when you did not have a cold or the flu?*
3. *In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?*

The risk factors encompassed all those used in the asthma analysis and the eczema analysis with the exception that heavy truck traffic (as used in the eczema paper) was selected rather than standard truck traffic (as used in the asthma paper).

The specific risk factors in this analysis for the younger age group are paracetamol use in the 1st year of life and in the past 12 months,[38] antibiotic use in the 1st year of life,[40] breast feeding,[41] cats and dogs in the home in the 1st year of life,[43] regular maternal contact with farm animals while pregnant and regular contact in the 1st year of life,[42] having 2 or more siblings,[50] heavy truck traffic,[39] fast food consumption,[46] television viewing,[45] parental smoking,[44] cooking

on an open fire,[47] and birth weight.[48] For the older age group, where early life factors were not available, we included heavy truck traffic,[39] fast food consumption,[46] television viewing,[45] parental smoking,[44] paracetamol use in the past 12 months,[51] open fire cooking,[47] and having 2 or more siblings.[50]

Most of these risk factors were "yes/no" questions in the environmental questionnaire. The exceptions were dichotomised: paracetamol use in the past 12 months (at least once per month vs. less than once per month), heavy truck traffic (frequently or almost the whole day vs. seldom or never), fast food consumption (once per week or more vs. less than once per week), television viewing (at least 1 hour per day vs. less than 1 hour per day), birth weight (less than 2.5 kg vs. at least 2.5 kg), and number of siblings (2 or more vs. 1 or fewer). More details of the individual risk factors can be found in Tables 3.1 and 3.8.

### 3.4.3 Results

**6-7-year-olds**

There were 221,280 children from 75 centres which met the initial data quality criteria (at least 1,000 children and a response rate of >60%). Of these, 210,928 children (from 2,903 schools, 75 centres, 32 countries) were from schools with at least 10 children and had data present for rhinoconjunctivitis symptoms, sex, maternal education and at least one of the exposures of interest, so contributed to the analyses for one or more exposures (the "maximum sample"), with 123,698 children (from 2,216 schools, 61 centres, 23 countries) having data present for all analysis variables (the "common sample"). See Figure 3.5 for more details. Individual- and school-level summary statistics are presented in Table 3.17 for the maximum sample and Table 3.18 for the common sample.

Comparing minimally adjusted associations between the common sample (Table 3.19) and the maximum sample (Table 3.20) at the individual level, we see very similar results indicating no evidence of introducing bias in restricting to the common sample. Comparing minimally adjusted to fully adjusted associations in Table 3.19, the effects are consistent but reduced in the fully adjusted sample. Only TV viewing showed some weak evidence of a protective association with rhinoconjunctivitis in the fully adjusted model but no evidence of effect in the minimally adjusted model.

| Total sample | |
|---|---|
| 221,280 individuals | |
| 3,167 schools | Median 44 (range 1-1,117) individuals per school |
| 75 centres | Median 3,000 (range 1,070-5,654) individuals per centre |
| 32 countries | Median 4,332 (range 1,070-43,918) individuals per country |

| Schools with at least 10 individuals | | Excluded |
|---|---|---|
| 219,853 individuals | | 1,427 individuals |
| 2,904 schools | Median 49 (range 10-1,117) individuals per school | 263 schools |
| 75 centres | Median 2,980 (range 999-5,603) individuals per centre | 0 centres |
| 32 countries | Median 4,314 (range 1,054-43,873) individuals per country | 0 countries |

| Individuals non-missing for outcome, confounders and at least one exposure | | Excluded |
|---|---|---|
| 210,928 individuals | | 8,925 individuals |
| 2,903 schools | Median 47 (range 8-1,030) individuals per school | 1 school |
| 75 centres | Median 2,820 (range 943-5,376) individuals per centre | 0 centres |
| 32 countries | Median 4,175 (range 992-41,756) individuals per country | 0 countries |

| Individuals non-missing for outcome, confounders and all exposures | | Excluded |
|---|---|---|
| 123,698 individuals | | 87,230 individuals |
| 2,216 schools | Median 38 (range 1-687) individuals per school | 687 schools |
| 61 centres | Median 2,080 (range 190-4,353) individuals per centre | 14 centres |
| 23 countries | Median 4,989 (range 992-41,756) individuals per country | 9 countries |

*Figure 3.5 Rhinoconjunctivitis data flowchart, age 6-7 years*

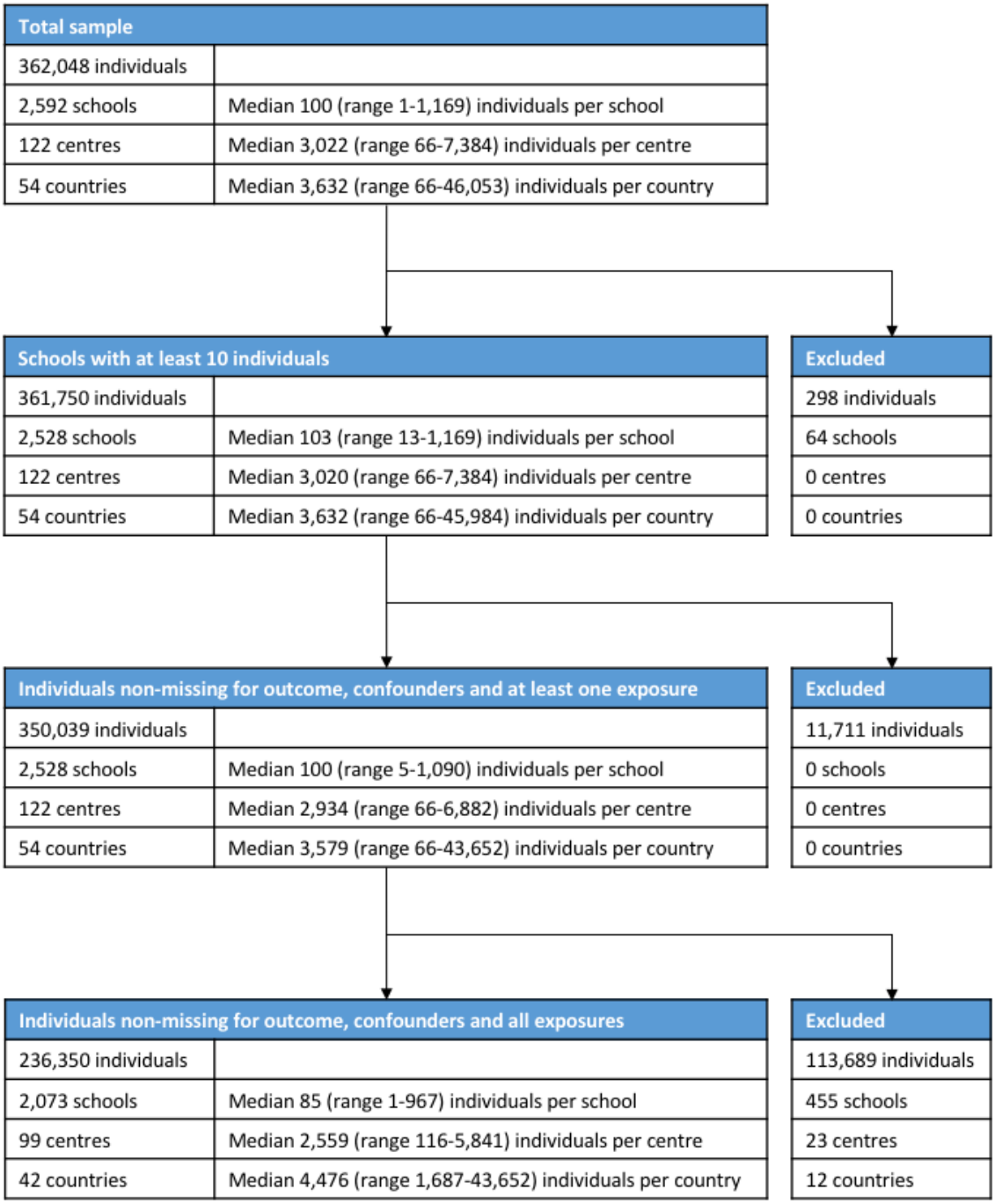


*Figure 3.6 Rhinoconjunctivitis data flowchart, age 13-14 years.*

*Table 3.17 Rhinoconjunctivitis - Summary statistics in the maximum sample*

In subjects with data on rhinoconjunctivitis symptoms, sex, maternal education and the exposure.

| Age group | Variable | Individual-level | | School-level | | |
|---|---|---|---|---|---|---|
| | | n | Prevalence | n | Median prevalence | Prevalence IQR |
| 6-7 years | Rhinoconjunctivitis in the last 12 months | 210,928 | 0.088 | 2,903 | 0.079 | (0.038, 0.128) |
| | Farm animals (in utero) | 187,393 | 0.098 | 2,682 | 0.076 | (0.033, 0.154) |
| | Low birthweight | 175,663 | 0.086 | 2,601 | 0.063 | (0.032, 0.106) |
| | Paracetamol (1st year) | 187,330 | 0.652 | 2,635 | 0.694 | (0.560, 0.822) |
| | Antibiotics (1st year) | 185,987 | 0.542 | 2,715 | 0.560 | (0.465, 0.645) |
| | Breastfed ever | 198,135 | 0.801 | 2,753 | 0.845 | (0.733, 0.929) |
| | Cat (1st year) | 195,731 | 0.118 | 2,753 | 0.102 | (0.047, 0.192) |
| | Dog (1st year) | 180,689 | 0.202 | 2,521 | 0.217 | (0.115, 0.324) |
| | Farm animals (1st year) | 187,542 | 0.113 | 2,686 | 0.094 | (0.043, 0.176) |
| | 2 or more siblings | 209,339 | 0.380 | 2,903 | 0.370 | (0.222, 0.538) |
| | Heavy Truck traffic (current) | 190,051 | 0.390 | 2,781 | 0.384 | (0.278, 0.500) |
| | Fast food (current) | 187,217 | 0.410 | 2,850 | 0.333 | (0.183, 0.512) |
| | Television (current) | 202,489 | 0.778 | 2,855 | 0.836 | (0.741, 0.909) |
| | Paternal tobacco (current) | 201,992 | 0.315 | 2,800 | 0.333 | (0.191, 0.467) |
| | Maternal tobacco (current) | 205,228 | 0.140 | 2,833 | 0.140 | (0.029, 0.300) |
| | Paracetamol (current) | 197,336 | 0.195 | 2,786 | 0.164 | (0.077, 0.308) |
| | Open fire cooking (current) | 190,910 | 0.031 | 2,776 | 0.000 | (0.000, 0.023) |
| 13-14 years | Rhinoconjunctivitis in the last 12 months | 350,039 | 0.143 | 2,528 | 0.139 | (0.083, 0.200) |
| | 2 or more siblings | 340,882 | 0.551 | 2,436 | 0.614 | (0.391, 0.806) |
| | Heavy Truck traffic (current) | 315,737 | 0.399 | 2,382 | 0.397 | (0.307, 0.514) |
| | Fast food (current) | 317,664 | 0.551 | 2,422 | 0.555 | (0.407, 0.698) |
| | Television (current) | 336,659 | 0.853 | 2,483 | 0.900 | (0.811, 0.943) |
| | Paternal tobacco (current) | 307,743 | 0.376 | 2,293 | 0.366 | (0.235, 0.485) |
| | Maternal tobacco (current) | 335,573 | 0.180 | 2,467 | 0.184 | (0.040, 0.333) |
| | Paracetamol (current) | 319,922 | 0.287 | 2,438 | 0.306 | (0.190, 0.435) |
| | Open fire cooking (current) | 309,668 | 0.076 | 2,355 | 0.012 | (0.000, 0.047) |

*Table 3.18 Rhinoconjunctivitis - Summary statistics in the common sample*

In subjects with data on rhinoconjunctivitis symptoms, sex, maternal education and all exposures.

| Age group | Variable | Individual-level (n = 123,698) | School-level (n = 2,216) | |
|---|---|---|---|---|
| | | Prevalence | Median prevalence | Prevalence IQR |
| 6-7 years | Rhinoconjunctivitis in the last 12 months | 0.089 | 0.077 | (0.029, 0.128) |
| | Farm animals (in utero) | 0.076 | 0.063 | (0.022, 0.125) |
| | Low birthweight | 0.078 | 0.056 | (0.023, 0.097) |
| | Paracetamol (1st year) | 0.662 | 0.702 | (0.571, 0.840) |
| | Antibiotics (1st year) | 0.558 | 0.573 | (0.475, 0.654) |
| | Breastfed ever | 0.805 | 0.837 | (0.733, 0.919) |
| | Cat (1st year) | 0.107 | 0.080 | (0.034, 0.167) |
| | Dog (1st year) | 0.193 | 0.192 | (0.095, 0.304) |
| | Farm animals (1st year) | 0.092 | 0.081 | (0.036, 0.146) |
| | 2 or more siblings | 0.347 | 0.333 | (0.188, 0.483) |
| | Heavy Truck traffic (current) | 0.383 | 0.379 | (0.271, 0.500) |
| | Fast food (current) | 0.395 | 0.307 | (0.165, 0.500) |
| | Television (current) | 0.798 | 0.849 | (0.750, 0.920) |
| | Paternal tobacco (current) | 0.320 | 0.352 | (0.211, 0.486) |
| | Maternal tobacco (current) | 0.161 | 0.167 | (0.041, 0.324) |
| | Paracetamol (current) | 0.177 | 0.138 | (0.057, 0.250) |
| | Open fire cooking (current) | 0.019 | 0.000 | (0.000, 0.017) |
| Age group | Variable | Individual-level (n = 236,350) | School-level (n = 2,073) | |
| | | Prevalence | Median prevalence | Prevalence IQR |
| 13-14 years | Rhinoconjunctivitis in the last 12 months | 0.142 | 0.136 | (0.077, 0.203) |
| | 2 or more siblings | 0.538 | 0.586 | (0.377, 0.793) |
| | Heavy Truck traffic (current) | 0.399 | 0.396 | (0.304, 0.500) |
| | Fast food (current) | 0.535 | 0.528 | (0.390, 0.680) |
| | Television (current) | 0.856 | 0.906 | (0.817, 0.947) |
| | Paternal tobacco (current) | 0.384 | 0.372 | (0.234, 0.494) |
| | Maternal tobacco (current) | 0.182 | 0.185 | (0.034, 0.357) |
| | Paracetamol (current) | 0.268 | 0.295 | (0.174, 0.412) |
| | Open fire cooking (current) | 0.052 | 0.006 | (0.000, 0.029) |

For the age 6-7-year group, the strongest (fully adjusted) associations with rhinoconjunctivitis at the individual-level were seen for current paracetamol use (OR = 2.02; 95% CI = 1.92, 2.12), antibiotic use in the 1st year of life (1.57; 1.49, 1.64) and paracetamol use in the 1st year of life (1.40; 1.33, 1.48) (see Table 3.19). At the school level, the associations of rhinoconjunctivitis with current paracetamol use (1.97; 1.39, 2.78) and antibiotic use in the 1st year of life (1.45; 1.08, 1.96) were very similar but the association with paracetamol use in the 1st year of life is not present at the school level (0.94; 0.70, 1.28).

Low birthweight showed no evidence of an association with rhinoconjunctivitis at the individual level (1.04; 0.96, 1.13) but at the school level the association was (2.38; 1.45, 3.93). Being breastfed showed no evidence of an effect at the individual level (1.00; 0.95, 1.05) but showed a strong protective association at the school level (0.61; 0.44, 0.86). Television watching showed a slight negative association at the individual level (0.93; 0.88, 0.99) but a positive association at the school level (1.46; 1.06, 2.00).

The ratios of the SEs from these rhinoconjunctivitis models and those in similar minimally adjusted models were calculated and we found no evidence of collinearity.

Stratifying by country affluence showed differences in 6-7-year-olds as follows. Contact with farm animals in the first year of life was associated with increased rhinoconjunctivitis symptoms in non-affluent countries (1.22; 1.10, 1.35) but not affluent countries (0.90; 0.77, 1.05). Having 2 or more siblings showed a negative association in affluent countries (0.88; 0.82, 0.94) but there was no evidence for this in non-affluent countries (1.05; 0.99, 1.11). For both of these there is strong evidence supporting a difference in effect between settings (Table 3.21).

**13-14-year-olds**

The 13-14-year-old participants included 362,048 children from 122 centres which met the initial data quality criteria (at least 1,000 children and a response rate of >70%). Of these, 350,039 children (from 2,528 schools, 122 centres, 54 countries) were from schools with at least 10 children and had data present for rhinoconjunctivitis symptoms, sex, maternal education and at least one of the exposures of interest so contributed to the analyses for one or more exposures (the “maximum sample”), with 236,350 children (from 2,073 schools, 99 centres, 42 countries) having data present for all analysis variables (the “common sample”). See Figure 3.6 for more details. Summary statistics at the individual- and school-level are presented in Table 3.17 for the maximum sample and Table 3.18 for the common sample.

Comparing minimally adjusted associations between the common sample (Table 3.19) and the maximum sample (Table 3.20) there are similar results at the individual level indicating no evidence of introducing bias in restricting to the common sample. Comparing minimally adjusted to fully adjusted associations in Table 3.19 there are reduced effects in the fully adjusted sample.

In the 13-14-year-old group, there were strong associations at the individual level with current paracetamol use (1.76; 1.71, 1.81) which was even stronger at the school-level (3.42; 2.62, 4.46) and heavy truck traffic (1.23; 1.20, 1.26) which was consistent at the school-level (1.16; 0.94, 1.44) though there was less precision on the estimate (Table 3.19). In addition, the positive association with open fire cooking was stronger at the school level (1.96; 1.36, 2.83) than at the individual level (1.16; 1.08, 1.25).

Similar to the other age group, the ratios of the SEs from the fully-adjusted and minimally adjusted models showed no evidence of collinearity.

Stratifying the adolescents by country affluence showed that paternal smoking and open fire cooking had positive associations in non-affluent countries (1.13; 1.10, 1.17) and (1.20; 1.11, 1.30) respectively but no evidence of associations in affluent countries (1.02; 0.97, 1.08) and (0.83; 0.64, 1.07). The association between open fire cooking and rhinoconjunctivitis in affluent countries was estimated as a negative effect, although was non-significant (Table 3.21).

### 3.4.4 Discussion

This is the first comprehensive analysis of lifestyle and environmental risk factor of allergic rhinoconjunctivitis among children in mutually adjusted models. There have been many papers on individual risk factors[38-51] but not one including all risk factors in one fully adjusted model. We also attempted to identify whether reverse causation could be a cause of these associations by comparing individual results to that of school level prevalence of risk factors.

*Table 3.19 Effects of individual- and school-level exposures on rhinoconjunctivitis symptoms in the last 12 months in the common sample*

In subjects non-missing for rhinoconjunctivitis symptoms, sex, maternal education and all exposures of interest. Mixed logistic regression models with random intercepts at the school, centre and country levels.

| Age group | Exposure | Individual-level exposure | | School-level exposure | |
|---|---|---|---|---|---|
| | | Minimally adjusted[a] | Fully adjusted[b] | Minimally adjusted[a] | Fully adjusted[b] |
| 6-7 years (n = 123,698) | Farm animals (in utero) | 1.37 (1.27, 1.47) | 1.17 (1.07, 1.28) | 1.55 (1.10, 2.20) | 1.16 (0.61, 2.18) |
| | Low birthweight | 1.11 (1.03, 1.20) | 1.04 (0.96, 1.13) | 2.83 (1.77, 4.54) | 2.38 (1.45, 3.93) |
| | Paracetamol (1st year) | 1.80 (1.71, 1.89) | 1.40 (1.33, 1.48) | 1.29 (0.98, 1.69) | 0.94 (0.70, 1.28) |
| | Antibiotics (1st year) | 1.82 (1.74, 1.91) | 1.57 (1.49, 1.64) | 1.49 (1.13, 1.96) | 1.45 (1.08, 1.96) |
| | Breastfed ever | 0.97 (0.92, 1.02) | 1.00 (0.95, 1.05) | 0.52 (0.37, 0.72) | 0.61 (0.44, 0.86) |
| | Cat (1st year) | 1.19 (1.11, 1.27) | 1.08 (1.01, 1.16) | 1.39 (0.96, 2.00) | 1.17 (0.77, 1.78) |
| | Dog (1st year) | 1.15 (1.10, 1.21) | 1.06 (1.01, 1.12) | 1.15 (0.85, 1.54) | 0.87 (0.63, 1.21) |
| | Farm animals (1st year) | 1.32 (1.23, 1.41) | 1.10 (1.01, 1.20) | 1.56 (1.12, 2.17) | 1.22 (0.67, 2.23) |
| | 2 or more siblings | 0.99 (0.95, 1.03) | 0.97 (0.93, 1.02) | 1.05 (0.85, 1.30) | 0.90 (0.71, 1.13) |
| | Heavy Truck traffic (current) | 1.25 (1.20, 1.30) | 1.17 (1.12, 1.22) | 1.10 (0.89, 1.36) | 0.90 (0.72, 1.13) |
| | Fast food (current) | 1.06 (1.01, 1.11) | 1.00 (0.96, 1.05) | 1.13 (0.90, 1.42) | 1.05 (0.83, 1.33) |
| | Television (current) | 0.98 (0.93, 1.04) | 0.93 (0.88, 0.99) | 1.58 (1.18, 2.11) | 1.46 (1.06, 2.00) |
| | Paternal tobacco (current) | 1.10 (1.05, 1.15) | 1.06 (1.01, 1.11) | 1.35 (1.04, 1.74) | 0.90 (0.66, 1.22) |
| | Maternal tobacco (current) | 1.13 (1.06, 1.19) | 1.05 (0.99, 1.12) | 1.63 (1.23, 2.17) | 1.33 (0.95, 1.87) |
| | Paracetamol (current) | 2.30 (2.18, 2.41) | 2.02 (1.92, 2.12) | 2.22 (1.61, 3.06) | 1.97 (1.39, 2.78) |
| | Open fire cooking (current) | 1.04 (0.87, 1.23) | 1.01 (0.84, 1.20) | 1.99 (1.05, 3.76) | 1.67 (0.84, 3.32) |
| 13-14 years (n = 236,350) | 2 or more siblings | 1.05 (1.02, 1.08) | 1.04 (1.01, 1.07) | 1.08 (0.88, 1.32) | 0.97 (0.79, 1.20) |
| | Heavy Truck traffic (current) | 1.27 (1.24, 1.31) | 1.23 (1.20, 1.26) | 1.36 (1.10, 1.67) | 1.16 (0.94, 1.44) |
| | Fast food (current) | 1.10 (1.07, 1.13) | 1.06 (1.03, 1.09) | 1.26 (1.03, 1.53) | 1.18 (0.97, 1.43) |
| | Television (current) | 1.03 (0.99, 1.07) | 1.00 (0.96, 1.04) | 1.37 (0.99, 1.90) | 1.25 (0.90, 1.75) |
| | Paternal tobacco (current) | 1.16 (1.13, 1.19) | 1.10 (1.07, 1.13) | 1.14 (0.89, 1.47) | 0.79 (0.59, 1.06) |
| | Maternal tobacco (current) | 1.20 (1.17, 1.24) | 1.13 (1.09, 1.17) | 1.49 (1.10, 2.00) | 1.54 (1.11, 2.14) |
| | Paracetamol (current) | 1.80 (1.75, 1.85) | 1.76 (1.71, 1.81) | 3.52 (2.71, 4.58) | 3.42 (2.62, 4.46) |
| | Open fire cooking (current) | 1.16 (1.08, 1.25) | 1.16 (1.08, 1.25) | 1.72 (1.20, 2.48) | 1.96 (1.36, 2.83) |

[a]Adjusted for sex and mother's level of education. [b]Additionally adjusted for all other variables in the table.

*Table 3.20 Minimally adjusted effects of individual- and school-level exposures on rhinoconjunctivitis symptoms in the last 12 months in the maximum sample.*

In subjects non-missing for rhinoconjunctivitis symptoms, sex, maternal education and the exposure of interest. Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Individual-level exposure | | School-level exposure | |
|---|---|---|---|---|---|
| | | n | OR (95% CI) | n | OR (95% CI) |
| 6-7 years | Farm animals (in utero) | 187,393 | 1.50 (1.42, 1.58) | 187,393 | 1.48 (1.12, 1.96) |
| | Low birthweight | 175,663 | 1.09 (1.02, 1.16) | 175,663 | 2.94 (1.94, 4.45) |
| | Paracetamol (1st year) | 187,330 | 1.82 (1.74, 1.89) | 187,330 | 1.27 (0.99, 1.63) |
| | Antibiotics (1st year) | 185,987 | 1.86 (1.80, 1.94) | 185,987 | 1.50 (1.17, 1.92) |
| | Breastfed ever | 198,135 | 0.95 (0.91, 0.99) | 198,135 | 0.54 (0.40, 0.73) |
| | Cat (1st year) | 195,731 | 1.32 (1.26, 1.39) | 195,731 | 1.48 (1.10, 2.01) |
| | Dog (1st year) | 180,689 | 1.26 (1.21, 1.31) | 180,689 | 1.43 (1.09, 1.86) |
| | Farm animals (1st year) | 187,542 | 1.50 (1.43, 1.58) | 187,542 | 1.63 (1.23, 2.15) |
| | 2 or more siblings | 209,339 | 0.98 (0.95, 1.02) | 209,339 | 1.06 (0.88, 1.27) |
| | Heavy Truck traffic (current) | 190,051 | 1.27 (1.23, 1.32) | 190,051 | 1.14 (0.94, 1.37) |
| | Fast food (current) | 187,217 | 1.06 (1.02, 1.09) | 187,217 | 1.21 (1.00, 1.46) |
| | Television (current) | 202,489 | 1.01 (0.97, 1.05) | 202,489 | 1.34 (1.06, 1.71) |
| | Paternal tobacco (current) | 201,992 | 1.13 (1.09, 1.17) | 201,992 | 1.18 (0.94, 1.49) |
| | Maternal tobacco (current) | 205,228 | 1.17 (1.12, 1.23) | 205,228 | 1.85 (1.43, 2.40) |
| | Paracetamol (current) | 197,336 | 2.24 (2.15, 2.32) | 197,336 | 1.60 (1.22, 2.09) |
| | Open fire cooking (current) | 190,910 | 1.02 (0.91, 1.15) | 190,910 | 2.69 (1.66, 4.38) |
| Age group | Exposure | Individual-level exposure | | School-level exposure | |
| | | n | OR (95% CI) | n | OR (95% CI) |
| 13-14 years | 2 or more siblings | 340,882 | 1.04 (1.01, 1.06) | 340,882 | 1.05 (0.87, 1.26) |
| | Heavy Truck traffic (current) | 315,737 | 1.26 (1.24, 1.29) | 315,737 | 1.35 (1.10, 1.65) |
| | Fast food (current) | 317,664 | 1.09 (1.06, 1.11) | 317,664 | 1.30 (1.08, 1.56) |
| | Television (current) | 336,659 | 1.04 (1.00, 1.07) | 336,659 | 1.27 (0.95, 1.69) |
| | Paternal tobacco (current) | 307,743 | 1.17 (1.14, 1.20) | 307,743 | 1.02 (0.81, 1.29) |
| | Maternal tobacco (current) | 335,573 | 1.22 (1.19, 1.25) | 335,573 | 1.75 (1.35, 2.26) |
| | Paracetamol (current) | 319,922 | 1.77 (1.73, 1.82) | 319,922 | 3.00 (2.36, 3.81) |
| | Open fire cooking (current) | 309,668 | 1.22 (1.15, 1.29) | 309,668 | 1.38 (1.05, 1.80) |

[a]Adjusted for sex and mother's level of education.

*Table 3.21 Fully adjusted effects of individual-level exposures on rhinoconjunctivitis symptoms in the last 12 months stratified by country affluence.*

In subjects non-missing for rhinoconjunctivitis symptoms, sex, maternal education and all exposures of interest (the "common sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Affluent Countries (n = 44,836) | | Non-Affluent countries (n = 78,862) | | Effect modification |
|---|---|---|---|---|---|---|
| | | Number exposed (%) | OR (95% CI) | Number exposed (%) | OR (95% CI) | p-value |
| 6-7 years | Farm animals (in utero) | 2,960 (6.6) | 1.16 (0.99, 1.37) | 6,433 (8.2) | 1.18 (1.06, 1.32) | 0.003 |
| | Low birthweight | 2,598 (5.8) | 1.02 (0.90, 1.16) | 6,992 (8.9) | 1.05 (0.95, 1.16) | 0.74 |
| | Paracetamol (1st year) | 27,967 (62.4) | 1.38 (1.27, 1.51) | 53,959 (68.4) | 1.42 (1.32, 1.51) | 0.99 |
| | Antibiotics (1st year) | 23,763 (53.0) | 1.60 (1.49, 1.71) | 45,235 (57.4) | 1.53 (1.44, 1.63) | 0.36 |
| | Breastfed ever | 30,729 (68.5) | 1.03 (0.96, 1.11) | 68,838 (87.3) | 0.96 (0.89, 1.04) | 0.24 |
| | Cat (1st year) | 6,699 (14.9) | 1.05 (0.95, 1.16) | 6,537 (8.3) | 1.10 (1.01, 1.21) | 0.17 |
| | Dog (1st year) | 8,088 (18.0) | 1.04 (0.95, 1.13) | 15,846 (20.1) | 1.07 (1.00, 1.14) | 0.16 |
| | Farm animals (1st year) | 3,672 (8.2) | 0.90 (0.77, 1.05) | 7,655 (9.7) | 1.22 (1.10, 1.35) | <0.001 |
| | 2 or more siblings | 13,388 (29.9) | 0.88 (0.82, 0.94) | 29,564 (37.5) | 1.05 (0.99, 1.11) | <0.001 |
| | Heavy Truck traffic (current) | 15,518 (34.6) | 1.16 (1.09, 1.24) | 31,809 (40.3) | 1.17 (1.10, 1.23) | 0.84 |
| | Fast food (current) | 13,817 (30.8) | 0.99 (0.93, 1.06) | 35,102 (44.5) | 1.01 (0.95, 1.08) | 0.73 |
| | Television (current) | 35,446 (79.1) | 0.88 (0.81, 0.95) | 63,306 (80.3) | 1.00 (0.92, 1.09) | 0.02 |
| | Paternal tobacco (current) | 17,921 (40.0) | 1.04 (0.97, 1.11) | 21,651 (27.5) | 1.08 (1.02, 1.16) | 0.22 |
| | Maternal tobacco (current) | 12,294 (27.4) | 1.06 (0.98, 1.15) | 7,671 (9.7) | 1.05 (0.96, 1.15) | 0.76 |
| | Paracetamol (current) | 5,019 (11.2) | 2.18 (2.00, 2.38) | 16,905 (21.4) | 1.94 (1.82, 2.07) | 0.05 |
| | Open fire cooking (current) | 259 (0.6) | 1.53 (1.07, 2.19) | 2,117 (2.7) | 0.90 (0.74, 1.10) | 0.02 |
| Age group | Exposure | Affluent Countries (n=50,491) | | Non-Affluent Countries (n=185,859) | | Effect modification |
| | | Number exposed (%) | OR (95% CI) | Number exposed (%) | OR (95% CI) | p-value |
| 13-14 years | 2 or more siblings | 18,895 (37.4) | 1.00 (0.95, 1.06) | 108,363 (58.3) | 1.05 (1.02, 1.09) | 0.09 |
| | Heavy Truck traffic (current) | 18,966 (37.6) | 1.21 (1.15, 1.28) | 75,427 (40.6) | 1.24 (1.20, 1.27) | 0.67 |
| | Fast food (current) | 25,483 (50.5) | 1.06 (1.00, 1.11) | 101,021 (54.4) | 1.06 (1.03, 1.09) | 0.89 |
| | Television (current) | 45,934 (91.0) | 0.98 (0.90, 1.07) | 156,498 (84.2) | 1.00 (0.96, 1.05) | 0.70 |
| | Paternal tobacco (current) | 20,610 (40.8) | 1.02 (0.97, 1.08) | 70,154 (37.7) | 1.13 (1.10, 1.17) | 0.001 |
| | Maternal tobacco (current) | 15,125 (30.0) | 1.11 (1.05, 1.18) | 27,856 (15.0) | 1.14 (1.10, 1.19) | 0.17 |
| | Paracetamol (current) | 13,437 (26.6) | 1.95 (1.85, 2.07) | 49,818 (26.8) | 1.70 (1.65, 1.76) | <0.001 |
| | Open fire cooking (current) | 536 (1.1) | 0.83 (0.64, 1.07) | 11,842 (6.4) | 1.20 (1.11, 1.30) | 0.006 |

[a]Adjusted for sex, mother's level of education and all other variables in the table.

*Table 3.22 Fully adjusted effects of school-level exposures on rhinoconjunctivitis symptom prevalence in the last 12 month stratified by country affluence.*

In subjects non-missing for rhinoconjunctivitis symptoms, sex, maternal education and all exposures of interest (the "common sample"). Mixed logistic regression models with random intercepts at the school, centre and country levels.[a]

| Age group | Exposure | Affluent countries (n = 44,836) | | Non-affluent countries (n = 78,862) | | Effect modification |
|---|---|---|---|---|---|---|
| | | Median prevalence | OR (95% CI) | Median prevalence | OR (95% CI) | p-value |
| 6-7 years | Farm animals (in utero) | 0.06 | 0.51 (0.19, 1.34) | 0.07 | 1.87 (0.79, 4.43) | 0.30 |
| | Low birthweight | 0.05 | 1.27 (0.54, 2.98) | 0.06 | 3.07 (1.60, 5.90) | 0.15 |
| | Paracetamol (1st year) | 0.75 | 1.58 (0.96, 2.61) | 0.68 | 0.73 (0.49, 1.09) | 0.002 |
| | Antibiotics (1st year) | 0.57 | 1.55 (1.01, 2.40) | 0.58 | 1.39 (0.92, 2.09) | 0.15 |
| | Breastfed ever | 0.74 | 0.68 (0.44, 1.03) | 0.89 | 0.63 (0.35, 1.13) | 0.86 |
| | Cat (1st year) | 0.09 | 1.16 (0.70, 1.93) | 0.07 | 0.94 (0.44, 1.98) | 0.96 |
| | Dog (1st year) | 0.18 | 0.85 (0.54, 1.36) | 0.20 | 0.92 (0.57, 1.47) | 0.65 |
| | Farm animals (1st year) | 0.07 | 2.10 (0.84, 5.27) | 0.08 | 0.90 (0.40, 2.01) | 0.98 |
| | 2 or more siblings | 0.29 | 0.67 (0.47, 0.94) | 0.36 | 1.08 (0.78, 1.50) | 0.09 |
| | Heavy Truck traffic (current) | 0.34 | 1.07 (0.78, 1.48) | 0.40 | 0.84 (0.62, 1.15) | 0.21 |
| | Fast food (current) | 0.27 | 0.87 (0.58, 1.30) | 0.36 | 1.14 (0.85, 1.53) | 0.56 |
| | Television (current) | 0.83 | 1.31 (0.86, 1.99) | 0.87 | 1.62 (0.99, 2.67) | 0.86 |
| | Paternal tobacco (current) | 0.42 | 0.73 (0.48, 1.11) | 0.29 | 1.06 (0.67, 1.69) | 0.26 |
| | Maternal tobacco (current) | 0.29 | 1.42 (0.94, 2.15) | 0.08 | 1.18 (0.65, 2.16) | 0.66 |
| | Paracetamol (current) | 0.11 | 3.53 (2.10, 5.94) | 0.17 | 1.59 (1.00, 2.54) | 0.02 |
| | Open fire cooking (current) | 0.00 | 5.42 (0.85, 34.78) | 0.00 | 1.32 (0.61, 2.84) | 0.33 |
| Age group | Exposure | Affluent countries (n = 50,491) | | Non-affluent countries (n = 185,859) | | Effect modification |
| | | Median prevalence | OR (95% CI) | Median prevalence | OR (95% CI) | p-value |
| 13-14 years | 2 or more siblings | 0.36 | 1.19 (0.82, 1.72) | 0.68 | 0.94 (0.73, 1.21) | 0.47 |
| | Heavy Truck traffic (current) | 0.37 | 0.82 (0.54, 1.25) | 0.40 | 1.26 (0.99, 1.61) | 0.08 |
| | Fast food (current) | 0.48 | 1.58 (1.04, 2.40) | 0.55 | 1.13 (0.90, 1.42) | 0.64 |
| | Television (current) | 0.92 | 0.58 (0.28, 1.21) | 0.90 | 1.46 (1.00, 2.13) | 0.04 |
| | Paternal tobacco (current) | 0.44 | 0.75 (0.44, 1.30) | 0.34 | 0.83 (0.59, 1.16) | 0.33 |
| | Maternal tobacco (current) | 0.35 | 1.59 (0.90, 2.79) | 0.13 | 1.60 (1.07, 2.38) | 0.51 |
| | Paracetamol (current) | 0.30 | 1.79 (1.10, 2.93) | 0.29 | 3.94 (2.88, 5.39) | 0.03 |
| | Open fire cooking (current) | 0.00 | 0.57 (0.06, 5.28) | 0.01 | 2.03 (1.37, 3.00) | 0.32 |

[a]Adjusted for sex, mother's level of education and all other variables in the table.

In the fully adjusted individual-level models, effects were reduced compared to minimally adjusted models (Table 3.19) which indicated some confounding between the risk factors. This was to be expected and one of the reasons to analyse the data in this way. Only TV viewing showed some weak evidence of a protective effect in the fully adjusted model but no evidence of effect in the minimally adjusted model. Fully adjusted school-level models showed a similar pattern of reduced effects compared to minimally adjusted.

There were only a few differences between school-level and individual-level results. Low birthweight had a much stronger effect at the school-level, which could be due to residual socio-economic confounding. There are many reasons for low birthweight at an individual level but at a community level it has been shown that, at least in England, poorer areas have higher prevalence of low birthweight, or Small for Gestational Age.[79] Maternal tobacco has a stronger effect at the school level for both age groups, which again could be residual socio-economic confounding. For adolescents, current paracetamol had an increased effect at the school level although it was a substantially harmful effect at both levels. For younger children the effect of both current paracetamol and paracetamol in the first year was reduced at the school level, although again both levels showed substantially harmful effects.

More generally, associations with school-level prevalences were similar in direction and magnitude to those ascertained at the individual level. Similar to results in the asthma and eczema papers[80,81] detailed earlier in the chapter, this helps to refute claims that effects are explained by reverse causation. Paracetamol and antibiotic use were thought to be related to early symptoms in advance of diagnosis and animal contact was believed to be avoided by those with a family history of allergies.

Rhinoconjunctivitis arises later in childhood than asthma or eczema. There is arguably less of an issue with reverse causation and early-life exposures as associations are less likely to arise from early disease (as with eczema) or prodromal chest illnesses (as with asthma). On the other hand, avoidance strategies may be put into place following symptoms of other allergic diseases in either the individual or other family members (e.g. removing pets, parental smoking cessation).

For many risk factors, associations were consistent between the two age groups (Table 3.19). The exceptions were a slightly lower effect of current paracetamol in adolescents and an increased effect of open fire cooking on adolescents. The latter could be because adolescents help more with the cooking than younger children. Associations were also consistent between

affluent and non-affluent countries (Table 3.20) with the exception of farm animal contact in the first year which was associated with rhinoconjunctivitis only in non-affluent countries and number of siblings which showed a protective effect in only affluent countries. These differences could be explained by different levels of contact with farm animals between living on a farm (or regularly visiting petting zoos) in affluent countries compared to rural living on farms in non-affluent countries, and secondly, housing with extended families in non-affluent countries could dilute any specific sibling effect.

Overall, this commonality of epidemiology suggests that there are common biological mechanisms operating in both affluent and less affluent settings.

***Strengths and limitations***

The main strength of ISAAC Phase III is the large sample size drawn from diverse study centres around the world. This enabled us to stratify results by affluent and non-affluent countries. In addition, all centres used a standardised method of data collection relying on symptom descriptions rather than doctor diagnoses. Although individuals may interpret/remember their symptom severity differently, levels of doctor diagnoses in different countries/centres is likely to be systematically different. The response rate was high at 85% overall and each centre required a minimum response rate of 70% for adolescents and 60% for children. This minimised concerns over selection bias.

Limitations include a lack of objective information on allergic sensitisation, but this is not possible to get from a questionnaire alone. Also, as with all questionnaires, there is a chance of misclassification due to recall bias or human error. If the misclassification is non-differential, then true associations may be stronger than shown in our results. Any differential misclassification could be either masking or exaggerating associations.

The definition of rhinoconjunctivitis is quite simple and it may be of benefit to do further analyses considering severity of disease or seasonality of symptoms (though this is made hard by the different seasonal patterns across the globe).

Rhinoconjunctivitis (in the absence of infectious disease) was used throughout this and previous ISAAC analyses rather than simply rhinitis because non-infectious inflammation of the nose and eyes is more specifically allergic than nasal symptoms alone. This was shown in ISAAC Phase Two with rhinoconjunctivitis having a stronger association with skin prick positivity.[32] In addition, later studies have replicated this in adolescents[82] and adults.[83]

In conclusion, these multi-level analyses provide additional evidence in favour of direct (rather than reverse) causation of the risk factors on symptoms of rhinoconjunctivitis, particularly paracetamol and antibiotic use. For paracetamol usage this is evidence against the theory of aspirin (or NSAID) avoidance as a form of reverse causation (avoiding aspirin and NSAIDs as they are known to exacerbate symptoms of nasal congestion in some people[84]). However, it is possible that NSAID usage (not measured here) could confound the association as ibuprofen is often used in conjunction with paracetamol in children (as opposed to aspirin which has not been recommended for children under 16 since the 1970s, due to Reye's syndrome).

## 3.5 Conclusion

There are similarities between the results of all three separate analyses. The main risk factors of paracetamol use and antibiotics have been identified to be strongly associated with symptoms of all three diseases of asthma, eczema and rhinoconjunctivitis. There was no evidence of potential reverse causation found from comparing individual-level with school-level models for any of the diseases. It would be useful to investigate the interaction between these diseases further as they seem to have many similarities. This will be considered in the next chapter.

# 4 Paper III: Comparison of individual-level and population-level risk factors for rhinoconjunctivitis, asthma and eczema in ISAAC Phase III

## Summary

This chapter compares the findings for individual-level and school-level risk factors for asthma, eczema and rhinoconjunctivitis. It comprises a published paper that investigates the similarities and differences in risk factors of asthma, eczema and rhinoconjunctivitis and different combinations of these diseases using novel methods for visualisation of the triad. Generally, the findings are similar for the three diseases, but there are a few notable differences.

## 4.1 Introduction

This paper uses the ISAAC Phase III data (see Section 2.4 for details) to identify similarities and differences between risk factors of asthma, eczema and rhinoconjunctivitis, and the various combinations of the diseases. All the analyses are based on the same sample, the "synthesis sample" which includes people with complete data for symptoms of all three diseases, data for all exposures (risk factors) and data for the confounders of sex and mother's level of education. This paper includes some results from rhinoconjunctivitis alone, similar to Section 3.4 but on the "Synthesis sample", comparing the individual- and school-level findings.

This paper was published in the World Allergy Organisation Journal in June 2020.

# 4.2 Article submitted

**SECTION A – Student Details**

| | | | |
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| **Student ID Number** | 1300807 | **Title** | Mrs |
| **First Name(s)** | Charlotte Emma | | |
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| **Thesis Title** | Multi-level modelling of international variations and time trends in asthma and allergic diseases in children. | | |
| **Primary Supervisor** | Neil Pearce | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

**SECTION B – Paper already published**

| | | | |
|---|---|---|---|
| Where was the work published? | World Allergy Organisation Journal | | |
| When was the work published? | June 2020 | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | Not applicable | | |
| Have you retained the copyright for the work?* | **Yes** | Was the work subject to academic peer review? | **Yes** |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

**SECTION C – Prepared for publication, but not yet published**

| | |
|---|---|
| Where is the work intended to be published? | |
| Please list the paper's authors in the intended authorship order: | |
| Stage of publication | |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role was running the analyses, creating the tables, writing the methods and results sections and reviewing all drafts. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | [redacted] |
| **Date** | 31/12/2021 |

| | |
|---|---|
| **Supervisor Signature** | [redacted] |
| **Date** | 23/03/2022 |

### 4.2.1 Abstract

**Background**

Symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema in children cluster at both the individual and population levels.

**Objectives**

To assess individual-level and school-level risk factors for symptoms of rhinoconjunctivitis and compare them to corresponding associations with symptoms of asthma and eczema in Phase Three of the International Study of Asthma and Allergies in Childhood.

**Methods**

We studied 116,863 children aged 6-7 years from 2,163 schools in 59 centres and 22 countries and 224,436 adolescents aged 13-14 years from 2,037 schools in 97 centres in 41 countries. Multilevel logistic regression models were fitted with random intercepts for school, centre and country, adjusting for sex and maternal education at the child level. Associations between symptoms and a range of lifestyle and environmental risk factors were assessed for both the child's exposure and mean exposure at the school. Models were fitted for rhinoconjunctivitis, asthma and eczema singly (unimorbidity) and for combinations of these conditions (multimorbidity).

**Results**

Generally, associations between symptoms and exposures at the school level were similar in direction and magnitude to those at the child level. Associations with multimorbidity were stronger than for unimorbidity, particularly in individuals with symptoms of all three diseases, but risk factor associations found in conventional single disease analyses persisted among children with only one condition, after excluding multimorbid groups.

Comparisons of individuals with only one disease showed that many risk factor associations were consistent across the three conditions. More strongly associated with asthma were low birthweight, cat exposure in infancy and current maternal smoking. Current paracetamol use was more strongly associated with asthma and rhinoconjunctivitis than eczema. Breastfeeding was more strongly associated with eczema than asthma or rhinoconjunctivitis.

The direction and magnitude of most risk factor associations were similar in affluent and non-affluent countries, although notable exceptions include farm animal contact in infancy and larger sibships, which were associated with increased risk of rhinoconjunctivitis in non-affluent countries but reduced risk in affluent countries. In both age groups, current paracetamol use increased risk of each disease to a greater extent in affluent countries than in non-affluent

countries. Effects of paracetamol and antibiotics in infancy were more consistent between richer and poorer settings.

**Conclusions**

Most of the environmental and lifestyle correlates of rhinoconjunctivitis, asthma and eczema in childhood display similarity across the three conditions, even in less affluent settings where allergic sensitisation is less likely to explain the concordant epidemiological patterns.

### 4.2.2 Introduction

The International Study of Asthma and Allergies in Childhood (ISAAC) has used standardised questionnaires to assess prevalence, time trends and epidemiological associations for symptoms of non-infective rhinoconjunctivitis, asthma and eczema among children from over 300 centres in more than 100 countries worldwide.[2,3] More detailed biomedical assessment in 30 diverse centres in ISAAC Phase Two[30,31,33] has demonstrated that allergic sensitisation accounts for a much lower proportion of rhinoconjunctivitis, asthma and eczema symptoms in centres from low- and middle-income countries than it does in more affluent settings which feature more prominently in the epidemiological literature.

Previous publications from ISAAC Phase Three have presented the associations of each of the three diseases with single environmental or lifestyle factors.[38-49] More recently, these have been summarised across multiple risk factors for symptoms of asthma[80] and eczema,[81] and comparisons made between the relationship of each of these diseases to exposures measured at the level of individuals and exposures averaged at the area level (schools).
In this paper, we apply the multi-level analytical approach to symptoms of rhinoconjunctivitis and extend our overview to assess similarities and differences in the epidemiological patterns of the three diseases, singly and in combination. We also compare these patterns between centres from higher-income and lower-income countries.

### 4.2.3 Methods

**Study design**

A brief summary of the ISAAC Phase Three methods is presented in this paper and more details are available elsewhere.[3] ISAAC Phase Three was a multi-centre, multi-country, cross-sectional study of children (age 6-7 years) and adolescents (age 13-14 years). Within a defined geographical area (centre), a sample of schools were chosen at random. All children within the age groups in those schools were asked to participate.[3] The Phase Three survey took place in 2000-2003 and included two standardised questionnaires (http://isaac.auckland.ac.nz); the

original symptom questionnaire from ISAAC Phase One[2,3] with information on symptoms of asthma, eczema and rhinoconjunctivitis, and an environmental questionnaire which collected data on a range of possible risk factors for the development of these disorders.[3]

**Variable definitions**

The three main outcomes of interest, asthma, eczema and rhinoconjunctivitis, are defined using previous ISAAC conventions.[2,3,30] These three diseases are likely to be undiagnosed in many cases as people seek to self-treat (particularly rhinoconjunctivitis), and the rate of doctor diagnoses is likely to vary widely from country to country. Thus, outcomes assessed in the ISAAC questionnaire are based on a description of symptoms rather than a diagnosis of disease.

Rhinoconjunctivitis is defined by positive responses to all of the following three questions:

*Have you [has your child] ever had a problem with sneezing, or a runny, or blocked nose when you did not have a cold or the flu?*

*In the past 12 months, have you [has your child] had a problem with sneezing, or a runny, or blocked nose when you [he/she] did not have a cold or the flu?*

*In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?*

Eczema is defined by positive responses to all of the following three questions:

*Have you [has your child] ever had an itchy rash which was coming and going for at least six months?*

*Have you [has your child] had this itchy rash at any time in the past 12 months?*

*Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?*

Asthma is defined by a positive response to the following question:

*Have you [has your child] had wheezing or whistling in the chest in the past 12 months?*

The environmental questionnaire for the 6-7-year-old age group contained more questions on early life exposures as this was completed by the parents of the child. We restricted our analyses to the risk factors which had shown associations with either rhinoconjunctivitis, asthma or eczema symptoms in the last 12 months in previous analyses at the individual level. Variables included for the younger age group (6-7 years) were paracetamol use in the first year of life and in the past 12 months,[38] antibiotic use in the first year of life,[40] breast feeding,[41] pets in the home in the first year of life,[43] regular contact with farm animals in the first year of life and prenatally through maternal contact,[42] truck traffic in the last 12 months,[39] fast food

consumption in the last 12 months,[46] television viewing in the last 12 months,[45] parental smoking in the last 12 months,[44] open fire cooking,[47] birth weight[48] and number of siblings.[50] For the older age group (13-14 years), truck traffic,[39] fast food consumption,[46] television viewing,[45] parental smoking[44] and paracetamol use,[51] all in the past 12 months, open fire cooking[47] and number of siblings[50] were included.

Most of the above risk factors were parameterised as binary variables from "yes/no" questions in the environmental questionnaire. The exceptions were: paracetamol use in the past 12 months (at least once per month vs. less than once per month), heavy truck traffic (frequently or almost the whole day vs. seldom or never), fast food consumption (once per week or more vs. less than once per week), television viewing (at least 1 hour per day vs. less than 1 hour per day), birth weight (less than 2.5 kg vs. at least 2.5 kg) and number of siblings (2 or more siblings vs. 1 or no siblings). Full definitions are in Table 4.1. The highest level of maternal education was recorded as primary, secondary, tertiary or missing/not stated.

Gross National Income (GNI) in 2002 was obtained from the World Bank website[61] where available, with gaps filled by the CIA World Factbook.[62] Countries were classified as 'affluent' or 'non-affluent' using a 2001 GNI value of US$9,205 per capita as a cut-off, which separates high-income countries from low and middle-income countries.[63]

**Statistical analyses**

Separate analyses were conducted for the two age groups. Centres with fewer than 1,000 individuals in an age group were excluded from the analyses for that age group. Each school was required to have at least 10 individuals to be included in the analyses for that age group. In addition, a response rate of at least 60% was required for children and at least 70% for adolescents for a centre to be included.

Mixed effect (multilevel) logistic regression models were used for all analyses with random intercepts at the 3 highest levels of the four-level hierarchy: individuals, schools, centres and countries (from lowest to highest). All analyses additionally adjusted for sex and maternal education as confounders at the individual level.

The potential risk factors for rhinoconjunctivitis symptoms were compared at individual level and at school level in a similar way to previous publications on asthma[80] and eczema.[81] The school-level risk factors are less prone to reverse causation bias than the individual-level risk factors as a change in behaviour of a few people with the disease will not greatly affect the

*Table 4.1 Risk factor definitions*

| **Risk Factors for ages 6-7** | **Question (asked to parent)** | **Positive Response** |
|---|---|---|
| Low birthweight | What was the weight of your child when he / she was born? | Less than 2.5kg |
| Breastfed ever | Was your child breastfed? | Yes |
| Farm animals (prenatal) | Has the child's mother had regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry) while being pregnant with this child? | Yes |
| Farm animals (1st year) | In your child's first year of life, did he / she have regular (at least once a week) contact with farm animals (e.g. cattle, pigs, goats, sheep or poultry)? | Yes |
| Cat (1st year) | Did you have a cat in your home during the first year of your child's life? | Yes |
| Dog (1st year) | Did you have a dog in your home during the first year of your child's life? | Yes |
| Paracetamol (1st year) | In the first 12 months of your child's life, did you usually give paracetamol for fever? | Yes |
| Antibiotics (1st year) | In the first 12 months of your child's life, did your child have any antibiotics? | Yes |
| 2 or more siblings | How many older and younger brothers and sisters does your child have? | Total of 2 or more |
| Heavy truck traffic (current) | How often do trucks pass through the street where you live, on weekdays? | Frequently or almost the whole day |
| Fast food (current) | In the past 12 months, how often, on average did your child eat fast food / burgers? | At least once a week |
| Television (current) | During a normal week, how many hours a day (24 hours) does your child watch television? | At least one hour per day |
| Paternal tobacco (current) | Does your child's father (or male guardian) smoke cigarettes? | Yes |
| Maternal tobacco (current) | Does your child's mother (or female guardian) smoke cigarettes? | Yes |
| Paracetamol (current) | In the past 12 months, how often, on average, have you given your child paracetamol? | At least once per month |
| Open fire cooking (current) | In your house, what fuels are usually used for cooking? Electricity, gas, open fires, other | Any that include open fires |

| **Risk Factors for ages 13-14** | **Question (asked to child)** | **Positive Response** |
|---|---|---|
| 2 or more siblings | How many older and younger brothers and sisters do you have? | Total of 2 or more |
| Heavy truck traffic (current) | How often do trucks pass through the street where you live, on weekdays? | Frequently or almost the whole day |
| Fast food (current) | In the past 12 months, how often, on average did you eat fast food / burgers? | At least once a week |

| | | |
|---|---|---|
| Television (current) | During a normal week, how many hours a day (24 hours) do you watch television? | At least one hour per day |
| Paternal tobacco (current) | Does your father (or male guardian) smoke cigarettes? | Yes |
| Maternal tobacco (current) | Does your mother (or female guardian) smoke cigarettes? | Yes |
| Paracetamol (current) | In the past 12 months, how often, on average, have you taken paracetamol? | At least once per month |
| Open fire cooking (current) | In your house, what fuels are usually used for cooking? Electricity, gas, open fires, other | Any that include open fires |

school-level prevalence of that risk factor. Thus, similar results at both levels can be interpreted as suggestive evidence against reverse causation influencing individual-level associations.

For comparison of risk factor associations between the three different diseases, three different modelling approaches were used:

i) Standard outcomes - modelling the three disease outcomes separately but within the same sample of children,

ii) Multimorbid outcomes - modelling each of the different combination of disease outcomes (i.e. asthma only, eczema only, rhinoconjunctivitis only, asthma and eczema, asthma and rhinoconjunctivitis, eczema and rhinoconjunctivitis, and all three) against those with no disease and comparing the resulting risk factor associations, and

iii) Unimorbid outcomes - comparing individuals with only asthma, only eczema or only rhinoconjunctivitis symptoms in the last 12 months and modelling the three combinations of disease pairs to evaluate if the risk factors are more associated with one disease than another.

In each of these modelling analyses we checked for collinearity between the risk factors by comparing the standard errors in the fully adjusted model (all risk factors and confounders) to those in minimally adjusted models (only the risk factor of interest and the confounders).

Additionally, we ran each model separately for 'affluent' and 'non-affluent' countries (with the exception of the multimorbid outcomes analyses where some of the sample sizes were too small). We also tested for an interaction between country affluence and each risk factor individually.

Analyses were conducted using Stata version 15.[85]

### 4.2.4 Results

**Derivation and characteristics of the sample analysed**

In the age 6-7 analyses there were 75 centres (comprising 221,280 children) that met the standard ISAAC inclusion criteria[3] of a minimum of 1,000 children and a response rate of at least 60%. For multi-level analysis, 263 schools (1,427 children in total) were excluded due to having fewer than 10 children and a further 102,990 children excluded for not having data available for all three outcomes (asthma, eczema and rhinoconjunctivitis symptoms), confounders (sex and mother's level of education) and all the included risk factors. The

remaining 116,863 children, on which these results are based (the "synthesis sample"), were from 2,163 schools within 59 centres, in 22 different countries (Figure 4.1).

The prevalence of rhinoconjunctivitis symptoms among the 6-7-year-olds included in this analysis was 8.9%, asthma symptoms was 9.7% and eczema symptoms was 7.3%. The overall prevalence of the exposures ranged from 1.8% for current open fire cooking to 80.5% for ever breastfed. These and further summary statistics for the synthesis sample are presented in Table 4.2.

For the 13-14 year-olds there were 122 centres (comprising 362,048 adolescents) meeting the ISAAC criteria[3] of a minimum of 1,000 per centre and a response rate of at least 70%. For multi-level analysis, 64 schools (comprising 298 individuals) were excluded due to having fewer than 10 adolescents. A further 137,314 individuals were excluded for not having data available for all three outcomes (asthma, eczema and rhinoconjunctivitis symptoms), confounders (sex and mother's level of education) and all the included risk factors of interest. The remaining "synthesis sample" contained 224,436 adolescents from 2,037 schools within 97 centres, in 41 different countries (Figure 4.2).

The prevalence of rhinoconjunctivitis symptoms among the 13-14-year-olds included in this analysis was 14.1%, asthma symptoms was 10.6% and eczema symptoms was 6.2%. The overall prevalence of the exposures ranged from 5.2% for current open fire cooking to 85.7% for watching television at least an hour a day. For further details, see Table 4.2.

**Multi-level models for rhinoconjunctivitis**

Table 4.3 presents associations at the individual level (within schools) and the area level (between schools, within centre) for exposures of interest, adjusted for sex and mother's educational level ("minimally adjusted") and for each other ("fully adjusted"), as derived from the multi-level model.

For the 6-7 age group, the strongest mutually adjusted associations with rhinoconjunctivitis at the individual level were current paracetamol use (odds ratio=2.02; 95% CI=1.92-2.13) and antibiotics in the first year (1.58; 1.51-1.66). These associations were very similar at the school level with odds ratios 2.04 (1.43-2.89) and 1.39 (1.03-1.88) respectively. However, the weaker child-level association with early paracetamol use (1.39;1.32-1.47) was not seen at the school level (0.99; 0.73-1.35).

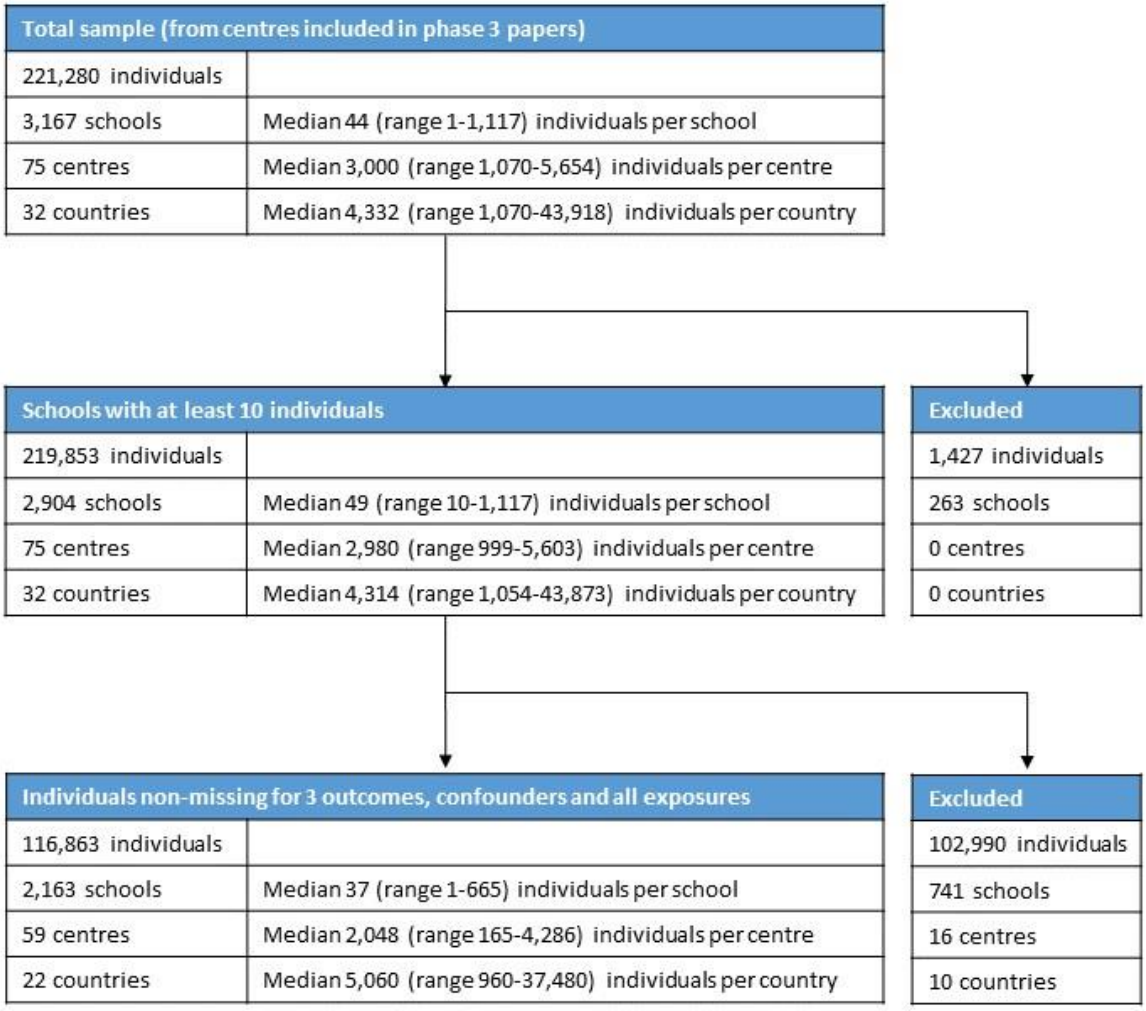


*Figure 4.1 Synthesis sample data flowchart, age 6-7 years*

*Shows the data flow through the exclusions to the final analysed sample for the 6-7 year-old children.*

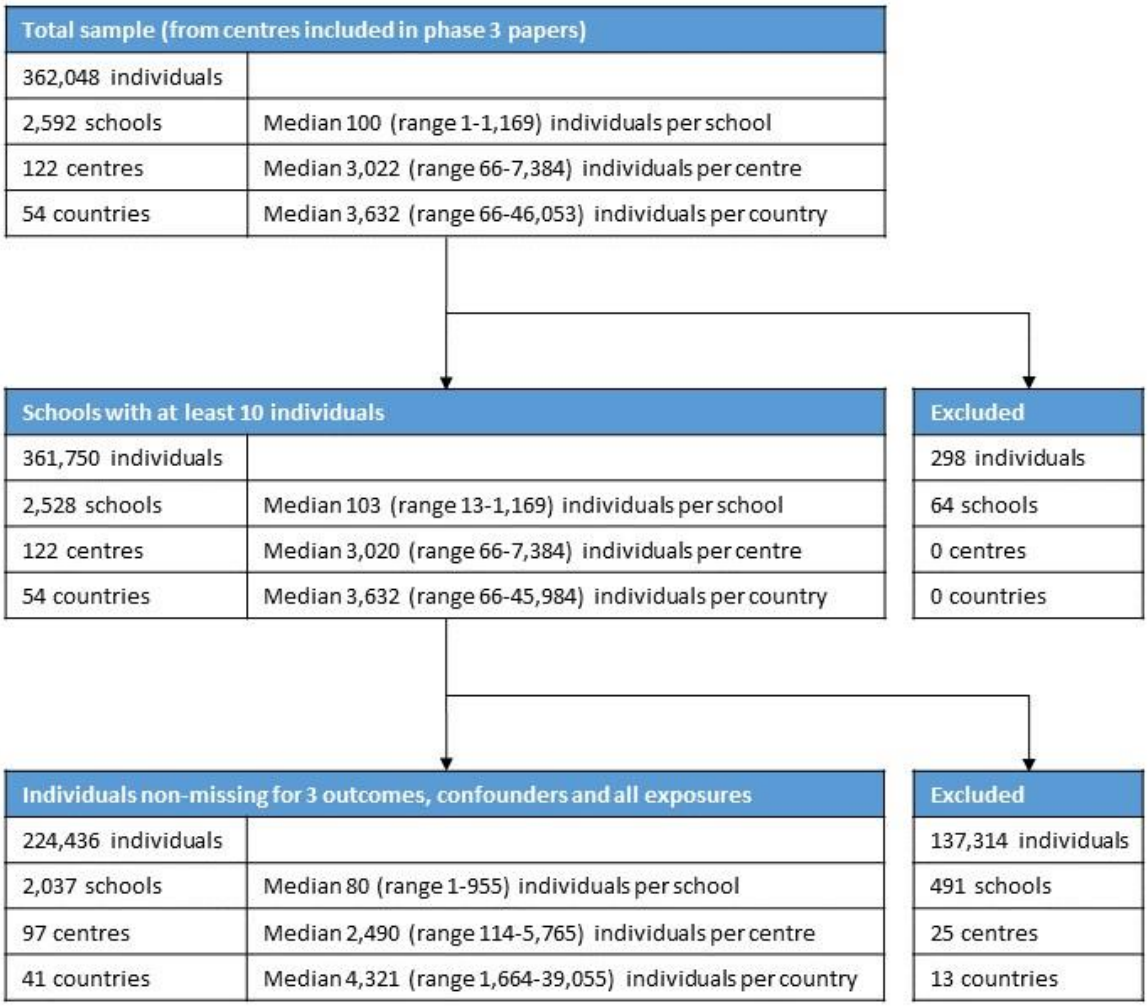


*Figure 4.2 Synthesis sample data flowchart, age 13-14 years*

***Shows the data flow through the exclusions to the final analysed sample for the 13-14 year-old adolescents.***

Similarly, a modest child-level association with heavy truck traffic (1.17; 1.12-1.22) was inconsistent with the inverse relationship at school level (odds ratio 0.92; 0.73-1.16). Low birthweight showed no evidence of an association with rhinoconjunctivitis at the individual level (1.04; 0.96-1.13) but at the school level the association was strong and significant (2.59; 1.56-4.29). Similarly, a school-level association was evident for television viewing (1.45;1.05-2.01) but not for children within schools (0.93; 0.88-0.98).

In the 13-14 age group, there was a strong association at the individual level with current paracetamol use (1.76; 1.71-1.81) which was even stronger at the school-level (3.48; 2.66-4.56). A less strong child-level association was observed for heavy truck traffic (1.23; 1.20-1.26) which was consistent at the school level (1.16; 0.94-1.44) though there was less precision on the latter estimate. Paternal and maternal smoking had similar effects at the individual-level but at the school level their associations were in opposite directions. For cooking by open fire, the school-level association (2.02;1.39-2.93) was much stronger than the child-level association (1.16;1.08-1.26).

The precision of estimates from the fully adjusted models and those from the corresponding minimally adjusted models (Table 4.3) were compared and no evidence of collinearity was found.

**Comparison of risk factor patterns for rhinoconjunctivitis, asthma and eczema**

Table 4.4 compares, by age group, the individual-level associations of each exposure with symptoms of rhinoconjunctivitis (from Table 4.3), asthma and eczema (previously published in slightly different samples,[80,81] but reanalysed here on the same "synthesis sample" as for rhinoconjunctivitis).

For younger children, the strongest associations in the fully adjusted analyses were similar across all three outcomes. They were: current paracetamol use (ORs for rhinoconjunctivitis symptoms 2.02; asthma symptoms 2.07; and eczema symptoms 1.46), antibiotic use in the first year of life (1.58; 1.66; 1.40, respectively), and paracetamol use in the first year of life (1.39; 1.34; 1.29). Heavy truck traffic showed a less strong but consistent association with all three outcomes (1.17; 1.19; 1.12). Similarly, cat ownership in the first year of life had a consistent direction of association, somewhat stronger with asthma (1.22) than with rhinoconjunctivitis (1.09) and eczema (1.10).

*Table 4.2 Summary statistics for variables and their prevalence in subjects who had data present for the 3 outcomes, the confounders sex and maternal education level and all other exposures of interest in the table (the "synthesis sample").*

| Variable Type | Variable | Age 6-7 years (n=116,863) | | | | | | Age 13-14 years (n=224,436) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Individual Level | Centre Level Prevalence (%) Quartiles | | | | | Individual Level | Centre Level Prevalence (%) Quartiles | | | | |
| | | Prevalence (%) | Min | Q1 | Med | Q3 | Max | Prevalence (%) | Min | Q1 | Med | Q3 | Max |
| Outcome | Rhinoconjunctivitis in the past 12 months | 8.9 | 0.9 | 3.7 | 7.5 | 12.2 | 25.2 | 14.1 | 1.2 | 8.8 | 13.2 | 18.5 | 31.7 |
| | Asthma symptoms in the past 12 months | 9.7 | 2.5 | 5.4 | 9.0 | 13.2 | 29.7 | 10.6 | 0.7 | 6.1 | 9.8 | 14.4 | 32.4 |
| | Eczema symptoms in the past 12 months | 7.3 | 0.6 | 2.5 | 6.0 | 10.9 | 18.9 | 6.2 | 0.1 | 3.0 | 4.7 | 8.0 | 23.8 |
| Multiple outcome | No symptoms | 80.1 | 62.2 | 74.1 | 80.1 | 89.0 | 95.0 | 76.0 | 51.8 | 69.6 | 75.8 | 83.5 | 98.2 |
| | Rhinoconjunctivitis only | 4.7 | 0.3 | 2.2 | 3.6 | 5.2 | 16.5 | 8.8 | 1.1 | 5.0 | 8.4 | 11.1 | 22.4 |
| | Asthma only | 5.8 | 1.7 | 3.6 | 5.0 | 7.4 | 26.1 | 6.1 | 0.6 | 3.7 | 5.5 | 8.0 | 19.6 |
| | Eczema only | 4.4 | 0.6 | 1.8 | 3.2 | 5.5 | 11.4 | 3.2 | 0.0 | 1.6 | 2.5 | 4.1 | 13.4 |
| | Rhinoconjunctivitis and Asthma | 2.1 | 0.2 | 0.8 | 2.0 | 3.3 | 4.9 | 2.9 | 0.0 | 1.4 | 2.6 | 4.0 | 10.3 |
| | Rhinoconjunctivitis and Eczema | 1.1 | 0.0 | 0.3 | 0.8 | 1.6 | 4.3 | 1.4 | 0.0 | 0.5 | 0.9 | 1.6 | 8.0 |
| | Asthma and Eczema | 0.9 | 0.0 | 0.3 | 0.6 | 1.3 | 3.9 | 0.7 | 0.0 | 0.2 | 0.5 | 1.0 | 2.9 |
| | Symptoms of all three | 0.9 | 0.0 | 0.2 | 0.8 | 1.4 | 3.3 | 0.9 | 0.0 | 0.3 | 0.8 | 1.2 | 4.1 |
| Early Life Exposure | Low birthweight | 7.7 | 0.0 | 5.2 | 6.2 | 9.4 | 39.4 | NA | NA | NA | NA | NA | NA |
| | Breastfed ever | 80.5 | 29.2 | 79.3 | 84.7 | 91.2 | 97.0 | NA | NA | NA | NA | NA | NA |
| | Farm animals (prenatal) | 7.7 | 0.7 | 4.5 | 7.5 | 10.7 | 24.2 | NA | NA | NA | NA | NA | NA |
| | Farm animals (1st year) | 9.3 | 1.9 | 6.2 | 9.3 | 13.5 | 24.9 | NA | NA | NA | NA | NA | NA |
| | Cat (1st year) | 10.9 | 1.2 | 4.9 | 8.3 | 11.9 | 53.8 | NA | NA | NA | NA | NA | NA |
| | Dog (1st year) | 19.8 | 0.7 | 10.6 | 18.2 | 27.6 | 46.3 | NA | NA | NA | NA | NA | NA |
| | Paracetamol (1st year) | 66.1 | 8.6 | 59.0 | 68.1 | 82.7 | 93.9 | NA | NA | NA | NA | NA | NA |
| | Antibiotics (1st year) | 55.6 | 18.8 | 52.0 | 57.8 | 62.3 | 77.7 | NA | NA | NA | NA | NA | NA |
| Current Exposure | 2 or more siblings | 34.7 | 12.4 | 21.9 | 31.8 | 45.3 | 83.1 | 53.9 | 3.9 | 37.9 | 57.6 | 73.3 | 100.0 |
| | Heavy truck traffic (past 12 months) | 37.9 | 6.3 | 32.1 | 37.8 | 43.8 | 67.4 | 39.5 | 15.2 | 32.3 | 38.0 | 45.0 | 90.9 |
| | Fast food (past 12 months) | 39.6 | 9.3 | 20.4 | 42.4 | 54.3 | 98.1 | 53.6 | 6.1 | 42.7 | 53.7 | 66.4 | 98.3 |
| | Television (past 12 months) | 80.1 | 40.1 | 72.9 | 82.2 | 89.1 | 95.3 | 85.7 | 42.9 | 80.9 | 90.0 | 93.2 | 98.0 |
| | Paternal tobacco (past 12 months) | 31.7 | 3.2 | 19.9 | 28.9 | 43.6 | 55.3 | 38.5 | 2.7 | 23.9 | 36.4 | 46.4 | 94.1 |
| | Maternal tobacco (past 12 months) | 16.3 | 0.0 | 1.6 | 12.6 | 24.5 | 46.6 | 18.3 | 0.4 | 2.7 | 14.1 | 28.9 | 93.7 |
| | Paracetamol (past 12 months) | 17.8 | 0.0 | 9.9 | 15.7 | 23.9 | 65.3 | 26.7 | 0.0 | 18.4 | 28.6 | 34.7 | 66.0 |
| | Open fire cooking | 1.8 | 0.0 | 0.3 | 1.1 | 2.0 | 44.8 | 5.2 | 0.0 | 0.6 | 1.3 | 4.1 | 86.1 |

*Table 4.3 Individual-level (within school) and school-level (between school) effects of exposures on rhinoconjunctivitis symptoms using the synthesis sample[a]. Mixed logistic regression models with random intercepts at the school, centre and country levels.*

| Age group | Exposures of Interest | Minimally adjusted model[b] | | Fully adjusted model[c] | |
|---|---|---|---|---|---|
| | | Individual-level OR (95% CI) | School-level OR (95% CI) | Individual-level OR (95% CI) | School-level OR (95% CI) |
| 6-7 years (n=116,863) | Low birthweight | 1.11 (1.02, 1.20) | 3.03 (1.88, 4.88) | 1.04 (0.96, 1.13) | 2.59 (1.56, 4.29) |
| | Breastfed ever | 0.97 (0.92, 1.02) | 0.52 (0.37, 0.73) | 1.00 (0.95, 1.06) | 0.62 (0.44, 0.88) |
| | Farm animals (prenatal) | 1.36 (1.27, 1.46) | 1.56 (1.10, 2.22) | 1.18 (1.07, 1.30) | 1.16 (0.61, 2.20) |
| | Farm animals (1st year) | 1.30 (1.21, 1.39) | 1.55 (1.11, 2.16) | 1.07 (0.98, 1.17) | 1.19 (0.65, 2.18) |
| | Cat (1st year) | 1.19 (1.11, 1.27) | 1.36 (0.94, 1.97) | 1.09 (1.01, 1.16) | 1.10 (0.72, 1.68) |
| | Dog (1st year) | 1.16 (1.10, 1.21) | 1.21 (0.89, 1.63) | 1.07 (1.01, 1.12) | 0.94 (0.67, 1.31) |
| | Paracetamol (1st year) | 1.80 (1.71, 1.89) | 1.32 (1.01, 1.75) | 1.39 (1.32, 1.47) | 0.99 (0.73, 1.35) |
| | Antibiotics (1st year) | 1.84 (1.75, 1.92) | 1.45 (1.09, 1.91) | 1.58 (1.51, 1.66) | 1.39 (1.03, 1.88) |
| | 2 or more siblings | 0.99 (0.95, 1.04) | 1.04 (0.83, 1.30) | 0.98 (0.94, 1.03) | 0.88 (0.69, 1.12) |
| | Heavy truck traffic (current) | 1.25 (1.20, 1.31) | 1.12 (0.90, 1.40) | 1.17 (1.12, 1.22) | 0.92 (0.73, 1.16) |
| | Fast food (current) | 1.04 (0.99, 1.09) | 1.13 (0.89, 1.42) | 0.99 (0.94, 1.03) | 1.04 (0.82, 1.32) |
| | Television (current) | 0.98 (0.92, 1.03) | 1.59 (1.18, 2.14) | 0.93 (0.88, 0.98) | 1.45 (1.05, 2.01) |
| | Paternal tobacco (current) | 1.11 (1.06, 1.16) | 1.34 (1.03, 1.74) | 1.07 (1.02, 1.12) | 0.86 (0.63, 1.19) |
| | Maternal tobacco (current) | 1.12 (1.06, 1.19) | 1.67 (1.25, 2.23) | 1.05 (0.99, 1.11) | 1.39 (0.98, 1.96) |
| | Paracetamol (current) | 2.30 (2.18, 2.42) | 2.30 (1.66, 3.20) | 2.02 (1.92, 2.13) | 2.04 (1.43, 2.89) |
| | Open fire cooking (current) | 1.03 (0.86, 1.23) | 2.21 (1.16, 4.22) | 0.99 (0.82, 1.19) | 1.85 (0.92, 3.71) |
| 13-14 years (n=224,436) | 2 or more siblings | 1.05 (1.02, 1.08) | 1.02 (0.83, 1.25) | 1.04 (1.01, 1.07) | 0.93 (0.75, 1.15) |
| | Heavy truck traffic (current) | 1.27 (1.24, 1.30) | 1.35 (1.09, 1.67) | 1.23 (1.20, 1.26) | 1.16 (0.94, 1.44) |
| | Fast food (current) | 1.10 (1.07, 1.13) | 1.31 (1.07, 1.61) | 1.06 (1.03, 1.08) | 1.24 (1.02, 1.51) |
| | Television (current) | 1.04 (1.00, 1.08) | 1.35 (0.97, 1.88) | 1.01 (0.97, 1.05) | 1.20 (0.86, 1.68) |
| | Paternal tobacco (current) | 1.16 (1.13, 1.19) | 1.08 (0.84, 1.40) | 1.10 (1.07, 1.13) | 0.75 (0.55, 1.00) |
| | Maternal tobacco (current) | 1.21 (1.17, 1.25) | 1.46 (1.08, 1.97) | 1.14 (1.10, 1.17) | 1.56 (1.12, 2.18) |
| | Paracetamol (current) | 1.80 (1.75, 1.85) | 3.52 (2.69, 4.60) | 1.76 (1.71, 1.81) | 3.48 (2.66, 4.56) |
| | Open fire cooking (current) | 1.16 (1.08, 1.25) | 1.73 (1.19, 2.49) | 1.16 (1.08, 1.26) | 2.02 (1.39, 2.93) |

[a]Synthesis sample contains individuals with data present for all 3 outcomes, sex, maternal education and all exposures of interest.
[b]Adjusted for sex and mothers level of education.
[c]Adjusted for sex, mothers level of education and all other variables in the table (within age group).

The three diseases differed in their associations with some other risk factors. Exposures showing a harmful association with asthma but no statistically significant association with rhinoconjunctivitis and eczema were cooking on an open fire and fast food. Low birthweight showed a harmful association with asthma (OR=1.15), a marginally statistically significant protective effect with eczema (OR=0.90) and no association with rhinoconjunctivitis. Breast feeding was associated with increased risk of eczema (1.11), a marginally statistically significant protective association with asthma (OR=0.95) and no association with rhinoconjunctivitis.

Among adolescents, exposures showing consistent associations with all three diseases were current paracetamol use (odds ratios for rhinoconjunctivitis 1.76; asthma 1.80; and eczema 1.58), heavy truck traffic (1.23; 1.20; 1.31, respectively), cooking on an open fire (1.16; 1.19; 1.49), mother smoking (1.14; 1.22; 1.11), and father smoking (1.10; 1.11; 1.15). Weaker associations with fast food were also consistent (1.06; 1.07; 1.06) across the three diseases (Table 4.4).

**Comparison of risk factor patterns in affluent and less affluent countries**

Figures 4.3-4.5 summarise the risk factor-disease associations by age group, stratified by national per capita GNI. (Numerical results are shown in Table 4.5) Many of the risk factor-disease associations are fairly consistent between affluent and non-affluent settings, with most differences being within the range expected by chance (interaction $p>0.01$). In the section below we focus upon the most significant inconsistencies (interaction $p<0.0001$ for one or more diseases).

For rhinoconjunctivitis among 6-7-year-olds (Figures 4.3, 4.4), notable differences by national per capita GNI are increased risk in non-affluent countries with farm animal contact in infancy (1.19; 1.07-1.33) and having more than two siblings (1.06; 1.00-1.13), whereas in affluent countries, these associations are protective (0.88; 0.75-1.03 and 0.87; 0.81-0.94, respectively).

For asthma among 6-7-year-olds (Figures 4.3, 4.4), farm animal exposure in pregnancy showed a harmful association in non-affluent countries (1.32; 1.18-1.49) but no significant effect in affluent countries (0.98; 0.83-1.14). Breastfeeding ever showed a protective effect in non-affluent countries (0.87; 0.81-0.94) but no significant effect in affluent countries (1.02; 0.96-1.10). Cat exposure in infancy increased risk of asthma symptoms in both settings but there was evidence of a stronger effect in non-affluent (1.36; 1.24-1.49) than affluent countries

(1.10; 1.01-1.20). Conversely, current paracetamol use elevated asthma risk to a significantly greater extent in affluent (2.36; 2.19-2.56) than non-affluent settings (1.90; 1.78-2.02).

For eczema among 6-7-year-olds (Figures 4.3 and 4.4), early cat exposure was a risk factor in non-affluent countries (1.23; 1.11-1.36) but not in affluent countries (0.99; 0.90-1.09). Farm animal exposure in infancy increased eczema risk in non-affluent (1.25; 1.11-1.40) but not in affluent countries (0.95; 0.80-1.13), and a similar pattern was evident for farm animal exposure in pregnancy. Current paracetamol use was more strongly associated with eczema symptoms in affluent (1.65; 1.50-1.81) than non-affluent settings (1.35; 1.25-1.46), although this heterogeneity (interaction p=0.003) was less significant than for asthma.

Stratifying the 13-14 year-old results in a similar manner (Figure 4.5 and Table 4.5), few risk factors demonstrate differential effects in affluent and non-affluent countries. For rhinoconjunctivitis, open fire cooking increased risk in non-affluent countries (1.20; 1.11-1.30) but not in affluent countries (0.82; 0.62-1.07) (interaction p=0.008). Across all three outcomes, current paracetamol use showed a harmful effect in both affluent and non-affluent countries but the effect was stronger in affluent countries (interaction p<0.0001 for rhinoconjunctivitis, p=0.0009 for asthma, p=0.009 for eczema).

**Multimorbid (combinations of disease) models**

In the 6-7-year-old synthesis sample, 80.1% of the children had no symptoms of any of the three outcomes. The proportion of children with only one disease was 14.9% (rhinoconjunctivitis 4.7%, asthma 5.8%, eczema 4.4%). The proportions with two diseases was 4.1% (rhinoconjunctivitis and asthma 2.1%, rhinoconjunctivitis and eczema 1.1%, and asthma and eczema 0.9%). Just 0.9% of the sample had symptoms of all three diseases (Table 4.2).

Using models comparing different combinations of disease outcomes to those with no disease (Table 4.6), we found that antibiotics in the first year of life showed a stronger effect among individuals with 2 or 3 diseases. Paracetamol in the first year had similar effects across any combination of the diseases, with a slightly stronger effect only noticed with individuals who have all 3 diseases. This was similar for current heavy truck traffic. Current paracetamol showed a stronger effect in asthma and rhinoconjunctivitis than eczema, as reflected in the combinations of multiple diseases with the strongest effects being in individuals with all three diseases or rhinoconjunctivitis and asthma (Table 4.6).

*Table 4.4 Single outcome models of fully adjusted[a], individual-level (within school) effects of exposures using the synthesis sample[b]. Mixed logistic regression models with random intercepts at the school, centre and country levels.*

| Age group | Exposures of Interest | Fully adjusted model[a] | | |
|---|---|---|---|---|
| | | Rhinoconjunctivitis symptoms OR (95% CI) | Asthma symptoms OR (95% CI) | Eczema symptoms OR (95% CI) |
| 6-7 years n=116,863 | Low birthweight | 1.04 (0.96, 1.13) | 1.15 (1.07, 1.25) | 0.90 (0.82, 0.99) |
| | Breastfed ever | 1.00 (0.95, 1.06) | 0.95 (0.90, 1.00) | 1.11 (1.04, 1.17) |
| | Farm animals (prenatal) | 1.18 (1.07, 1.30) | 1.19 (1.08, 1.30) | 1.12 (1.01, 1.24) |
| | Farm animals (1st year) | 1.07 (0.98, 1.17) | 0.98 (0.89, 1.06) | 1.13 (1.03, 1.25) |
| | Cat (1st year) | 1.09 (1.01, 1.16) | 1.22 (1.14, 1.30) | 1.10 (1.02, 1.18) |
| | Dog (1st year) | 1.07 (1.01, 1.12) | 1.03 (0.98, 1.08) | 1.06 (1.00, 1.12) |
| | Paracetamol (1st year) | 1.39 (1.32, 1.47) | 1.34 (1.27, 1.41) | 1.29 (1.22, 1.37) |
| | Antibiotics (1st year) | 1.58 (1.51, 1.66) | 1.66 (1.59, 1.74) | 1.40 (1.33, 1.47) |
| | 2 or more siblings | 0.98 (0.94, 1.03) | 0.97 (0.92, 1.01) | 0.94 (0.90, 0.99) |
| | Heavy truck traffic (current) | 1.17 (1.12, 1.22) | 1.19 (1.14, 1.24) | 1.12 (1.06, 1.17) |
| | Fast food (current) | 0.99 (0.94, 1.03) | 1.08 (1.04, 1.13) | 0.99 (0.94, 1.05) |
| | Television (current) | 0.93 (0.88, 0.98) | 1.05 (0.99, 1.11) | 0.96 (0.90, 1.02) |
| | Paternal tobacco (current) | 1.07 (1.02, 1.12) | 1.10 (1.05, 1.16) | 1.04 (0.99, 1.10) |
| | Maternal tobacco (current) | 1.05 (0.99, 1.11) | 1.20 (1.14, 1.27) | 1.05 (0.99, 1.12) |
| | Paracetamol (current) | 2.02 (1.92, 2.13) | 2.07 (1.97, 2.17) | 1.46 (1.38, 1.55) |
| | Open fire cooking (current) | 0.99 (0.82, 1.19) | 1.21 (1.04, 1.42) | 1.14 (0.96, 1.35) |
| 13-14 years n=224,436 | 2 or more siblings | 1.04 (1.01, 1.07) | 1.02 (0.99, 1.06) | 1.08 (1.04, 1.12) |
| | Heavy truck traffic (current) | 1.23 (1.20, 1.26) | 1.20 (1.16, 1.23) | 1.31 (1.26, 1.36) |
| | Fast food (current) | 1.06 (1.03, 1.08) | 1.07 (1.04, 1.10) | 1.06 (1.02, 1.10) |
| | Television (current) | 1.01 (0.97, 1.05) | 1.02 (0.97, 1.07) | 1.07 (1.01, 1.14) |
| | Paternal tobacco (current) | 1.10 (1.07, 1.13) | 1.11 (1.07, 1.14) | 1.15 (1.11, 1.20) |
| | Maternal tobacco (current) | 1.14 (1.10, 1.17) | 1.22 (1.18, 1.27) | 1.11 (1.06, 1.17) |
| | Paracetamol (current) | 1.76 (1.71, 1.81) | 1.80 (1.75, 1.86) | 1.58 (1.52, 1.65) |
| | Open fire cooking (current) | 1.16 (1.08, 1.26) | 1.19 (1.10, 1.30) | 1.49 (1.34, 1.65) |

[a]Adjusted for sex, mothers level of education and for all other variables in the table (within age group).

[b]Synthesis sample contains individuals with data present for all 3 outcomes, sex, maternal education and all exposures of interest.

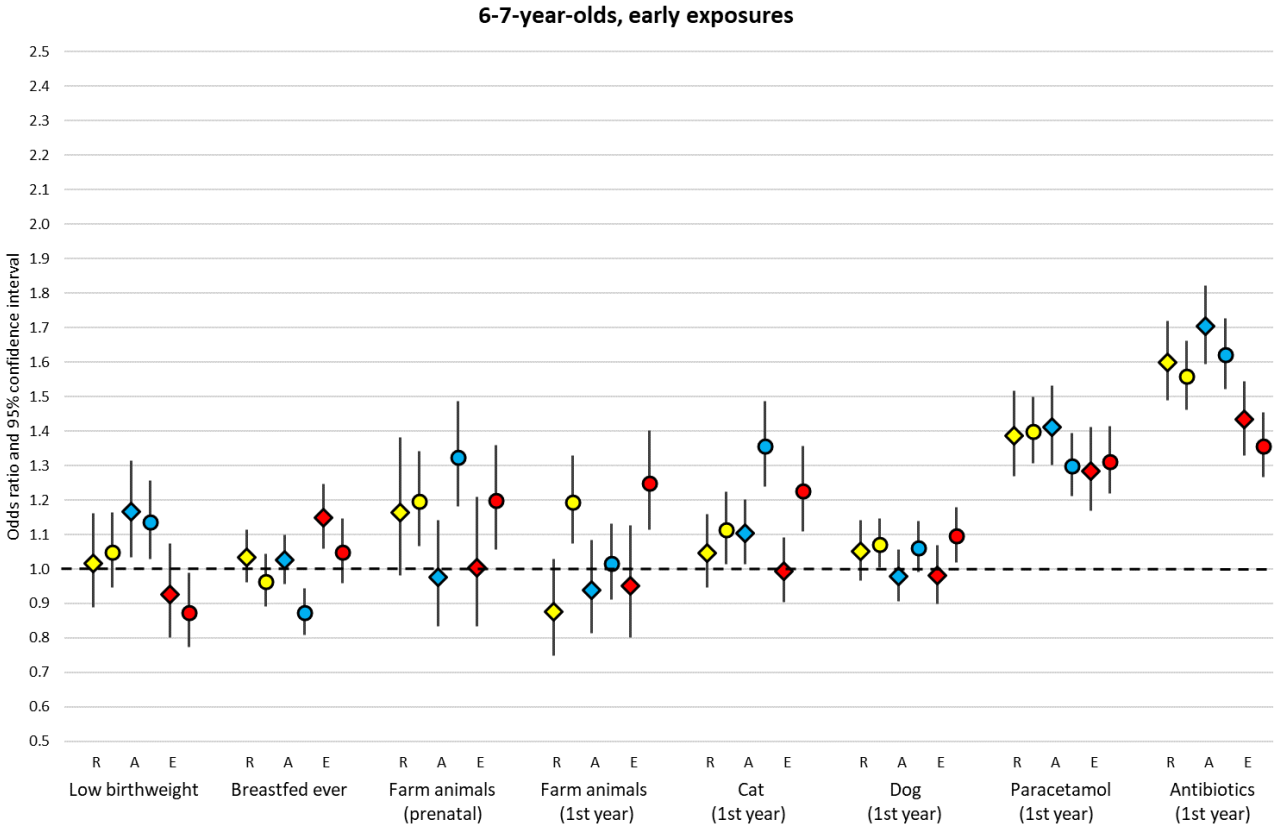


*Figure 4.3 Mutually adjusted odds ratios and 95% confidence intervals for individual-level associations between risk factors and each of the three diseases, in affluent countries and non-affluent countries for age 6-7, early exposures.*

Results from mixed logistic regression models with random intercepts at the school, centre and country levels. Adjusted for sex. Mother's level of education and all other variables shown for the same age group. Based on the synthesis sample as shown in Table 4.4, stratified by country-level affluence. Results for affluent countries shown as diamonds (N = 41,831 aged 6-7; N = 46,932 aged 13-14). Results for non-affluent countries shown as circles (N = 75,032 aged 6-7; N = 177,504 aged 13-14). Results for rhinoconjunctivitis symptoms (R) shown in yellow; Results for asthma symptoms (A) shown in blue; Results for eczema symptoms (E) shown in red.

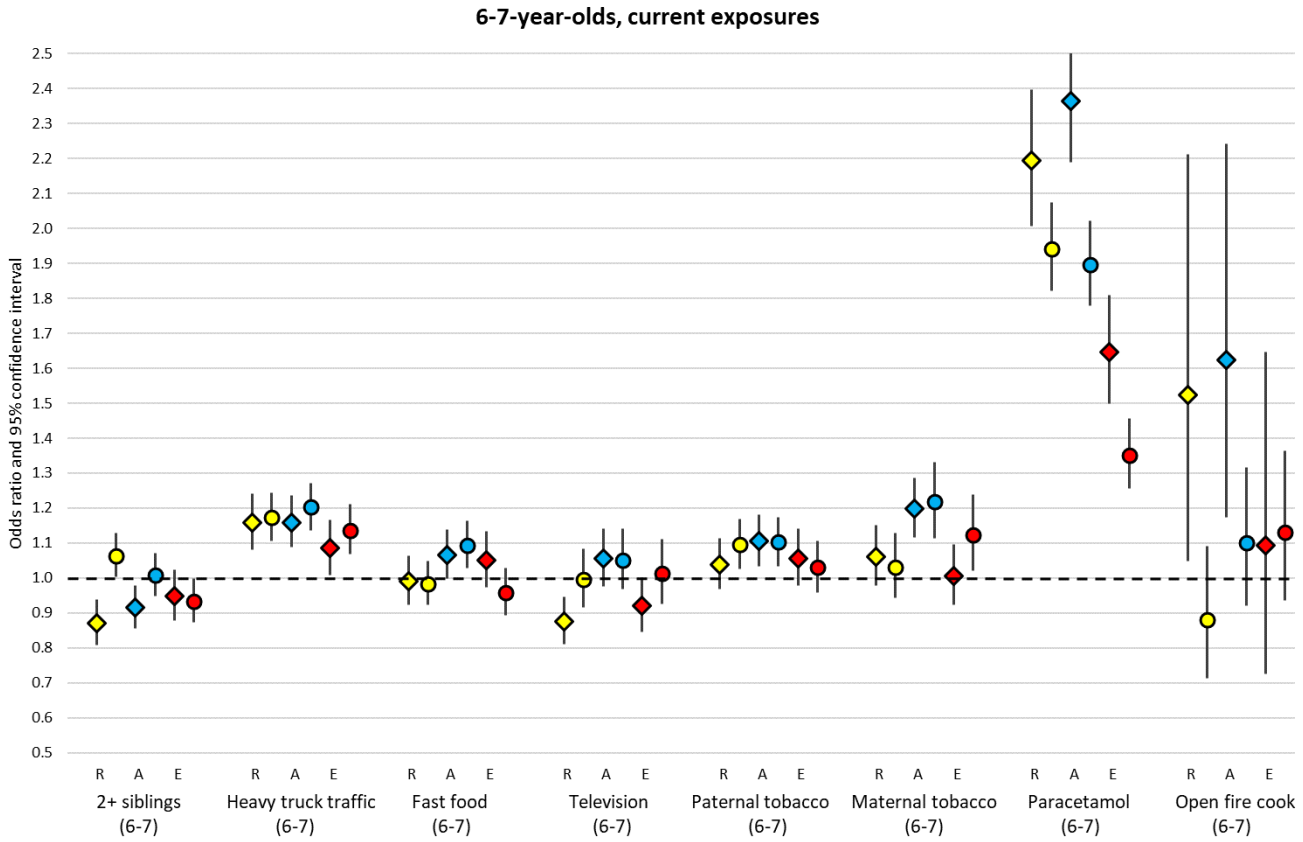


*Figure 4.4 Mutually adjusted odds ratios and 95% confidence intervals for individual-level associations between risk factors and each of the three diseases, in affluent countries and non-affluent countries for age 6-7, current exposures.*

Results from mixed logistic regression models with random intercepts at the school, centre and country levels. Adjusted for sex. Mother's level of education and all other variables shown for the same age group. Based on the synthesis sample as shown in Table 4.4, stratified by country-level affluence. Results for affluent countries shown as diamonds (N = 41,831 aged 6-7; N = 46,932 aged 13-14). Results for non-affluent countries shown as circles (N = 75,032 aged 6-7; N = 177,504 aged 13-14). Results for rhinoconjunctivitis symptoms (R) shown in yellow; Results for asthma symptoms (A) shown in blue; Results for eczema symptoms (E) shown in red.

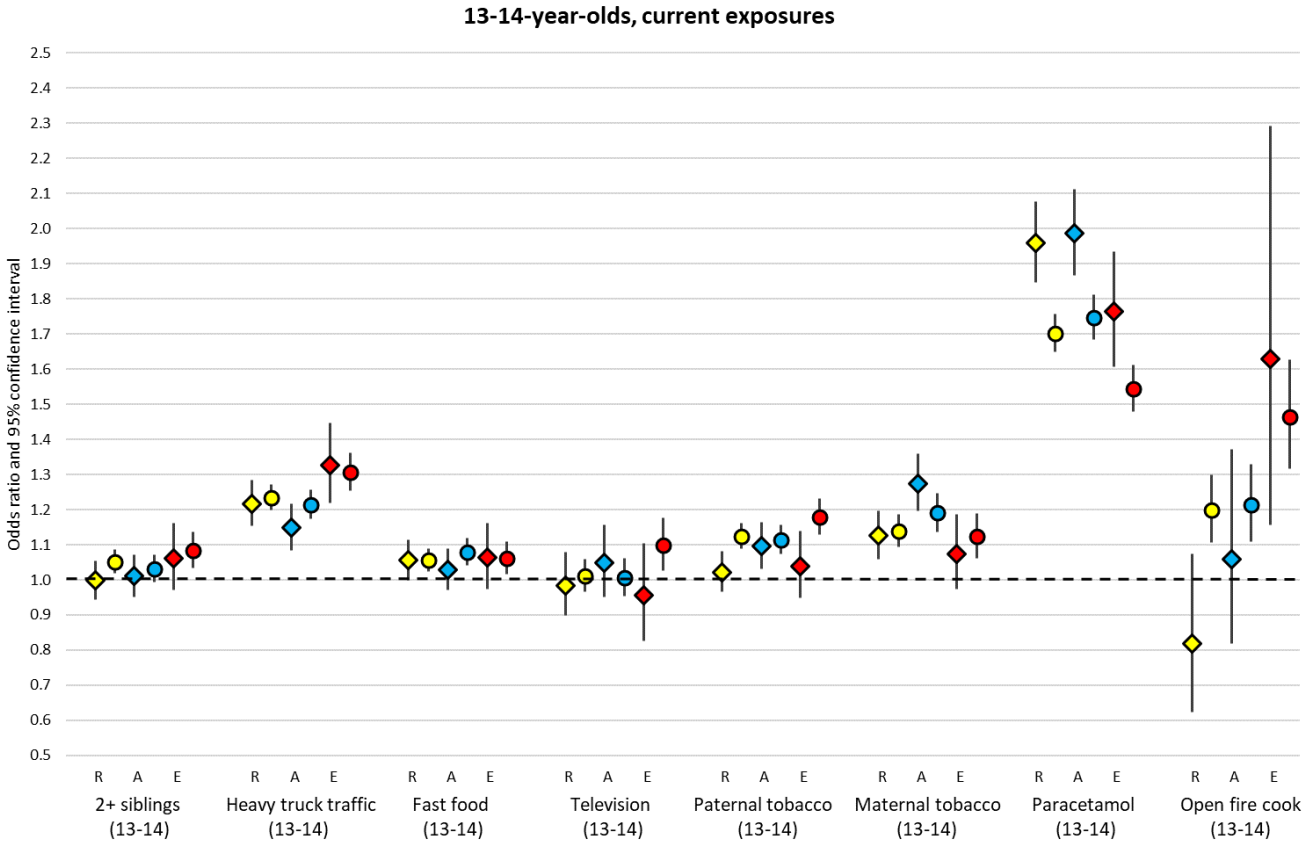


*Figure 4.5 Mutually adjusted odds ratios and 95% confidence intervals for individual-level associations between risk factors and each of the three diseases, in affluent countries and non-affluent countries for age 13-14, current exposures.*

Results from mixed logistic regression models with random intercepts at the school, centre and country levels. Adjusted for sex. Mother's level of education and all other variables shown for the same age group. Based on the synthesis sample as shown in Table 4.4, stratified by country-level affluence. Results for affluent countries shown as diamonds (N = 41,831 aged 6-7; N = 46,932 aged 13-14). Results for non-affluent countries shown as circles (N = 75,032 aged 6-7; N = 177,504 aged 13-14). Results for rhinoconjunctivitis symptoms (R) shown in yellow; Results for asthma symptoms (A) shown in blue; Results for eczema symptoms (E) shown in red.

*Table 4.5 Single outcome models of fully adjusted[a] within school effects of exposures using the synthesis sample[b], stratified by country-level affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.*

| Age | Exposure | Affluent Countries (n = 41,831) | | | Non-affluent Countries (n = 75,032) | | |
|---|---|---|---|---|---|---|---|
| | | Rhinoconjunctivitis | Asthma | Eczema | Rhinoconjunctivitis | Asthma | Eczema |
| 6-7 years | Low birthweight | 1.02 (0.89, 1.16) | 1.17 (1.03, 1.31) | 0.93 (0.80, 1.07) | 1.05 (0.95, 1.16) | 1.14 (1.03, 1.26) | 0.87 (0.77, 0.99) |
| | Breastfed ever | 1.03 (0.96, 1.11) | 1.02 (0.96, 1.10) | 1.15 (1.06, 1.25) | 0.96 (0.89, 1.04) | 0.87 (0.81, 0.94) | 1.05 (0.96, 1.15) |
| | Farm animals (prenatal) | 1.16 (0.98, 1.38) | 0.98 (0.83, 1.14) | 1.00 (0.83, 1.21) | 1.20 (1.07, 1.34) | 1.32 (1.18, 1.49) | 1.20 (1.06, 1.36) |
| | Farm animals (1st year) | 0.88 (0.75, 1.03) | 0.94 (0.81, 1.08) | 0.95 (0.80, 1.13) | 1.19 (1.07, 1.33) | 1.02 (0.91, 1.13) | 1.25 (1.11, 1.40) |
| | Cat (1st year) | 1.05 (0.95, 1.16) | 1.10 (1.01, 1.20) | 0.99 (0.90, 1.09) | 1.11 (1.01, 1.22) | 1.36 (1.24, 1.49) | 1.23 (1.11, 1.36) |
| | Dog (1st year) | 1.05 (0.97, 1.14) | 0.98 (0.91, 1.06) | 0.98 (0.90, 1.07) | 1.07 (1.00, 1.15) | 1.06 (0.99, 1.14) | 1.10 (1.02, 1.18) |
| | Paracetamol (1st year) | 1.39 (1.27, 1.52) | 1.41 (1.30, 1.53) | 1.28 (1.17, 1.41) | 1.40 (1.31, 1.50) | 1.30 (1.21, 1.39) | 1.31 (1.22, 1.41) |
| | Antibiotics (1st year) | 1.60 (1.49, 1.72) | 1.70 (1.59, 1.82) | 1.43 (1.33, 1.54) | 1.56 (1.46, 1.66) | 1.62 (1.52, 1.73) | 1.36 (1.27, 1.45) |
| | 2 or more siblings | 0.87 (0.81, 0.94) | 0.91 (0.85, 0.98) | 0.95 (0.88, 1.02) | 1.06 (1.00, 1.13) | 1.01 (0.95, 1.07) | 0.93 (0.87, 1.00) |
| | Heavy truck traffic (current) | 1.16 (1.08, 1.24) | 1.16 (1.09, 1.24) | 1.08 (1.01, 1.17) | 1.17 (1.11, 1.24) | 1.20 (1.14, 1.27) | 1.14 (1.07, 1.21) |
| | Fast food (current) | 0.99 (0.92, 1.06) | 1.07 (1.00, 1.14) | 1.05 (0.97, 1.13) | 0.98 (0.92, 1.05) | 1.09 (1.03, 1.16) | 0.96 (0.89, 1.03) |
| | Television (current) | 0.88 (0.81, 0.95) | 1.05 (0.98, 1.14) | 0.92 (0.85, 1.00) | 1.00 (0.92, 1.08) | 1.05 (0.97, 1.14) | 1.01 (0.93, 1.11) |
| | Paternal tobacco (current) | 1.04 (0.97, 1.11) | 1.11 (1.03, 1.18) | 1.06 (0.98, 1.14) | 1.10 (1.03, 1.17) | 1.10 (1.03, 1.17) | 1.03 (0.96, 1.11) |
| | Maternal tobacco (current) | 1.06 (0.98, 1.15) | 1.20 (1.12, 1.29) | 1.01 (0.92, 1.10) | 1.03 (0.94, 1.13) | 1.22 (1.11, 1.33) | 1.12 (1.02, 1.24) |
| | Paracetamol (current) | 2.19 (2.01, 2.40) | 2.36 (2.19, 2.56) | 1.65 (1.50, 1.81) | 1.94 (1.82, 2.07) | 1.90 (1.78, 2.02) | 1.35 (1.25, 1.46) |
| | Open fire cooking (current) | 1.52 (1.05, 2.21) | 1.62 (1.17, 2.24) | 1.09 (0.72, 1.65) | 0.88 (0.71, 1.09) | 1.10 (0.92, 1.32) | 1.13 (0.94, 1.36) |
| Age | Exposure | Affluent Countries (n = 46,932) | | | Non-Affluent Countries (n = 177,504) | | |
| | | Rhinoconjunctivitis | Asthma | Eczema | Rhinoconjunctivitis | Asthma | Eczema |
| 13-14 years | 2 or more siblings | 1.00 (0.94, 1.05) | 1.01 (0.95, 1.07) | 1.06 (0.97, 1.16) | 1.05 (1.02, 1.09) | 1.03 (0.99, 1.07) | 1.08 (1.03, 1.14) |
| | Heavy truck traffic (current) | 1.22 (1.15, 1.28) | 1.15 (1.08, 1.22) | 1.33 (1.22, 1.45) | 1.23 (1.20, 1.27) | 1.21 (1.17, 1.26) | 1.31 (1.25, 1.36) |
| | Fast food (current) | 1.06 (1.00, 1.11) | 1.03 (0.97, 1.09) | 1.06 (0.97, 1.16) | 1.06 (1.02, 1.09) | 1.08 (1.04, 1.12) | 1.06 (1.02, 1.11) |
| | Television (current) | 0.98 (0.90, 1.08) | 1.05 (0.95, 1.16) | 0.95 (0.83, 1.10) | 1.01 (0.97, 1.06) | 1.01 (0.95, 1.06) | 1.10 (1.03, 1.18) |
| | Paternal tobacco (current) | 1.02 (0.97, 1.08) | 1.10 (1.03, 1.16) | 1.04 (0.95, 1.14) | 1.12 (1.09, 1.16) | 1.11 (1.07, 1.16) | 1.18 (1.13, 1.23) |
| | Maternal tobacco (current) | 1.13 (1.06, 1.20) | 1.27 (1.20, 1.36) | 1.07 (0.97, 1.19) | 1.14 (1.09, 1.19) | 1.19 (1.14, 1.25) | 1.12 (1.06, 1.19) |
| | Paracetamol (current) | 1.96 (1.85, 2.08) | 1.99 (1.87, 2.11) | 1.76 (1.61, 1.93) | 1.70 (1.65, 1.76) | 1.75 (1.68, 1.81) | 1.54 (1.48, 1.61) |
| | Open fire cooking (current) | 0.82 (0.62, 1.07) | 1.06 (0.82, 1.37) | 1.63 (1.16, 2.29) | 1.20 (1.11, 1.30) | 1.21 (1.11, 1.33) | 1.46 (1.32, 1.63) |

[a]Adjusted for sex, mother's level of education and all other variables in the table for that age group.

[b]Synthesis sample contains individuals with data present for all 3 outcomes, sex, maternal education and all exposures of interest.

Among the 13-14-year-old synthesis sample, 76.0% had no symptoms of any of the three outcomes. The proportion of adolescents with only one disease was 18.1% (rhinoconjunctivitis 8.8%, asthma 6.1%, eczema 3.2%). A further 5.0% had symptoms of two of the diseases (rhinoconjunctivitis and asthma 2.9%, rhinoconjunctivitis and eczema 1.4% and asthma and eczema 0.7%). Only 0.9% had symptoms of all three diseases (Table 4.2).

Current paracetamol showed a stronger effect in individuals with more than one disease, with the strongest effect in those with all 3 diseases. Open fire cooking showed a stronger effect in all combinations that contain eczema (Table 4.6).

Importantly, in both age groups, risk factor associations with each disease in the whole population (Table 4.4) persisted among children with only one condition, after exclusion of multimorbid groups (Table 4.6).

**Unimorbid (single disease case-only) models**

Table 4.7 shows the results of three separate models, each comparing two of the unimorbid outcomes. Corresponding results, stratified by per capita GNI, are shown as Table 4.8 in the Supporting Material. Triangle plots appear as Figures 4.6-4.11 in the Supporting Material. An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases, the further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. In the plots the odds ratios displayed are all greater than or equal to one; they relate to whichever disease has the stronger effect (the corner they are closest to compared to the opposite corner).

In the 6-7-year-old age group, low birthweight was most strongly associated with asthma and more strongly associated with rhinoconjunctivitis than eczema. Early life antibiotic exposure showed a similar pattern but to a slightly reduced extent. Being breastfed ever showed a stronger association with eczema than both asthma and rhinoconjunctivitis. Owning a cat in the first year of life was most strongly associated with asthma but more strongly associated with eczema than rhinoconjunctivitis.

Some differences were evident between affluent and non-affluent countries (Table 4.8 and Figure 4.9). Farm animal contact during pregnancy had effects in non-affluent countries which were more balanced between the diseases, but in affluent countries the effect was stronger on eczema and rhinoconjunctivitis than asthma. In contrast, early cat contact had more balanced

effects in affluent countries but in non-affluent countries there was a much stronger effect on asthma and eczema than rhinoconjunctivitis.

Among the current exposures for 6-7 year-olds, current paracetamol use was more strongly associated with asthma and rhinoconjunctivitis than with eczema. Open fire cooking was more strongly associated with both asthma and eczema than rhinoconjunctivitis but the confidence intervals were wide. Maternal smoking was more strongly associated with asthma than with eczema or rhinoconjunctivitis. Affluent centres showed a stronger effect of open fire cooking on asthma and rhinoconjunctivitis, whereas in non-affluent centres the stronger effect was on asthma and eczema.

Among 13-14 year-olds, similar to the younger children, maternal smoking had a stronger association with asthma than with either eczema or rhinoconjunctivitis, and current paracetamol showed a stronger association with asthma and rhinoconjunctivitis than with eczema. The biggest difference between affluent and non-affluent countries was observed for open fire cooking. In affluent countries, there were stronger associations with eczema than with asthma or rhinoconjunctivitis although it is important to note that the confidence intervals were exceptionally large due to the rarity of cooking on open fires in the affluent centres.

### 4.2.5 Discussion

**Overview of findings**

This is the largest and broadest overview to date of lifestyle and environmental risk factors for symptoms of non-infective rhinoconjunctivitis among children. It is the first comprehensive analysis of this condition, which models multiple risk factors together to compare their mutually adjusted individual-level and population (school)-level associations in a multilevel framework. Due to the multiple comparisons made, and the large size of our sample, we concentrate our interpretation upon the overall patterns of results and on specific findings with more extreme levels of statistical significance.

*Table 4.6 Multi outcome models of fully adjusted[a] within school effects of exposures compared to a reference group with no disease. Mixed logistic regression models with random intercepts at the school, centre and country levels.*

| | Rhinoconjunctivitis only OR (95% CI) | Asthma only OR (95% CI) | Eczema only OR (95% CI) | Rhinoconjunctivitis and Asthma OR (95% CI) | Rhinoconjunctivitis and Eczema OR (95% CI) | Asthma and Eczema OR (95% CI) | Rhinoconjunctivitis, Asthma and Eczema OR (95% CI) |
|---|---|---|---|---|---|---|---|
| Age 6-7 years | Reference group with no disease, $n_0$=93,554 | | | | | | |
| Exposures of Interest | $n_1$=5,508 | $n_1$=6,720 | $n_1$=5,099 | $n_1$=2,503 | $n_1$=1,310 | $n_1$=1,074 | $n_1$=1,095 |
| Low birthweight | 0.98 (0.88, 1.10) | 1.16 (1.05, 1.27) | 0.85 (0.75, 0.96) | 1.14 (0.98, 1.33) | 0.96 (0.76, 1.20) | 0.90 (0.70, 1.16) | 1.14 (0.91, 1.44) |
| Breastfed ever | 0.98 (0.91, 1.05) | 0.93 (0.87, 1.00) | 1.12 (1.03, 1.21) | 0.96 (0.86, 1.06) | 1.10 (0.95, 1.28) | 0.98 (0.84, 1.15) | 1.12 (0.96, 1.32) |
| Farm animals (prenatal) | 1.17 (1.03, 1.34) | 1.14 (1.01, 1.28) | 1.06 (0.93, 1.22) | 1.22 (1.01, 1.47) | 1.07 (0.84, 1.37) | 1.19 (0.89, 1.58) | 1.56 (1.20, 2.03) |
| Farm animals (1st year) | 1.11 (0.99, 1.25) | 1.03 (0.92, 1.15) | 1.17 (1.03, 1.32) | 0.97 (0.82, 1.16) | 1.40 (1.13, 1.74) | 1.04 (0.80, 1.35) | 0.86 (0.66, 1.12) |
| Cat (1st year) | 0.97 (0.88, 1.07) | 1.21 (1.12, 1.31) | 1.08 (0.99, 1.18) | 1.29 (1.14, 1.47) | 1.19 (1.00, 1.42) | 1.06 (0.89, 1.27) | 1.16 (0.97, 1.39) |
| Dog (1st year) | 1.07 (1.00, 1.15) | 1.01 (0.94, 1.08) | 1.07 (1.00, 1.15) | 1.08 (0.98, 1.20) | 1.05 (0.92, 1.20) | 0.99 (0.86, 1.15) | 1.14 (0.99, 1.32) |
| Paracetamol (1st year) | 1.38 (1.29, 1.48) | 1.32 (1.24, 1.41) | 1.26 (1.17, 1.35) | 1.45 (1.30, 1.62) | 1.49 (1.29, 1.72) | 1.35 (1.14, 1.60) | 1.82 (1.52, 2.18) |
| Antibiotics (1st year) | 1.44 (1.36, 1.54) | 1.56 (1.47, 1.65) | 1.25 (1.17, 1.33) | 1.95 (1.77, 2.15) | 1.82 (1.60, 2.07) | 2.13 (1.84, 2.47) | 2.37 (2.03, 2.76) |
| 2 or more siblings | 0.98 (0.92, 1.04) | 0.96 (0.90, 1.01) | 0.94 (0.88, 1.00) | 0.98 (0.90, 1.08) | 0.91 (0.81, 1.03) | 0.88 (0.77, 1.01) | 0.99 (0.86, 1.13) |
| Heavy truck traffic (current) | 1.13 (1.06, 1.20) | 1.18 (1.12, 1.24) | 1.08 (1.01, 1.15) | 1.19 (1.09, 1.29) | 1.15 (1.02, 1.29) | 1.11 (0.98, 1.26) | 1.50 (1.32, 1.71) |
| Fast food (current) | 0.96 (0.90, 1.02) | 1.08 (1.02, 1.15) | 0.96 (0.90, 1.03) | 1.06 (0.97, 1.16) | 1.01 (0.89, 1.14) | 1.21 (1.05, 1.38) | 0.98 (0.86, 1.13) |
| Television (current) | 0.91 (0.85, 0.98) | 1.07 (0.99, 1.15) | 0.97 (0.90, 1.05) | 1.02 (0.91, 1.14) | 0.85 (0.73, 0.99) | 1.05 (0.88, 1.25) | 0.95 (0.80, 1.12) |
| Paternal tobacco (current) | 1.05 (0.98, 1.12) | 1.08 (1.02, 1.15) | 1.02 (0.96, 1.10) | 1.12 (1.03, 1.23) | 0.93 (0.82, 1.06) | 1.12 (0.97, 1.29) | 1.22 (1.06, 1.40) |
| Maternal tobacco (current) | 1.02 (0.94, 1.11) | 1.24 (1.16, 1.33) | 1.05 (0.97, 1.14) | 1.21 (1.09, 1.36) | 1.11 (0.94, 1.30) | 1.30 (1.11, 1.53) | 1.05 (0.89, 1.24) |
| Paracetamol (current) | 1.90 (1.77, 2.04) | 1.96 (1.84, 2.08) | 1.34 (1.24, 1.45) | 2.86 (2.59, 3.15) | 1.91 (1.66, 2.19) | 2.17 (1.88, 2.51) | 2.92 (2.53, 3.37) |
| Open fire cooking (current) | 0.97 (0.75, 1.25) | 1.28 (1.07, 1.55) | 1.18 (0.96, 1.45) | 1.17 (0.83, 1.67) | 1.09 (0.70, 1.72) | 1.21 (0.77, 1.91) | 0.77 (0.43, 1.39) |
| Age 13-14 years | Reference group with no disease, $n_0$=170,542 | | | | | | |
| Exposures of Interest | $n_1$=19,858 | $n_1$=13,585 | $n_1$=7,104 | $n_1$=6,557 | $n_1$=3,219 | $n_1$=1,554 | $n_1$=2,017 |
| 2 or more siblings | 1.02 (0.98, 1.06) | 1.01 (0.97, 1.05) | 1.06 (1.00, 1.12) | 1.05 (0.99, 1.11) | 1.18 (1.09, 1.29) | 1.06 (0.95, 1.19) | 1.12 (1.01, 1.24) |
| Heavy truck traffic (current) | 1.19 (1.16, 1.23) | 1.14 (1.09, 1.18) | 1.26 (1.20, 1.33) | 1.30 (1.23, 1.37) | 1.44 (1.34, 1.55) | 1.47 (1.33, 1.64) | 1.56 (1.42, 1.71) |
| Fast food (current) | 1.04 (1.01, 1.08) | 1.06 (1.02, 1.10) | 1.06 (1.00, 1.12) | 1.13 (1.07, 1.19) | 1.12 (1.04, 1.21) | 1.13 (1.01, 1.26) | 1.13 (1.02, 1.24) |
| Television (current) | 1.03 (0.98, 1.08) | 1.08 (1.02, 1.15) | 1.09 (1.01, 1.19) | 0.97 (0.89, 1.06) | 1.23 (1.08, 1.41) | 1.21 (1.01, 1.46) | 0.80 (0.69, 0.92) |
| Paternal tobacco (current) | 1.08 (1.04, 1.11) | 1.10 (1.05, 1.14) | 1.13 (1.07, 1.19) | 1.14 (1.07, 1.20) | 1.22 (1.13, 1.32) | 1.16 (1.04, 1.30) | 1.26 (1.14, 1.39) |
| Maternal tobacco (current) | 1.09 (1.05, 1.14) | 1.20 (1.15, 1.26) | 1.07 (0.99, 1.14) | 1.27 (1.19, 1.35) | 1.19 (1.08, 1.31) | 1.22 (1.06, 1.39) | 1.32 (1.18, 1.49) |
| Paracetamol (current) | 1.62 (1.56, 1.68) | 1.69 (1.62, 1.76) | 1.36 (1.29, 1.44) | 2.34 (2.21, 2.47) | 2.16 (2.00, 2.34) | 2.12 (1.89, 2.36) | 2.98 (2.71, 3.29) |
| Open fire cooking (current) | 1.15 (1.05, 1.27) | 1.12 (1.01, 1.25) | 1.33 (1.15, 1.53) | 1.09 (0.92, 1.28) | 1.50 (1.22, 1.84) | 1.93 (1.49, 2.50) | 2.22 (1.76, 2.81) |

[a]Adjusted for sex, mother's level of education and all other variables in the table for that age group.

*Table 4.7 Fully adjusted[a] unimorbid two-way models. Mixed logistic regression models with random intercepts at the school, centre and country levels.*

| Age group | Exposures of Interest | Asthma v Eczema (n=11,819) OR (95% CI) | Asthma v Rhinoconjunctivitis (n=12,228) OR (95% CI) | Rhinoconjunctivitis v Eczema (n=10,607) OR (95% CI) |
|---|---|---|---|---|
| 6-7 years | Low birthweight | 1.40 (1.19, 1.64) | 1.16 (0.99, 1.35) | 1.11 (0.94, 1.32) |
| | Breastfed ever | 0.85 (0.76, 0.94) | 0.94 (0.85, 1.05) | 0.89 (0.80, 1.00) |
| | Farm animals (prenatal) | 1.03 (0.85, 1.23) | 0.99 (0.82, 1.18) | 1.04 (0.86, 1.26) |
| | Farm animals (1st year) | 0.90 (0.76, 1.06) | 0.89 (0.75, 1.05) | 0.98 (0.83, 1.17) |
| | Cat (1st year) | 1.12 (0.99, 1.26) | 1.27 (1.11, 1.44) | 0.83 (0.73, 0.96) |
| | Dog (1st year) | 0.94 (0.85, 1.04) | 0.97 (0.87, 1.07) | 0.95 (0.86, 1.05) |
| | Paracetamol (1st year) | 1.05 (0.95, 1.16) | 0.96 (0.86, 1.06) | 1.07 (0.96, 1.19) |
| | Antibiotics (1st year) | 1.26 (1.16, 1.38) | 1.12 (1.03, 1.23) | 1.14 (1.03, 1.25) |
| | 2 or more siblings | 1.01 (0.93, 1.10) | 0.99 (0.90, 1.08) | 1.03 (0.94, 1.13) |
| | Heavy truck traffic (current) | 1.08 (1.00, 1.17) | 1.05 (0.97, 1.14) | 1.06 (0.97, 1.16) |
| | Fast food (current) | 1.12 (1.02, 1.22) | 1.12 (1.03, 1.23) | 1.00 (0.91, 1.10) |
| | Television (current) | 1.13 (1.01, 1.26) | 1.16 (1.04, 1.29) | 0.92 (0.82, 1.03) |
| | Paternal tobacco (current) | 1.03 (0.94, 1.12) | 1.03 (0.94, 1.13) | 1.02 (0.92, 1.12) |
| | Maternal tobacco (current) | 1.16 (1.04, 1.29) | 1.21 (1.08, 1.35) | 0.94 (0.84, 1.07) |
| | Paracetamol (current) | 1.45 (1.31, 1.60) | 1.03 (0.93, 1.14) | 1.48 (1.32, 1.65) |
| | Open fire cooking (current) | 1.02 (0.77, 1.35) | 1.32 (0.95, 1.83) | 0.72 (0.51, 1.01) |
| Age group | Exposures of Interest | Asthma v Eczema (n=20,689) OR (95% CI) | Asthma v Rhinoconjunctivitis (n=33,443) OR (95% CI) | Rhinoconjunctivitis v Eczema (n=26,962) OR (95% CI) |
| 13-14 years | 2 or more siblings | 0.94 (0.87, 1.01) | 0.99 (0.94, 1.05) | 0.96 (0.90, 1.03) |
| | Heavy truck traffic (current) | 0.92 (0.86, 0.99) | 0.97 (0.92, 1.02) | 0.93 (0.87, 0.98) |
| | Fast food (current) | 1.01 (0.94, 1.08) | 0.99 (0.94, 1.04) | 1.00 (0.94, 1.06) |
| | Television (current) | 0.98 (0.88, 1.09) | 1.06 (0.98, 1.15) | 0.96 (0.87, 1.06) |
| | Paternal tobacco (current) | 0.96 (0.89, 1.03) | 1.01 (0.96, 1.06) | 0.96 (0.90, 1.03) |
| | Maternal tobacco (current) | 1.15 (1.06, 1.26) | 1.13 (1.06, 1.21) | 1.02 (0.94, 1.11) |
| | Paracetamol (current) | 1.17 (1.09, 1.26) | 1.02 (0.97, 1.08) | 1.16 (1.09, 1.24) |
| | Open fire cooking (current) | 0.89 (0.74, 1.06) | 1.05 (0.91, 1.21) | 0.80 (0.68, 0.95) |

[a]Adjusted for sex, mother's level of education and all other variables in the table for that age group.

*Table 4.8 Fully adjusted[a] unimorbid two-way models split by country affluence. Mixed logistic regression models with random intercepts at the school, centre and country levels.*

| Exposure of Interest | Asthma v Eczema | | Rhinoconjunctivitis v Asthma | | Eczema v Rhinoconjunctivitis | |
|---|---|---|---|---|---|---|
| Age 6-7 years | Affluent countries n=5,172 | Non-affluent countries n=6,647 | Affluent countries n=5,189 | Non-affluent countries n=7,039 | Affluent countries n=4,347 | Non-affluent countries n=6,260 |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| Low birthweight | 1.42 (1.10, 1.82) | 1.40 (1.13, 1.72) | 0.81 (0.63, 1.05) | 0.90 (0.74, 1.09) | 0.85 (0.63, 1.14) | 0.93 (0.75, 1.15) |
| Breastfed ever | 0.86 (0.75, 0.99) | 0.84 (0.72, 0.99) | 1.03 (0.89, 1.18) | 1.09 (0.94, 1.27) | 1.12 (0.96, 1.31) | 1.10 (0.93, 1.29) |
| Farm animals (prenatal) | 0.85 (0.63, 1.16) | 1.13 (0.90, 1.42) | 1.23 (0.90, 1.68) | 0.92 (0.74, 1.15) | 0.85 (0.60, 1.20) | 1.01 (0.80, 1.27) |
| Farm animals (1st year) | 1.08 (0.82, 1.43) | 0.82 (0.67, 1.02) | 1.00 (0.76, 1.33) | 1.21 (0.98, 1.48) | 1.02 (0.75, 1.40) | 0.99 (0.81, 1.23) |
| Cat (1st year) | 1.08 (0.92, 1.27) | 1.17 (0.98, 1.39) | 0.91 (0.75, 1.09) | 0.69 (0.57, 0.82) | 1.06 (0.87, 1.29) | 1.35 (1.12, 1.63) |
| Dog (1st year) | 1.02 (0.87, 1.18) | 0.89 (0.78, 1.01) | 1.09 (0.93, 1.29) | 1.00 (0.88, 1.14) | 0.93 (0.78, 1.11) | 1.12 (0.98, 1.27) |
| Paracetamol (1st year) | 1.15 (0.99, 1.35) | 0.98 (0.86, 1.11) | 1.04 (0.88, 1.23) | 1.05 (0.92, 1.20) | 0.88 (0.73, 1.05) | 0.97 (0.86, 1.11) |
| Antibiotics (1st year) | 1.26 (1.11, 1.43) | 1.27 (1.12, 1.43) | 0.87 (0.76, 1.00) | 0.90 (0.80, 1.02) | 0.93 (0.81, 1.08) | 0.84 (0.75, 0.95) |
| 2 or more siblings | 0.98 (0.86, 1.12) | 1.04 (0.93, 1.18) | 0.89 (0.77, 1.03) | 1.11 (0.99, 1.24) | 1.11 (0.96, 1.30) | 0.89 (0.79, 1.00) |
| Heavy truck traffic (current) | 1.03 (0.91, 1.17) | 1.11 (1.00, 1.24) | 0.91 (0.80, 1.05) | 0.98 (0.88, 1.09) | 1.04 (0.90, 1.20) | 0.89 (0.80, 1.00) |
| Fast food (current) | 0.99 (0.87, 1.13) | 1.20 (1.07, 1.36) | 0.93 (0.81, 1.07) | 0.87 (0.77, 0.97) | 1.07 (0.92, 1.25) | 0.96 (0.85, 1.09) |
| Television (current) | 1.19 (1.02, 1.38) | 1.06 (0.90, 1.24) | 0.83 (0.71, 0.97) | 0.88 (0.76, 1.02) | 1.09 (0.92, 1.28) | 1.13 (0.96, 1.33) |
| Paternal tobacco (current) | 1.02 (0.89, 1.17) | 1.01 (0.90, 1.15) | 0.93 (0.81, 1.07) | 1.00 (0.89, 1.13) | 1.04 (0.89, 1.21) | 0.96 (0.85, 1.09) |
| Maternal tobacco (current) | 1.28 (1.11, 1.48) | 1.00 (0.84, 1.19) | 0.81 (0.70, 0.95) | 0.84 (0.71, 1.00) | 0.93 (0.78, 1.10) | 1.22 (1.03, 1.45) |
| Paracetamol (current) | 1.58 (1.34, 1.87) | 1.39 (1.22, 1.58) | 0.94 (0.79, 1.12) | 1.00 (0.89, 1.13) | 0.67 (0.55, 0.82) | 0.67 (0.59, 0.77) |
| Open fire cooking (current) | 1.21 (0.62, 2.35) | 1.00 (0.73, 1.38) | 1.00 (0.50, 2.03) | 0.72 (0.49, 1.04) | 0.82 (0.37, 1.81) | 1.54 (1.04, 2.26) |
| Age 13-14 years | Affluent countries n=4,774 | Non-affluent countries n=15,915 | Affluent countries n=7,941 | Non-affluent countries n=25,502 | Affluent countries n=5,557 | Non-affluent countries n=21,405 |
| | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) | OR (95% CI) |
| 2 or more siblings | 0.93 (0.80, 1.07) | 0.95 (0.87, 1.03) | 0.98 (0.89, 1.09) | 1.01 (0.95, 1.08) | 1.07 (0.93, 1.23) | 1.03 (0.95, 1.11) |
| Heavy truck traffic (current) | 0.90 (0.78, 1.04) | 0.93 (0.87, 1.01) | 1.08 (0.98, 1.19) | 1.01 (0.96, 1.08) | 1.07 (0.93, 1.23) | 1.08 (1.01, 1.15) |
| Fast food (current) | 0.92 (0.80, 1.06) | 1.03 (0.95, 1.11) | 1.01 (0.91, 1.11) | 1.02 (0.96, 1.08) | 1.07 (0.93, 1.23) | 0.99 (0.92, 1.06) |
| Television (current) | 1.08 (0.85, 1.38) | 0.96 (0.85, 1.08) | 0.92 (0.77, 1.08) | 0.95 (0.87, 1.04) | 1.03 (0.81, 1.29) | 1.05 (0.94, 1.17) |
| Paternal tobacco (current) | 1.06 (0.92, 1.24) | 0.93 (0.86, 1.01) | 0.90 (0.81, 1.00) | 1.03 (0.96, 1.09) | 1.04 (0.90, 1.21) | 1.04 (0.97, 1.12) |
| Maternal tobacco (current) | 1.30 (1.11, 1.53) | 1.09 (0.98, 1.21) | 0.83 (0.74, 0.93) | 0.92 (0.85, 1.00) | 0.92 (0.79, 1.09) | 0.99 (0.90, 1.09) |
| Paracetamol (current) | 1.29 (1.10, 1.51) | 1.15 (1.06, 1.24) | 0.97 (0.87, 1.08) | 0.98 (0.92, 1.05) | 0.79 (0.68, 0.92) | 0.87 (0.81, 0.94) |
| Open fire cooking (current) | 0.77 (0.41, 1.45) | 0.92 (0.76, 1.11) | 0.73 (0.45, 1.19) | 0.97 (0.84, 1.13) | 1.87 (0.97, 3.59) | 1.20 (1.01, 1.44) |

[a]Adjusted for sex, mother's level of education and all other variables in the table for that age group.

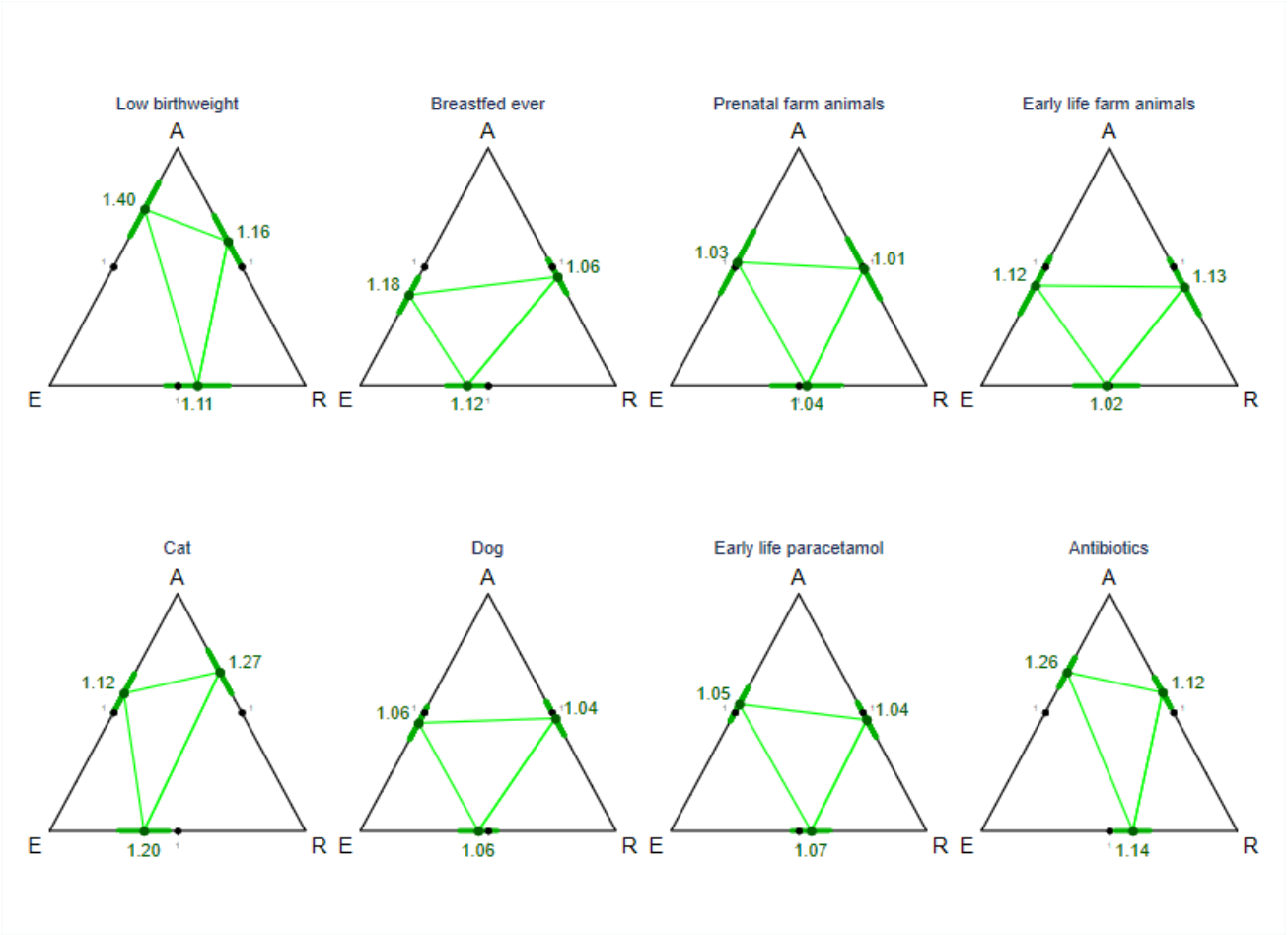


*Figure 4.6 Triangular graphs showing unimorbid two-way comparisons of early life risk factor effects for 6-7-year-old children.*

*Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals. The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Early life risk factors in 6-7 year-old children includes factors from the first year of the child's life (except prenatal farm animals which is mother's contact with farm animals during pregnancy with the child). The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.*

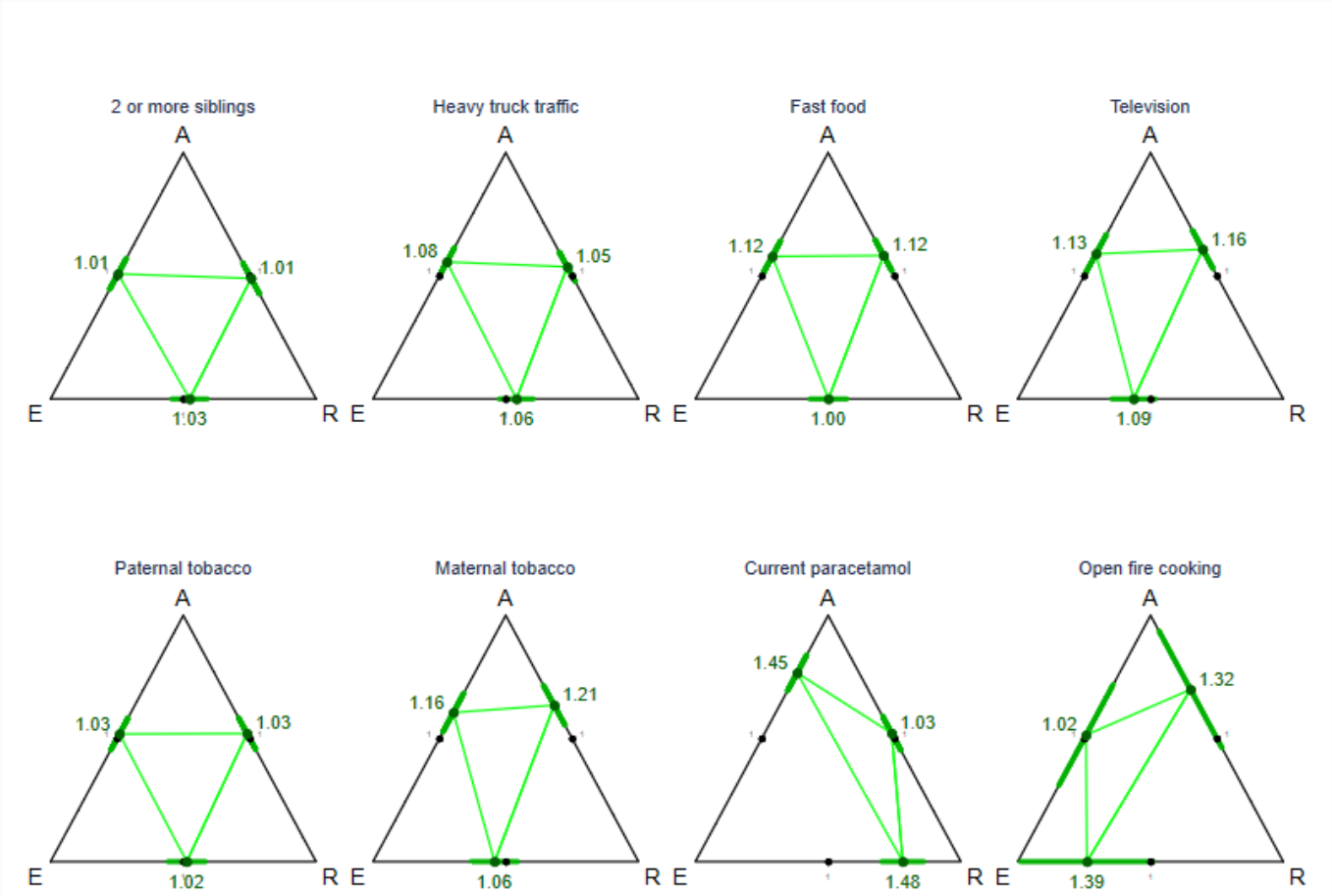


*Figure 4.7 Triangular graphs showing unimorbid two-way comparisons of current risk factor effects for 6-7-year-old children.*

*Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals. The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 6-7 year-old children includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.*

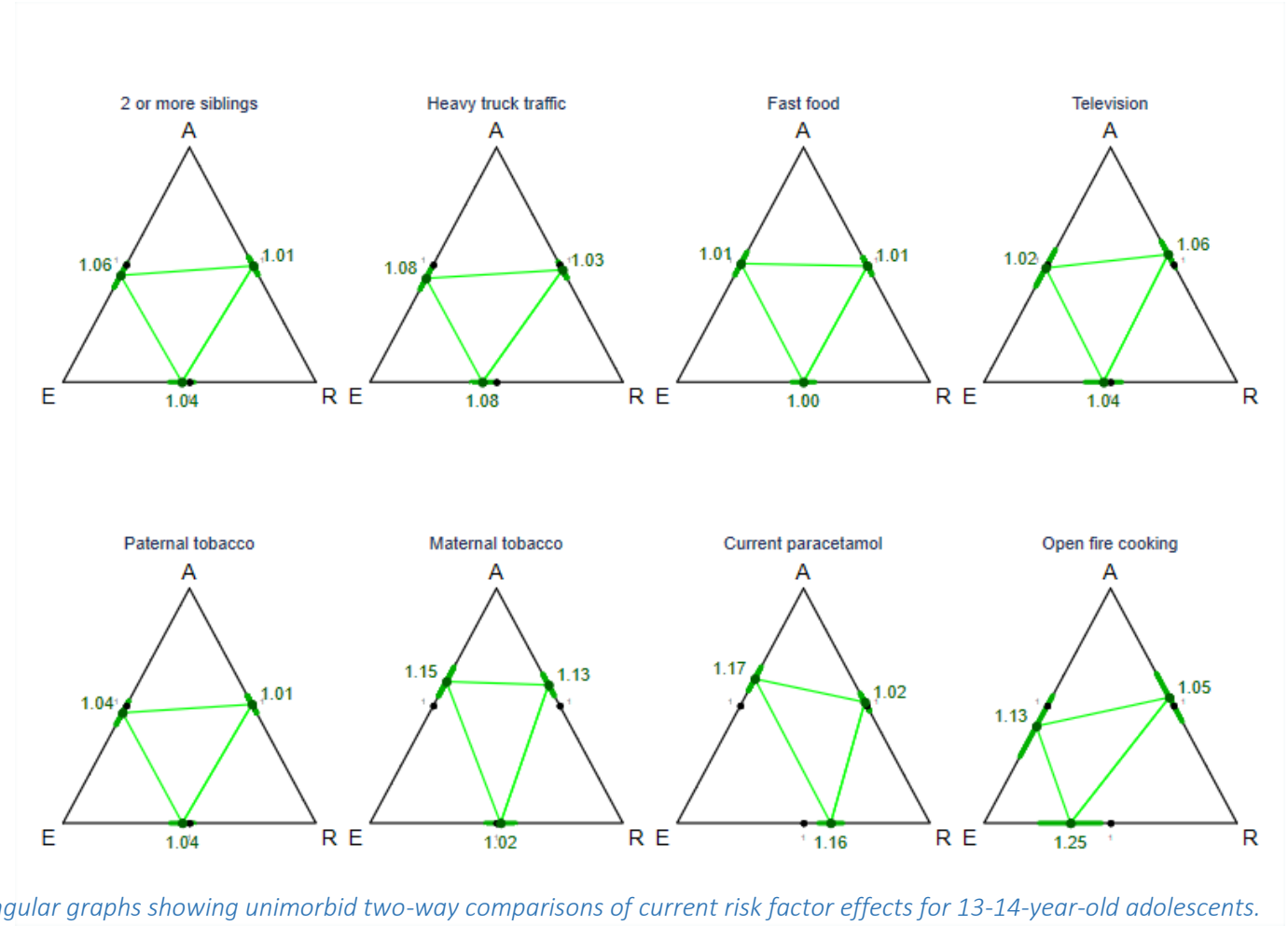


*Figure 4.8 Triangular graphs showing unimorbid two-way comparisons of current risk factor effects for 13-14-year-old adolescents.*

*Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals. The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 13-14 year-old adolescents includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.*

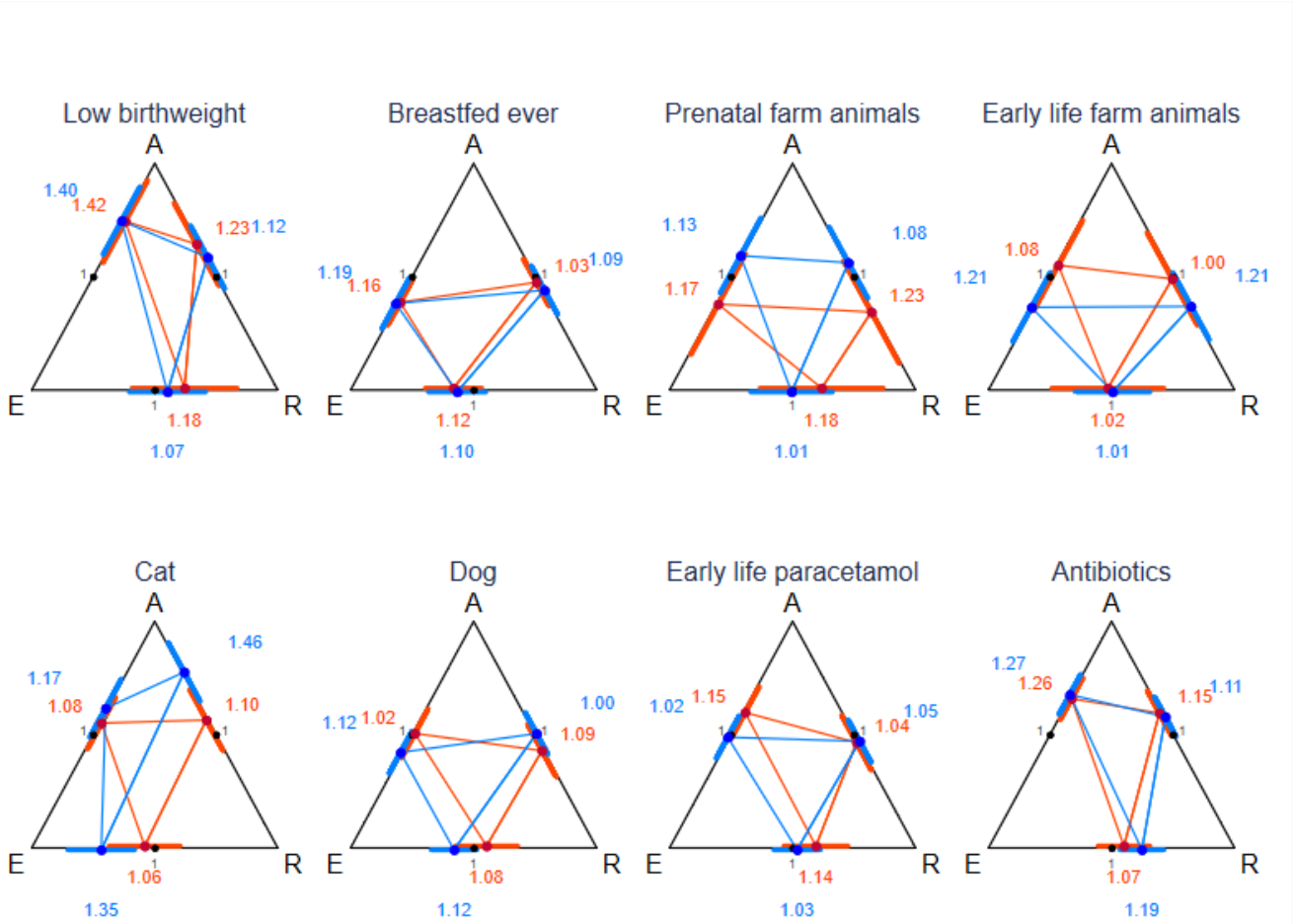


*Figure 4.9 Triangular graphs showing unimorbid two-way comparisons of effects of early life risk factors for 6-7-year-old children in affluent and non-affluent countries.*

*Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals, stratified by affluent countries (red) and non-affluent countries (blue). The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Early life risk factors in 6-7 year-old children includes factors from the first year of the child's life (except prenatal farm animals which is mother's contact with farm animals during pregnancy with the child). The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.*

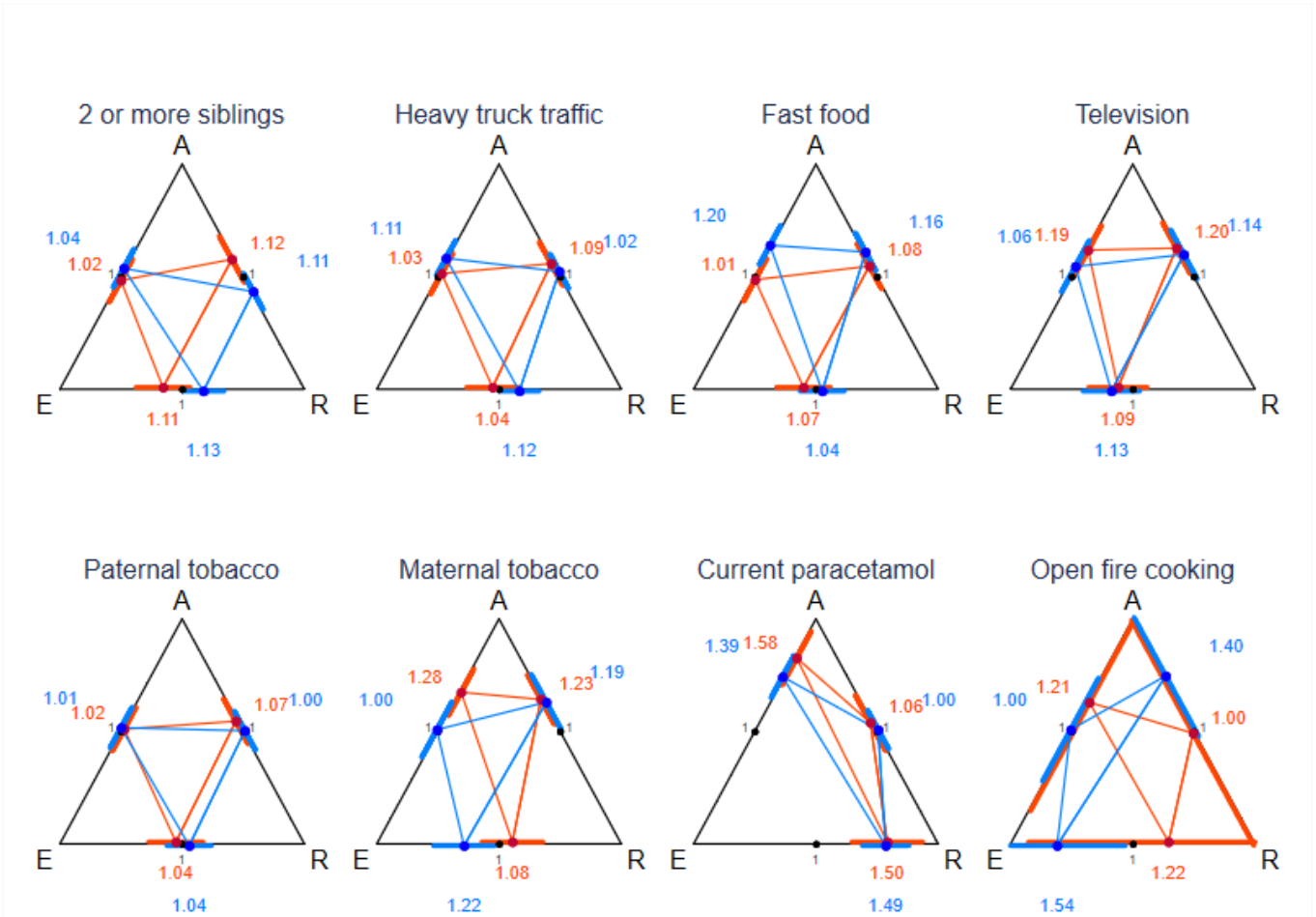


*Figure 4.10 Triangular graphs showing unimorbid two-way comparisons of effects of current risk factors for 6-7-year-old children in affluent and non-affluent countries.*

*Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals, stratified by affluent countries (red) and non-affluent countries (blue). The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 6-7 year-old children includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale*

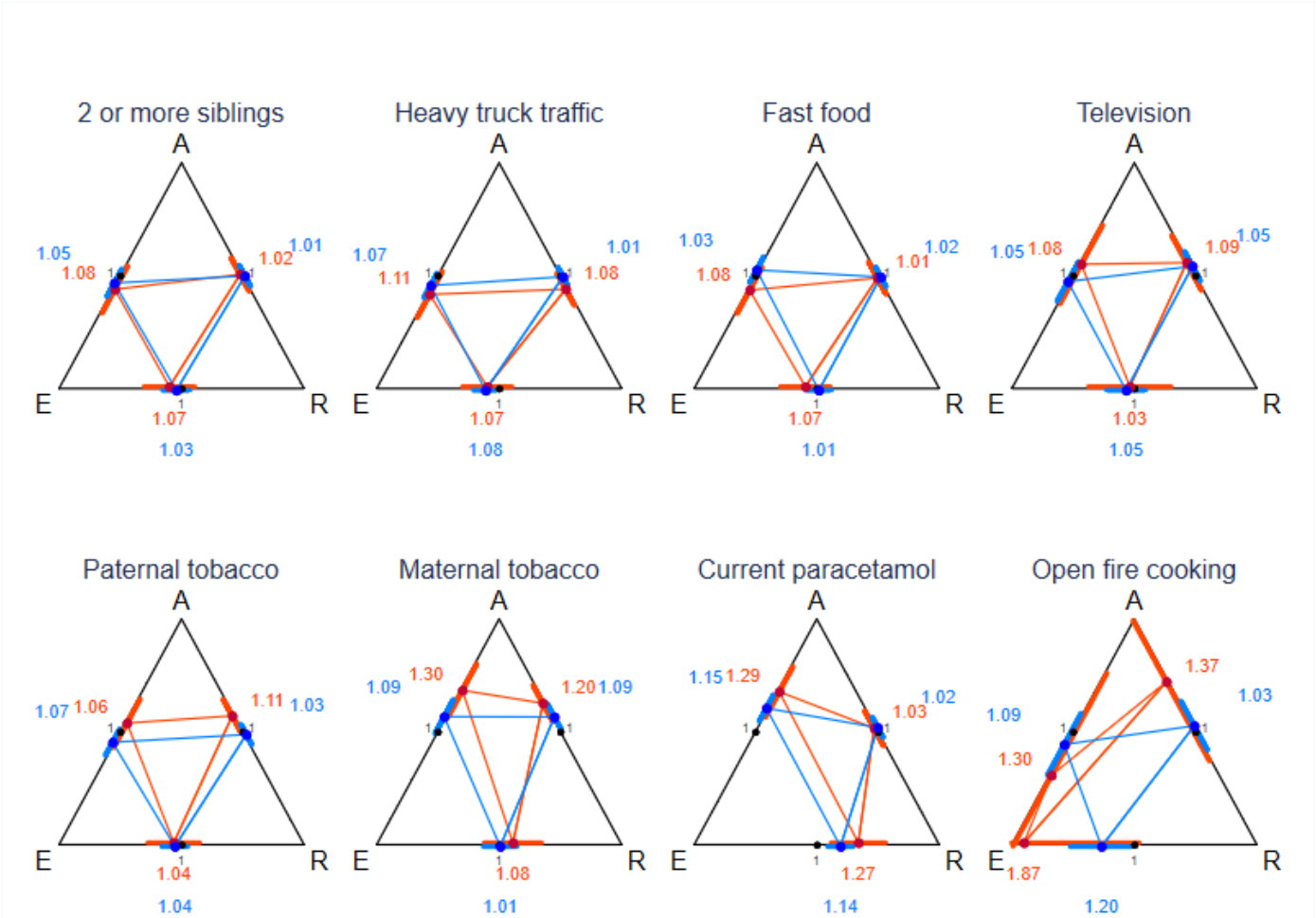


*Figure 4.11 Triangular graphs showing unimorbid two-way comparisons of effects of current risk factors for 13-14-year-old adolescents in affluent and non-affluent countries.*

***Each triangular plot shows the OR (labelled) and 95% confidence interval for two-way associations between the risk factor and two of the three diseases Asthma (A), Eczema (E) and Rhinoconjunctivitis (R) using a sample of unimorbid individuals, stratified by affluent countries (red) and non-affluent countries (blue). The odds ratio is always over 1 and relates to the increased chance of an individual with that risk factor as having one disease over the other. It indicates a relative strength of association (one disease compared to another) rather than an absolute strength of association (a disease compared to no disease). An equilateral central triangle denotes a risk factor that has a similar strength of effect on all three diseases. The further from equilateral the triangle is, the more that risk factor effect differs in strength between diseases. Current risk factors in 13-14 year-old adolescents includes factors from the previous 12 months. The possible range of OR graphed is from 1 in the centre to 2 at either extreme, on the log scale.***

Generally, associations with exposures averaged at the school level were similar in direction and magnitude to those ascertained at the child level, as we found also for symptoms of asthma and eczema. As we have argued elsewhere[80-81] this helps to exclude reverse causation, particularly for exposures such as early paracetamol and antibiotic use which may be related to prodromal disease, or pets which may be avoided by allergic families. An exception are the results for breastfeeding, showing a borderline significant inverse association with asthma symptoms, a significantly positive association with eczema symptoms and a null association with rhinoconjunctivitis at the individual level (Table 4.4). Nevertheless, the association of breastfeeding with rhinoconjunctivitis at the school level is strongly and significantly inverse (Table 4.3), perhaps indicating confounding by socioeconomic or other unmeasured characteristics of the school catchment population. This contrasts with the pattern of school-level associations of breastfeeding with symptoms of asthma[80] and eczema,[81] which were weakly positive but non-significant.

Many of the risk factor associations observed for symptoms of rhinoconjunctivitis were similar to those previously reported for symptoms of asthma or eczema in ISAAC Phase Three.[6-51,80,81] Since the three diseases cluster together at the individual level, it is possible that associations observed for one disease could be influenced by risk factors for other conditions in the triad. An innovative use of ISAAC data in this paper is the analysis of rhinoconjunctivitis, asthma and eczema, singly and in combination.

As expected, we found that associations with multimorbidity (combinations of two or three diseases) were stronger than for each disease alone (unimorbidity). However, the relationships of risk factors with each disease in the absence of the others were of similar direction and magnitude to the results for each condition modelled separately. Thus, multimorbidity is not the sole explanation of the common epidemiological patterns across these three diseases.

For many risk factors, associations were consistent across the three diseases, between the two age groups, and between countries with different levels of per capita Gross National Income. This similarity of epidemiology strongly suggests that there are common biological mechanisms for these three diseases, which operate in both affluent and less affluent settings. The most striking example of this in our ISAAC dataset is current paracetamol exposure, which was consistently associated with each of the three diseases, within schools and between schools, in both age groups and in richer and poorer countries, although somewhat more strongly with rhinoconjunctivitis and asthma than with eczema.

Shared mechanisms do not exclude the possibility of disease-specific pathways, which may differ between higher and lower income countries. An example of the latter is the inverse association of seasonal rhinoconjunctivitis with number of siblings and childhood exposure to the farm environment. This is well established from large epidemiological studies in Europe and confirmed by objective markers of allergic sensitisation.[86] This pattern is consistent with our findings for rhinoconjunctivitis symptoms in affluent countries but contrasts with the increased risk of these symptoms among children from larger families and those exposed to farm animals in poorer countries.

**Strengths and limitations**

ISAAC Phase Three has substantial advantages in terms of large sample sizes drawn from diverse study centres worldwide, who adopted standardised methods of data collection. Reliance solely upon questionnaires completed by parents (for the 6-7-year-olds) or participants (for the 13-14-year-olds) is a limitation, both for definition of disease outcomes and for ascertainment of risk factors. On the other hand, the questionnaire methodology maintained high response rates in each centre.

Misclassification of disease or risk factor information could be non-systematic, leading to weaker associations, or systematic, potentially exaggerating or masking associations. A particular concern would be individual differences in the threshold for reporting of symptoms, which could exaggerate clustering of the three complaints within individual children. This is unlikely to affect risk factor associations in our unimorbid analysis, where similarity in the epidemiological patterns for the each of the three diseases (in the absence of the others, Table 4.6) would be biased only if reporting of all three diseases were altered by the presence of the risk factor (or conversely, reporting of the common risk factor were biased to a similar degree by the presence of each of the three diseases).

A particular limitation of ISAAC Phase Three is the lack of objective information on allergic sensitisation. This was measured by skin prick testing and serum allergen-specific IgE in a separate study of more than 50,000 10-11-year-old children in 30 centres from 22 countries (ISAAC Phase Two).[30-33] Although (as expected) symptoms of rhinoconjunctivitis, asthma and eczema were more common among children with positive skin prick tests, these associations were substantially weaker in less affluent settings. The proportion of each disease attributable to skin prick positivity in centres from lower-income countries (per capita GNI < USD 9,200 in 2001) was 14% for rhinoconjunctivitis, 20% for asthma but only 1% for eczema. The

corresponding population attributable fractions (PAFs) in higher-income countries were 61% for rhinoconjunctivitis, 46% for asthma and 28% for eczema. The PAF estimates were very similar when serum allergen-specific IgE was used as the measure of allergic sensitisation.[31]

Throughout, ISAAC has focused upon the combination of nasal and conjunctival symptoms (in the absence of intercurrent infection) as the most relevant definition of rhinoconjunctivitis because non-infective rhinitis alone (without itchy eyes) is less strongly associated with skin prick positivity (PAFs of 5% in less affluent centres and 10% in more affluent centres).[32] More recent studies, among adolescents[82] and adults[83] have confirmed a stronger association of allergic sensitisation with rhinoconjunctivitis than with rhinitis alone.

**A shared non-allergic mechanism for "atopic diseases"?**

In recent decades, two models of multimorbidity have been proposed to explain the occurrence of two or more "atopic diseases" (asthma, rhinitis and eczema, sometimes extended also to food allergy). The term "united airway disease" has been proposed for the coexistence of asthma and rhinitis in the same patient at the same time.[87-89] The concept of the "atopic march" applies to the sequential development of eczema, asthma and rhinitis (usually in that order) through childhood and adolescence.[90.91] Discussion of both concepts has tended to focus upon IgE-mediated allergic mechanisms and Th2-immune inflammatory pathways as an explanation for concurrent and longitudinal clustering of the three diseases.

However, it is recognised that several distinct pathways and mechanisms are likely to be involved in the atopic march, some of them common and some disease-specific.[91] Non-allergic airway inflammation, defects of mucosal defence, and exogenous cofactors (including microbes, pollutants and smoking) have been proposed as "treatable traits" underlying united airway disease,[89] in addition to the close association of both asthma and rhinitis with IgE sensitisation, particularly to multiple allergens.[92]

Genome-wide association studies have shown a mixture of common and disease-specific signals for asthma, hay fever and eczema[93] illustrated by triangle plots derived from unimorbid case-only comparisons similar to those we have shown in Table 4.8 and Figures 4.6-4.11. Filaggrin (*FLG*) variants are specifically associated with eczema, whereas other genome-wide significant loci such as *IL6R* show almost perfect symmetry in association with each of the three diseases. A bioinformatics (data-mining) analysis of protein interactions found that asthma, rhinitis and eczema shared more associated proteins than would be expected by

chance and identified 15 pathways potentially involved in the multimorbidity of asthma, rhinitis and eczema, although many of these are related to Th2-immune signalling pathways.[94]

Epidemiological evidence for non-allergic mechanisms underlying coexistence of asthma, rhinitis and eczema emerges from the collaborative analysis of European birth cohorts by the MeDALL consortium.[95] Among over 8,000 children followed from birth to 4 and 8 years of age, IgE sensitisation to common food and aero-allergens at age 4 years accounted for only 38% of the co-occurrence of two or more conditions (asthma, rhinitis and eczema) at age 8 years. In relative terms, the strength of the association among the three diseases was higher in non-sensitised children, although the excess comorbidity was greater among those who were sensitised, due to a higher baseline risk of disease. Among the sensitised children, about a quarter of the observed comorbidity was not due to chance, whereas among non-sensitised children the non-chance proportion was more than half at age 8 years. Comorbidity at age 4 years was strongly predictive of comorbidity at age 8 years. All these observations led the MeDALL investigators to propose "a new vision of multimorbidity independent of IgE sensitisation",[96] which would be entirely consistent with our observations of common epidemiological patterns for symptoms of rhinoconjunctivitis, asthma and eczema in two age groups of children in both affluent and non-affluent countries worldwide.

**Conclusions**

Most of the environmental and lifestyle correlates of rhinoconjunctivitis, asthma and eczema in childhood display similarity across the three conditions, even in less affluent settings where allergic sensitisation (as conventionally defined) is less likely to explain the concordant epidemiological patterns. This supports the view that mechanisms other than IgE-mediated tissue inflammation may contribute a substantial proportion of the clustering of these "atopic diseases" within individuals (concurrently and sequentially) and at the population level.

# 5 Paper IV: Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I cross-sectional study

## Summary

This chapter examines worldwide trends in the burden of asthma symptoms in school-aged children. It comprises a paper published in the Lancet describing changes in prevalence of asthma symptoms around the world from the start of ISAAC Phase I in 1992 up to GAN Phase I 2020, i.e. over a 27-28-year period. There was evidence that time trends in asthma symptom prevalence were associated with country income level and region, with decreases found in low-income countries, increases in lower-middle-income countries, and no evidence of change across upper-middle- and high-income countries.

## 5.1 Introduction

This chapter uses GAN Phase I data along with ISAAC data from Phase I and Phase III to explore changes over time within and between centres around the world. There are 3 published peer-reviewed papers covering the main time trend findings. This part of the thesis concentrates on asthma and this chapter includes a co-authored paper published in *The Lancet*. The other two co-authored papers are a paper on rhinoconjunctivitis, published in *Pediatric Allergy and Immunology* in August 2021 (Appendix D) and a paper on eczema submitted to *The Journal of Allergy and Clinical Immunology* in November 2021 and pending a decision as of March 2022 (Appendix E).

The included paper has been reformatted to the style of this thesis but no text changes have been made. Supplementary material from the published paper is available with open access at http://thelancet.com/journals/lancet/article/PIIS0140-6736(21)01450-1/fulltext. This includes

six individual maps, which have been reformatted into the two figures 5.2 and 5.3. It also includes extended versions of tables 5.3 and 5.4 which are not included in this thesis due to their size. The additional data they contain are not referred to in the text.

Note that where this paper refers to current wheeze this means the same as current asthma symptoms in the rest of the thesis.

# 5.2 Article submitted

**SECTION A – Student Details**

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300807 | **Title** | Mrs |
| **First Name(s)** | Charlotte Emma | | |
| **Surname/Family Name** | Rutter | | |
| **Thesis Title** | Multi-level modelling of international variations and time trends in asthma and allergic diseases in children. | | |
| **Primary Supervisor** | Neil Pearce | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

**SECTION B – Paper already published**

| | | | |
|---|---|---|---|
| Where was the work published? | The Lancet | | |
| When was the work published? | 30th October 2021 | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | **Yes** | Was the work subject to academic peer review? | **Yes** |

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**SECTION C – Prepared for publication, but not yet published**

| | |
|---|---|
| Where is the work intended to be published? | |
| Please list the paper's authors in the intended authorship order: | |
| Stage of publication | |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role was running the analyses, creating the tables and figures, and reviewing/editing the drafts (CER in the below, taken from the paper).<br><br>MIA, KB, C-YC, AES, PE, LG-M, GBM, NP, and DPS conceptualised the study. EE, PE, LG-M, EM, VP-F, CER, SR, and RJS curated the data. NP, CER, and DPS did the formal analysis. MIA handled the investigation and the resources. MIA, C-YC, PE, LG-M, NP, CER, DPS, and RJS were responsible for the methods. MIA, EE, and PE were responsible for project administration. LG-M, NP, DPS, and RJS supervised the study. PE validated the data. EE, PE, and CER handled data visualisation. MIA and CER wrote the original draft. KB, C-YC, AES, EE, PE, LG-M, EM, KM, VP-F, NP, DPS, RJS, and the Global Asthma Network Phase I Study Group reviewed and edited the manuscript. The Global Asthma Network Phase I Study Group contributed original data for the analyses. CER, NP, VP-F, and DPS verified the underlying data. The writing group authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | [redacted] |
| **Date** | 26/01/2022 |

| | |
|---|---|
| **Supervisor Signature** | [redacted] |
| **Date** | 23/03/2022 |

### 5.2.1 Abstract

**Background**

Asthma is the most common chronic disease in children globally. The Global Asthma Network (GAN) Phase I study aimed to determine if the worldwide burden of asthma symptoms is changing.

**Methods**

This updated cross-sectional study used the same methods as the International Study of Asthma and Allergies in Childhood (ISAAC) Phase III. Asthma symptoms were assessed from centres that completed GAN Phase I and ISAAC Phase I (1993-95), ISAAC Phase III (2001-03), or both. We included individuals from two age groups (children aged 6-7 years and adolescents aged 13-14 years) who self-completed written questionnaires at school. We estimated the 10-year rate of change in prevalence of current wheeze, severe asthma symptoms, ever having asthma, exercise wheeze, and night cough (defined by core questions in the questionnaire) for each centre, and we estimated trends across world regions and income levels using mixed-effects linear regression models with region and country income level as confounders.

**Findings**

Overall, 119,795 participants from 27 centres in 14 countries were included: 74,361 adolescents (response rate 90%) and 45,434 children (response rate 79%). About one in ten individuals of both age groups had wheeze in the preceding year, of whom almost half had severe symptoms. Most centres showed a change in prevalence of 2 SE or more between ISAAC Phase III to GAN Phase I. Over the 27-year period (1993-2020), adolescents showed a significant decrease in percentage point prevalence per decade in severe asthma symptoms (-0·37, 95% CI -0·69 to -0·04) and an increase in ever having asthma (1·25, 0·67 to 1·83) and night cough (4·25, 3·06 to 5·44), which was also found in children (3·21, 1·80 to 4·62). The prevalence of current wheeze decreased in low-income countries (-1·37, -2·47 to -0·27, in children and -1·67, -2·70 to -0·64, in adolescents) and increased in lower-middle-income countries (1·99, 0·33 to 3·66, in children and 1·69, 0·13 to 3·25, in adolescents), but it was stable in upper-middle-income and high-income countries.

**Interpretation**

Trends in prevalence and severity of asthma symptoms over the past three decades varied by age group, country income, region, and centre. The high worldwide burden of severe asthma symptoms would be mitigated by enabling access to effective therapies for asthma.

**Funding**

International Union Against Tuberculosis and Lung Disease, Boehringer Ingelheim New Zealand, Astra Zeneca Educational Grant, National Institute for Health Research, UK Medical Research Council, European Research Council, and Instituto de Salud Carlos III.

### 5.2.2 Introduction

Asthma is the most common non-communicable disease in children and one of the most common chronic diseases in adulthood.[58,97] It is a major global health problem, with estimated 495,100 deaths from asthma in 2017,[98] and 22·8 million disability-adjusted life-years in 2017.[99] More than 1000 asthma deaths each day are similar to the number of deaths from malaria.[100] Cross-sectional comparisons of the prevalence of asthma in populations require standardised methods that can be implemented in a wide range of settings, and the International Study of Asthma and Allergies in Childhood (ISAAC) is the only worldwide study to achieve this.[101] ISAAC Phase I (1993-95), repeated in Phase III (2001-03), identified that the prevalence of asthma symptoms (current wheeze) in school-aged children (aged 6-7 years and 13-14 years) was rising in some low-income and middle-income countries.[54,102]

The Global Asthma Network (GAN) was established in 2012, building on the success of ISAAC and incorporating a new collaboration with the International Union Against Tuberculosis and Lung Disease. One of GAN's core activities, GAN Phase I (building on ISAAC and using an identical approach and methods)[4] includes global surveillance of prevalence and severity of asthma symptoms,[21] making it the only source of new population-based data on worldwide trends in prevalence of asthma symptoms directly comparable to data from ISAAC Phases I and III. Public health interventions need to be based on science, with up-to-date evidence of the size and trends of health issues.

We hypothesised that globally, the burden (prevalence and severity) of asthma symptoms is changing in school-aged children worldwide. The aim was to conduct asthma symptom surveillance around the world in two age groups of school pupils to examine time trends in prevalence and severity of asthma symptoms from centres that completed GAN Phase I and ISAAC Phase I, Phase III, or both.[21]

### 5.2.3 Methods

**Study design and participants**

ISAAC Phase I and Phase III were multicentre, multi-country, cross-sectional, population studies in school-aged children, following standardised methods that have been well described[2,3] and are highly replicable.[103] This enabled comparisons of prevalence and severity of asthma symptoms between ISAAC Phase I and Phase III and GAN Phase I. Centres that completed GAN Phase I and ISAAC Phase I, Phase III, or both were the study centres for this analysis, and key personnel at the GAN Global Centre (Auckland, New Zealand) were the same throughout ISAAC Phase I, ISAAC Phase III, and GAN Phase I.

Each GAN Phase I investigator completed a registration document and followed the GAN manual.[104] They gained approval from their local ethics committee and replicated the methods that had been used in their centres for ISAAC; this was documented in the centre report,[104] which enabled checks to ensure the use of the same geographical sampling frame, sample size, age groups, method of selecting pupils, time of year for data collection, and translations as had been used in ISAAC.[105] From the sampling frame, ten or more schools were selected at random (or all schools if fewer than ten). The GAN Global Centre checked each centre report with the investigator for validity.

As in ISAAC, the compulsory age group was individuals aged 13-14 years (adolescents) who self-completed written questionnaires at school. The inclusion of individuals aged 6-7 years (children) was optional, and their questionnaires were completed at home by their parents or caregivers. All students of the specified age within schools were included and selected by grade, level, or year or by chronological age. Local ethics committees determined the method of consent (either passive or written) from parents or caregivers of both age groups; however, GAN recommended passive consent as written consent could reduce response rate,[106] and the adolescents agreed by participating. Additionally, GAN Phase I included questionnaires completed by the parents about themselves, not reported here.

**Procedures**

We used seven core written asthma questions for comparisons in this Article. Current wheeze was defined as a positive answer to the question *"*have you (has this child) had wheezing or whistling in the chest in the past 12 months?" Severe asthma symptoms were defined as participants with current wheeze who, in the preceding 12 months, had four or more attacks of wheeze, one or more nights per week with sleep disturbance from wheeze, or wheeze

affecting their speech.[36] Ever having asthma (asthma ever) was defined as a positive answer to the question ‘‘have you (has this child) ever had asthma?’’ Exercise wheeze was defined by a positive answer to the question “in the past 12 months, has your (has this child’s) chest sounded wheezy during or after exercise?” And lastly, night cough was defined as a positive answer to the question “in the past 12 months have you (has this child) had a dry cough at night, apart from associated with a cold or chest infection?”

Data and the centre report from each participating centre were submitted to the GAN Global Centre, and quality control checks were completed. Centres with minor deviations from the methods were included in analyses, and these deviations are specified in footnotes in the tables, as in ISAAC.[16] The data were then transferred to one of two designated GAN Phase I data centres for checking and analysis: Murcia (Spain) for Spanish-speaking and Portuguese-speaking centres and London (UK) for all other languages. A uniform approach to data processing, checking, and analysis was developed, using Stata versions 13-15.[85]

The mean date of questionnaire completion in each centre was used, rather than the year alone as had occurred in ISAAC time-trend studies.[54,102] High levels of participation were required for inclusion because absent school pupils might be away from school due to asthma symptoms: response rate was required to be at least 80% for adolescents and 70% for children.[2,4,16] The response rate was defined as the number of core asthma symptom questionnaires returned with at least some symptom data, divided by the number of pupils in the age group. Three of the centre datasets received (one for adolescents and two for children) were excluded from the analyses due to poor (<50%) response rates.

In each centre, estimates of prevalence of symptoms for each age group were obtained by dividing the number of positive responses to each question by the number of completed questionnaires. If apparent inconsistencies were found between responses to a main question and a branched question (one dependent on the response to a main question), these were accepted and not recoded. For regional and global summaries, data for each centre were weighted by the sample size.

We obtained country income categories from the World Bank, with countries categorised into low-income, lower-middle-income, upper-middle-income, and high-income countries.[107] The gross national income 2001 classification was used, because it was close to the timing of ISAAC Phase III, from which most data were available. Countries were allocated to four regions corresponding to WHO regions of the world, with Southeast Asia and Western Pacific regions combined and Africa and Eastern Mediterranean regions combined, because of the small

number of centres in these regions. WHO regions and country income category are not synonymous.

**Outcomes and statistical analysis**

We sought a sample size of 3000 participants for each age group (with a minimum of 1000 deemed acceptable), a stringent requirement because of the number of hypotheses being tested.

We examined changes in prevalence over time from ISAAC Phase I to GAN Phase I. We calculated the 10-year change in prevalence of symptoms for each centre using the difference between the two timepoints (e.g. GAN Phase I and ISAAC Phase III) divided by the number of decades between the mean data collection dates of those timepoints.

We derived estimates of the absolute 10-year rate of change in current wheeze, severe asthma symptoms, ever having asthma, exercise wheeze, and night cough for each centre. We calculated the SE of this change to account for school-level clustering. We used Bland Altman plots to examine the relationship between change in prevalence and average prevalence between timepoints, to remove the influence of sampling error (regression to the mean)[108] when comparing the trends in higher or lower prevalence areas. The relationship was assessed with Spearman's rank correlation.

To examine trends over time in different types of countries or centres, multilevel modelling was undertaken. Along with GAN Phase I centres who participated in ISAAC, we included ISAAC-only centres with data from both ISAAC Phases I and III[54] (94 centres with adolescents and 57 centres with children). This enabled us to estimate trends in prevalence across the full 27-year period (1993-2020) using all available time trends of centres in one mixed-effects linear regression model. Some centres had complete three-point time trend data available for the periods of ISAAC Phase I to ISAAC Phase III to GAN Phase I, whereas others had only ISAAC Phase III to GAN Phase I, ISAAC Phase I to GAN Phase I, or ISAAC Phase I to ISAAC Phase III. We included country-level and centre-level random intercepts in the mixed-effects linear regression models. The estimated time trend could therefore be interpreted as the within-centre absolute change in percentage point prevalence per decade. Data from both age groups were included in the one model to improve model efficiency. We included age group as an a-priori confounder and effect modifier to assess time trends in each age group separately.

We considered country income category and region as confounders and effect modifiers of the time trend. Therefore, our analyses controlled, by stratification, for age group, region of the world, and country income level. In all centres, boys and girls were approximately evenly distributed, so we did not control for sex. We also tested for evidence against a linear form for the time trend through the introduction of a quadratic term. The main models were additionally fitted to estimate the time trend in severe wheeze, exercise wheeze, night cough, and ever having asthma.

To consider the effect of the level of prevalence of current wheeze on the change in prevalence of current wheeze, we additionally fitted separate models that included level of prevalence in ISAAC Phase III (or midpoint if no ISAAC Phase III data were available).

**Role of the funding source**

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report; and no role in the decision to submit the paper for publication.

### 5.2.4 Results

Data were available for 27 centres, in 14 countries in all four regions (Africa and Eastern Mediterranean, America, Europe, and Southeast Asia and Western Pacific) that had completed ISAAC Phase I, Phase III, or both and for which GAN Phase I methods and data checks were completed by Jan 29, 2021. Overall, 119,795 participants from GAN Phase I were included: 74,361 adolescents in 27 centres (response rate 90%, range 68-100) and 45,434 children in 19 centres (response rate 79%, range 55-100) (Table 5.1). For the 27 centres in GAN Phase I with data available for adolescents, 13 had data from ISAAC Phase III alone, 13 had data from both ISAAC Phases I and III, and one (Athens) had data for ISAAC Phase I alone.

For the 19 centres in GAN Phase I with data available for children, nine had data from ISAAC Phase III alone, nine had data from both ISAAC Phases I and III, and one (Chandigarh) had data from ISAAC Phase I alone.

*Table 5.1 GAN Phase I data collection details in each study centre*

| Country (centre) | 13-14-years age group | | | | 6-7-years age group | | | |
|---|---|---|---|---|---|---|---|---|
| | Principal investigator | GAN response rate, %* | Mean data collection date | Years between Phases† | Principal investigator | GAN response rate, %* | Mean data collection date | Years between Phases† |
| **Africa and Eastern Mediterranean** | | | | | | | | |
| Nigeria (Ibadan) | A Falade | 85·0% | May 2018 | 16·7 | .. | .. | .. | .. |
| South Africa (Cape Town) | H J Zar | 84·4% | Aug 2017 | 15·2 | .. | .. | .. | .. |
| Sudan (Khartoum) | M Nour | 99·9% | Mar 2017 | 14·1 | .. | .. | .. | .. |
| Syria (Lattakia) | G Dib | 99·6% | Apr 2019 | 17·3 | Y Mohammad | 93·0% | May 2019 | 16·2 |
| Region total | .. | .. | Dec 2017 | 15·7 | .. | .. | May 2019 | 16·2 |
| **Americas** | | | | | | | | |
| Chile (South Santiago) | J Mallol | 81·9% | Mar 2015 | 13·3 | .. | .. | .. | .. |
| Costa Rica (Costa Rica) | M Soto-Martinez | 67·5% | Feb 2018 | 16·1 | M Soto-Martinez | 64·5% | Jan 2018 | 16·0 |
| Ecuador (Quito) | A Cabrera Aguilar | 100·0% | Apr 2019 | 15·9 | .. | .. | .. | .. |
| Mexico (Ciudad Victoria) | R García-Almaráz | 82·3% | Dec 2015 | 12·7 | R García-Almaráz | 81·5% | Feb 2016 | 12·9 |
| Mexico (Mexicali) | J V Mérida-Palacio | 83·7% | Apr 2016 | 13·7 | J V Mérida-Palacio | 77·0% | Mar 2016 | 13·3 |
| Mexico (Mexico City North Area) | B E Del Río Navarro | 93·8% | Sep 2015 | 12·9 | B E Del Río Navarro | 86·7% | Jun 2016 | 13·6 |
| Mexico (Monterrey) | S N González-Díaz | 88·0% | Dec 2017 | 16·7 | .. | .. | .. | .. |
| Mexico (Toluca Urban Area) | E M Navarrete- Rodriguez | 98·1% | Oct 2015 | 13·1 | E M Navarrete- Rodriguez | 95·7% | Apr 2016 | 13·5 |
| Nicaragua (Managua) | J F Sánchez | 90·5% | Nov 2018 | 16·5 | J F Sánchez | 87·9% | Nov 2018 | 16·4 |
| Region total | .. | .. | Dec 2016 | 14·5 | .. | .. | Jan 2017 | 14·4 |
| **Europe** | | | | | | | | |
| Spain (A Coruña) | A López-Silvarrey Varela | 92·1% | Jan 2019 | 15·2 | A López-Silvarrey Varela | 71·0% | Jan 2019 | 15·3 |
| Spain (Bilbao) | C González Díaz | 91·1% | Sep 2018 | 16·8 | C González Díaz | 55·2% | Aug 2018 | 16·7 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Spain (Cartagena) | L García-Marcos | 73·8% | Jan 2016 | 13·9 | L García-Marcos | 65·9% | Jan 2016 | 14·0 |
| Region total | .. | .. | Dec 2017 | 15·4 | .. | .. | Nov 2017 | 15·3 |
| **South-East Asia and Western Pacific** | | | | | | | | |
| India (Bikaner) | M Sabir | 90·1% | Nov 2017 | 16·3 | .. | .. | .. | .. |
| India (Chandigarh) | M Singh | 100·0% | Oct 2017 | 15·9 | .. | .. | .. | .. |
| India (Jaipur) | V Singh | 98·7% | Nov 2017 | 16·3 | V Singh | 75·8% | Nov 2017 | 16·3 |
| India (Kottayam) | T U Sukumaran | 85·3% | Oct 2017 | 15·3 | T U Sukumaran | 68·4% | Dec 2017 | 15·5 |
| India (Lucknow) | S Awasthi | 94·0% | Oct 2017 | 16·0 | S Awasthi | 91·3% | Oct 2017 | 15·9 |
| India (New Delhi) | S K Kabra | 100·0% | Nov 2017 | 16·0 | S K Kabra | 80·9% | Jan 2018 | 16·1 |
| India (Pune) | S Salvi | 99·6% | Oct 2017 | 15·9 | S Salvi | 79·8% | Oct 2017 | 15·9 |
| New Zealand (Auckland) | M I Asher | 85·5% | Oct 2018 | 16·7 | M I Asher | 63·7% | Jul 2018 | 16·4 |
| Taiwan (Taipei) | J-L Huang | 93·0% | Oct 2017 | 15·8 | J-L Huang | 76·3% | Oct 2017 | 15·8 |
| Thailand (Bangkok) | S Chinratanapisit | 97·9% | Sep 2017 | 16·1 | S Chinratanapisit | 86·3% | Aug 2017 | 16·1 |
| Region total | .. | .. | Nov 2017 | 16·0 | .. | .. | Nov 2017 | 16·0 |
| World total | .. | .. | Aug 2017 | 15·4 | .. | .. | Aug 2017 | 15·3 |

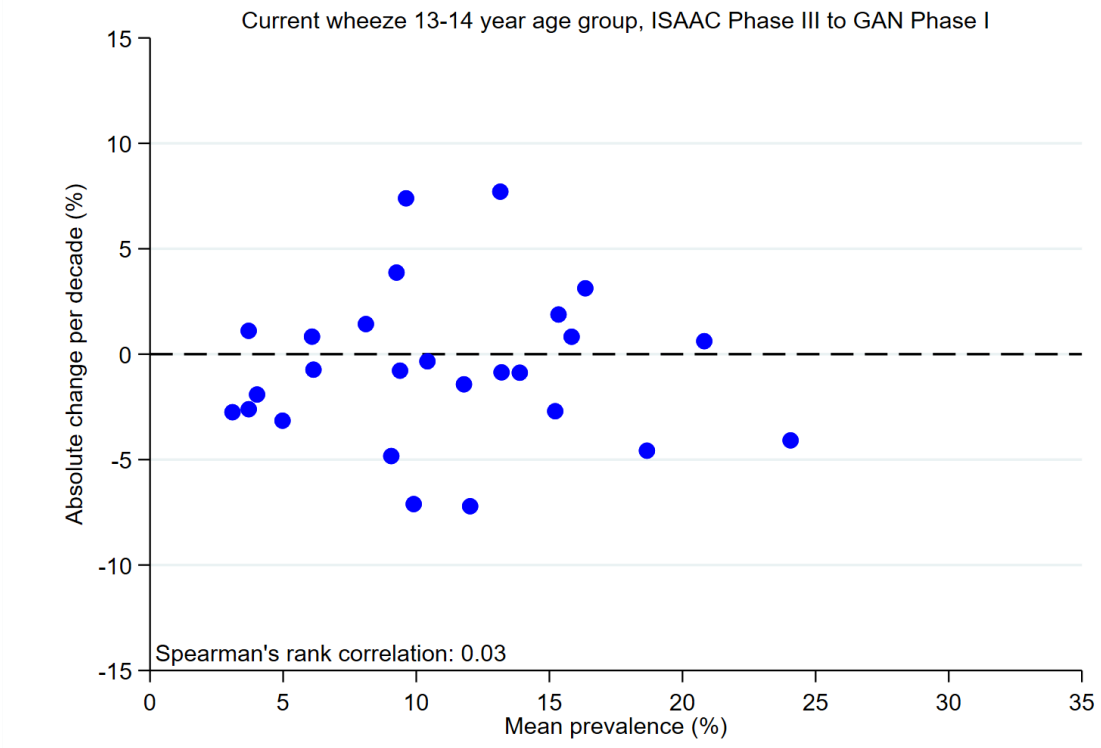
The Athens centre is not presented because its ISAAC data are from Phase I alone; the Chandigarh centre is not presented in the 6-7-years age group because its ISAAC data are from Phase I alone. For the 13-14-years age group, methodology notes for centres with GAN Phase I data alone are the following: no date of birth on the questionnaire (Ibadan, Taipei); response rate lower than 80% (Costa Rica, Cartagena); age and birth date showed high inconsistencies (Quito); fewer than ten schools used when ten or more schools were available (Ciudad Victoria, Mexico City [north area], Toluca Urban Area, Auckland, Bangkok); only age was reported reliably (Monterrey); single data entry (Monterrey); no age on the questionnaire (Chandigarh, New Delhi); questionnaires completed at home by parents (Kottayam); and more than 20% of questionnaires missing age and date of birth (Bangkok). For the 6–7-years age group, methodology notes for centres with GAN Phase I data alone are the following: response rate lower than 70% (Costa Rica, Bilbao, Cartagena, Kottayam, Auckland); no date of birth on the questionnaire (Taipei); no age on the questionnaire (New Delhi); fewer than ten schools used when ten or more schools were available (Bangkok); and more than 20% of questionnaires missing age and date of birth (Bangkok). *GAN Phase I. †ISAAC Phase III to GAN Phase I.

GAN Phase I was undertaken between March 2, 2015 and Feb 28, 2020, with the date of data collection varying by centre. There was an average of 15·4 years (range 12·7-17·3) between ISAAC Phase III and GAN Phase I and 22·7 years (19·5-25·5) between ISAAC Phase I and GAN Phase I; dates of data collection were similar between the adolescent group and children group.

For current wheeze, in GAN Phase I, the prevalence in adolescents ranged from 0·9% (New Delhi, India) to 21·3% (Cape Town, South Africa), with a mean of 10·4% (95% CI 7·8-12·8); and the prevalence in children ranged from 1·1% (Lucknow, India) to 23·2% (Costa Rica), with a mean of 9·9% (7·3-12·4; Tables 5.2, 5.3). The Bland Altman plots showed that the underlying prevalence of current wheeze was not associated with the magnitude of change (Figure 5.1).

We assessed the changes within centres in absolute prevalence of current wheeze from ISAAC (Phases I and III) to GAN Phase I (Figure 5.2). Within each age group, most centres in both age groups showed significant (≥2 SE up or down) changes in current wheeze and severe asthma symptoms. For prevalence of current wheeze in adolescents, ten centres showed an SE decrease of 2 or more, seven showed an SE increase of 2 or more, and nine showed an SE change lower than 2 (Figure 5.3a). For prevalence of current wheeze in children, nine centres showed an SE decrease of 2 or more, five showed an SE increase of 2 or more, and four showed an SE change lower than 2 (Figure 5.4a). Within centres and in both age groups, the pattern of changes in prevalence of severe asthma symptoms (Figures 5.3b, 5.4b) and ever having asthma (Figures 5.3c, 5.4c) was similar to the changes in current wheeze. Additionally, the pattern of changes in prevalence of exercise wheeze and night cough was similar to those in current wheeze in both age groups (Tables 5.2, 5.3).

The regression models examined whether within-centre changes were, collectively, compatible with chance or real trends. The models showed the effects of age group, region, and country income group upon time trends in current wheeze to be minimally altered by adjustment for their mutual confounding (data not shown). Although we observed no evidence for age group as an effect modifier (p=0·67), we decided a priori to stratify on this variable due to the importance of showing age group-specific results. We observed evidence of an additional effect modification with both income group (p=0·002) and region (p=0·0002), but the low number of centres in each stratum meant that we did not consider these effect modifiers together.



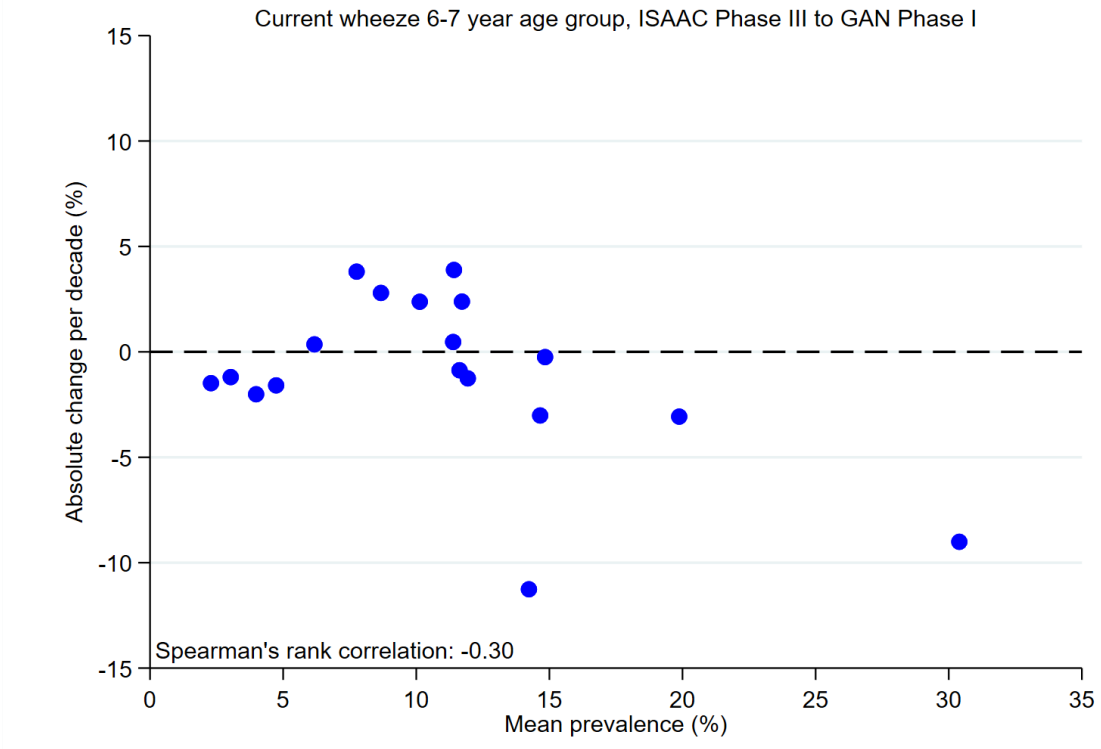




*Figure 5.1 Bland Altman plots which examined, for current wheeze, the relationship between change in prevalence and average prevalence between time points for both age groups.*

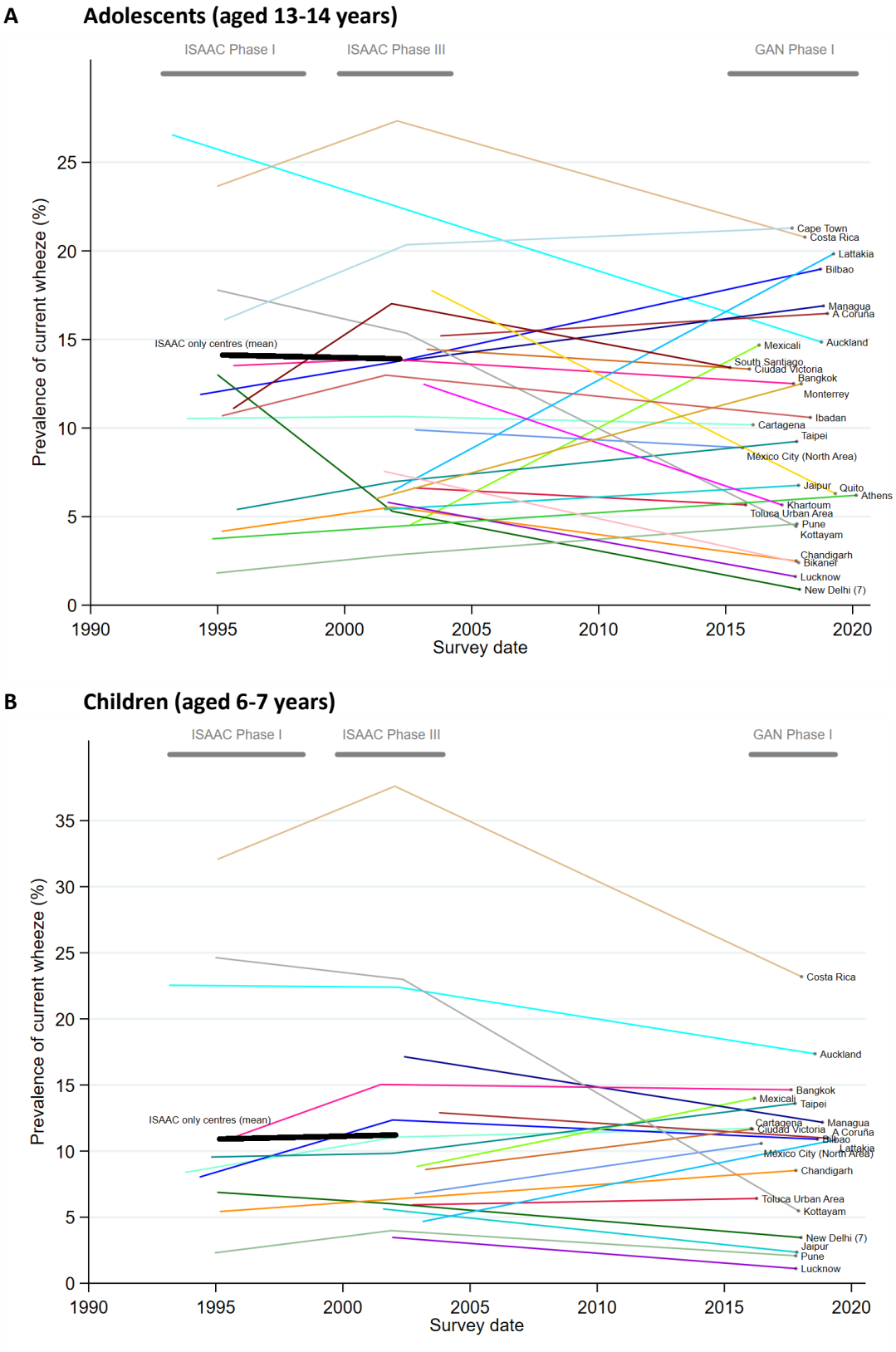



*Figure 5.2 Absolute changes over time in prevalence of current wheeze for adolescents (A) and children (B) by survey date*

Each thin line represents one centre. The thick line shows the average absolute change from ISAAC Phase I to Phase III for those centres that did not participate in GAN Phase I. The span of the years of data collection for ISAAC Phase I, ISAAC Phase III and GAN Phase I are shown.

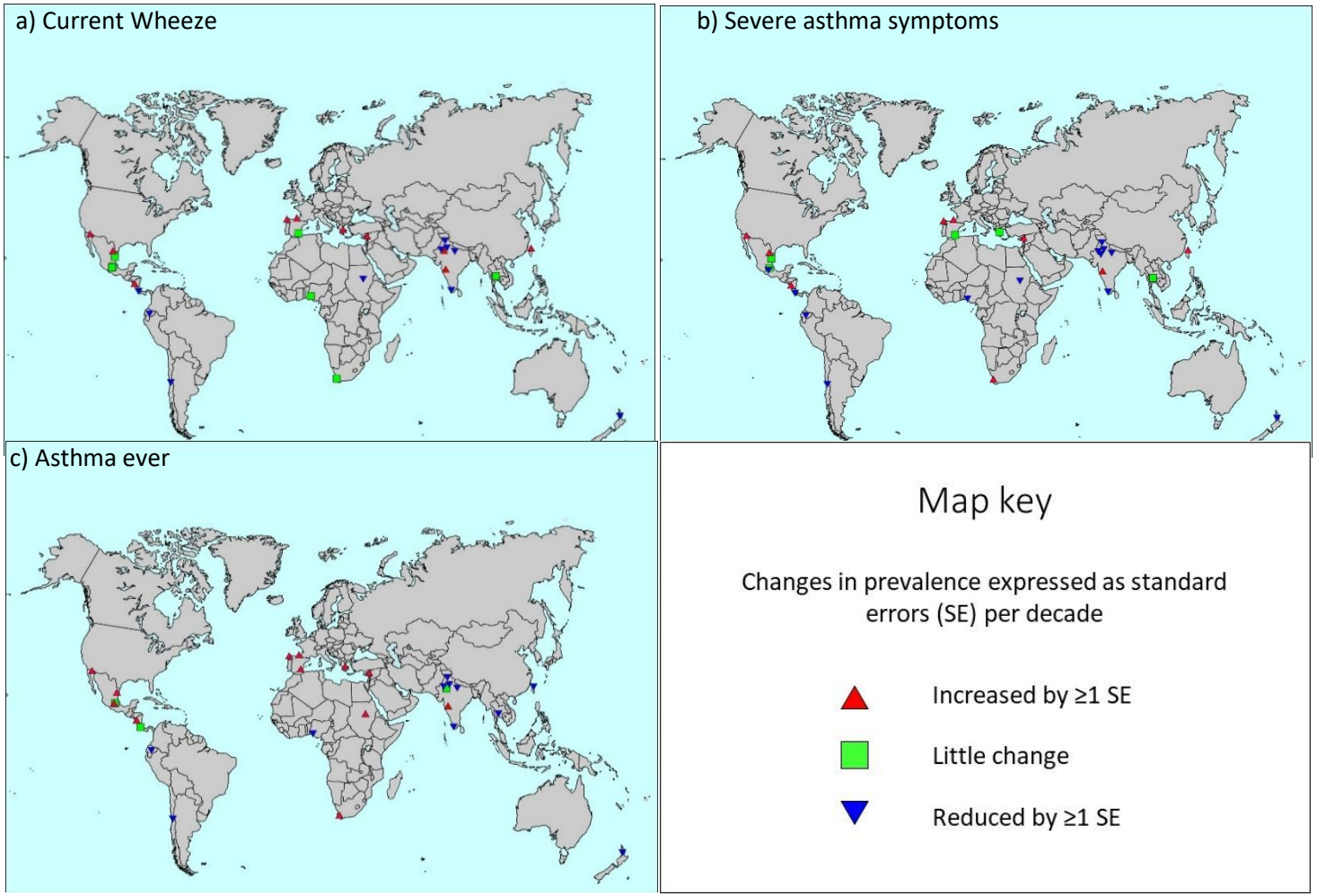



*Figure 5.3 World maps of centres, for 13-14 year olds (adolescents) showing changes in prevalence per decade expressed in standard errors (SE)*

ISAAC Phase III to GAN Phase I except Athens which undertook ISAAC Phase I but not ISAAC Phase III

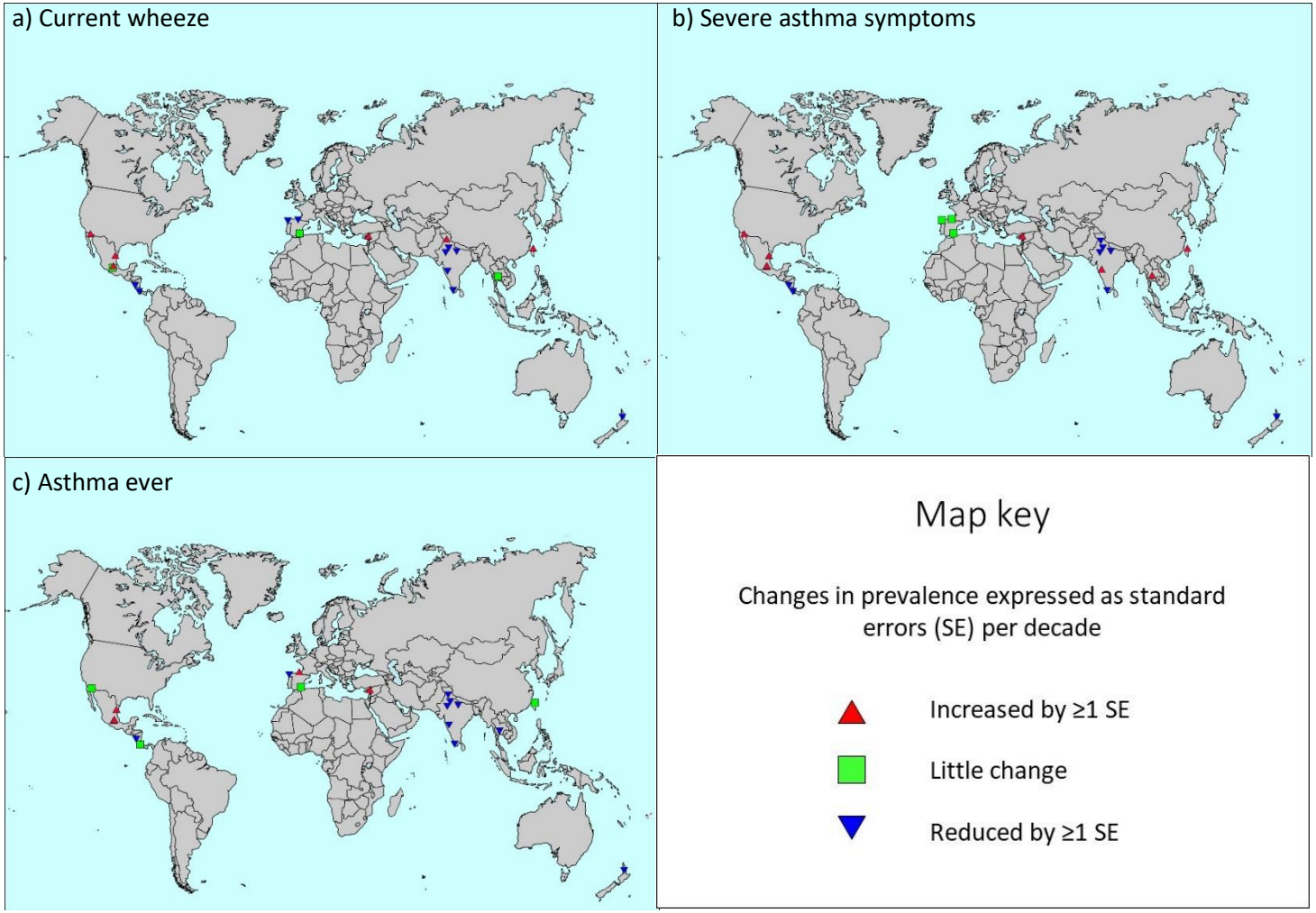



*Figure 5.4 World maps of centres, for 6-7 year olds (children) showing changes in prevalence per decade expressed in standard errors (SE)*

ISAAC Phase III to GAN Phase I except Chandigarh which undertook ISAAC Phase I but not ISAAC Phase III

*Table 5.2 12-month prevalence of asthma symptoms and absolute change per decade for the 13-14-years age group in each study centre*

| Country (centre) | Number of individuals* | Wheeze in past 12 months | | | Asthma ever | | | Severe asthma symptoms in past 12 months | | | Exercise wheeze in past 12 months | | | Night cough in past 12 months | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change |
| Africa and Eastern Mediterranean | | | | | | | | | | | | | | | | |
| Nigeria (Ibadan) | 2,897 | 10·6 | -1·4 | -1·0 | 3·7 | -4·8 | -5·3 | 6·2 | -1·3 | -1·2 | 32·0 | -1·3 | -0·7 | 23·6 | -2·5 | -1·8 |
| South Africa (Cape Town) | 3,979 | 21·3 | 0·6 | 0·5 | 16·6 | 1·4 | 1·5 | 12·0 | 1·7 | 2·7 | 36·0 | 2·2 | 1·3 | 41·4 | 3·1 | 2·4 |
| Sudan (Khartoum) | 1,785 | 5·7 | -4·8 | -3·9 | 18·2 | 1·9 | 1·2 | 3·5 | -2·7 | -3·2 | 28·1 | 9·6 | 3·4 | 40·4 | 14·4 | 7·2 |
| Syrian Arab Republic (Lattakia) | 1,215 | 19·8 | 7·7 | 4·4 | 10·9 | 2·8 | 4·9 | 10·6 | 4·7 | 4·3 | 35·8 | 13·6 | 4·6 | 54·4 | 19·4 | 8·6 |
| Region total | 9,876 | 15·1 | 0·7 | NA | 12·4 | 0·1 | NA | 8·6 | 0·8 | NA | 33·4 | 5·4 | NA | 37·6 | 6·2 | NA |
| America | | | | | | | | | | | | | | | | |
| Chile (South Santiago) | 2,750 | 13·4 | -2·7 | -3·2 | 13·7 | -1·7 | -2·4 | 3·9 | -1·4 | -3·2 | 16·7 | -3·0 | -3·5 | 32·9 | -5·7 | -5·6 |
| Costa Rica (whole country) | 1,338 | 20·8 | -4·1 | -3·9 | 22·0 | -0·7 | -0·6 | 9·4 | -2·7 | -3·7 | 14·4 | -3·3 | -4·4 | 31·2 | 3·0 | 2·7 |
| Ecuador (Quito) | 3,000 | 6·3 | -7·2 | -6·5 | 4·5 | -1·5 | -2·5 | 3·0 | -1·4 | -2·5 | 18·2 | 4·8 | 3·3 | 28·0 | 12·7 | 9·4 |
| México (Ciudad Victoria) | 2,468 | 13·3 | -0·9 | -0·4 | 8·6 | 2·2 | 2·6 | 5·8 | 0·4 | 0·7 | 16·6 | -3·9 | -1·5 | 25·8 | -5·6 | -2·0 |
| México (Mexicali) | 2,479 | 14·7 | 7·4 | 11·5 | 8·7 | 5·4 | 11·6 | 7·5 | 3·9 | 8·4 | 21·3 | 11·2 | 7·3 | 25·7 | 16·4 | 11·7 |
| México (México City (North Area)) | 3,375 | 8·9 | -0·8 | -0·6 | 7·4 | -0·4 | -0·4 | 3·7 | -0·2 | -0·3 | 15·5 | 1·9 | 1·3 | 14·8 | -13·2 | -4·7 |
| México (Monterrey) | 2,641 | 12·5 | 3·9 | 6·9 | 11·3 | 2·5 | 4·2 | 5·5 | 1·7 | 4·0 | 23·1 | 8·0 | 7·6 | 31·2 | -2·6 | -1·1 |
| México (Toluca Urban Area) | 2,650 | 5·7 | -0·7 | -0·7 | 6·2 | 0·8 | 1·8 | 2·3 | -0·9 | -1·3 | 11·0 | -5·2 | -1·6 | 16·1 | -3·4 | -1·2 |
| Nicaragua (Managua) | 3,131 | 16·9 | 1·9 | 2·3 | 20·1 | 3·0 | 4·1 | 9·8 | 1·3 | 2·2 | 21·9 | -2·6 | -2·6 | 43·8 | 0·2 | 0·2 |
| Region total | 23,832 | 11·9 | -0·5 | NA | 10·8 | 0·9 | NA | 5·4 | 0·0 | NA | 17·8 | 1·2 | NA | 27·5 | 0·2 | NA |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Europe | | | | | | | | | | | | | | | | |
| Spain (A Coruña) | 3,462 | 16·5 | 0·8 | 1·1 | 20·6 | 1·4 | 1·9 | 8·1 | 1·2 | 2·5 | 21·3 | 0·2 | 0·2 | 35·7 | 4·9 | 4·6 |
| Spain (Bilbao) | 3,379 | 19·0 | 3·1 | 4·8 | 29·9 | 4·8 | 6·4 | 9·6 | 2·2 | 5·9 | 26·9 | 2·8 | 3·0 | 35·3 | 8·9 | 8·6 |
| Spain (Cartagena) | 3,437 | 10·2 | -0·3 | -0·5 | 14·9 | 2·3 | 3·4 | 4·1 | 0·1 | 0·3 | 13·9 | -0·8 | -0·9 | 23·6 | -2·8 | -3·0 |
| Region total | 10,278 | 15·2 | 1·4 | NA | 21·7 | 3·1 | NA | 7·3 | 1·3 | NA | 20·7 | 1·0 | NA | 31·5 | 4·0 | NA |
| South-East Asia and Western Pacific | | | | | | | | | | | | | | | | |
| India (Bikaner) | 2,702 | 2·4 | -3·2 | -3·2 | 3·5 | -0·7 | -1·1 | 1·6 | -0·9 | -1·7 | 8·7 | -0·1 | -0·1 | 22·5 | -2·5 | -2·4 |
| India (Chandigarh) | 3,000 | 2·5 | -1·9 | -5·6 | 1·2 | -1·7 | -5·0 | 0·7 | -1·2 | -5·8 | 10·4 | 3·2 | 2·2 | 39·1 | 7·8 | 3·8 |
| India (Jaipur) | 3,060 | 6·8 | 0·8 | 1·1 | 6·2 | 0·2 | 0·3 | 2·1 | -0·5 | -1·6 | 9·8 | 3·3 | 5·9 | 45·8 | 11·4 | 8·2 |
| India (Kottayam) | 2,091 | 4·4 | -7·1 | -5·9 | 4·3 | -3·0 | -2·0 | 1·5 | -5·0 | -4·1 | 4·8 | -4·5 | -4·1 | 17·3 | -7·6 | -5·0 |
| India (Lucknow) | 2,969 | 1·6 | -2·6 | -4·6 | 1·3 | -1·2 | -2·6 | 0·8 | -1·2 | -3·1 | 9·5 | 2·0 | 1·5 | 22·7 | -4·9 | -1·5 |
| India (New Delhi (7)) | 3,024 | 0·9 | -2·8 | -4·2 | 0·3 | -3·9 | -5·2 | 0·5 | -1·8 | -4·7 | 6·6 | 1·2 | 1·7 | 27·3 | 13·1 | 12·6 |
| India (Pune) | 3,030 | 4·6 | 1·1 | 2·2 | 7·9 | 1·7 | 2·3 | 2·0 | 1·2 | 5.1 | 10·6 | 2·6 | 2·7 | 33·0 | 14·2 | 9·0 |
| New Zealand (Auckland) | 1,885 | 14·9 | -4·6 | -3·4 | 22·6 | -3·2 | -3·0 | 5·1 | -2·2 | -3·6 | 22·7 | -5·8 | -5·2 | 24·9 | -3·6 | -2·6 |
| Taiwan (Taipei) | 3,474 | 9·2 | 1·4 | 2·9 | 14·2 | -1·7 | -2·7 | 3·3 | 0·7 | 2·7 | 25·0 | 3·6 | 4·8 | 27·7 | 9·6 | 13·5 |
| Thailand (Bangkok) | 3,206 | 12·5 | -0·9 | -0·7 | 8·8 | -4·4 | -5·9 | 5·8 | -0·4 | -0·6 | 14·8 | -2·0 | -1·4 | 30·0 | -0·7 | -0·2 |
| Region total | 28,441 | 5·8 | -2·1 | NA | 6·7 | -2·5 | NA | 2·3 | -1·2 | NA | 12·4 | -0·1 | NA | 29·7 | 4·3 | NA |
| World total | 72,427 | 10·4 | -0·7 | NA | 11·0 | -0·3 | NA | 4·9 | -0·2 | NA | 18·2 | 1·2 | NA | 30·3 | 3·2 | NA |

The Athens centre is not presented because its ISAAC data are from Phase I alone. NA=not applicable. Methodology notes for centres with GAN Phase I data alone are the following: no date of birth on the questionnaire (Ibadan, Taipei); response rate lower than 80% (Costa Rica, Cartagena); age and birth date showed high inconsistencies (Quito); fewer than ten schools used when ten or more schools were available (Ciudad Victoria, Mexico City [north area], Toluca Urban Area, Auckland, Bangkok); only age was reported reliably (Monterrey); single data entry (Monterrey); no age on the questionnaire (Chandigarh, New Delhi); questionnaires completed at home by parents (Kottayam); and more than 20% of questionnaires missing age and date of birth (Bangkok).

*GAN Phase I. †ISAAC Phase III to GAN Phase I.

*Table 5.3 12-month prevalence of asthma symptoms and absolute change per decade for the 6-7-years age group in each study centre*

| Country (centre) | Number of individuals* | Wheeze in past 12 months | | | Asthma ever | | | Severe asthma symptoms in past 12 months | | | Exercise wheeze in past 12 months | | | Night cough in past 12 months | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change | Prevalence, %* | Absolute change per decade, %† | SE change |
| Africa and Eastern Mediterranean | | | | | | | | | | | | | | | | |
| Syrian Arab Republic (Lattakia) | 1,116 | 10·8 | 3·8 | 5·1 | 11·9 | 4·9 | 5·2 | 5·4 | 1·7 | 3·2 | 11·6 | 5·5 | 6·7 | 29·1 | 8·6 | 4·4 |
| Region total | 1,116 | 10·8 | 3·8 | NA | 11·9 | 4·9 | NA | 5·4 | 1·7 | NA | 11·6 | 5·5 | NA | 29·1 | 8·6 | NA |
| America | | | | | | | | | | | | | | | | |
| Costa Rica (whole country) | 1,936 | 23·2 | -9·0 | -7·5 | 29·3 | 0·9 | 0·6 | 13·2 | -3·2 | -4·1 | 12·2 | -3·0 | -3·5 | 45·9 | 5·6 | 5·5 |
| México (Ciudad Victoria) | 2,444 | 11·7 | 2·4 | 3·9 | 6·5 | 1·4 | 2·5 | 5·8 | 1·8 | 4·4 | 10·0 | 4·5 | 7·1 | 22·7 | -4·6 | -4·3 |
| México (Mexicali) | 2,001 | 14·0 | 3·9 | 5·7 | 7·5 | -0·2 | -0·4 | 7·6 | 3·3 | 5·9 | 14·8 | 7·0 | 10·3 | 23·0 | -3·4 | -2·8 |
| México (México City (North Area)) | 2,515 | 10·6 | 2·8 | 4·2 | 5·1 | 0·5 | 1·0 | 4·3 | 1·5 | 4·1 | 9·1 | 4·2 | 7·5 | 19·8 | -7·9 | -5·6 |
| México (Toluca Urban Area) | 2,712 | 6·4 | 0·4 | 0·4 | 3·4 | 1·0 | 2·6 | 2·9 | 0·7 | 1·4 | 6·5 | 2·2 | 3·2 | 18·0 | -0·6 | -0·5 |
| Nicaragua (Managua) | 3,162 | 12·2 | -3·0 | -3·0 | 14·0 | -1·8 | -1·9 | 5·9 | -2·1 | -3·2 | 7·9 | -4·9 | -5·9 | 32·5 | -7·2 | -3·7 |
| Region total | 14,770 | 12·5 | -1·5 | NA | 10·4 | -0·4 | NA | 6·3 | -0·3 | NA | 9·7 | 0·8 | NA | 26·5 | -3·4 | NA |
| Europe | | | | | | | | | | | | | | | | |
| Spain (A Coruña) | 3,407 | 11·0 | -1·3 | -2·3 | 9·7 | -2·6 | -4·5 | 4·4 | -0·2 | -0·4 | 4·9 | -0·8 | -2·0 | 30·9 | 4·8 | 5·1 |
| Spain (Bilbao) | 2,707 | 10·9 | -0·9 | -1·4 | 22·7 | 1·2 | 1·4 | 4·1 | 0·2 | 0·4 | 6·4 | -0·1 | -0·3 | 27·8 | 4·2 | 5·0 |
| Spain (Cartagena) | 3,509 | 11·7 | 0·5 | 0·9 | 10·3 | -0·3 | -0·6 | 4·4 | 0·2 | 0·4 | 6·1 | 0·7 | 1·7 | 27·4 | 4·7 | 5·6 |
| Region total | 9,623 | 11·2 | -0·6 | NA | 13·6 | -1·1 | NA | 4·3 | 0·1 | NA | 5·7 | -0·1 | NA | 28·7 | 4·6 | NA |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| South-East Asia and Western Pacific | | | | | | | | | | | | | | | | |
| India (Jaipur) | 2,296 | 2·4 | -2·0 | -2·1 | 2·2 | -2·2 | -2·3 | 0·8 | -1·7 | -2·0 | 2·5 | -0·6 | -0·5 | 19·9 | -2·9 | -2·3 |
| India (Kottayam) | 2,099 | 5·5 | -11·3 | -13·4 | 3·5 | -5·2 | -3·7 | 2·9 | -5·3 | -4·8 | 1·8 | -7·1 | -6·2 | 20·9 | -0·3 | -0·2 |
| India (Lucknow) | 2,969 | 1·1 | -1·5 | -3·3 | 0·6 | -1·1 | -3·7 | 0·5 | -0·6 | -2·7 | 1·9 | 0·2 | 0·6 | 6·7 | -5·7 | -5·0 |
| India (New Delhi (7)) | 2,516 | 3·5 | -1·6 | -2·6 | 0·4 | -3·9 | -5·7 | 0·8 | -1·1 | -5·8 | 2·7 | -0·2 | -0·6 | 22·9 | 9·8 | 7·8 |
| India (Pune) | 2,404 | 2·1 | -1·2 | -3·4 | 1·8 | -1·0 | -3·6 | 0·7 | 0·4 | 4·1 | 4·4 | 0·8 | 1·7 | 19·8 | 5·0 | 5·3 |
| New Zealand (Auckland) | 1,538 | 17·4 | -3·1 | -3·6 | 19·2 | -5·5 | -4·5 | 6·7 | -2·0 | -3·4 | 12·0 | -2·1 | -2·3 | 24·8 | -2·7 | -2·7 |
| Taiwan (Taipei) | 3,036 | 13·6 | 2·4 | 4·2 | 14·5 | 0·1 | 0·2 | 3·7 | 1·0 | 3·7 | 6·9 | 1·3 | 3·8 | 32·8 | 7·4 | 14·7 |
| Thailand (Bangkok) | 3,067 | 14·6 | -0·2 | -0·3 | 6·1 | -2·9 | -4·2 | 6·8 | 0·9 | 1·9 | 3·0 | -1·7 | -3·6 | 24·2 | -4·2 | -5·1 |
| Region total | 19,925 | 7·4 | -2·5 | NA | 5·6 | -3·4 | NA | 2·8 | -1·0 | NA | 4·1 | -1·3 | NA | 21·4 | 0·5 | NA |
| World total | 45,434 | 9·9 | -1·5 | NA | 9·0 | -1·6 | NA | 4·3 | -0·5 | NA | 6·4 | -0·2 | NA | 24·8 | 0·5 | NA |

The Chandigarh centre is not presented because its ISAAC data are from Phase I alone. NA=not applicable. Methodology notes for centres with GAN Phase I data alone are the following: response rate lower than 70% (Costa Rica, Bilbao, Cartagena, Kottayam, Auckland); no date of birth on the questionnaire (Taipei); no age on the questionnaire (New Delhi); fewer than ten schools used when ten or more schools were available (Bangkok); and more than 20% of questionnaires missing age and date of birth (Bangkok).
*GAN Phase I. †ISAAC Phase III to GAN Phase I.

*Table 5.4 Model results of estimated change in all asthma related outcomes over 10 years*

| Strata | | Outcome | | | | | N* in strata |
|---|---|---|---|---|---|---|---|
| | | Current wheeze | Severe asthma symptoms | Exercise wheeze | Night cough | Asthma ever | |
| **Model stratified by age group** | | | | | | | |
| Age 6-7 years | | -0·22 (-1·00, 0·57) | -0·24 (-0·63, 0·15) | 0·78 (-0·31, 1·87) | 3·21 (1·80, 4·62) | 0·56 (-0·13, 1·24) | 161 |
| Age 13-14 years | | -0·43 (-1·10, 0·23) | -0·37 (-0·69, -0·04) | 0·34 (-0·58, 1·26) | 4·25 (3·06, 5·44) | 1·25 (0·67, 1·83) | 255 |
| **Model stratified by age group and income group** | | | | | | | |
| Age 6-7 years | Low income | -1·37 (-2·47, -0·27) | -0·84 (-1·37, -0·30) | -0·02 (-1·54, 1·50) | 3·33 (1·34, 5·32) | -1·56 (-2·48, -0·65) | 31 |
| | Lower-middle income | 1·99 (0·33, 3·66) | 1·32 (0·51, 2·12) | 3·66 (1·36, 5·96) | 5·29 (2·28, 8·29) | 0·06 (-1·33, 1·44) | 15 |
| | Upper-middle income | 0·50 (-0·82, 1·82) | 0·20 (-0·44, 0·84) | 1·66 (-0·17, 3·48) | 1·41 (-0·98, 3·80) | 1·19 (0·09, 2·28) | 43 |
| | High income | -0·22 (-1·24, 0·80) | -0·39 (-0·88, 0·11) | 0·25 (-1·16, 1·66) | 3·48 (1·63, 5·32) | 2·07 (1·22, 2·92) | 72 |
| Age 13-14 years | Low income | -1·67 (-2·70, -0·64) | -1·03 (-1·53, -0·53) | -0·58 (-2·00, 0·85) | 4·31 (2·45, 6·17) | -0·84 (-1·70, 0·02) | 47 |
| | Lower-middle income | 1·69 (0·13, 3·25) | 1·13 (0·37, 1·88) | 3·10 (0·95, 5·25) | 6·26 (3·46, 9·07) | 0·78 (-0·52, 2·08) | 40 |
| | Upper-middle income | 0·19 (-1·06, 1·45) | 0·01 (-0·60, 0·62) | 1·10 (-0·63, 2·83) | 2·38 (0·12, 4·65) | 1·91 (0·86, 2·95) | 62 |
| | High income | -0·52 (-1·47, 0·43) | -0·58 (-1·04, -0·12) | -0·31 (-1·62, 1·00) | 4·45 (2·73, 6·17) | 2·79 (2·00, 3·58) | 106 |
| **Model stratified by age group and grouped region** | | | | | | | |
| Age 6-7 years | Africa and Eastern Mediterranean | 2·61 (0·76, 4·46) | 1·46 (0·57, 2·35) | 4·99 (2·41, 7·57) | 6·64 (3·28, 9·99) | 0·21 (-1·38, 1·79) | 10 |
| | America | 0·01 (-1·29, 1·31) | 0·13 (-0·50, 0·76) | 1·23 (-0·56, 3·03) | 1·43 (-0·92, 3·77) | 0·88 (-0·24, 1·99) | 29 |
| | Europe† | 1·08 (-0·08, 2·24) | 0·43 (-0·13, 0·99) | 1·60 (-0·01, 3·21) | 4·67 (2·57, 6·78) | 2·73 (1·74, 3·73) | 64 |
| | South-East Asia and Western Pacific | -1·35 (-2·28, -0·41) | -0·96 (-1·41, -0·51) | -0·33 (-1·64, 0·98) | 2·71 (1·01, 4·42) | -0·69 (-1·49, 0·11) | 58 |
| Age 13-14 years | Africa and Eastern Mediterranean | 2·09 (0·40, 3·78) | 1·15 (0·33, 1·96) | 4·15 (1·80, 6·51) | 7·41 (4·34, 10·47) | 0·78 (-0·68, 2·23) | 34 |
| | America | -0·51 (-1·73, 0·71) | -0·19 (-0·77, 0·40) | 0·39 (-1·29, 2·07) | 2·20 (0·00, 4·40) | 1·45 (0·40, 2·50) | 50 |
| | Europe† | 0·56 (-0·51, 1·63) | 0·11 (-0·40, 0·63) | 0·76 (-0·73, 2·25) | 5·45 (3·50, 7·39) | 3·30 (2·38, 4·22) | 100 |
| | South-East Asia and Western Pacific | -1·87 (-2·78, -0·96) | -1·28 (-1·72, -0·84) | -1·17 (-2·44, 0·10) | 3·49 (1·83, 5·14) | -0·12 (-0·90, 0·66) | 71 |

Data are absolute percentage points difference (95% CI). Results from mixed model with random intercepts for country and centre, incorporating effect modification, fully adjusted for age group, income group, and grouped region (n=416).

*N=number of surveys contributing to each stratified analysis.

†Malta was in ISAAC's Eastern Mediterranean region but has been moved to the European region in modelling for this analysis.

After stratifying by age group, adolescents showed a decrease in percentage point prevalence per decade of severe asthma symptoms and an increase in ever having asthma and night cough, which was also found in children (Table 5.4). Stratification by country income group (adjusted for region) showed a decrease in prevalence of current wheeze among low-income countries in both age groups. However, we found an increase in prevalence of current wheeze among both age groups in lower-middle-income countries, but no change in upper-middle-income and high-income countries (Table 5.4). Stratification by world region (adjusted for income group) showed an increase in prevalence of current wheeze in the Africa and Eastern Mediterranean region for both age groups, whereas the Southeast Asia and Western Pacific regions showed decreased prevalence of current wheeze (Table 5.4). We observed no evidence of a change in prevalence for the regions of America and Europe in either age group. We assessed nine strata across two age groups and five symptom outcomes, but not all of these are statistically independent. Within-centre trends in prevalence of related symptoms, and of a given symptom across age groups, might be correlated.

The results of the models for the other four outcome variables showed that the pattern for prevalence of severe asthma symptoms and exercise wheeze was similar to that of current wheeze (Table 5.4). However, ever having asthma showed a different pattern, with increases in high-income countries and Europe. For night cough, we found a consistent pattern of increase in point prevalence in both age groups, all country income groups, and most regions.

### 5.2.5 Discussion

To our knowledge, GAN Phase I has provided the first standardised global estimates of trends over time in prevalence and severity of asthma symptoms in school-aged children since 2003. The study included almost 120,000 children from 27 centres in 14 countries using the same instruments and methods as ISAAC.[4,21] We identified a substantial burden of asthma symptoms in school-aged children: in both age groups, about one in ten had wheeze in the preceding year, of whom almost half had severe symptoms. We modelled all ISAAC Phases I and III and GAN Phase I prevalence data over time to determine patterns of change over nearly three decades (1993-2020) and found prevalence and severity to vary by age group, country income, region, and centre.

We observed change in prevalence of all asthma symptoms by 2 SE or more in most centres, suggesting more than just random variation. In seven countries, we found a decrease in prevalence of most asthma symptoms, whereas increases were found in seven countries.

There is evidence from the 27-year modelling of an overall decrease in prevalence for severe asthma symptoms in adolescents and an overall increased report of ever having asthma and night cough in both age groups. We also found regional differences, with evidence of increasing prevalence of current wheeze and severe asthma symptoms in Africa and Eastern Mediterranean and decreasing mean prevalence in Southeast Asia and Western Pacific regions. Country income was associated with changes in prevalence of asthma symptoms, with low-income countries showing a significant decrease but lower-middle-income countries showing an increase, with no evidence of change in more affluent countries. These broad patterns overlie a substantial heterogeneity of trends both between and within countries. This limits the generalisability of conclusions from any single centre or country.

The interpretation of these patterns is complex because a wide range of risk factors exists and environmental changes are at play. Some centres had changes of particular interest. For example, large variations were found within India, and the reasons for this are subject to a national study. A few centres with high prevalence saw a progressive decrease from ISAAC Phases I to III[54,102] to GAN Phase I. Some low-prevalence centres showed increased prevalence of asthma symptoms, including severe asthma symptoms, contributing to the burden of asthma. A large increase in prevalence was found in Lattakia, in war-torn Syria. In two centres (Cape Town and Bilbao), the increase in prevalence of severe asthma symptoms was more than that of asthma symptoms; whether this is due to barriers to asthma care remains to be investigated. The influence of asthma programmes, accessibility of asthma medicines, or other environmental changes[58] on these variations needs to be determined. National asthma programmes can be effective ways of reducing the burden of severe asthma symptoms: Costa Rica, India, and Taiwan reported national asthma strategies in 2013-14,[109] which might be a factor in the decreased burden in Costa Rica and India, but not in Taiwan. The role of macro-environmental changes affecting populations is worthy of exploration.

The Global Burden of Disease Study (GBD) has reported estimates of global asthma prevalence (for all ages) over a similar period as this analysis. The GBD case definition for asthma differed from ours in that it was a reported diagnosis by a physician (which varies between countries) combined with wheezing in the preceding 12 months. The GBD estimates over 2000-17 showed large and unexplained variations between 220·4 and 339·4 million people.[97,110-115] Since 2003, no new worldwide standardised studies of asthma symptom prevalence were done until GAN Phase I, which also included additional 36 centres in 11 countries that did not undertake ISAAC, not included in this Article, and should contribute to future GBD analyses.

Our study has many strengths, especially the standardised methods used to estimate asthma prevalence from symptoms in a wide range of settings in the world.[101] Tight quality control checks along with the same key personnel in ISAAC and GAN meant that replication of the standardised methods from ISAAC Phase I to Phase III to GAN Phase I was successful, as evidenced by the low number of centres excluded or with footnotes related to the methods. Response rates were high. The study includes many centres from low-income, middle-income, and high-income countries from all regions of the world except North America. In about half of the centres, GAN Phase I was the first paired standardised study of asthma symptom prevalence; these included centres in five countries with no previous time-trend data (centres in Ecuador, Greece, Nicaragua, Sudan, and Syria), and nine centres that had no previous time-trend data (although different centres in those countries had provided ISAAC time-trend data).[102]

Our study has some limitations, which include the smaller number of GAN Phase I centres compared with that of ISAAC Phase I to Phase III, which makes it difficult to generalise the findings to global prevalence changes. Centres were self-selecting, and thus not representative of countries except for Costa Rica, which was a whole country study. Within an individual country, wide differences of prevalence can occur such as rural versus urban locations and high-income areas in a low-income or middle-income country. Despite the simplicity of the GAN and ISAAC approach, these surveys are more difficult to undertake now than at the time of ISAAC Phases I and III. Factors that increase this difficulty include reluctance of schools to being involved in research due to increased curriculum demands; more stringent ethical requirements, meaning that obtaining passive consent for adolescents is less easy than in previous decades[106]; funders not prioritising population-based research; parents being busier and having less time for participation; and epidemics or pandemics (currently COVID-19) and conflicts that disrupt schools and people's lives.

Future GAN Phase I reports will contribute an estimate of the global burden of asthma, which will include the GAN Phase I centres in this Article as well as centres without time-trend data, and analyses in children and adolescents assessing rhinoconjunctivitis and eczema and other asthma risk factors, similar to ISAAC Phase III reports, as well as studies in adults. Extensive risk factor analyses were undertaken in ISAAC Phase III.[80,116] Equivalent analyses will be undertaken with use of GAN Phase I data in conjunction with ISAAC Phase III data to determine to what extent changes in risk factor prevalences over time can account for the observed changes in prevalence and severity of asthma symptoms. We will also examine the relationship of management of asthma and symptoms. Abundant evidence exists that in many locations in the

world, asthma management is suboptimal, contributing to a relatively high prevalence of severe asthma symptoms,[58,98] and there are strategies to improve this even in localities within low-resource settings.[58,117] As the legacy of severe asthma in childhood can be chronic obstructive pulmonary disease in adults, reducing the burden of severe asthma symptoms in children is of crucial importance.[97]

These data suggest that, while the overall worldwide prevalence of asthma symptoms is relatively stable, about one in 20 school-aged children have severe asthma symptoms, and they need to gain better asthma control to lessen the associated avoidable asthma morbidity and mortality; little has changed over 27 years. The UN 2030 Sustainable Development Goal 3 aims to "ensure healthy lives and promote wellbeing at all ages".[58] Our findings emphasise the urgency of ensuring that the high worldwide burden of severe asthma symptoms in children is mitigated by enabling equitable and affordable access to the effective therapies for asthma that have been available to those who can afford them for decades.

# 6 Risk factors for time trends in prevalence of asthma symptoms

## Summary

This chapter considers centre-level risk factor associations with asthma symptoms, using those risk factors identified at the individual level in Section 3.2.

In the first part, the risk factors are considered at a single time point (ISAAC Phase III), and associations are estimated between these risk factors and the centre-level asthma symptom prevalences.

The second part incorporates ISAAC Phase I and GAN Phase I data to assess whether the centre-level (ISAAC Phase III) prevalence of risk factors can explain either the centre-level prevalence of asthma symptoms (in ISAAC Phase III) or time trends in prevalence across the three surveys.

## 6.1 Introduction

Section 3.2 found individual-level risk factors that were associated with an increased or decreased risk of experiencing asthma symptoms. Assessing whether these same risk factors may affect time trends in prevalence is more complex since the data does not include information from the same children (or even schools) at different time points. Not only is this information not available, but it is also not appropriate, since the participants in ISAAC Phase I (for example), were considerably older at the time of ISAAC Phase III and GAN Phase I, and prevalence of asthma symptoms varies by age as well as time. Therefore, assessing time trends requires estimating the prevalence of asthma symptoms in groups of children and adolescents of the same age at different points in time. Thus centre-level prevalence of risk factors and asthma symptoms is used (separate for each age group). Thus an ecological analysis is presented here, that assesses risk factors for time trends at the population (centre) level, and not at the individual level.

There are different forms for an ecological analysis. The first possibility is to consider simply the effect of risk factors on prevalence at one time-point. i.e. similar to the analysis in Section 3.2 using ISAAC Phase III data, but here using centre-level as opposed to individual and school-level prevalence of outcome and exposures. This assesses whether the risk factors previously identified at individual- and school-level are also associated with symptom prevalence at the centre-level. The associations may be quite different at the centre-level compared with the individual-level findings. For example, a very strong individual-level risk factor that has the same prevalence across all centres would not show an effect at the ecological level.[118]

The above analysis only uses asthma symptom prevalence data from one time-point along with risk factor data from one time-point (in this case the same time-point). The second form of ecological analysis still considers risk factors at one time-point, but within a time trend model of asthma symptom prevalence (centre-level longitudinal analysis but with risk factors not time varying). This can identify associations between risk factors and the change in prevalence of symptoms at the centre level. For the purpose of these analyses, the risk factor data from ISAAC Phase III was used, because this is roughly the mid-point of the studies and includes the largest number of centres with risk factor data.

A third form of ecological analysis would use risk factor data specific to each time point, to model the associations with time trends in symptom prevalence (centre-level longitudinal with time-varying risk factor covariates). However, this method requires measures of risk factor prevalence (as well as outcome prevalence) in each centre at multiple time-points. In ISAAC Phase I there were no risk factor data, and the overlap between ISAAC Phase III and GAN Phase I centres is quite small. Such an analysis would be based on only 26 centres which would be underpowered to detect most associations. Therefore, this method is not considered further in this thesis. There are other methods for assessing time trends for example directly modelling the change in prevalence of asthma symptoms and the change in risk factors, but these also require centres with multiple values in order to calculate the change.

In summary, the intention of this chapter is to assess at the ecological (centre) level whether:

i) the prevalence of a risk factor in a centre is associated with the prevalence of asthma symptoms at the same point in time (ISAAC Phase III); and

ii) the prevalence of a risk factor in a centre (ISAAC Phase III) is associated with a change in prevalence of asthma symptoms (ISAAC Phase I, ISAAC Phase III, GAN Phase I).

## 6.2 Association between centre-level risk factor prevalence and asthma symptom prevalence in ISAAC Phase III

### 6.2.1 Methods

The same risk factors used in the paper on asthma symptoms in Section 3.2 were considered for this analysis (details in Table 3.1). For a centre's risk factor prevalence to be included in the analysis there was a requirement that at least 70% of respondents in the respective age group gave a valid answer for the question on that particular risk factor (i.e. a question specific response rate of $\geq$70%).

Each risk factor prevalence was defined as the number of respondents answering positively to the relevant question divided by the number of respondents with a valid (non-missing) response. Asthma symptom prevalence (the outcome) was an exception and was defined as the number of respondents answering positively divided by the total number of respondents. (This is to remain consistent with other published centre-level results; a missing value to a question on symptoms was taken to mean a negative response given that questionnaires with no answers to any symptom questions were excluded from the original study data).

Plots and summary statistics of the centre-level risk factor prevalences were checked for outliers and to quantify whether the distribution of prevalence values was sufficiently variable to allow discrimination between centres. Those risk factors with an IQR smaller than 5% were removed from further analyses. Then a simple ecological analysis was run, to identify associations between risk factor prevalence and asthma symptom prevalence in ISAAC Phase III (for comparison to the individual- and school-level results from Section 3.2). This involved a change from a hierarchical dataset of hundreds of thousands of individuals down to a dataset of hundreds of centres. Simple linear regression models were fitted, adjusted for country income group and region. The risk factors were scaled to show the effect of 10 percentage point increments in prevalence as this is a meaningful level of difference between centres, the same as that used in the paper in Chapter 5. Mixed-effects models with country as a cluster level were considered but many of the clusters only contained one record as there were a high number of countries with only one centre. This means a small amount of dependency may be included in the model between centres in the same country. Separate models were fitted for each age group due to the different risk factor information available (early-life risk factors were only on the children's questionnaire). Minimally adjusted models (adjusting for an

individual risk factor plus country income group and region) were fitted for each risk factor in turn in both a "maximum sample" (all centres with valid prevalence for that risk factor) and the "common sample" (centres with valid prevalence for all risk factors in that age group). Then fully adjusted models were fitted, adjusting for all risk factors for that age group plus income group and region. For comparability with the older age group, partially adjusted models were also fitted to the younger age group, adjusting separately for all current risk factors and all early-life risk factors. Analyses of both age groups were checked for collinearity between pairs of risk factors.

### 6.2.2 Results

**Descriptive results**

Valid prevalence was available for at least one risk factor for 121 of the 233 ISAAC Phase III centres for adolescents and 75 of the 144 centres for children (Figure 6.1). The main reason for the drop in numbers is that the questionnaire on risk factors was optional (in addition to the symptom questionnaire) and only around half of centres completed it. Median and inter-quartile range (IQR) for each risk factor's centre prevalence, within the maximum sample for that risk factor, are shown in Table 6.1.

*Table 6.1 Median centre prevalence and IQR of current asthma symptoms and risk factors*

| Risk factor | Age 13-14 | | Age 6-7 | |
|---|---|---|---|---|
| | n | Median (IQR) centre prevalence | n | Median (IQR) centre prevalence |
| Current asthma symptoms (outcome) | 121 | 0.10 (0.06, 0.15) | 75 | 0.09 (0.06, 0.15) |
| Current paracetamol use | 114 | 0.30 (0.19, 0.40) | 73 | 0.16 (0.11, 0.28) |
| Current truck traffic | 113 | 0.85 (0.77, 0.90) | 70 | 0.82 (0.75, 0.88) |
| Current regular fast food | 110 | 0.55 (0.44, 0.67) | 68 | 0.41 (0.23, 0.53) |
| Current paternal smoking | 108 | 0.36 (0.25, 0.46) | 73 | 0.30 (0.20, 0.44) |
| Currently maternal smoking | 117 | 0.17 (0.03, 0.28) | 74 | 0.11 (0.03, 0.24) |
| Current open fire cooking | 110 | 0.02 (0.01, 0.05) | 70 | 0.01 (0.00, 0.03) |
| Current frequent TV viewing | 119 | 0.89 (0.83, 0.93) | 74 | 0.82 (0.72, 0.88) |
| Paracetamol in first year | NA | NA | 69 | 0.67 (0.56, 0.81) |
| Antibiotics in first year | NA | NA | 71 | 0.57 (0.51, 0.62) |
| Breastfed ever | NA | NA | 72 | 0.84 (0.76, 0.91) |
| Cat in first year | NA | NA | 71 | 0.09 (0.05, 0.14) |
| Farm animals in first year | NA | NA | 69 | 0.10 (0.07, 0.15) |
| Low birthweight | NA | NA | 63 | 0.06 (0.05, 0.09) |

Open fire cooking and low birthweight were removed from further analysis as they showed very little variability in prevalence between centres. The common sample with valid centre prevalence for all 11 remaining risk factors included 84 centres for 13-14-year-olds and 54 centres for 6-7-year-olds (Figure 6.1).

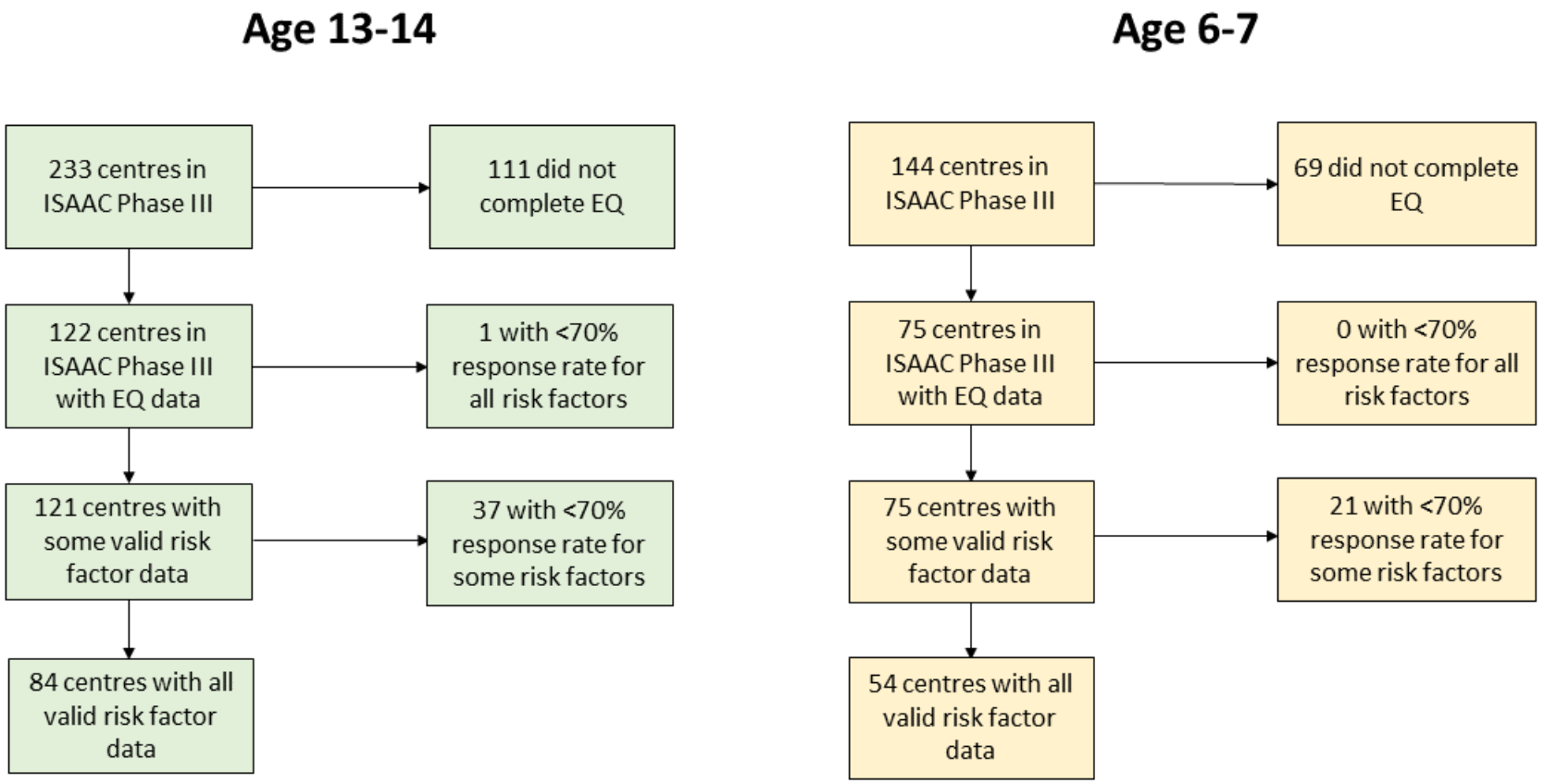



*Figure 6.1 Data flowchart for ISAAC Phase III centre-level risk factor prevalence*

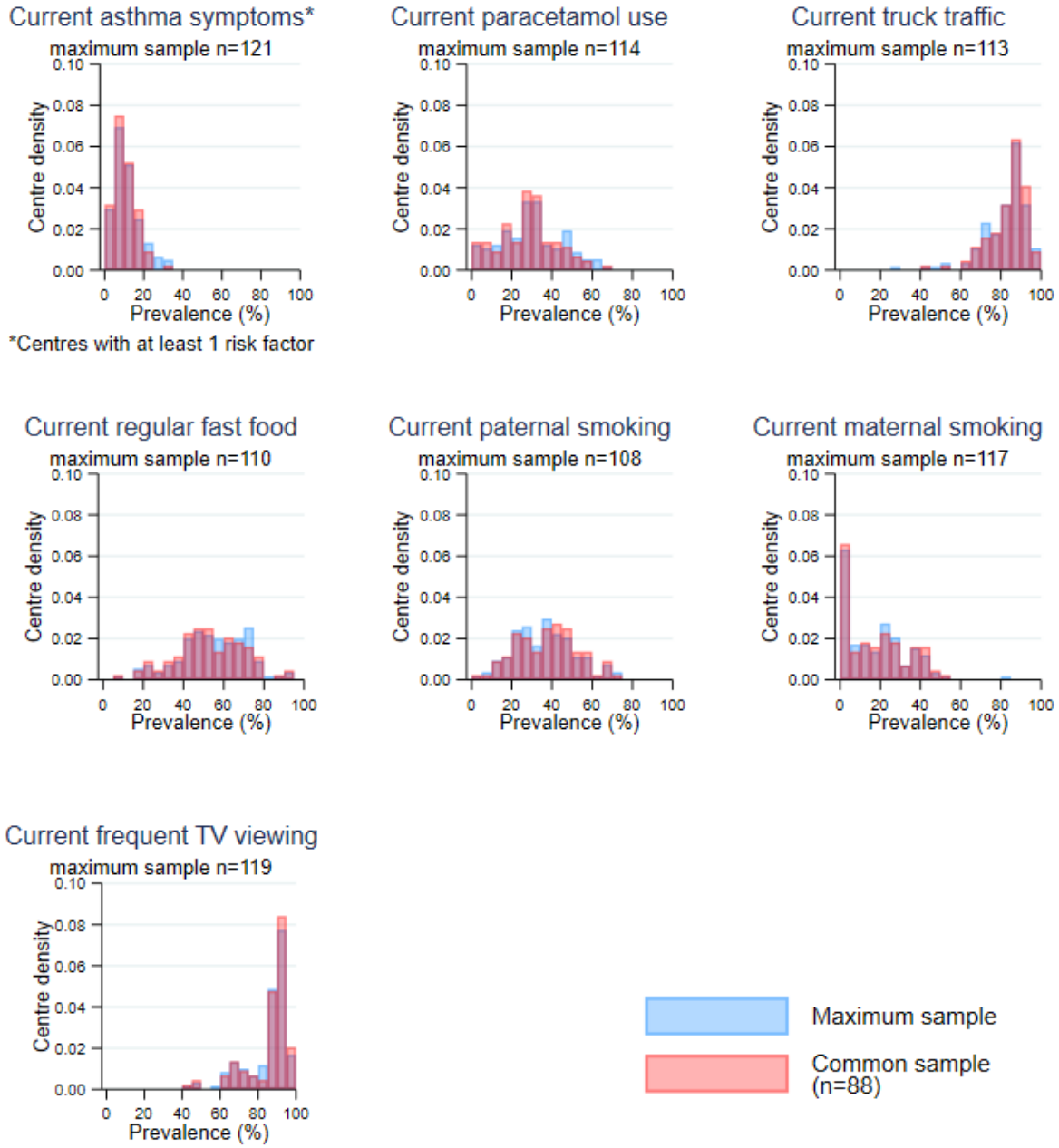



*Figure 6.2 Distribution of outcome and risk factors in ISAAC Phase III for age 13-14*

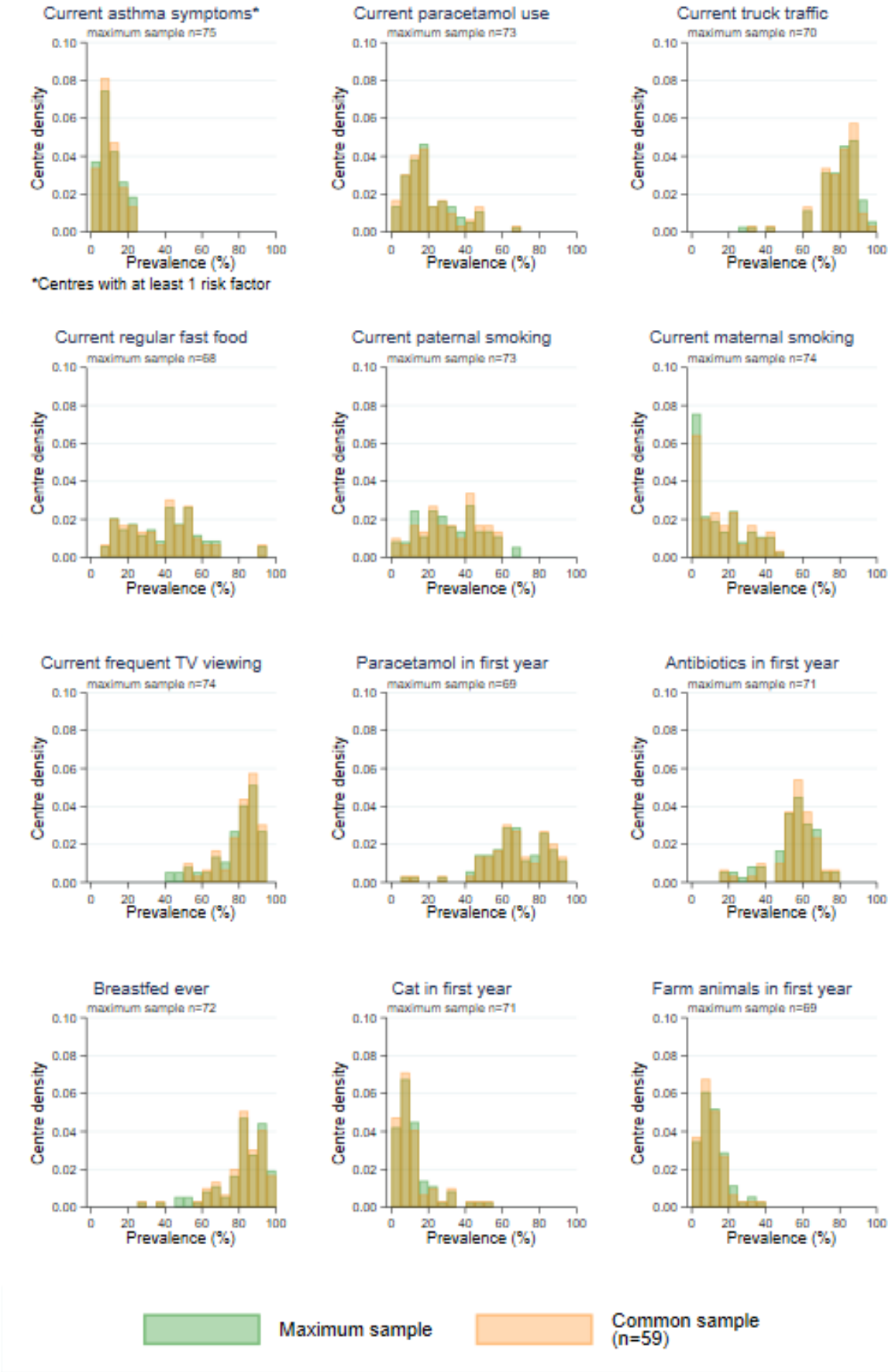



*Figure 6.3 Distribution of outcome and risk factors in ISAAC Phase III for age 6-7*

Histograms of the remaining risk factors, in the maximum and common samples, are shown in Figure 6.2 for 13-14-year-olds and Figure 6.3 for 6-7-year-olds. There was a very slight bias in the common sample towards low asthma symptom prevalence centres in the older age group and to low fast food prevalence centres in both age groups. There was also a very slight bias towards higher prevalence centres for maternal smoking and television viewing in the younger age group. Distributions of other risk factors looked similar between the maximum and common samples across both age groups.

**Associations between risk factors and asthma symptom prevalence**

For the 13-14-year-olds, in the minimally adjusted model on the maximum sample, there was evidence that increased levels of current paracetamol (1.21 percentage point increase per 10% higher paracetamol; 95% CI= 0.42, 2.00), regular fast food (1.11; 0.40, 1.81), maternal smoking (1.03; 0.03, 2.02) and frequent television (2.00; 0.70, 3.29) were associated with higher asthma symptom prevalence and that paternal smoking (-1.51; -2.33, -0.69) was associated with lower asthma symptom prevalence (Table 6.2). However, there were large differences when the common sample was used and only the association with regular fast food remained (0.59; 0.03, 1.16). In the fully adjusted models (adjusted for the other risk factors) there was no evidence that fast food or any other risk factor was associated with higher asthma symptom prevalence (Table 6.2).

For the younger age group, in the minimally adjusted models on the maximum sample there was evidence that paracetamol in the first year (1.44; 0.75, 2.14), antibiotics in the first year (1.18; 0.19, 2.17), cat in the first year (2.40; 1.23, 3.58), current paracetamol (1.82; 0.57, 3.08) and maternal smoking (1.68; 0.31, 3.05) were associated with higher asthma symptom prevalence. There was also evidence that paternal smoking (-1.29; -2.34, -0.24) was associated with lower asthma symptom prevalence (Table 6.2). The same model on the common sample showed evidence that higher prevalence of paracetamol in the first year (1.51; 0.93, 2.08), cat in the first year (1.99; 0.91, 3.07), current paracetamol (1.16; 0.02, 2.31) and regular fast food (0.75; 0.02, 1.48) stayed associated with a higher prevalence of asthma symptoms and paternal smoking with a lower prevalence of asthma symptoms (-1.25; -2.29, -0.21). In the partially adjusted model for current risk factors, there was marginal evidence that higher prevalence of regular fast food (0.67; 0.00, 1.34) and maternal smoking (1.24; 0.01, 2.47) were associated with higher asthma symptom prevalence and paternal smoking (-1.06; -2.64, -0.55) with lower asthma symptom prevalence. In the early life partially-adjusted model there was evidence for only paracetamol in the first year, which was positively associated with asthma symptom prevalence (1.38; 0.47, 2.29). In the fully adjusted models for age 6-7, this

association between paracetamol in the first year and asthma symptom prevalence remained (1.50; 0.43, 2.57) (Table 6.2).

Overall for the younger age group, there was some evidence, in all versions of the models, that higher levels of early-life paracetamol were associated with higher prevalence of asthma symptoms (Table 6.2). However, many of the risk factors identified in the individual-level analysis in Section 3.2 were not associated with increased risks at the ecological centre-level.

Pairwise checks for collinearity resulted in standard errors increasing by a maximum multiple of 1.15 in adolescents and 1.23 in children with the addition of other risk factors, so little or no evidence of collinearity was detected between risk factors (details not shown).[65]

### 6.2.3 Discussion

Generally, the centre-level associations between risk factors and asthma symptom prevalence were quite weak, which is different to the previous findings at the individual- and school-levels. From Section 3.2, the risk factors that showed the strongest associations at the individual-level (within school, centre and country) were current paracetamol (age 13-14: OR = 1.80; 95% CI = 1.75, 1.86, age 6-7: 2.06; 1.97, 2.16), open fire cooking (age 13-14: 1.32; 1.22, 1.43, age 6-7: 1.44; 1.26, 1.65), early-life antibiotics (age 6-7: 1.65; 1.58, 1.73) and early-life paracetamol (age 6-7: 1.33; 1.27, 1.40). Others showed evidence of a small association such as low birthweight, cat in first year, farm animals in first year, truck traffic, regular fast food, and both paternal and maternal smoking. In the school-level analysis from Section 3.2 (within centre, between school effects, based on individual-level outcome), these risk factor associations were still evident, except early-life paracetamol (children only) and paternal smoking.

By contrast, in this chapter's centre-level ecological analysis (of between centre effects), very few associations were evident. In fully adjusted analysis for both age groups, current paracetamol use was not associated with higher prevalence of asthma symptoms. However, for children, also after full adjustment, higher prevalence of asthma symptoms was associated with higher prevalence of paracetamol use in the first year (similar to the individual-level but in contrast to the school-level) but not antibiotics in the first year (in contrast to both the individual- and school-levels). No risk factors were associated with asthma symptoms in the fully adjusted adolescent model.

*Table 6.2 Linear regression models on the association between centre level prevalence of asthma symptoms and risk factors in ISAAC Phase III, adjusting for income group and region.*

| Risk factor (effect per 10 percentage point higher prevalence) | Maximum sample[a] | | Common sample[b] | | | |
|---|---|---|---|---|---|---|
| | n | Minimally adjusted[c] Change in asthma symptom prevalence (95% CI) | n | Minimally adjusted[c] Change in asthma symptom prevalence (95% CI) | Partially adjusted[d] Change in asthma symptom prevalence (95% CI) | Fully adjusted[e] Change in asthma symptom prevalence (95% CI) |
| Age 13-14 | | | | | | |
| Current paracetamol | 114 | 1.21 (0.42, 2.00) | 88 | 0.05 (-0.76, 0.87) | NA | 0.01 (-0.82, 0.84) |
| Current truck traffic | 113 | 0.38 (-0.74, 1.50) | 88 | 0.97 (-0.17, 2.11) | NA | 0.99 (-0.20, 2.18) |
| Current regular fast food | 110 | 1.11 (0.40, 1.81) | 88 | 0.59 (0.03, 1.16) | NA | 0.34 (-0.28, 0.96) |
| Current paternal smoking | 108 | -1.51 (-2.33,-0.69) | 88 | -0.59 (-1.43, 0.25) | NA | -0.58 (-1.55, 0.38) |
| Current maternal smoking | 117 | 1.03 (0.03, 2.02) | 88 | -0.09 (-1.10, 0.92) | NA | 0.14 (-0.92, 1.20) |
| Current frequent television | 119 | 2.00 (0.70, 3.29) | 88 | 0.83 (-0.27, 1.92) | NA | 1.10 (-0.05, 2.25) |
| Age 6-7 | | | | | | |
| Current paracetamol | 73 | 1.82 (0.57, 3.08) | 59 | 1.16 (0.02, 2.31) | 0.47 (-0.63, 1.56) | 0.38 (-0.84, 1.59) |
| Current truck traffic | 70 | 0.40 (-0.68, 1.47) | 59 | -0.01 (-1.05, 1.04) | 0.73 (-0.30, 1.77) | 0.93 (-0.08, 1.93) |
| Current regular fast food | 68 | 0.32 (-0.46, 1.11) | 59 | 0.75 (0.02, 1.48) | 0.67 (0.00, 1.34) | 0.31 (-0.37, 0.99) |
| Current paternal smoking | 73 | -1.29 (-2.34,-0.24) | 59 | -1.25 (-2.29,-0.21) | -1.60 (-2.64, -0.55) | -0.39 (-1.63, 0.84) |
| Current maternal smoking | 74 | 1.68 (0.31, 3.05) | 59 | 1.13 (-0.24, 2.50) | 1.24 (0.01, 2.47) | 1.26 (-0.04, 2.57) |
| Current frequent television | 74 | 0.97 (-0.69, 2.62) | 59 | 1.19 (-0.55, 2.92) | 1.47 (-0.18, 3.13) | 0.49 (-1.25, 2.24) |
| Paracetamol in first year | 69 | 1.44 (0.75, 2.14) | 59 | 1.51 (0.93, 2.08) | 1.38 (0.47, 2.29) | 1.50 (0.43, 2.57) |
| Antibiotics in first year | 71 | 1.18 (0.19, 2.17) | 59 | 0.50 (-0.49, 1.50) | -0.28 (-1.27, 0.71) | -0.62 (-1.68, 0.44) |
| Breastfed ever | 72 | 1.03 (-0.07, 2.13) | 59 | 1.05 (-0.01, 2.12) | -0.12 (-1.30, 1.07) | -0.40 (-1.63, 0.83) |
| Cat in first year | 71 | 2.40 (1.23, 3.58) | 59 | 1.99 (0.91, 3.07) | 0.66 (-0.88, 2.19) | 0.05 (-1.53, 1.63) |
| Farm animals in first year | 69 | 1.67 (-0.06, 3.39) | 59 | 0.29 (-1.48, 2.06) | -0.07 (-1.88, 1.73) | 0.30 (-1.81, 2.40) |

[a] maximum sample includes all centres with valid data for that risk factor
[b] common sample includes all centres with valid data for all risk factors
[c] minimally adjusted for income group and region only
[d] partially adjusted for income group, region and all other current or early life risk factors (above or below the thick line)
[e] fully adjusted for income group, region and all other risk factors in the table

In summary, early-life paracetamol was associated with an increased risk of asthma symptoms in 6-7-year-olds using either individual- or centre-level analysis, but not at the school-level. Current paracetamol is an important risk factor at the individual- and school-levels in both age groups, but not at the centre-level.

These differences could be due to some risk factors at the centre-level acting as a proxy for unmeasured variables, or it could be because a strong individual effect is not reflected at the centre-level, a type of reverse "ecological fallacy", which is where factors that are associated with population prevalences may not be associated with disease in individuals[119]. These differences between findings at the individual-level and the centre-level are clearly important in terms of scientific inference. It is generally assumed that the individual-level analyses will be more valid,[120] although this is not always the case.[80,81,120,121] In the current context, as discussed above, the focus is on whether risk factors may explain differences between centre-level prevalences, or trends over time, so these centre-level analyses are necessary and appropriate. The next section therefore incorporates the other time points of data to assess whether risk factor prevalence at the time of ISAAC Phase III can partially explain changes in centre-level prevalence over time.

## 6.3 Risk factors and time trends

### 6.3.1 Methods

Similar to Chapter 5, multi-level models of the time trends in prevalence of asthma symptoms were fitted, for the centres with more than one time-point, but only those that had risk factor prevalence data from ISAAC Phase III. These models differed from the previously presented time trends analysis (Chapter 5) as the age groups were modelled separately to include different risk factors for each age group. The risk factors incorporated were those used in the previous ecological analysis in Section 6.2.

Each model otherwise used the same format as the previous analyses in Chapter 5, i.e. 3-level mixed-effects linear regression models with random intercepts for country and centre (and the lowest level being data from one time-point). All models were adjusted for income group and region, along with their separate interactions with time trend. Risk factors, both main effect and interaction with time, were included singly for minimally adjusted models and all together for fully adjusted models. In addition, partially adjusted models were used for the younger age group, one containing all the current risk factors and one with all the early-life risk factors.

The time period was centred as at the start of ISAAC Phase III, i.e. 1st Jan 2002. This is similar to the time the risk factor data was captured and means the main effect of a risk factor on asthma prevalence can be interpreted as an effect on the ISAAC Phase III prevalence (also termed the "mid-point prevalence"). This is compared to the interaction effect of a risk factor with time which is interpreted as the effect of that risk factor on the change in asthma symptom prevalence per decade.

All models were run on the common sample of centres with risk factor prevalence data available for all risk factors used in the analysis of the relevant age group.

### 6.3.2 Results

Of the 84 centres with all risk factor data for adolescents (Figure 6.1), there were 50 that were time trends centres. For children 41 out of the 54 were time trends centres. Distributions of the risk factors comparing the time trends centres to all the centres are shown in Figure 6.4 for adolescents and Figure 6.5 for children. No systemic differences were found between the two datasets with regard to the distributions of risk factor prevalence.

For adolescents (Table 6.3), in the minimally adjusted models there was evidence that a 10% increase in prevalence of regular fast food (-0.61 percentage points per decade; 95% CI=-1.14, -0.07) and regular television viewing (-1.14; -2.13, -0.14) were associated with decreasing asthma symptom prevalence. There was also evidence that higher prevalence of truck traffic was associated with high asthma symptom prevalence at the mid-point (1.52; 0.42, 2.61) and weak evidence that higher prevalence of paternal smoking was associated with lower asthma symptom prevalence at the mid-point (-0.90; -1.81, 0.02). In the fully adjusted model, the associations with regular fast food and frequent television disappeared (-0.49; -1.07, 0.10 and -1.08; -2.24, 0.08 respectively) and there was no evidence of any other associations between the risk factors and change in asthma symptom prevalence. Truck traffic was still associated with a higher mid-point asthma symptom prevalence (1.55; 0.49, 2.62) and paternal smoking with a lower asthma symptom prevalence (-1.19; -2.28, -0.11) but no other risk factors showed an association with mid-point prevalence.

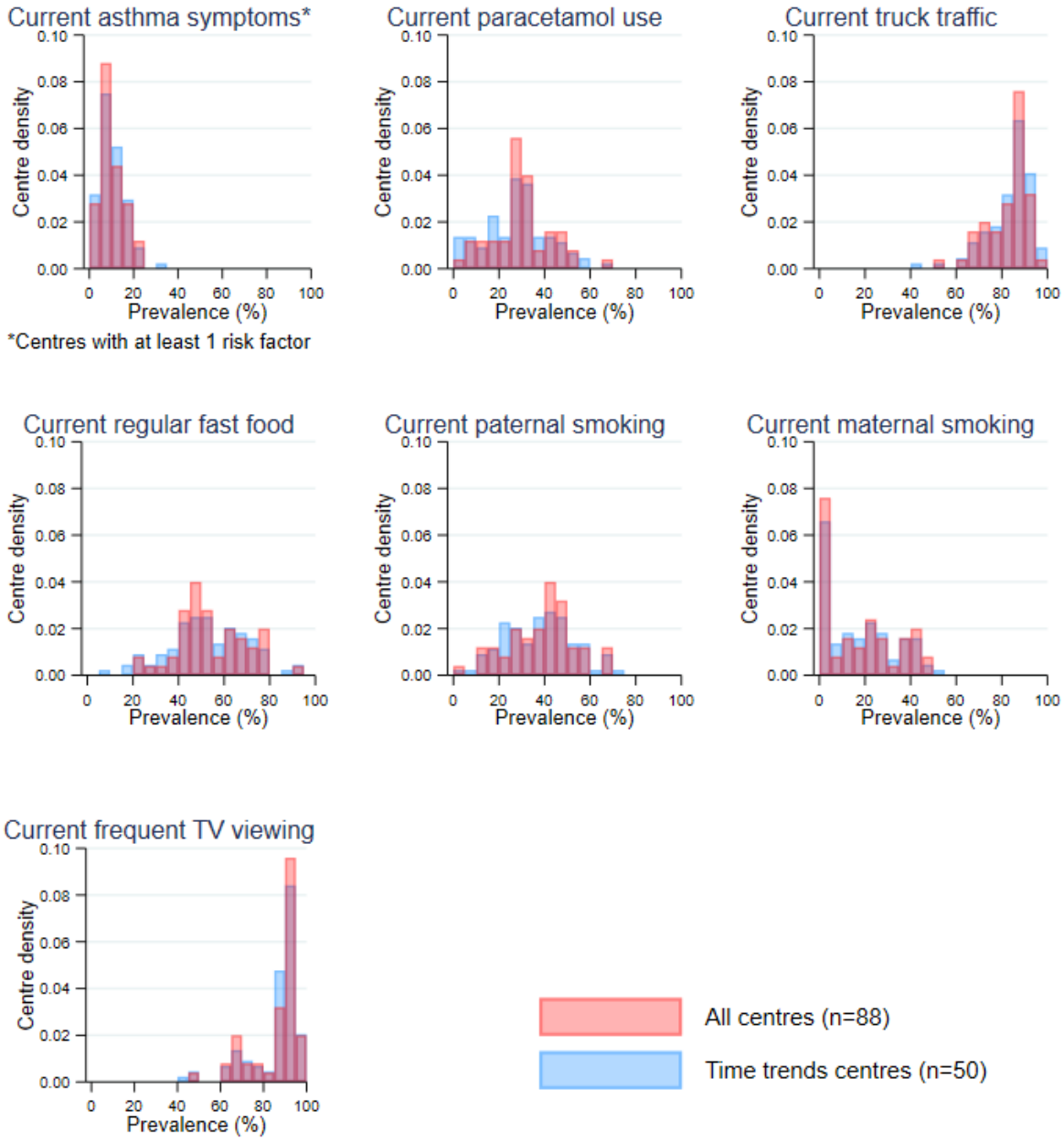



*Figure 6.4 Risk factor distribution in time trends centres and all centres, age 13-14*

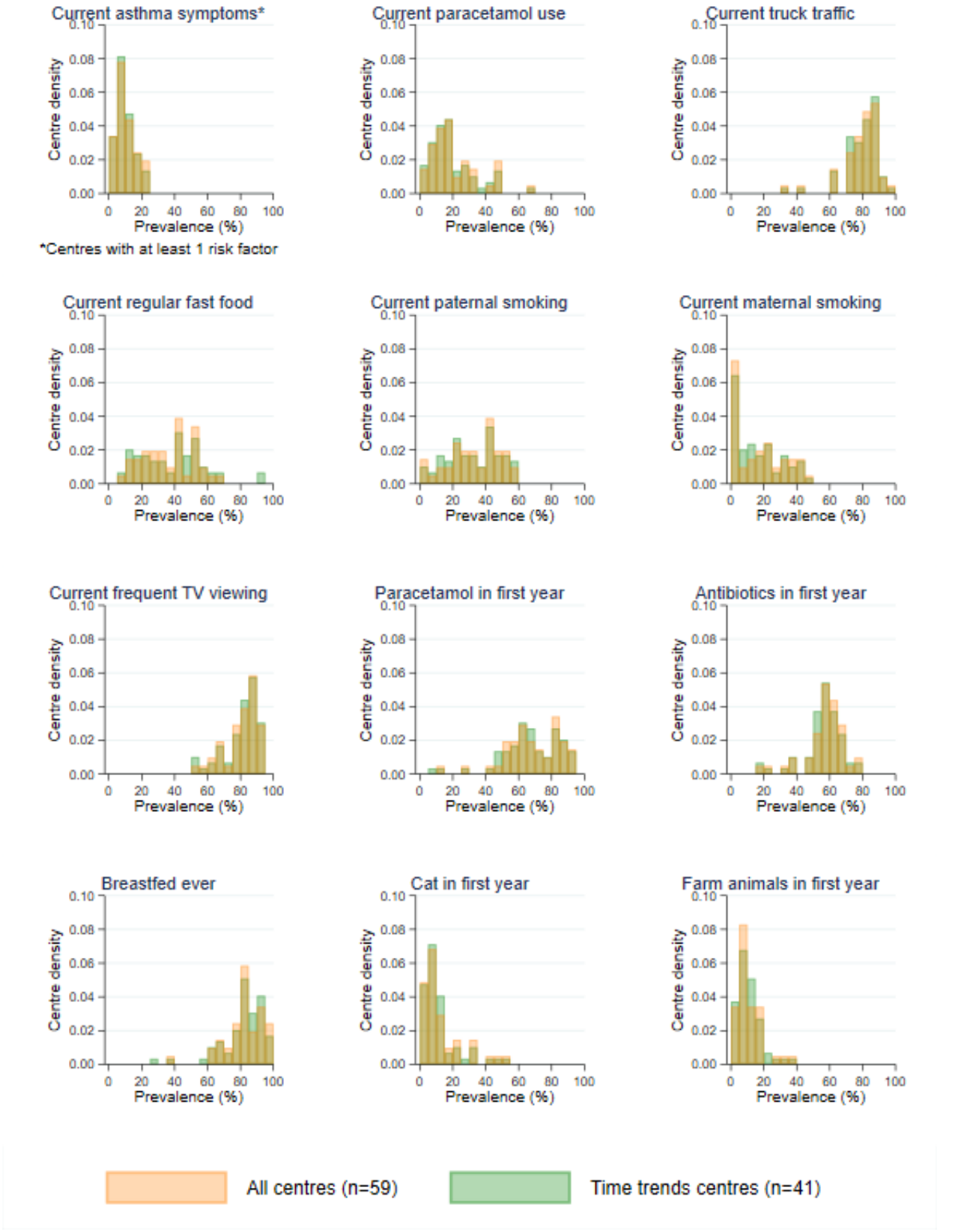



*Figure 6.5 Risk factor distribution in time trends centres and all centres, age 6-7*

*Table 6.3 Risk factor associations with prevalence and time trends of asthma symptoms with random intercepts for centre and country, age 13-14*

| Risk factor (effect of 10 percentage point higher prevalence) | Minimally adjusted[a] models (n=108) | | Fully adjusted[b] model (n=108) | |
|---|---|---|---|---|
| | Effect on asthma symptom prevalence at 1st Jan 2002 (95% CI) | Effect on change in asthma symptom prevalence per decade (95% CI) | Effect on asthma symptom prevalence at 1st Jan 2002 (95% CI) | Effect on change in asthma symptom prevalence per decade (95% CI) |
| Current paracetamol | 0.20 (-0.91, 1.31) | 0.09 (-0.92, 1.10) | 0.18 (-0.85, 1.22) | 0.08 (-0.96, 1.11) |
| Current truck traffic | 1.52 (0.42, 2.61) | -0.66 (-1.73, 0.41) | 1.55 (0.49, 2.62) | -0.81 (-1.91, 0.29) |
| Current regular fast food | 0.23 (-0.33, 0.80) | -0.61 (-1.14, -0.07) | 0.17 (-0.36, 0.71) | -0.49 (-1.07, 0.10) |
| Current paternal smoking | -0.90 (-1.81, 0.02) | 0.21 (-0.83, 1.25) | -1.19 (-2.28, -0.11) | 0.85 (-0.45, 2.16) |
| Current maternal smoking | -0.45 (-1.54, 0.64) | -0.01 (-0.91, 0.90) | 0.08 (-1.14, 1.30) | -0.43 (-1.55, 0.69) |
| Current frequent TV | 0.63 (-0.55, 1.80) | -1.14 (-2.13, -0.14) | 1.24 (0.08, 2.39) | -1.08 (-2.24, 0.08) |

[a]Minimally adjusted for income group and region

[b]Fully adjusted for income group, region and all other risk factors in the table.

*Table 6.4 Risk factor associations with prevalence and time trends of asthma symptoms with random intercepts for centre and country, age 6-7*

| Risk factor (effect of 10% absolute increase) | Minimally adjusted[a] models (n=88) | | Partially adjusted[b] models (n=88) | | Fully adjusted[c] model (n=88) | |
|---|---|---|---|---|---|---|
| | Effect on asthma symptom prevalence at 1st Jan 2002 (95% CI) | Effect on change in asthma symptom prevalence per decade (95% CI) | Effect on asthma symptom prevalence at 1st Jan 2002 (95% CI) | Effect on change in asthma symptom prevalence per decade (95% CI) | Effect on asthma symptom prevalence at 1st Jan 2002 (95% CI) | Effect on change in asthma symptom prevalence per decade (95% CI) |
| Current paracetamol | 1.05 (-0.09, 2.19) | -0.82 (-1.45, -0.19) | 0.68 (-0.44, 1.81) | -0.94 (-1.82, -0.06) | 0.73 (-0.35, 1.81) | -0.91 (-2.03, 0.21) |
| Current truck traffic | -0.11 (-1.07, 0.85) | -0.96 (-1.66, -0.26) | 0.30 (-0.60, 1.20) | -0.72 (-1.41, -0.04) | 0.94 (0.15, 1.73) | -0.52 (-1.29, 0.25) |
| Current regular fast food | 0.50 (-0.15, 1.15) | 0.09 (-0.44, 0.62) | 0.32 (-0.38, 1.02) | 0.33 (-0.22, 0.89) | 0.16 (-0.61, 0.93) | 0.07 (-0.61, 0.76) |
| Current paternal smoking | -0.23 (-1.48, 1.02) | 0.51 (-0.21, 1.22) | -1.01 (-2.33, 0.31) | 0.01 (-0.80, 0.82) | 0.26 (-1.14, 1.65) | -0.31 (-1.61, 0.98) |
| Current maternal smoking | 0.40 (-0.84, 1.63) | -0.90 (-1.64, -0.16) | 0.79 (-0.57, 2.14) | -0.36 (-1.18, 0.47) | 1.10 (0.01, 2.19) | 0.21 (-0.81, 1.24) |
| Current frequent television | 0.60 (-0.75, 1.95) | -0.35 (-1.20, 0.49) | 0.58 (-0.92, 2.08) | 0.19 (-0.76, 1.13) | -0.34 (-1.79, 1.12) | 0.53 (-0.69, 1.75) |
| Paracetamol in first year | 1.27 (0.46, 2.08) | -0.40 (-0.69, -0.11) | 1.55 (0.46, 2.64) | 0.17 (-0.51, 0.85) | 2.53 (1.43, 3.63) | 0.22 (-0.89, 1.32) |
| Antibiotics in first year | 0.23 (-0.47, 0.93) | -0.84 (-1.24, -0.45) | 0.06 (-0.66, 0.79) | -0.65 (-1.25, -0.05) | -0.34 (-1.22, 0.55) | -0.39 (-1.19, 0.41) |
| Breastfed ever | 0.30 (-1.06, 1.66) | -0.82 (-1.30, -0.34) | -0.21 (-1.64, 1.22) | -0.34 (-1.38, 0.71) | -0.88 (-2.22, 0.46) | -0.48 (-1.65, 0.70) |
| Cat in first year | 0.31 (-1.00, 1.63) | -0.74 (-1.31, -0.17) | -0.51 (-2.24, 1.23) | -0.41 (-1.74, 0.93) | -0.89 (-2.62, 0.84) | -0.54 (-2.07, 0.99) |
| Farm animals in first year | -0.47 (-1.97, 1.03) | -0.45 (-1.58, 0.68) | -0.56 (-2.14, 1.03) | 0.47 (-0.76, 1.69) | -0.48 (-2.14, 1.17) | 0.72 (-0.77, 2.22) |

[a]Minimally adjusted for income group and region

[b]Partially adjusted for all risk factors on the same side of the thick line

[c]Fully adjusted for income group, region and all other risk factors in the table

For children (Table 6.4), minimally adjusted models showed evidence that current paracetamol (-0.82; -1.45, -0.19), truck traffic (-0.96; -1.66, -0.26), maternal smoking (-0.90; -1.64, -0.16), paracetamol in the first year (-0.40; -0.69, -0.11), antibiotics in the first year (-0.84; -1.24, -0.45), breastfed ever (-0.82; -1.30, -0.34) and cat in the first year (-0.74; -1.31, -0.17) were all associated with a decreasing trend in asthma symptom prevalence and paracetamol in the first year was also associated with a higher level of asthma symptom prevalence at the mid-point (1.27; 0.46, 2.08).

In the partially adjusted model for current risk factors, the associations with current paracetamol (-0.94; -1.82, -0.06) and truck traffic (-0.72; -1.41, -0.04) remained, but not maternal smoking. In the partially adjusted model for early-life risk factors only the association with antibiotics remained (-0.65; -1.25, -0.05) along with the association of paracetamol in the first year with asthma symptom prevalence at the mid-point (1.55; 0.46, 2.64). However, in the fully adjusted model there was no evidence that any risk factors were associated with a trend in asthma symptom prevalence, though there was some evidence that truck traffic (0.94; 0.15, 1.73) and paracetamol in the first year (2.53; 1.43, 3.63) were associated with higher asthma symptom prevalence at the mid-point, along with weak evidence for maternal smoking (1.10; 0.01, 2.19).

### 6.3.4 Discussion

The analyses showed that for adolescents aged 13-14 years, in a fully adjusted model, there was little evidence that any particular risk factor was associated with a change in asthma symptom prevalence. The model did show that higher prevalence of truck traffic was associated with higher asthma symptom prevalence at the mid-point, along with paternal smoking being associated with a lower prevalence at the mid-point. These estimates were consistent in direction and magnitude with those in the prior ecological analysis (Section 6.2) although the effect estimates in that model had relatively wide confidence intervals. The time trends model was based on more data points, with the addition of data from ISAAC Phase I and GAN Phase I, despite centres without time trends being excluded.

For children aged 6-7 there was again no evidence that any risk factor was associated with a change in asthma symptom prevalence after adjusting for all other risk factors. However, there was strong evidence that paracetamol in the first year was associated with higher asthma symptom prevalence at mid-point along with truck traffic and maternal smoking. This effect of paracetamol in the first year of life is consistent with, though greater in magnitude than,

findings in the simple ecological analysis in Section 6.2. This detection of a larger effect could be because of the difference in the sample, there are 50% more data points in the time trends model for this age group. Interestingly, in the models adjusting for only current risk factors or early-life risk factors separately there were associations with time trend found (current paracetamol and truck traffic for the current risk factor model and antibiotics in the first year for the early-life model). It could be that the fully adjusted model was underpowered to detect effects using so many parameters. All the confidence intervals are wider in this model indicating loss of precision.

## 6.4 Comparison of multi-level risk factor associations

This Chapter included two different methods for estimating the effect of centre-level risk factor data on centre prevalence of asthma symptoms. Combined with the analyses in Section 3.2 at the individual- and school-level there are multiple ways to interpret risk factor effects. These results, from the fully adjusted models, are shown together in Table 6.5.

The interpretation is different for each type of model. The individual-level shows the odds ratio between an individual with the risk factor and an individual without the risk factor, within the same school, relating to the chance of that individual having current asthma symptoms. At the school-level this is similar except the odds ratio is between an individual at a school where everyone has the risk factor and an individual at another school (within the same centre) where no-one has the risk factor (therefore necessarily between an individual having and not having the risk factor). The centre-level model is slightly different as both the exposure and outcome are centre prevalences, so the effect is the estimated percentage point change in asthma symptom prevalence between one centre and another centre (regardless of country) that has a 10% lower prevalence of the risk factor. The centre-level time trends model has two separate effects and contains multiple time-points of outcomes per centre (either two or three). The first is the estimated percentage point change in asthma symptom prevalence at 1$^{st}$ Jan 2002 (approximate mid-point) between one centre and another centre, within the same country, that has a 10% lower prevalence of the risk factor. The second is the estimated percentage point change in the asthma symptom prevalence time trend per decade between one centre and another centre, within the same country, that has a 10% lower prevalence of

*Table 6.5 Comparison of associations between risk factors and asthma symptoms across different hierarchical levels*

| Age group | Risk factor | Individual-level models | School-level models | Centre-level models | Centre-level time trend models | |
|---|---|---|---|---|---|---|
| | | OR (95% CI) | OR for 0% to 100% prevalence (95% CI) | Effect of 10% higher prevalence (95% CI) | Effect of 10% higher prevalence at 1st Jan 2001 (95% CI) | Effect of 10% higher prevalence on change per decade (95% CI) |
| 13-14 years | Current paracetamol | 1.80 (1.75, 1.86) | 2.31 (1.71, 3.12) | 0.01 (-0.82, 0.84) | 0.18 (-0.85, 1.22) | 0.08 (-0.96, 1.11) |
| | Current truck traffic | 1.16 (1.12, 1.21) | 1.28 (0.92, 1.79) | 0.99 (-0.20, 2.18) | 1.55 (0.49, 2.62) | -0.81 (-1.91, 0.29) |
| | Current regular fast food | 1.07 (1.04, 1.10) | 1.21 (0.96, 1.51) | 0.34 (-0.28, 0.96) | 0.17 (-0.36, 0.71) | -0.49 (-1.07, 0.10) |
| | Current paternal smoking | 1.12 (1.08, 1.15) | 0.51 (0.37, 0.70) | -0.58 (-1.55, 0.38) | -1.19 (-2.28, -0.11) | 0.85 (-0.45, 2.16) |
| | Current maternal smoking | 1.23 (1.18, 1.27) | 2.51 (1.74, 3.61) | 0.14 (-0.92, 1.20) | 0.08 (-1.14, 1.30) | -0.43 (-1.55, 0.69) |
| | Current frequent TV | 1.02 (0.97, 1.07) | 2.01 (1.36, 2.96) | 1.10 (-0.05, 2.25) | 1.24 (0.08, 2.39) | -1.08 (-2.24, 0.08) |
| | Current open fire cooking | 1.32 (1.22, 1.43) | 1.28 (0.85, 1.94) | NA | NA | NA |
| 6-7 years | Current paracetamol | 2.06 (1.97, 2.16) | 2.05 (1.55, 2.71) | 0.38 (-0.84, 1.59) | 0.73 (-0.35, 1.81) | -0.91 (-2.03, 0.21) |
| | Current truck traffic | 1.17 (1.11, 1.23) | 1.25 (0.97, 1.62) | 0.93 (-0.08, 1.93) | 0.94 (0.15, 1.73) | -0.52 (-1.29, 0.25) |
| | Current regular fast food | 1.07 (1.03, 1.12) | 1.80 (1.47, 2.20) | 0.31 (-0.37, 0.99) | 0.16 (-0.61, 0.93) | 0.07 (-0.61, 0.76) |
| | Current paternal smoking | 1.12 (1.07, 1.17) | 1.51 (1.20, 1.89) | -0.39 (-1.63, 0.84) | 0.26 (-1.14, 1.65) | -0.31 (-1.61, 0.98) |
| | Current maternal smoking | 1.20 (1.14, 1.27) | 2.22 (1.72, 2.87) | 1.26 (-0.04, 2.57) | 1.10 (0.01, 2.19) | 0.21 (-0.81, 1.24) |
| | Current frequent TV | 1.04 (0.99, 1.10) | 2.08 (1.61, 2.69) | 0.49 (-1.25, 2.24) | -0.34 (-1.79, 1.12) | 0.53 (-0.69, 1.75) |
| | Current open fire cooking | 1.44 (1.26, 1.65) | 1.95 (1.15, 3.29) | NA | NA | NA |
| | Paracetamol in first year | 1.33 (1.27, 1.40) | 1.42 (1.11, 1.82) | 1.50 (0.43, 2.57) | 2.53 (1.43, 3.63) | 0.22 (-0.89, 1.32) |
| | Antibiotics in first year | 1.65 (1.58, 1.73) | 1.49 (1.17, 1.90) | -0.62 (-1.68, 0.44) | -0.34 (-1.22, 0.55) | -0.39 (-1.19, 0.41) |
| | Breastfed ever | 0.96 (0.91, 1.01) | 0.80 (0.60, 1.09) | -0.40 (-1.63, 0.83) | -0.88 (-2.22, 0.46) | -0.48 (-1.65, 0.70) |
| | Cat in first year | 1.22 (1.15, 1.29) | 1.44 (1.06, 1.94) | 0.05 (-1.53, 1.63) | -0.89 (-2.62, 0.84) | -0.54 (-2.07, 0.99) |
| | Farm animals in first year | 1.12 (1.06, 1.20) | 1.47 (1.11, 1.94) | 0.30 (-1.81, 2.40) | -0.48 (-2.14, 1.17) | 0.72 (-0.77, 2.22) |
| | Low birthweight | 1.12 (1.05, 1.21) | 2.43 (1.60, 3.69) | NA | NA | NA |

[a]Individual-level: Logistic regression with binary asthma symptom outcome and individual binary risk factors, adjusts for all risk factors in age group and sex and mother's education level.
[b]School-level: Logistic regression with binary asthma symptom outcome and school-level risk factor prevalence, adjusts for all risk factors in age group plus sex and mother's education level.
[c]Centre-level: Linear regression with centre-level asthma symptom prevalence and risk factor prevalence, adjusts for all risk factors in age group plus country income group and region.
[d]Centre-level time trend: Linear regression with time-point specific asthma symptom centre prevalence and ISAAC Phase III risk factor centre prevalence, adjusts for all risk factors in age group and country income group and region plus time-point and the interaction with the time-point of each risk factor, income group and region.

the risk factor (i.e. the part of the change in asthma symptom prevalence per decade that is attributable to a 10% change in risk factor prevalence).

Although the estimands are not therefore directly comparable, the general level of evidence of an effect, as well as the magnitude compared to other risk factors, can be assessed. The strongest effects were found at the individual-level, where all risk factors except TV viewing and breastfeeding showed an association with higher odds of asthma symptoms. School-level results were more volatile with some risk factors show stronger effects and some weaker, and generally there is lower precision (with wider confidence intervals). The most important risk factor for children at the centre-level was paracetamol in the first year, which showed a substantial effect on centre-level asthma symptom prevalence, although no effect on the time trend of asthma symptom prevalence. Other risk factors with some evidence of association with centre-level prevalence were truck traffic and TV viewing for adolescents and truck traffic and maternal smoking for children, however these were also not associated with time trends in asthma symptom prevalence. All other risk factors showed no effect at the centre-level.

In order for a true risk factor with a strong association at the individual level to be evident at the centre-level there are other criteria that must be met. Firstly, the prevalence of that risk factor must vary significantly between centres. Risk factors with very little variation in prevalence between centres were excluded from this analysis but the amount of variation required to notice an effect may be substantial. Secondly, the prevalence of the outcome must vary substantially between centres, which in this case does seem to be met. Thirdly, there must not be unmeasured confounders that mask the association at the centre-level, which almost certainly could be an issue as there is considerable unexplained variation at the centre-level which could likely be explained by other as yet unknown factors (and is unlikely to all be due to random fluctuations).

So these findings may be a true reflection, as it is possible that strong individual-level determinants do not affect the centre-level.[119] However, it may also be that individually centre-level effects are quite weak and unable to be detected here, but taken together they might still be able to aid prediction of trends and latest prevalence estimates for asthma symptoms. This will be considered in the next chapter, although bearing in mind the sample size of the time trends dataset is reduced when including risk factors.

# 7 Predicting 2019 prevalence of asthma symptoms

## Summary

This chapter uses the determinants of time trends in prevalence to predict current prevalences of asthma symptoms.

In the previous chapter, the associations between the prevalences of asthma symptoms (at one time-point and time trends) and key risk factors were identified. This chapter uses the same risk factors, but extends the models to predict the marginal time trends and current prevalence of asthma symptoms, across all centres that have data for at least two time-points. The findings are given as estimates of asthma symptom prevalence in 2019, and time trend per decade (over the previous 27 years). Overall estimates, as well as estimates stratified by age group, income group and region are presented.

## 7.1 Introduction

In the previous two chapters, linear regression models were fitted to assess factors associated with time trends in wheeze prevalence in centres with data from at least two time points in ISAAC and GAN. Firstly, country level factors (income group and region), available for all centres were analysed; secondly, centre prevalences of risk factors from ISAAC Phase III were added to the analysis. In Chapter 5, there was evidence that time trends in asthma prevalence were modified by income group and region. Centres in low-income countries were more likely to experience a decrease in prevalence of current asthma symptoms whereas those in lower-middle-income countries experienced increases. Prevalence remained stable on average across centres in upper-middle and high-income countries.

In this chapter, the findings from this simple model are compared with more advanced methods for analysing time trends and predicting outside the sample. The rationale for these further analyses are to:

i) obtain estimates of the overall prevalence per age group as at GAN Phase I (2019) as well as prevalence by country, income group and region; and

ii) refine these estimates by incorporating risk factor data.

The two approaches both use modelled parameters to estimate the trends and prevalence on a wider range of data, such as different time-points and age groups. One is a frequentist method and the second is Bayesian. The results from these two approaches are compared to the results from Chapter 5, on the same two underlying models (with interaction terms for age and income group, and for age and region) to check for consistency of results. The more appropriate model was determined and the analysis extended to incorporate data on risk factors.

Predictions for wheeze prevalence and time trends are summarised overall, by age group, and by age group stratified on either income or region. These are marginal effects standardised across the levels of other factors for which analysing interaction was not of interest (i.e. age group summaries marginalise across income group or region and all extended models marginalise across included risk factor values).

The extension to incorporate life-style risk factors used all risk factors from Chapter 6. None had been shown to have particularly strong associations with country or centre-level prevalence but it was still considered possible that levels of these risk factors could in part explain time trends, which was the object of the current analyses. These analyses incorporating risk factors were based on a smaller dataset of only those centres with risk factor information. Moreover, the analyses were conducted separately for each age group, since these included different risk factor information, and even the same risk factor could have a different interpretation in each age group.

If the set of risk factors that were considered were associated with centre prevalences and time trends of asthma symptoms, then a better fitting model would be expected when these risk factors were included in the model. However, comparisons between models need to weigh up these potential gains in improved estimation with loss of power and precision from the smaller sample size due to fewer centres being included in the model.

## 7.2 Methods

**Frequentist approach**

The frequentist approach considered here was adapted from that previously presented by Cousens et al[122]. In summary, a regression model was fitted for centres with more than one time-point of data and then the parameter estimates were used to predict the prevalence of wheeze as at GAN Phase I (1st January 2019) and the change in prevalence per decade across the preceding 27 years. Bootstrapping was used to estimate confidence intervals around these estimates, which were summarised at age group, income group and regional levels.

Firstly, a mixed effects model was fitted, with random effects at the country and centre levels. The BLUPS for country and centre (best linear unbiased prediction of the random intercepts) were stored. Then only one observation per centre per age group was retained (i.e. one time-point), with any extra discarded, and the dataset was expanded to ensure that there was an observation for each age group for each centre (i.e. the predicted value was used if no data was available for that age-group for that centre). This formed the basis of the prediction sample. The index time-point was set as 1/1/2019, and fitted values (from the fixed effects) were predicted and added to the stored BLUPS to create a predicted prevalence per centre. This was repeated with the index time-point 1/1/1992, and then the predicted time trend per decade was estimated from the difference between these two values. The mean of these prevalence and time trend predictions was calculated at required levels (overall, age group and either income group or region within age group).

This process was bootstrapped 10,000 times to gain (normal-approximation) confidence intervals around the mean prevalence and time trends predictions. Resampling was taken at the observation level, i.e. a specific time-point for a study centre. Although this is a clustered dataset, resampling was not selected at the centre and country level, as each centre could choose separately to take part in any individual phase. The accounting for clustering in these time trend models is done simply to take account of the expected similarity between surveys in the same centre, and centres in the same country. The fact that resampling was at the observation level means that any single bootstrap replicate may contain centres with only one time-point. Although centres with only one time-point were removed from the original dataset, since they would not provide any information on time trends, they are not removed here as excluding them from the bootstrapped sample could introduce bias. Additionally, in some bootstrap replicates, centres or countries could be missing entirely, or missing within an age group, therefore without a BLUP or BLUPs. Where a BLUP was missing, it was either copied

from another observation of the same centre or country, or if there were none, a value was randomly selected from the distribution for the relevant random intercept, i.e. using a random draw from N(0, $\sigma^2$) where sigma is the standard deviation estimated in the model.

Every bootstrap replicate therefore provided predictions that encompassed the same centres from the prediction sample, one in each age group, even though the underlying regression model was based on a traditional bootstrap sample (with some records excluded and some repeated). This whole process was run separately for each of the two underlying models from Chapter 5, both with interaction terms for time and age and one with an additional interaction term for time and income group, and the other for time and region. Both models were adjusted for age, income group and region. This analysis was run on Stata[85] version 15 and code is provided in Appendix F.

**Bayesian approach**

The Bayesian hierarchical models, to estimate the association between time and asthma symptom prevalence, used random intercepts for centre and country, and adjusted for income group, region and age group, as well as including terms for the interaction between time and age. One model then had an additional interaction between time, age and income, and the other model had an interaction between time, age and region. This is the same parameter structure as the previous frequentist model, but under the Bayesian framework. Bayesian predictions can be produced with credible intervals without further bootstrapping, by using the MCMC samples. This uses the model parameters to estimate the prevalence of asthma symptoms as at 1/1/2019 and the change in prevalence per decade.

The models were assigned uninformative priors for all covariates. There were random intercepts for country and centre with priors of the form N(0, $\tau_i^2$) with inverse-gamma(0.01, 0.01) hyper priors for both $\tau^2_{\text{country}}$ and $\tau^2_{\text{centre}}$. The regression coefficients for age group, income group, region and relevant interactions all used priors of N(0, $100^2$). The likelihood model was normally distributed with mean of the linear fixed effects and variance from the hyper prior inverse-gamma(0.01, 0.01).

To minimise autocorrelation, the burn-in period was set to 25,000, the MCMC sample size was 50,000 which was thinned by 1 in 5. The hyper parameters were in a separate block from the regression coefficients. The Bayesian analysis was run on Stata[123] version 17 which included new functionality for Bayesian hierarchical models. The code used is provided in Appendix G.

**Extension for selected approach**

The selected approach was also fitted on slightly extended models that allowed for a three-way interaction between time, age and income, or time, age and region. This was to check if the effects of income group or region differed between the two age groups. There was a requirement to balance the flexibility of allowing these associations to differ by age group, with the extra model efficiency gained by borrowing information from one age group to inform the analysis of the other age group in a simpler model with fewer parameters. A likelihood ratio test was then used to compare model fit. Full predictions for 2019 asthma symptom prevalence split by age, income group and region were estimated for both versions of the model.

Finally, the risk factors from Chapter 6 were incorporated into the selected model, as standard covariates and as interactions with time. Models with risk factors and models without risk factors were fitted on the same sample (i.e. centres with all risk factor data available) for further comparison and then compared to the previous models which included no risk factor information on the wider dataset. For the younger age group, the early-life risk factors and the current risk factors were included in separate models because together (adjusted for and as interaction with time) there were too many parameters for the model to converge in all the bootstrap replicates.

## 7.3 Results

**Income and region based results**

The estimates for the frequentist prediction models, when predicting only on the strata included in the model, were almost identical to those in Chapter 5, as expected since these have identical underlying models (Table 7.1). The accompanying confidence intervals were wider, but comparable to those using boot strapped standard errors in the original models.

The overall predicted values of current wheeze prevalence as at 1/1/2019 differed slightly, dependent on the model used (Table 7.2). When restricting the effect of income/region to be the same across both age groups, the model stratifying by income group showed an overall prevalence estimate of 12.8% (95% CI=11.4%, 14.2%), and the model stratifying by region showed 13.2% (11.9%, 14.6%). Using income group gave a slightly more precise estimate (i.e. a narrower confidence interval).

The prevalence of wheeze in low-income countries (age 6-7: 5.2%; 95% CI = 2.5% ,7.8%; age 13-14: 5.3%; 2.8%, 7.8%) was lower than that in lower-middle-, upper-middle- and high-income countries. There was no evidence of a difference between the latter three groups which were estimated around 14-15% prevalence in both age groups. Centres in the South-East Asia and the Western Pacific region had lower current prevalence of asthma symptoms (age 6-7: 7.8%; 5.5%, 10.2%; age 13-14: 7.6%; 5.3%, 9.8%) than centres in the Americas and Europe in both age groups, and lower than in Africa and Eastern Mediterranean region in 13-14-year-olds. The highest estimated regional prevalence was for America (age 6-7: 16.3%; 13.2%, 19.4%; age 13-14: 16.0%; 12.9%, 19.1%), although this was not much higher than the estimated prevalence in Europe or Africa and Eastern Mediterranean regions (Table 7.2).

When the effect of income/region was allowed to vary by age group (three-way models) then the point estimates were not substantially different to those from the two-way models, but the confidence intervals were considerably wider, particularly in the younger age group (Table 7.2). This is likely due to low power for detecting further interactions. However, the likelihood ratio tests showed that although the three-way model was not a better fit for the income stratified version (p=0.17), it was a better fit in the version that was stratified by region (p=0.004).

The main results from the Bayesian time trend models are shown in Table 7.1 compared to the models in Chapter 5. The trend is similar to that from the frequentist method, which is reassuring, though there are some minor differences. However, there were issues with high auto correlation for many of the regression coefficients (less so for the random effect variances), despite the mitigation methods of extended burn-in, larger sample size and sample thinning detailed above. The efficiencies of most of the parameters were below 1% which indicates that the posterior distribution was not accurately sampled from. Despite these issues, the overall predictions for all time trends centres using the Bayesian models were 12.4% (11.4%, 13.5%) for the age and income model and 12.5% (11.4%, 13.6%) for the age and region model; these findings are consistent with those from the frequentist models. Unfortunately, it was not possible to calculate predictions at the group level with the Bayes model using Stata. This technical issue combined with the previous problem of autocorrelation mean this method was not taken further and the frequentist prediction method was chosen for the further analyses which incorporated information on the risk factors.

*Table 7.1 Model comparison of time trend effects between simple models, frequentist prediction method and Bayesian method (n=416)*

| Lancet model | Strata | | Number of centres | Models in Chapter 5 | Chapter 5 models but with bootstrapped CI[a] | Frequentist predictions[a] | Bayesian model |
|---|---|---|---|---|---|---|---|
| | | | | Estimate (95% CI) | Estimate (95% CI) | Estimate (95% CI) | Estimate (95% CrI) |
| Age and income interactions with time trend | 6-7 years | Low income | 14 | -1·37 (-2·47, -0·27) | -1.37 (-2.87, 0.14) | -1.37 (-2.86, 0.12) | -1.39 (-1.84, -0.85) |
| | | Lower-middle | 7 | 1·99 (0·33, 3·66) | 1.99 (-0.51, 4.49) | 1.99 (-0.50, 4.49) | 1.97 (0.35, 3.58) |
| | | Upper-middle | 21 | 0·50 (-0·82, 1·82) | 0.50 (-1.20, 2.20) | 0.50 (-1.21, 2.21) | 0.73 (0.13, 1.55) |
| | | High income | 34 | -0·22 (-1·24, 0·80) | -0.22 (-1.37, 0.93) | -0.22 (-1.39, 0.95) | -0.04 (-0.70, 0.69) |
| | 13-14 years | Low income | 21 | -1·67 (-2·70, -0·64) | -1.67 (-3.09, -0.25) | -1.67 (-3.07, -0.27) | -1.75 (-2.44, -1.10) |
| | | Lower-middle | 19 | 1·69 (0·13, 3·25) | 1.69 (-0.93, 4.31) | 1.69 (-0.92, 4.30) | 1.61 (0.10, 3.06) |
| | | Upper-middle | 30 | 0·19 (-1·06, 1·45) | 0.19 (-1.49, 1.88) | 0.19 (-1.49, 1.88) | 0.37 (-0.41, 1.20) |
| | | High income | 51 | -0·52 (-1·47, 0·43) | -0.52 (-1.74, 0.70) | -0.52 (-1.75, 0.70) | -0.40 (-1.16, 0.35) |
| Age and region interactions with time trend | 6-7 years | Africa and Eastern Mediterranean | 5 | 2·61 (0·76, 4·46) | 2.61 (0.08, 5.14) | 2.61 (0.04, 5.18) | 1.92 (1.30, 2.58) |
| | | America | 14 | 0·01 (-1·29, 1·31) | 0.01 (-1.75, 1.77) | 0.01 (-1.75, 1.77) | -0.10 (-0.92, 0.69) |
| | | Europe | 31 | 1·08 (-0·08, 2·24) | 1.08 (-0.07, 2.23) | 1.08 (-0.06, 2.22) | 1.08 (0.11, 1.97) |
| | | South-East Asia and Western Pacific | 26 | -1·35 (-2·28, -0·41) | -1.35 (-2.62, -0.07) | -1.35 (-2.58, -0.11) | -1.43 (-2.21, -0.69) |
| | 13-14 years | Africa and Eastern Mediterranean | 16 | 2·09 (0·40, 3·78) | 2.09 (-0.41, 4.58) | 2.09 (-0.43, 4.60) | 1.56 (0.62, 2.50) |
| | | America | 24 | -0·51 (-1·73, 0·71) | -0.51 (-2.27, 1.25) | -0.51 (-2.29, 1.27) | -0.46 (-1.37, 0.52) |
| | | Europe | 49 | 0·56 (-0·51, 1·63) | 0.56 (-0.60, 1.71) | 0.56 (-0.60, 1.71) | 0.72 (-0.31, 1.74) |
| | | South-East Asia and Western Pacific | 32 | -1·87 (-2·78, -0·96) | -1.87 (-3.04, -0.69) | -1.87 (-3.04, -0.69) | -1.79 (-2.63, -0.96) |

[a]bootstraps used 10,000 replicates [b]includes 3 way interactions between time, age and income, and time, age and region. CI=Confidence interval; CrI=Credible interval

*Table 7.2 Estimated 2019 wheeze prevalence and trend, from frequentist prediction method with mixed-effect models with random intercepts at country and centre levels, and interactions between time trend, age and income group and time trend, age and region.*

| Summary level of predictions | | Number of centres in model | Number of centres predicted | Model with 2-way interactions between time and each of the strata[a] | | Model with a 3-way interaction between time and the two strata[a] | |
|---|---|---|---|---|---|---|---|
| | | | | Estimated time trend per decade (95% CI[b]) | Estimated 2019 prevalence (95% CI[b]) | Estimated time trend per decade (95% CI[b]) | Estimated 2019 prevalence (95% CI[b]) |
| Models with age and income group strata[a] | | | | | | | |
| Overall | | 124 | 124 | -0.06 (-0.79, 0.67) | 12.82 (11.40, 14.24) | -0.05 (-0.88, 0.77) | 12.80 (11.14, 14.46) |
| 6-7 years | | 76 | 124 | 0.09 (-0.82, 1.00) | 12.75 (11.01, 14.49) | 0.10 (-1.10, 1.30) | 12.70 (10.21, 15.20) |
| 13-14 years | | 121 | 124 | -0.21 (-1.16, 0.74) | 12.89 (11.02, 14.75) | -0.20 (-1.23, 0.82) | 12.90 (10.87, 14.92) |
| 6-7 years | Low income countries | 14 | 22 | -1.37 (-2.86, 0.12) | 5.15 (2.54, 7.76) | -1.55 (-3.54, 0.43) | 4.85 (1.57, 8.14) |
| | Lower-middle countries | 7 | 19 | 1.99 (-0.50, 4.49) | 14.25 (9.27, 19.23) | 2.00 (-3.72, 7.73) | 13.47 (0.83, 26.10) |
| | Upper-middle countries | 21 | 30 | 0.50 (-1.21, 2.21) | 14.83 (11.63, 18.04) | 0.09 (-1.88, 2.06) | 15.10 (11.39, 18.80) |
| | High income countries | 34 | 53 | -0.22 (-1.39, 0.95) | 14.18 (11.83, 16.53) | 0.10 (-1.24, 1.45) | 14.34 (11.60, 17.08) |
| 13-14 years | Low income countries | 21 | 22 | -1.67 (-3.07, -0.27) | 5.29 (2.81, 7.77) | -1.54 (-3.15, 0.07) | 5.50 (2.59, 8.41) |
| | Lower-middle countries | 19 | 19 | 1.69 (-0.92, 4.30) | 14.39 (9.15, 19.62) | 1.69 (-2.04, 5.43) | 14.58 (7.18, 21.98) |
| | Upper-middle countries | 30 | 30 | 0.19 (-1.49, 1.88) | 14.97 (11.83, 18.11) | 0.55 (-1.36, 2.46) | 15.07 (11.45, 18.69) |
| | High income countries | 51 | 53 | -0.52 (-1.75, 0.70) | 14.32 (11.85, 16.79) | -0.76 (-2.28, 0.77) | 14.13 (11.02, 17.24) |
| Models with age and region strata[a] | | | | | | | |
| Overall | | 124 | 124 | 0.16 (-0.52, 0.83) | 13.24 (11.94, 14.55) | 0.11 (-1.44, 1.67) | 13.10 (9.72, 16.49) |
| 6-7 years | | 76 | 124 | 0.42 (-0.47, 1.31) | 13.38 (11.66, 15.10) | 0.23 (-2.72, 3.18) | 12.96 (6.47, 19.45) |
| 13-14 years | | 121 | 124 | -0.11 (-0.97, 0.76) | 13.10 (11.42, 14.78) | 0.00 (-0.90, 0.89) | 13.25 (11.49, 15.01) |
| 6-7 years | Africa and Eastern Mediterranean | 5 | 16 | 2.61 (0.04, 5.18) | 15.06 (9.99, 20.13) | 2.83 (-19.24, 24.89) | 12.80 (-36.14, 61.75) |
| | America | 14 | 25 | 0.01 (-1.75, 1.77) | 16.30 (13.18, 19.42) | -1.10 (-3.01, 0.81) | 16.29 (12.90, 19.67) |
| | Europe | 31 | 50 | 1.08 (-0.06, 2.22) | 15.05 (12.76, 17.33) | 0.92 (-0.28, 2.12) | 14.46 (12.02, 16.89) |
| | South-East Asia and Western Pacific | 26 | 33 | -1.35 (-2.58, -0.11) | 7.83 (5.46, 10.21) | -1.07 (-2.59, 0.46) | 8.25 (5.35, 11.15) |
| 13-14 years | Africa and Eastern Mediterranean | 16 | 16 | 2.09 (-0.43, 4.60) | 14.78 (9.80, 19.76) | 1.86 (-1.17, 4.88) | 14.84 (8.83, 20.86) |
| | America | 24 | 25 | -0.51 (-2.29, 1.27) | 16.02 (12.90, 19.14) | 0.31 (-1.74, 2.36) | 16.61 (12.96, 20.27) |
| | Europe | 49 | 50 | 0.56 (-0.60, 1.71) | 14.77 (12.40, 17.13) | 0.65 (-0.85, 2.14) | 15.09 (12.03, 18.14) |
| | South-East Asia and Western Pacific | 32 | 33 | -1.87 (-3.04, -0.69) | 7.56 (5.32, 9.79) | -2.12 (-3.42, -0.83) | 7.15 (4.65, 9.64) |

[a]all models adjusted for age, income group and region; [b]CI=Confidence intervals calculated using bootstrapping with 10,000 replicates.

**Risk factor based results**

The addition of risk factors to the model reduced the sample size from one combined age dataset of 416 records (made up of 124 centres) to two separate age group datasets of 108 for adolescents and 94 for children. This was because not all ISAAC Phase III centres took part in the optional environmental risk factor questionnaire.

For adolescents, the findings from the (smaller) risk factor dataset, but without including risk factors in the model (Table 7.3), gave estimates of 2019 prevalence that were consistent with the previous model on the full data set (Table 7.2). For the trends, there were some differences. High income countries showed evidence of increasing prevalence (1.70%; 95% CI 0.29%, 3.11%), whereas the analysis on the original dataset showed little evidence of this (despite a small positive point estimate). When risk factors were included in the model, there was very little change to predicted prevalence and predicted trends, but the confidence intervals were wider (Table 7.3).

For children, the model without risk factors (but on the smaller dataset) (Table 7.4) yielded estimates of 2019 prevalence that were consistent with the model on the larger dataset (Table 7.2). However, the time trend results were different to those in the previous larger dataset and all groups showed little evidence of any trend. When risk factors were included in the model, there was very little change to predicted prevalence and trends. The confidence intervals were relatively wide; in particular, for the Africa and Eastern Mediterranean region they were exceptionally wide due to low numbers in that stratum, and although the point estimate looked reasonable the confidence interval lower bound was negative (theoretically not possible for a prevalence estimate), showing that there was not enough data to properly estimate the results for this group (Table 7.4).

*Table 7.3 Estimated 2019 asthma symptom prevalence and trend, from frequentist prediction method with mixed-effect models with random intercepts for country and centre. Centres with time trends and risk factor data available, with and without risk factors included, age 13-14 (n=108).*

| Strata for predictions | Number of centres in model | Without risk factors | | With risk factors[a] (adjusted for and as interaction with time trend) | |
|---|---|---|---|---|---|
| | | Estimated time trend per decade (95% CI[b]) | Estimated 2019 prevalence (95% CI[b]) | Estimated time trend per decade (95% CI[b]) | Estimated 2019 prevalence (95% CI[b]) |
| Models with interaction between income group and time, also adjusted for region | | | | | |
| Overall | 50 | 1.06 (-0.19, 2.30) | 12.34 (10.08, 14.59) | 1.19 (-0.32, 2.71) | 12.60 (9.73, 15.47) |
| Low income | 10 | -1.48 (-3.50, 0.54) | 2.92 (-0.48, 6.32) | -1.63 (-3.74, 0.48) | 2.78 (-1.26, 6.82) |
| Lower-middle | 10 | 3.09 (-0.81, 6.98) | 17.58 (9.98, 25.17) | 3.52 (-1.06, 8.10) | 18.37 (9.28, 27.46) |
| Upper-middle | 15 | 0.75 (-1.82, 3.32) | 13.12 (8.86, 17.39) | 1.07 (-1.79, 3.93) | 13.68 (8.85, 18.52) |
| High income | 15 | 1.70 (0.29, 3.11) | 14.33 (11.49, 17.17) | 1.65 (-0.12, 3.43) | 14.22 (10.67, 17.76) |
| Models with interaction between region and time, also adjusted for income group | | | | | |
| Overall | 50 | 0.70 (-0.57, 1.97) | 11.63 (9.30, 13.95) | 0.98 (-0.77, 2.73) | 12.15 (8.93, 15.37) |
| Africa and Eastern Mediterranean | 8 | 2.54 (-1.62, 6.70) | 16.31 (7.78, 24.85) | 3.05 (-0.82, 6.93) | 17.09 (9.50, 24.67) |
| America | 9 | 0.26 (-3.35, 3.87) | 16.15 (10.96, 21.34) | 0.56 (-4.26, 5.38) | 16.40 (9.15, 23.65) |
| Europe | 16 | 2.05 (0.46, 3.64) | 14.64 (11.40, 17.87) | 2.32 (-0.50, 5.13) | 15.19 (9.94, 20.43) |
| South-East Asia and Western Pacific | 17 | -1.21 (-3.23, 0.81) | 4.19 (0.51, 7.87) | -1.04 (-3.25, 1.17) | 4.71 (0.45, 8.97) |

[a]current paracetamol, truck traffic, fast food, maternal smoking, paternal smoking, and television viewing.
[b]CI=Confidence intervals calculated using bootstrapping with 10,000 replicates.

*Table 7.4 Estimated 2019 asthma symptom prevalence and trend, from frequentist prediction method with mixed-effect models with random intercepts for country and centre. Centres with time trends and risk factor data available, with and without risk factors included, age 6-7 (n=88).*

| Strata for predictions | Number of centres | Without risk factors | | With early-life risk factors[a] (adjustment and interaction with time trend) | | With current risk factors[b] (adjustment and interaction with time trend) | |
|---|---|---|---|---|---|---|---|
| | | Estimated time trend per decade (95% CI[c]) | Estimated 2019 prevalence (95% CI[c]) | Estimated time trend per decade (95% CI[c]) | Estimated 2019 prevalence (95% CI[c]) | Estimated time trend per decade (95% CI[c]) | Estimated 2019 prevalence (95% CI[c]) |
| Models with interaction between income group and time, also adjusted for region | | | | | | | |
| Overall | 41 | 0.80 (-1.67, 3.28) | 11.83 (7.01, 16.66) | 0.88 (-0.67, 2.42) | 11.91 (8.90, 14.93) | 0.71 (-2.42, 3.84) | 11.65 (5.61, 17.69) |
| Low income | 7 | -0.98 (-3.17, 1.20) | 2.01 (-2.74, 6.77) | -0.51 (-2.66, 1.65) | 3.09 (-1.03, 7.20) | -1.07 (-6.49, 4.35) | 1.78 (-10.09, 13.65) |
| Lower-middle | 5 | 3.07 (-15.95, 22.09) | 14.23 (-23.16, 51.62) | 3.77 (-8.34, 15.88) | 15.57 (-8.24, 39.38) | 2.32 (-19.93, 24.57) | 12.61 (-29.85, 55.06) |
| Upper-middle | 13 | 1.45 (-0.26, 3.15) | 12.45 (9.27, 15.62) | 1.30 (-0.89, 3.49) | 12.05 (8.02, 16.09) | 1.60 (-1.09, 4.29) | 12.90 (7.77, 18.03) |
| High income | 16 | 0.35 (-1.13, 1.83) | 14.88 (12.08, 17.68) | 0.23 (-1.36, 1.83) | 14.52 (11.40, 17.63) | 0.26 (-1.69, 2.21) | 14.66 (10.80, 18.52) |
| Models with interaction between region and time, also adjusted for income group | | | | | | | |
| Overall | 41 | 1.03 (-4.09, 6.14) | 12.22 (0.38, 24.06) | 0.83 (-5.32, 6.98) | 11.77 (-2.50, 26.04) | 0.98 (-1.56, 3.51) | 12.10 (7.15, 17.05) |
| Africa and Eastern Mediterranean | 5 | 4.10 (-37.29, 45.49) | 14.95 (-81.43, 111.34) | 4.62 (-45.08, 54.32) | 16.07 (-99.87, 132.00) | 3.64 (-14.56, 21.85) | 13.83 (-22.15, 49.80) |
| America | 7 | 1.79 (-0.96, 4.55) | 15.03 (10.51, 19.55) | 1.64 (-1.69, 4.96) | 14.66 (9.29, 20.03) | 1.41 (-2.85, 5.66) | 14.21 (7.11, 21.32) |
| Europe | 13 | 1.11 (-0.26, 2.49) | 12.38 (9.69, 15.07) | 1.04 (-0.84, 2.93) | 12.17 (8.44, 15.91) | 1.59 (-0.33, 3.52) | 13.41 (9.58, 17.23) |
| South-East Asia and Western Pacific | 16 | -0.34 (-1.77, 1.09) | 10.01 (7.25, 12.76) | -0.89 (-2.68, 0.91) | 8.83 (5.25, 12.42) | -0.54 (-2.13, 1.04) | 9.56 (6.46, 12.67) |

[a] early-life factors (in first year): paracetamol, antibiotics, breastfed ever, cat contact, farm animal contact.
[b] current risk factors (in past 12 months): paracetamol, truck traffic, fast food, maternal smoking, paternal smoking, and television viewing.
[c] CI=Confidence intervals calculated using bootstrapping with 10,000 replicates.

## 7.4 Discussion

In this chapter, the findings from the simpler frequentist multi-level model (Chapter 5) were compared with those obtained using a more advanced frequentist multi-level method (Cousens[122] method) and a Bayesian hierarchical method for analysing time trends and predicting outside the sample. Both approaches yielded findings that were consistent with the models in Chapter 5 when comparing the same underlying models.

There were some issues in running the Bayesian models with problems of high autocorrelation that could not be fixed. This meant that the MCMC sample was not representative of the posterior distribution due to dependence between consecutive draws. Possible solutions were to further increase the chain, although the length required would likely make the running time prohibitive. More thinning is not advised[124] as this is no better than increasing the chain and just discards information. Reparameterisation of the random effects is another solution[125] but would make comparison with the other models harder. For these reasons, the Bayesian model was not taken forward.

The frequentist method was therefore selected to provide full predictions for 2019 prevalence of asthma symptoms along with estimated trends per decade over the 27 years. The findings showed an estimated prevalence of about 13%, with very little difference between age-groups. Low-income countries are predicted to have lower prevalence of asthma symptoms, with evidence of a decreasing trend in adolescents. Centres in the South East Asia and Western Pacific region are predicted to have lower prevalence than other regions, and it appears that their prevalence is also decreasing.

There seemed no benefit to allowing the effects of income group or region on trend to vary by age group. The difference between age groups is small compared to the unexplained variability between centres (seen as width of confidence intervals).

Adding risk factors to the model had the problem of reducing the size of the dataset, since not all centres had risk factor data. Also the dataset was then split by age group to allow for differing risk factor availability; this prevented the borrowing of information from one age group to the other as was the case in previous models. This reduced the power of the study and although the breadth of available information was large (i.e. a large number of risk

factors), there were not enough centres with risk factors and time trends to allow these associations to be fully investigated.

The models analysing time trends across all centres, and including income group and region, have showed that these high level factors do in fact have large enough effects to be identified in these analyses, and there is strong evidence that low-income countries have a generally lower prevalence of asthma symptoms (although these analyses have not considered differences in severity of symptoms), and that prevalence may actually be decreasing in these countries. This finding is unexpected, since it has been hypothesized that prevalence would increase in these countries with increasing westernisation.[126]

The method of predicting prevalence at one time-point works well, and could be used again if further data were to become available. The added advantage is that other time-varying explanatory data could be added for multiple time-points from other sources, to refine the predictions without new centres becoming available. An example is risk factor information from a general country level. This would be susceptible to other ecological biases (compared to the risk factor prevalences here summarised from the individuals who actually took part in the survey) but could be a way to get risk factor information for all centres, and even include changes in risk factors over time. This is briefly discussed in the final chapter as one type of further analysis that could be done in future.

# 8 Discussion

## Summary

This final chapter brings together the findings from all the previous chapters. The strengths and limitations of the study data are discussed along with an analysis of statistical issues raised during the course of this PhD. Then possible opportunities for further analyses of the existing data, as well as suggestions for further studies, are considered.

Finally, conclusions are drawn of what this work adds to the existing understanding of global asthma prevalence patterns and trends.

## 8.1 Overview

The purpose of this thesis was to explore methods for analysing international patterns and time trends of asthma, eczema and rhinitis, while taking account of the multi-level structure of the available data.

This was achieved through the following four specific objectives.

1. Investigate the role of bias due to reverse causation within cross-sectional data for risk factors of asthma, eczema and rhinoconjunctivitis, by utilising cluster information. (Chapters 3 and 4)
2. Incorporate newly available data to estimate time trends in global symptom prevalence and differences around the world. (Chapter 5)
3. Estimate the effects of risk factors on time trends in symptom prevalence, even when some clusters have missing time points. (Chapter 6)
4. Use modelled time trends to estimate an up to date prevalence of symptoms for all studies that have taken part in multiple ISAAC/GAN studies, even those that did not complete the most recent phase. (Chapter 7)

The findings from each chapter are summarised and discussed below. The strengths and limitations of these analyses have been discussed in each of the prior chapters, and these will not be repeated in detail, but some issues related to the study data, which impact all of the analyses, will be considered. Additionally, some of the key statistical issues that arose during the analyses will be discussed along with any potential implications. Opportunities for further research are then detailed, followed by the overall conclusions of the thesis.

## 8.2 Synopsis of findings

***Risk factors for prevalence***

The first objective was to investigate risk factors for asthma, eczema and rhinoconjunctivitis, by utilising cluster level information in order to explore the role of bias due to reverse causation. Studies at the individual-level may be biased due to reverse causation, e.g. if parents rehouse the family cat if a child becomes sensitised. Population-level studies can in part remove these biases, but in turn they may suffer from population-level confounding (the ecological fallacy), and lack of individual exposure data. Chapters 3 and 4 used four-level mixed-effects logistic regression models to take account of clustering within schools, centres and countries and adjusted all analyses for all of the risk factors being considered, along with sex and mother's level of education (as a proxy for individual-level, within school and centre, socio-economic status). Results were compared between models with individual-level risk factors and models with school-level prevalences of risk factors.

The paper in Section 3.2 on asthma symptoms showed that for adolescents, where only current risk factors were available, the strongest effects at the individual-level were seen for current paracetamol use (OR=1.80; 95% CI = 1.75, 1.86), followed by open fire cooking (1.32; 1.22, 1.43), and maternal smoking (1.23; 1.18, 1.27), with weaker effects seen for truck traffic, paternal smoking and fast food. Only regular television watching showed no effect. At the school-level, the findings were similar except for television watching, which showed a strong association at the school-level (2.01; 1.36, 2.96) and no association at the individual-level (1.02; 0.97, 1.07); similarly, paternal smoking showed a change in direction from individual- compared to school-level (1.12; 1.08, 1.15 and 0.51; 0.37, 0.70 respectively). For some other risk factors, the strength of association became weaker, but the power of the school level study was lower because of the loss of information, and the confidence intervals were therefore generally wider.

For children, the risk factors with the strongest individual associations with asthma symptoms were current paracetamol use (2.06; 1.97, 2.16), followed by early life antibiotic use (1.65; 1.58, 1.73), open fire cooking (1.44; 1.26, 1.65) and early-life paracetamol use (1.33; 1.27, 1.40) with weaker associations for low birthweight, cat contact, farm animal contact, truck traffic, fast food, paternal smoking and maternal smoking. No associations were found for breastfeeding and television viewing. The school-level analyses showed similar findings, except for paracetamol in the first year and current paternal smoking, which showed no evidence of association. The strength of association was weaker for cat contact in the first year and current truck traffic, but the results were still consistent with those at the individual-level.

The similar analyses for eczema symptoms, from the paper in Section 3.3, showed that for adolescents, the strongest individual-level risk factors were current paracetamol use, open fire cooking and heavy truck traffic, and these effects remained at the school-level, with the paracetamol association becoming stronger (1.57; 1.51, 1.63 to 2.57; 1.84, 3.59). Paternal smoking showed a weak adverse effect at the individual-level, and a protective effect at the school-level (1.15; 1.10, 1.19 and 0.64; 0.44, 0.94 respectively), similar to results on asthma. A difference was that fast food was only weakly associated at the individual level (1.05; 1.02, 1.10), but much more strongly at the school level (2.11; 1.66, 2.70).

For children, eczema symptoms were most associated at the individual-level with current paracetamol use (1.45; 1.37, 1.54), early-life antibiotic use (1.41; 1.34, 1.48) and early-life paracetamol use (1.28; 1.21, 1.36), with weaker effects for low birthweight (protective), breastfeeding, early-life cat and farm animal exposure, heavy truck traffic and 2 or more siblings (protective). There was no evidence of increased or decreased risks for mothers' contact with farm animals during pregnancy, early-life dog exposure, current fast food, paternal and maternal smoking and open fire cooking. At the school-level there was no evidence of an association with early-life paracetamol use (0.94; 0.69, 1.28). Most other variables yielded consistent findings at both levels, although the confidence intervals at the school-level were considerably wider. A notable exception was low birthweight which showed a marginally protective effect at the individual-level but a considerable adverse effect at the school-level (0.89; 0.81, 0.97 and 1.78; 1.07, 2.95). Given that birthweight is not a choice and always occurs before asthma symptoms are manifested, these findings are puzzling. Perhaps the most likely explanation is that a high proportion of low birthweight children in an area is associated with some other unmeasured confounder, resulting in ecological bias.

In Section 3.4, for rhinitis in adolescents, the strongest risk factors at the individual-level were current paracetamol use (1.76; 1.71, 1.81) and heavy truck traffic (1.23; 1.20, 1.26) with weaker associations for open fire cooking, maternal tobacco, paternal tobacco, fast food, and 2 or more siblings. There was no association with television viewing. At the school-level the association with current paracetamol was much stronger (3.42; 2.62, 4.46). Other differences at the school-level included paternal smoking with the estimate changing direction, although at the school-level there was no evidence of an effect (1.10; 1.07, 1.13 to 0.79; 0.59, 1.06) and open fire cooking getting stronger (1.16; 1.08, 1.25 to 1.96; 1.36, 2.83). Other risk factors were consistent at both levels.

For children the strongest individual-level association was again with current paracetamol use (2.02; 1.92, 2.12) which was maintained at the school-level (1.97; 1.39, 2.78). Early-life antibiotic use also had a strong association that was maintained (1.57; 1.49, 1.64 to 1.45; 1.08, 1.96). Early-life paracetamol use had a strong effect at the individual-level (1.40; 1.33, 1.48) but this disappeared at the school-level (0.94; 0.70, 1.28). There was a very marginal protective effect of television viewing at the individual-level (0.93; 0.88,0.99) but there was an adverse effect at the school-level (1.46; 1.06, 2.00). Heavy truck traffic had an adverse effect at the individual-level (1.17; 1.12, 1.22) but not at the school-level (0.90; 0.72, 1.13). Breast feeding was protective at the school-level (0.61; 0.44, 0.86) but with no effect at the individual-level (1.00; 0.95, 1.05).

In summary, of the variables previously hypothesised to be potentially affected by reverse causation, the associations for current paracetamol and early-life antibiotic use were found unlikely to be due to this potential bias as the findings for all three diseases were consistent at the individual- and school-level. However, the association with early-life paracetamol use could be due to reverse causation, as for all three diseases the association was strong at the individual-level, but disappeared when using school-level prevalence. One possible mechanism is that families with a history of asthma, eczema or rhinoconjunctivitis may avoid using ibuprofen (and previously aspirin) with their young children and so use paracetamol instead. However, it is not clear why this would only affect the use of paracetamol for fevers as a baby and not paracetamol for pain relief as a young child or adolescent.

Paternal smoking (particularly for adolescents) yielded surprising findings for all three diseases that are not fully explained. This showed an adverse effect in all individual-level analyses, although not particularly strong, but in school-level analyses this effect disappeared and in some cases the odds ratios were less than 1.0, i.e. a protective effect. Once again, the

unexpected school-level effect could be due to ecological confounding where the proportion of fathers who smoke is associated with some unmeasured confounder.

This method of investigating reverse causation cannot give definitive answers, but does provide very useful additional information over that provided by the individual-level analyses. Triangulating the two sets of analyses[127] is highly informative. In some instances, if similar results are obtained with the two approaches, this may indicate that they are unlikely to be due to bias, whereas differing results indicates that bias is present in at least one of the analyses.

Undertaking this work for all three diseases highlighted how similar the risk factors were. In Chapter 4 this was formalised in the synthesis paper using the same sample for all conditions (where data for the three outcomes and all risk factors and confounders were present). It is known that the three diseases tend to occur together in an individual (even if occurring at different time points in life) so it is possible that a risk factor is identified for one disease when it is actually a risk factor for only the other disease (which confounds the first association). However, models of combinations of diseases were included in this paper and showed that for individuals with symptoms of more than one of the conditions, the associations with risk factors were stronger (although not doubled or tripled). This indicated that the risk factors are indeed likely to affect each of the diseases, at least in part.

***Time trends***

The analyses discussed so far in this chapter have all been from ISAAC Phase III alone, since the focus was on risk factors for prevalence, and ISAAC Phase III was the largest dataset that included risk factor information. In the subsequent analyses, all three surveys were included in order to analyse the time trends, particularly for asthma prevalence.

In Chapter 5, the global trends were analysed to identify patterns of similarity and difference (Objective 2). The time trends were assessed across the maximum possible number of centres, i.e. all those centres with symptom data for more than one time-point (from ISAAC Phase I, Phase III and GAN Phase I). Adjustment was made for the country level factors of income group (from the World bank[2]) and region of the world. The findings showed that overall the prevalence of current asthma symptoms had not changed much over the 27 years of these studies; there was a very small decrease for adolescents (-0.43 percentage points per decade; 95% CI -1.10, 0.23), and there was no evidence of a change for children (-0.22; -1.00, 0.57). However, many individual centre prevalences had changed by more than 2 SE between ISAAC

Phase III and GAN Phase I indicating either random fluctuations, or more likely differing local trends in particular areas. Stratification by income group and region separately, showed where some differences were occurring. Prevalence decreased across both age groups in low-income countries (age 6-7: -1.37; -2.47, -0.27, age 13-14: -1.67; -2.70, -0.64), increased in lower-middle-income countries (age 6-7: 1.99; 0.33, 3.66, age 13-14: 1.69; 0.13, 3.25) and there was no evidence of change in upper-middle- and high-income countries. When stratifying by region, prevalence rose in Africa and the Eastern Mediterranean (age 6-7: 2.61; 0.76, 4.46, age 13-14: 2.09; 0.40, 3.78), decreased in South-East Asia and the Western Pacific (age 6-7: -1.35; -2.28, -0.41, age 13-14: -1.87; -2.78, -0.96), and there was no evidence of change in Europe or the Americas. It is hard to tell if the driver is really income or region due to the crossover between the two. The data at centre-level was too sparse to stratify by both factors together.

Even within the strata, there was substantial heterogeneity between centres that may be explained by other risk factors or possible external events, e.g. Syria showed a very high increase in asthma symptoms following an extended period of civil war. Forest plots could be used to explore and visualise this heterogeneity of time-trends, as used in the analysis on rhinoconjunctivitis in Appendix D,[128] although this can only be used with complete case data.

***Risk factors for time trends***

The analyses of the effects of risk factors on time trends are necessarily ecological (we only have risk factor data for centres, not for the same individuals over time). Therefore, before conducting the analyses of the effects of risk factors on centre-level time trends, in Chapter 6 ecological centre-level models were fitted, one for each age group, using both risk factor and asthma symptom prevalence data from ISAAC Phase III. The findings showed that, despite well distributed centre prevalences for each risk factor, fewer associations were found with asthma symptoms than at the individual- or school-level. In particular, the previous strong effects of current paracetamol at the individual-level (age 13-14: OR = 1.80; 95% CI = 1.75,1.86, age 6-7: 2.06; 1.97, 2.16) and school-level were not evident at the centre-level with effects of 10% increase in risk factor prevalence (age 13-14: change in prevalence = 1.80%; 95% CI = -0.82%, 0.84%, age 6-7: 0.38%; -0.84%, 1.59%), although for the younger age group early-life paracetamol was still associated with higher prevalence (1.50%; 0.43%, 2.57%).

For the main analysis on time trends, models incorporating centre-level asthma symptom prevalence at different time-points were fitted (ISAAC Phase I, III and GAN Phase I), although with risk factor prevalence only at ISAAC Phase III. These analyses showed that the associations of the risk factors with asthma symptom prevalence were weak or non-existent, i.e. the risk

factors were associated with asthma symptoms at the individual level, but did not explain the population time trends. In the fully adjusted models, for adolescents, there was no evidence that any of the risk factors were associated with changes in prevalence of asthma symptoms. For children there was weak evidence that current paracetamol use was associated with a decreasing trend in asthma symptom prevalence. When the younger age group was restricted to early life risk factors only (partially adjusted model), then there was an association between higher prevalence of antibiotic use in the first year of life and decreasing trend in asthma symptoms. In this case, higher prevalence of paracetamol use in the first year of life was associated with higher asthma symptom prevalence as at 2002 (ISAAC Phase III) but not with trends in prevalence.

Overall, the risk factors at the centre level do not show associations with asthma symptom prevalence and change, despite being good indicators of risk at the individual-level. Furthermore, incorporating the risk factors into these models restrict the sample, as not all ISAAC Phase III centres included the risk factor questionnaire.

***Prediction of asthma symptom prevalence in 2019***

To predict asthma symptom prevalence in 2019, including centres without recent data, the previous models from Chapter 5 were extended. The most appropriate approach was the frequentist, which involved fitting a mixed effects model (with country and centre clusters) where each individual observation includes time varying centre prevalence of outcome, country income and region. The estimated 2019 prevalence for all centres that had taken part in more than one ISAAC or GAN Phase I, predicting in both age groups for each centre, was 12.8% (95% CI 11.4%, 14.2%) if using income group as the main predictor and 13.2% (11.9%, 14.6%) if using region.

There was little difference between the two age groups (estimated difference of 0.3%), even when allowing a three-way interaction between time, age and income/region. The findings showed that the prevalence of asthma symptoms in adolescents in low-income countries was reducing (-1.7% per decade; 95% CI -3.1%, -0.3%) with no evidence of a pattern of change in other income categories. Regionally, there was evidence that prevalence in both age groups was decreasing in South-East Asia and Western Pacific region (age 13-14: -1.9%; -3.0%, -0.7%, age 6-7: -1.4%; -2.6%, -0.1%) whereas children age 6-7 in Africa and Eastern Mediterranean region and marginally in Europe were increasing (2.6%; 0.04%, 5.2% and 1.1%; -0.1%, 2.2% respectively).

The addition of risk factors to the models made little or no difference to the predictions of 2019 prevalence or time trends, but did reduce the precision, due to the smaller sample size available with risk factor data.

## 8.3 Findings in context

Many studies of childhood asthma have been conducted using similar methods to ISAAC and GAN, but usually within a single country. The most convincing evidence comes from various infant cohort studies, but even these do not generally provide consistent findings. For example, several infant cohort studies have investigated the effects of breastfeeding on asthma, some showing protective effects, some no effect, and some showing harmful effects.[129-131] The findings in this thesis concluded that breastfeeding was probably mildly protective.

A number of studies have shown positive associations between second-hand tobacco smoke (e.g. parental smoking) and asthma incidence in children[132, 133] which was confirmed in a meta-analysis[134] and was consistent with the findings in this thesis at the individual level.

Paracetamol use during pregnancy has been reported as a risk factor for asthma in children aged 6–7 years.[135] Similarly, several cross-sectional and longitudinal studies have reported a dose-response relationship between paracetamol use and an increase in asthma in children and asthma incidence in adults.[136, 137] In this thesis, paracetamol use (including in the first year of life) was consistently associated with higher prevalence of wheeze, and the school-level analyses indicated that this was unlikely to be due to confounding by indication.

When considering global differences there are few studies that included multiple countries. The European Community Respiratory Health Survey (ECRHS) was a survey of adults aged 20-44 from 48 centres (mainly from Europe but with 9 non-European centres) that showed the highest prevalence to be in English speaking countries,[138] which is similar to what was found in ISAAC and GAN in adolescents and children. However very few non-affluent countries were included. A direct comparison of the ISAAC and ECRHS findings, for those countries which took part in both surveys, found that although there were differences in the absolute levels of prevalence observed in the two surveys, there was good overall agreement between findings from the studies with regard to international prevalence patterns.[139]

Considering time trends, there are mainly single country studies[140] which have shown a levelling off of asthma prevalence in affluent countries over the last 20 years following larger increases in previous decades. These time trends analyses were mainly in European and other affluent countries, and few studies have investigated time trends in non- affluent countries. These findings from single-country studies are consistent with the finding in this thesis that asthma prevalence has in general not increased in high income countries since the initial ISAAC Phase I survey in the early 1990s.

## 8.4 Strengths and limitations of the study data

The main strength of the ISAAC and GAN surveys was the standardised methodology used around the world across three phases of data collection. It was a considerable challenge to ensure that different centres run by different PIs in different languages could follow the same methodology. This was achieved through central management by the global GAN centre (and previously ISAAC) with additional support from the London and Murcia data centres in GAN. Standardised questionnaires included descriptions of symptoms, as these are less affected by healthcare practices and differences in diagnoses. When questionnaires were translated, they were then back translated by someone else and the questions compared. Data input was achieved by following a standard data coding manual that was sent to every centre. In GAN the London and Murcia data centres helped by liaising with centre PIs during data checking to ensure that the manual was correctly followed and any errors in data coding or data entry were fixed.

The large number of participants and high response rate within the studies was also a strength, providing the power to identify risk factors with smaller effects. However, this benefit was diluted when moving to a centre prevalence level dataset for the time trends analysis.
A limitation was the number of centres that took part in GAN Phase I. There were a large number of centres that expressed interest, but not all could actually conduct the surveys. This limited the overlap of centres between ISAAC and GAN, and therefore the data available for analysing time trends; in particular, there were very few centres that took part in all three surveys. Additionally, the centres were not representative of the world as a whole, with some countries providing data from multiple centres while many countries were not represented at all, making it difficult to produce valid global estimates.

For these reasons, when examining time trends, some of the data were omitted (i.e. for those centres which only did one phase of the survey), and hence there was a loss of statistical power. It should also be noted that the three surveys involved different individuals (for obvious reasons as this is not a life course study, but rather a series of cross-sectional surveys with different participants), and often involved different schools. It may have been useful to use the same schools so that trends could be followed at school-level which would keep more information than centre-level, although on the other hand, this could mean that the surveys became non-representative since they would not include newly established schools. As it is, all outcomes and risk factors were summarised to centre prevalence level so there was only one record per centre per time point. For example, paracetamol use may have a substantial effect

at the individual level but there would have to be large differences in the prevalence of paracetamol use between different centres in order for an association to be reflected at the centre-level.

## 8.5 Statistical issues

The structure of the data involved multiple cluster levels, achieved through a complex recruitment and sampling process. More usually, a clustered analysis would have two levels but the ISAAC and GAN studies had four: countries, centres, schools and individuals. Centres were the highest true study unit. They were not randomly selected, and participation was dependent on finding enthusiastic local investigators who could obtain funding. In some countries multiple centres took part, resulting in an extra higher level to account for dependence between centres in the same country, which added complexity to all the models and their interpretation. In each centre, schools were randomly selected from all schools in the geographical area served by the centre (unless there were fewer than 10 schools, in which case all were selected). Within each school, the individuals were comprised of all available children in the right age-range (i.e. not those off sick or who opted out of completion).

With any cross-sectional survey there are always concerns about bias, which can take many forms. The temporality of exposures and outcomes needs to be considered. In the ISAAC and GAN questionnaires, both the outcome and most of the current risk factors are assessed over the past year. In the child questionnaire the early life questions are based on the first year of life which is probably before the onset of asthma,[10] (although less so for eczema[11]).

Another area that might cause bias is misclassification of the exposure(s) and/or the outcome. Most questions in the ISAAC and GAN studies were categorical, and were transformed to binary variables for the analyses. If there is non-differential (random) misclassification in an exposure from participants accidentally answering wrongly then in general this should bias results towards the null.[141] However, in a fully adjusted model, even if misclassification is non-differential, if it occurs in more than one of the exposures or confounders then effects could be biased in either direction. In addition, non-differential misclassification of the outcome would usually bias results towards the null, making it harder to detect associations[4].

Of perhaps more concern is differential misclassification where the answers given are related to the outcome. In particular, for the early-life questions in the children's questionnaire, recall bias could be an issue. For example, it may be easier to remember things about your child's

past if you had thought about these issues following an asthma diagnosis. However, many of the questions were on fairly easy to remember facts which would not be as susceptible to recall bias (e.g. pets, breastfeeding, parental smoking, birthweight).

Missing data can also cause problems, particularly if the reason for missingness is related to the outcome or exposure. Generally, for the ISAAC and GAN studies the overall response rates were high, but there were still participants who didn't take part or who missed out some questions. If outcomes or risk factors are missing completely at random (MCAR) then only the power of the study, or sample size, is affected. If responses are missing at random (MAR), i.e. all of the determinants of the missingness can be adjusted for, then results should also not be biased (e.g. if boys are more likely to miss out questions then sex can be included as a confounder and the data assumed MCAR within each sex category). If on the other hand data is missing not at random (MNAR), i.e. the missingness is related to unknown but relevant facts, then there could be biased results (e.g. people with asthma being off school and unable to complete the questionnaire).

Chapter 3 showed how for ISAAC Phase III, the common sample (those non-missing for all risk factors) was one-third smaller than the maximum sample (those with at least one non-missing risk factor). However, this was not based on one low response question, but rather a large number of questions where there were a few missing values. This seemed to imply a random missingness as there was no identifiable pattern. Once summarised up to the centre-level for time trends analysis, missing data became less of an issue, as individual values were not being compared so summaries could be based on the maximum number with data for a risk factor. Thus the proportion of missing values decreased to around 10% on average for each risk factor.

Unmeasured or residual confounding is also likely to be an issue in these analyses. The exposure measures were mainly binary, such as maternal smoking. There is a difference between a social smoker and a regular smoker, for example, which is not captured by the ISAAC questions. There is also considerable unexplained variation in symptom prevalence between centres which implies there is unmeasured confounding. This is not surprising, as there is still a great deal that is not known about the causes of asthma. There is also the possibility of collider bias if one of the risk factors adjusted for is actually a collider rather than a confounder i.e. if it is a common effect of another risk factor in the model and an unmeasured confounder (or of two risk factors in the model). Adjusting for such a variable

would open a back door pathway which would have been blocked if the relevant variable (collider) had not been adjusted for.[142]

In the time trends analyses, all models were fitted using an assumption of linearity in the time trend. Although statistically there was no evidence against linearity overall in the models (Chapter 5), it is likely that many centres had non-linear changes in prevalence, and there could be different true patterns for different groups. However, given the lack of improvement to the model using a quadratic, and the available sample size for the analysis, more complex models of the time trends would have been unlikely to see improvements in fit or predictions. The models would certainly be underpowered to detect different shapes of time trend in different groups.

## 8.6 Recommendations for future work

Further work with the existing ISAAC and GAN data sets could involve assessing whether changes in risk factor prevalence are associated with changes in symptom prevalence. This was not included as part of this thesis as there were very few centres with two time-points of risk factor data. Risk factor data were not available in ISAAC Phase I, so any assessment of changes in risk factor prevalence would be restricted to the overlap between ISAAC Phase III (those centres who did the environmental questionnaire) and GAN Phase I. However, if more centres complete GAN Phase I (as late centres), or if a future GAN Phase is larger, then this work would be valuable. It may also be possible to collect information on population-level changes in risk factors (e.g. changes in smoking rates or air pollution levels); this is discussed more below.

Another piece of work that could be conducted is to repeat part of the analysis from Chapter 3 using GAN Phase I data, i.e. fitting fully adjusted multi-level models on the same risk factors to compare results between the two studies (GAN Phase I and ISAAC Phase III). This could assess whether the same risk factors are still associated with symptoms at an individual level. Given that 15 years has passed since ISAAC Phase III, up to date information on risk factor effects at the individual-level would be very useful, and differences may provide insights into the nature of the observed associations.

Future work could also involve expanding the predictive time trend analyses using data available at the country level in order to better predict asthma (or eczema or rhinoconjunctivitis) prevalence at the global level. This would more fully utilise the method of using predictions. However, it would involve building almost a whole new exposure dataset

from information such as the World Bank indicators[143] and WHO Global Health Observatory[144]. There would need to be many different exposures and almost all countries included, along with population size, for useful global (or stratified global) predictions, similar to methods used in GBD.[98,99]

Finally, principal components analysis (PCA) was considered for use with the available risk factors in the time trends model so that one summary exposure variable could be used in the model for stratification, representing a mix of risk factors. However, there were few risk factors that showed any effect on time trends, so this did not seem appropriate. It could however be a way to incorporate many more possible risk factors, given that the questionnaires contain much more data, particularly on dietary patterns, than the items that have been considered in the publications to date. If each has a small effect, then a combination of exposures may be a better way to identify groups of countries with similar characteristics.

## 8.7 Conclusions

The ISAAC and GAN data sets are large and unique. Using these data sets, the best overall estimate of the current prevalence of asthma symptoms is 12.8% (95% CI=11.4%, 14.2%), with no significant difference between age groups, incorporating all 124 centres that took part in more than one ISAAC/GAN survey.

The risk factors that were identified at the individual level do not seem to explain the differences between centres and countries, or the time trends. Income group and region account for some of the differences, but the unexplained variation is still very high. Perhaps other types of higher-level risk factors (e.g. summary markers of Westernisation[126]) may have more explanatory power.

Statistically, this work demonstrates that even very large studies can have problems with lack of precision depending on the methods used. In a multi-level model, the analysis level used is very important and can change the findings dramatically. There is always a need to interpret effects carefully with hierarchical data. All levels need to be accounted for in order to gain correct inferences at the relevant level, but collapsing the data to a higher level necessarily loses information and power. To ask the question, “What factors influence asthma symptoms around the world?” gives very different answers if you interpret this as a question about

individual- or population-level exposures. The risk factors in individuals may not be the same as the risk factors that affect population prevalence.[145] Both are valid and important questions.

Using the different levels of analysis, it was found that reverse causation was probably not a major factor in the identified individual-level associations of risk factors with asthma, eczema or rhinoconjunctivitis, with the possible exception of paracetamol use in the first year of life. The estimated time trends showed differences between income group and region, although still with a large amount of unexplained variation. The effects of risk factors on time trends were very small, or non-existent, at the centre-level, despite strong individual-level associations with asthma symptom prevalence.

Global patterns in asthma symptoms are extremely complex with substantial variation in both absolute levels and trends. From the analyses in this thesis there is no clear overall change in prevalence, but this conclusion may hide problem areas where the prevalence of asthma is increasing greatly. There is also the concern that even in areas where prevalence is not increasing, the burden of asthma may still be substantial, and asthma management may be poor.

# Appendices

# A Relevant publications

List of relevant papers, both published and submitted, co-written by the author during the period of this PhD.

**Published articles**

1. Silverwood RJ, Rutter CE, Mitchell EA, et al. Are environmental risk factors for current wheeze in the International Study of Asthma and Allergies in Childhood (ISAAC) phase three due to reverse causation? *Clinical and Experimental Allergy.* 2019; 1–12. DOI:10.1111/cea.13325
   Contribution: Lead analyst and support writer. In thesis in Chapter 3.

2. Rutter CE, Silverwood RJ, Williams HC, et al. Are environmental factors for atopic eczema in ISAAC Phase Three due to reverse causation? *Journal of Investigative Dermatology* (2019) 139, 1023e1036. DOI:10.1016/j.jid.2018.08.035
   Contribution: Lead analyst and lead author. In thesis in Chapter 3.

3. Rutter CE, Silverwood RJ, Asher MI, et al. Comparison of individual-level and population-level risk factors for rhinoconjunctivitis, asthma, and eczema in the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *World Allergy Organization Journal.* 2020; 13:100123. DOI:10.1016/j.waojou.2020.100123
   Contribution: Lead analyst and lead author. In thesis in Chapter 4.

4. Ellwood P, Ellwood E, Rutter CE, et al. Global Asthma Network Phase I Surveillance: Geographical Coverage and Response Rates. *Journal of Clinical Medicine.* 2020, 9, 3688. DOI:10.3390/jcm9113688
   Contribution: Support analyst and support writer. Not in thesis.

5. Asher MI, Rutter CE, Bissell K, et al. Worldwide trends in the burden of asthma symptoms in school-aged children: Global Asthma Network Phase I cross-sectional study. *Lancet.* 2021; 398:1569-80. DOI:10.1016/S0140-6736(21)01450-1
   Contribution: Lead analyst and co-lead author. In thesis in Chapter 5.

6. Strachan DP, Rutter CE, et al. Worldwide time trends in prevalence of symptoms of rhinoconjunctivitis in children: Global Asthma Network Phase I. *Pediatric Allergy and Immunology.* 2022 Jan;33(1):e13656. DOI:10.1111/pai.13656. Epub 2021 Sep 21. PMID: 34453861.
   Contribution: Support analyst and support writer. In thesis in Appendix D.

7. García-Marcos L, Asher MI, Pearce N, et al. The burden of asthma, hay fever and eczema in children in 25 countries: GAN Phase I study. *Eur Respir J.* 2022 Feb 10:2102866. DOI:10.1183/13993003.02866-2021. Epub ahead of print. PMID: 35144987.
   Contribution: Support analyst and editing/reviewing. Not in thesis.

8. Mortimer K, Lesosky M, García-Marcos L, et al. The burden of asthma, hay fever and eczema in adults in 17 countries: GAN Phase I study. Eur Respir J. 2022 Feb 24:2102865. DOI:10.1183/13993003.02865-2021. Epub ahead of print. PMID: 35210319.
   Contribution: Editing and reviewing. Not in thesis.

**Submitted articles**

9. Langan SM, Mulick AR, Rutter CE, et al. Is the prevalence of eczema in school age children still increasing globally? A Global Asthma Network Phase One Study. *Allergy* (submitted May 2022)
   Contribution: Lead analysis lead and support writer. In thesis in Appendix E.

**Other publications**

10. Global Asthma Network. The Global Asthma Report 2018. Auckland, New Zealand: Global Asthma Network; 2018
    Contribution: Co-author of chapter 7 on Factors Affecting Asthma. Not in thesis.

11. Global Asthma Network. The Global Asthma Report 2022. Auckland, New Zealand: Global Asthma Network; in print.
    Contribution: Lead author of chapter 3 on The Global Burden of Asthma and co-author of chapter 4 on Asthma Mortality. Not in thesis.

# B Evidence of copyright retention for papers I, II, III, IV, V and VI

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## Paper IV (DOI:10.1016/S0140-6736(21)01450-1)



## Paper V (DOI:10.1111/pai.13656)



## Paper VI

This is not yet published.

# C ISAAC Phase III previously published results summary

*Table C.1 ISAAC Phase III world-wide papers on risk factor exposures for age 6-7*

| Paper | Exposure | Sample type* | Asthma symptoms in last 12 mths OR (95% CI) | Eczema symptoms in last 12 mths OR (95% CI) | Rhinoconjunctivitis in last 12 mths OR (95% CI) | Covariates |
|---|---|---|---|---|---|---|
| Paracetamol[38] | Paracetamol given in 1st year | Maximum | 1.76 (1.68,1.85) | 1.54 (1.47,1.61) | 1.78 (1.69,1.86) | Sex, region, language, GNI |
| | | Common | 1.77 (1.66,1.89) | 1.54 (1.44,1.64) | 1.74 (1.62,1.87) | Sex, region, language, GNI |
| | | Common | 1.46 (1.36,1.56) | 1.35 (1.26,1.45) | 1.48 (1.38,1.60) | Sex, region, language, GNI, mother's education, antibiotics in 1st year of life, breastfed, mother currently smokes, father currently smokes, fruit, vegetables, pulses, any younger siblings, any older siblings |
| | Paracetamol - None in last 12 months[R]<br>At least once in last 12 months<br>At least once per month for last 12 months | Maximum | 1.00<br>1.55 (1.46,1.65)<br>3.45 (3.22,3.69) | 1.00<br>1.26 (1.18,1.33)<br>1.94 (1.81,2.07) | 1.00<br>1.37 (1.28,1.45)<br>2.85 (2.65,3.06) | Sex, region, language, GNI |
| | Paracetamol - None in last 12 months[R]<br>At least once in last 12 months<br>At least once per month for last 12 months | Common | 1.00<br>1.74 (1.58,1.91)<br>3.73 (3.35,4.14) | 1.00<br>1.25 (1.14,1.37)<br>2.05 (1.85,2.28) | 1.00<br>1.42 (1.29,1.56)<br>3.11 (2.79,3.47) | Sex, region, language, GNI |
| | Paracetamol - None in last 12 months[R]<br>At least once in last 12 months<br>At least once per month for last 12 months | Common | 1.00<br>1.61 (1.46,1.77)<br>3.23 (2.91,3.60) | 1.00<br>1.18 (1.08,1.30)<br>1.87 (1.68,2.08) | 1.00<br>1.32 (1.20,1.46)<br>2.81 (2.52,3.14) | Sex, region, language, GNI, mother's education, antibiotics in 1st year of life, breastfed, mother currently smokes, father currently smokes, fruit, vegetables, pulses, any younger siblings, any older siblings |
| Truck Traffic[39] | Truck Traffic – All day<br>Frequently<br>Seldom<br>Never[R] | Maximum | 1.46 (1.36,1.56)<br>1.31 (1.24,1.39)<br>1.09 (1.03,1.15)<br>1.00 | 1.37 (1.28,1.48)<br>1.20 (1.13,1.28)<br>1.08 (1.02,1.14)<br>1.00 | 1.44 (1.34,1.54)<br>1.24 (1.17,1.32)<br>1.07 (1.01,1.13)<br>1.00 | Sex, region, language, GNI |
| | Truck Traffic – All day<br>Frequently<br>Seldom<br>Never[R] | Common | 1.48 (1.34,1.63)<br>1.35 (1.25,1.46)<br>1.08 (1.01,1.16)<br>1.00 | 1.42 (1.29,1.56)<br>1.21 (1.11,1.31)<br>1.08 (1.00,1.16)<br>1.00 | 1.43 (1.29,1.59)<br>1.20 (1.10,1.30)<br>1.01 (0.93,1.09)<br>1.00 | Sex, region, language, GNI |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Truck Traffic – All day<br>Frequently<br>Seldom<br>Never[R] | Common | 1.35 (1.22,1.48)<br>1.27 (1.17,1.38)<br>1.05 (0.98,1.13)<br>1.00 | 1.36 (1.23,1.50)<br>1.18 (1.09,1.28)<br>1.07 (0.99,.1.15)<br>1.00 | 1.33 (1.20,1.48)<br>1.14 (1.05,1.24)<br>0.99 (0.91,1.07)<br>1.00 | Sex, region, language, GNI, mother's education, cooking fuel, mother currently smokes, father currently smokes, TV viewing, exercise, any older siblings, any younger siblings, fast food, current paracetamol use |
| Antibiotics[40] | Antibiotics in 1st year of life | Maximum | 1.95 (1.88,2.03) | 1.60 (1.53,1.67) | 1.86 (1.78,1.94) | Sex, region, language, GNI |
| | | Common | 1.96<br>(1.85,2.07) | 1.58<br>(1.49,1.68) | 1.8<br>(1.70,1.92) | Sex, region, language, GNI |
| | | Common | 1.70 (1.60,1.80) | 1.42 (1.33,1.51) | 1.56 (1.46,1.66) | Sex, region, language, GNI, mother's education, breastfed, mother currently smokes, father currently smokes, veg, pulses, fruit, paracetamol in 1st year of life, current paracetamol use, any older siblings, any younger siblings |
| Breastfeeding[41] | Was Breastfed | Maximum | 0.95 (0.91,1,00) | 1.08 (1.03,1.13) | 0.97 (0.92,1.01) | Sex, region, language, GNI |
| | | Common | 0.94 (0.88,1.00) | 1.02 (0.95,1.10) | 0.98 (0.91,1.06) | Sex, region, language, GNI |
| | | Common | 0.99 (0.92,1.05) | 1.05 (0.97,1.12) | 1.00 (0.93,1.08) | Sex, region, language, GNI, birthweight, mother's education, mother smoked in 1st year of life, cat or dog in 1st year of life, paracetamol in 1st year of life, antibiotics in 1st year of life, any older siblings, farm animal exposure in utero, farm animal exposure in 1st year of life |
| Farm Animals[42] | Contact with Farm animals in 1st year of life | Maximum | 1.27 (1.20,1.35) | 1.33 (1.25,1.41) | 1.31 (1.24,1.40) | Sex, region, language, GNI |
| | | Common A | 1.14 (1.05,1.24) | 1.19 (1.10,1.30) | 1.22 (1.12,1.34) | Sex, region, language, GNI |
| | | Common A | 1.09 (1.00,1.18) | 1.16 (1.07,1.27) | 1.18 (1.08,1.30) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Maternal contact with farm animals while pregnant | Maximum | 1.36 (1.28,1.44) | 1.30 (1.22,1.39) | 1.33 (1.25,1.42) | Sex, region, language, GNI |
| | | Common B | 1.19 (1.09,1.30) | 1.21 (1.10,1.32) | 1.29 (1.17,1.43) | Sex, region, language, GNI |
| | | Common B | 1.13 (1.03,1.24) | 1.17 (1.07,1.29) | 1.24 (1.12,1.37) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |
| Cat and Dogs[43] | Had a Cat in 1st year of life | Maximum | 1.30 (1.23,1.36) | 1.21 (1.14,1.28) | 1.19 (1.13,1.27) | Sex, region, language, GNI |
| | | Common A | 1.19 (1.10,1.28) | 1.09 (1.01,1.18) | 1.10 (1.01,1.19) | Sex, region, language, GNI |
| | | Common A | 1.17 (1.09,1.26) | 1.09 (1.01,1.17) | 1.09 (1.00,1.18) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |
| | Has a Cat currently | Maximum | 1.18 (1.12,1.23) | 1.12 (1.07,1.18) | 1.10 (1.04,1.16) | Sex, region, language, GNI |
| | | Common B | 1.11 (1.03,1.18) | 1.06 (0.99,1.13) | 1.08 (1.00,1.16) | Sex, region, language, GNI |
| | | Common B | 1.07 (1.00,1.14) | 1.05 (0.98,1.12) | 1.07 (0.99,1.15) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |
| | Had a Dog in 1st year of life | Maximum | 1.19 (1.14,1.24) | 1.13 (1.08,1.19) | 1.17 (1.11,1.22) | Sex, region, language, GNI |
| | | Common C | 1.07 (1.01,1.14) | 1.05 (0.99,1.12) | 1.09 (1.02,1.17) | Sex, region, language, GNI |
| | | Common C | 1.03 (0.97,1.09) | 1.04 (0.97,1.10) | 1.06 (0.99,1.14) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Has a Dog currently | Maximum | 1.10 (1.06,1.15) | 1.03 (0.98,1.07) | 1.06 (1.01,1.11) | Sex, region, language, GNI |
| | | Common D | 1.03 (0.97,1.09) | 1.04 (0.97,1.10) | 1.04 (0.98,1.12) | Sex, region, language, GNI |
| | | Common D | 0.98 (0.92,1.04) | 1.03 (0.97,1.09) | 1.03 (0.96,1.10) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |
| Tobacco[44] | Father currently smokes | Maximum | 1.17 (1.12,1.21) | 1.09 (1.04,1.13) | 1.08 (1.04,1.13) | Sex, region, language, GNI |
| | Mother currently smokes | Maximum | 1.28 (1.22,1.34) | 1.15 (1.09,1.21) | 1.12 (1.06,1.18) | Sex, region, language, GNI |
| | Mother smoked in first year of life | Maximum | 1.36 (1.29,1.43) | 1.20 (1.13,1.27) | 1.17 (1.10,1.24) | Sex, region, language, GNI |
| | Neither parent currently smokes[R]<br>Only mother currently smokes<br>Only father currently smokes<br>Both parents currently smoke | Maximum | 1.00<br>1.31 (1.22,1.41)<br>1.13 (1.08,1.18)<br>1.37 (1.29,1.45) | 1.00<br>1.15 (1.06,1.24)<br>1.07 (1.02,1.12)<br>1.19 (1.11,1.27) | 1.00<br>1.13 (1.04,1.23)<br>1.07 (1.02,1.12)<br>1.16 (1.09,1.24) | Sex, region, language, GNI |
| | Mother smoked at neither time[R]<br>Mother smoked first year of life only<br>Mother smokes currently only<br>Mother smoked at both times | Maximum | 1.00<br>1.38 (1.24,1.53)<br>1.23 (1.14,1.32)<br>1.39 (1.31,1.47) | | 1.00<br>1.18 (1.05,1.33)<br>1.07 (0.99,1.16)<br>1.16 (1.09,1.24) | Sex, region, language, GNI |
| | Father currently smokes – None[R]<br>1-9 cigarettes per day<br>10-19 cigarettes per day<br>20 or more cigarettes per day | Maximum | 1.00<br>1.06 (1.00,1.12)<br>1.15 (1.08,1.22)<br>1.27 (1.19,1.35) | 1.00<br>1.08 (1.02,1.15)<br>1.04 (0.97,1.11)<br>1.11 (1.04,1.20) | 1.00<br>1.04 (0.98,1.11)<br>1.06 (0.99,1.13)<br>1.10 (1.03,1.18) | Sex, region, language, GNI |
| | Mother currently smokes – None[R]<br>1-9 cigarettes per day<br>10-19 cigarettes per day<br>20 or more cigarettes per day | Maximum | 1.00<br>1.25 (1.17,1.34)<br>1.29 (1.20,1.38)<br>1.44 (1.31,1.59) | 1.00<br>1.17 (1.08,1.26)<br>1.13 (1.04,1.23)<br>1.15 (1.02,1.30) | 1.00<br>1.18 (1.09,1.27)<br>1.02 (0.94,1.11)<br>1.14 (1.02,1.28) | Sex, region, language, GNI |

| | | | | | | |
|---|---|---|---|---|---|---|
| BMI, Exercise and TV[45] | BMI - Underweight<br>Normal[R]<br>Overweight<br>Obese | Common | 0.96 (0.88,1.06)<br>1.00<br>1.20 (1.09,1.31)<br>1.27 (1.12,1.44) | 0.92 (0.83,1.01)<br>1.00<br>1.08 (0.98,1.19)<br>1.20 (1.05,1.37) | 0.97 (0.88,1.06)<br>1.00<br>0.99 (0.91,1.09)<br>0.99 (0.87,1.12) | Sex, region, language, GNI, exercise, TV viewing, BMI measurement type |
| | Exercise - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Common | 1.00<br>1.04 (0.96,1.12)<br>0.83 (0.76,0.91) | 1.00<br>1.02 (0.95,1.11)<br>0.97 (0.88,1.06) | 1.00<br>1.11 (1.03,1.19)<br>0.98 (0.89,1.07) | Sex, region, language, GNI, BMI, TV viewing, BMI measurement type |
| | TV - less than 1 hr per day[R]<br>1hr but less than 3hrs per day<br>3hrs but less than 5hrs per day<br>5hrs or more per day | Common | 1.00<br>1.04 (0.96,1.13)<br>1.12 (1.01,1.25)<br>1.26 (1.07,1.47) | 1.00<br>0.98 (0.91,1.07)<br>0.99 (0.89,1.10)<br>1.05 (0.90,1.23) | 1.00<br>0.93 (0.86,1.00)<br>1.00 (0.90,1.11)<br>1.02 (0.86,1.20) | Sex, region, language, GNI, exercise, BMI, BMI measurement type |
| Diet[46] | Butter - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.96 (0.91,1.01)<br>0.99 (0.94,1.05) | 1.00<br>0.99 (0.93,1.04)<br>0.96 (0.91,1.02) | 1.00<br>1.00 (0.94,1.05)<br>0.98 (0.92,1.04) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Cereals - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.95 (0.86,1.05)<br>0.93 (0.84,1.02) | 1.00<br>0.98 (0.89,1.08)<br>1.00 (0.91,1.10) | 1.00<br>1.04 (0.94,1.16)<br>0.97 (0.88,1.08) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Eggs - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.80 (0.75,0.85)<br>0.76 (0.70,0.81) | 1.00<br>0.78 (0.73,0.84)<br>0.76 (0.71,0.82) | 1.00<br>0.82 (0.76,0.88)<br>0.82 (0.76,0.89) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Fast food - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>1.08 (1.03,1.13)<br>1.17 (1.08,1.27) | 1.00<br>1.04 (0.99,1.09)<br>1.04 (0.95,1.14) | 1.00<br>1.00 (0.95,1.05)<br>1.20 (1.11,1.31) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Fruit - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.96 (0.88,1.05)<br>0.87 (0.80,0.95) | 1.00<br>0.96 (0.88,1.05)<br>0.90 (0.82,0.98) | 1.00<br>0.88 (0.80,0.96)<br>0.83 (0.76,0.91) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Margarine - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.98 (0.92,1.03)<br>1.00 (0.95,1.06) | 1.00<br>1.00 (0.95,1.06)<br>1.01 (0.95,1.07) | 1.00<br>1.06 (1.00,1.12)<br>1.11 (1.04,1.18) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Meat - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.86 (0.79,0.95)<br>0.86 (0.78,0.94) | 1.00<br>0.87 (0.80,0.96)<br>0.85 (0.78,0.93) | 1.00<br>0.88 (0.80,0.96)<br>0.87 (0.79,0.96) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Milk - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.88 (0.80,0.96)<br>0.83 (0.76,0.90) | 1.00<br>0.80 (0.73,0.88)<br>0.73 (0.67,0.79) | 1.00<br>0.88 (0.79,0.97)<br>0.77 (0.71,0.85) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Nuts - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.90 (0.86,0.95)<br>0.86 (0.79,0.94) | 1.00<br>0.87 (0.82,0.91)<br>0.90 (0.82,0.99) | 1.00<br>0.93 (0.88,0.97)<br>0.96 (0.88,1.05) | Sex, region, language, GNI, exercise, TV viewing,<br>mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Pasta - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.96 (0.90,1.03)<br>0.96 (0.89,1.03) | 1.00<br>0.95 (0.89,1.02)<br>1.00 (0.93,1.08) | 1.00<br>0.96 (0.89,1.03)<br>1.02 (0.94,1.11) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Potato - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.96 (0.89,1.03)<br>0.97 (0.90,1.05) | 1.00<br>0.92 (0.86,0.98)<br>0.92 (0.85,0.99) | 1.00<br>0.91 (0.85,0.97)<br>0.90 (0.84,0.97) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Pulses - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.93 (0.88,0.98)<br>0.94 (0.88,1.00) | 1.00<br>0.89 (0.84,0.95)<br>0.90 (0.84,0.96) | 1.00<br>0.93 (0.87,0.98)<br>0.95 (0.88,1.02) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Rice - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.98 (0.91,1.05)<br>0.96 (0.89,1.04) | 1.00<br>0.98 (0.90,1.06)<br>1.01 (0.93,1.11) | 1.00<br>0.97 (0.90,1.05)<br>1.05 (0.96,1.14) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Seafood - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.90 (0.86,0.95)<br>0.88 (0.82,0.94) | 1.00<br>0.92 (0.87,0.97)<br>0.92 (0.85,0.99) | 1.00<br>0.96 (0.91,1.01)<br>0.95 (0.88,1.02) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |
| | Vegetables - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>0.89 (0.83,0.95)<br>0.88 (0.82,0.94) | 1.00<br>0.94 (0.88,1.01)<br>0.93 (0.87,0.99) | 1.00<br>0.91 (0.84,0.97)<br>0.92 (0.86,0.99) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes, mother smoked in 1st year of life |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cooking Fuels[47] | Any use of open fire for cooking | Common A | 1.78 (1.51,2.10) | 0.93 (0.73,1.21) | 1.24 (0.97,1.59) | Sex, region, language, GNI |
| | | Common A | 1.51 (1.25,1.81) | 1.14 (0.96,1.35) | 1.06 (0.86,1.30) | Sex, region, language, GNI, mother's education, mother currently smokes, father currently smokes, TV viewing, exercise, any older siblings, any younger siblings, fast food, level of truck traffic, current paracetamol use |
| | Cooking on open fire only | Common B | 1.79 (1.52,2.10) | 1.10 (0.91,1.33) | 1.02 (0.80,1.30) | Sex, region, language, GNI |
| | | Common B | 2.17 (1.64,2.87) | 1.08 (0.75,1.55) | 1.12 (0.74,1.69) | Sex, region, language, GNI, mother's education, mother currently smokes, father currently smokes, TV viewing, exercise, any older siblings, any younger siblings, fast food, level of truck traffic, current paracetamol use |
| Birthweight[48] | Birthweight <2.5kg | Maximum | 1.20 (1.12,1.30) | 0.93 (0.85,1.01) | 1.08 (1.00,1.17) | Sex, region, language, GNI, mother smoked in 1st year of life |
| | 2.5kg <= Birthweight < 3kg | | 1.08 (1.03,1.14) | 1.00 (0.94,1.05) | 1.01 (0.96,1.07) | |
| | 3kg <= Birthweight < 4kg[R] | | 1.00 | 1.00 | 1.00 | |
| | 4kg <= Birthweight < 4.5kg | | 1.01 (0.93,1.09) | 0.96 (0.88,1.05) | 0.96 (0.88,1.05) | |
| | Birthweight >= 4.5kg | | 1.05 (0.93,1.19) | 1.07 (0.94,1.23) | 1.01 (0.88,1.16) | |
| Migration[49] | Migration | Maximum | 0.79 (0.72,0.88) | 0.74 (0.66,0.83) | 0.91 (0.81,1.01) | Sex, region, language, GNI |
| | | Maximum | 0.87 (0.77,0.98) | 0.80 (0.70,0.91) | 0.93 (0.81,1.06) | Sex, region, language, GNI, eggs, fruit, meat, milk, vegetables, nuts, pulses, seafood, potato, current paracetamol use, antibiotics in 1st year of life, mother's education and mother currently smokes |
| Siblings[50] | Siblings – None[R] | Maximum | 1.00 | 1.00 | 1.00 | Sex, region, language, GNI |
| | One | | 0.99 (0.94,1.04) | 1.09 (1.03,1.15) | 1.00 (0.95,1.06) | |
| | Two | | 0.96 (0.91,1.02) | 1.01 (0.98,1.08) | 0.95 (0.90,1.01) | |
| | Three or more | | 0.99 (0.92,1.05) | 1.04 (0.97,1.12) | 0.96 (0.90,1.04) | |
| | Older siblings (each extra sibling) | Common | 1.01 (0.99,1.03) | 0.98 (0.96,1.00) | 0.98 (0.96,1.00) | Sex, region, language, GNI, younger siblings |
| | Younger siblings (each extra sibling) | Common | 0.96 (0.93,0.98) | 1.06 (1.03,1.09) | 1.03 (1.00,1.06) | Sex, region, language, GNI, older siblings |

*Common (or common X) is the same sample within paper. [R]Reference category.

*Table C.2 ISAAC Phase III world-wide papers on risk factor exposures for age 13-14*

| Paper | Exposure | Sample Type* | Asthma symptoms in last 12 mths OR (95% CI) | Eczema symptoms in last 12 mths OR (95% CI) | Rhinoconjunctivitis in last 12 mths OR (95% CI) | Covariates |
|---|---|---|---|---|---|---|
| Acetominaphen[51] | Paracetamol - None in last 12 months[R]<br>At least once in last 12 months<br>At least once per month for last 12 months | Maximum | 1.00<br>1.38 (1.31,1.46)<br>2.36 (2.24,2.50) | 1.00<br>1.28 (1.20,1.36)<br>1.90 (1.78,2.03) | 1.00<br>1.34 (1.28,1.40)<br>2.23 (2.13,2.35) | Sex, region, language, GNI |
| | Paracetamol - None in last 12 months[R]<br>At least once in last 12 months<br>At least once per month for last 12 months | Common | 1.00<br>1.42 (1.34,1.52)<br>2.47 (2.31,2.64) | 1.00<br>1.31 (1.22,1.41)<br>1.97 (1.82,2.12) | 1.00<br>1.38 (1.31,1.47)<br>2.40 (2.26,2.55) | Sex, region, language, GNI |
| | Paracetamol - None in last 12 months[R]<br>At least once in last 12 months<br>At least once per month for last 12 months | Common | 1.00<br>1.43 (1.33,1.53)<br>2.51 (2.33,2.70) | 1.00<br>1.31 (1.21,1.42)<br>1.99 (1.82,2.16) | 1.00<br>1.38 (1.29,1.47)<br>2.39 (2.24,2.55) | Sex, region, language, GNI, mother's education, mother currently smokes, fruit, vegetables, pulses, any younger siblings, any older siblings |
| Truck Traffic[38] | Truck Traffic – All day<br>Frequently<br>Seldom<br>Never[R] | Maximum | 1.46 (1.36,1.56)<br>1.33 (1.25,1.41)<br>1.13 (1.07,1.19)<br>1.00 | 1.59 (1.47,1.72)<br>1.35 (1.25,1.44)<br>1.09 (1.03,1.17)<br>1.00 | 1.49 (1.41,1.59)<br>1.28 (1.21,1.35)<br>1.09 (1.03,1.14)<br>1.00 | Sex, region, language, GNI |
| | Truck Traffic – All day<br>Frequently<br>Seldom<br>Never[R] | Common | 1.47 (1.33,1.62)<br>1.31 (1.20,1.43)<br>1.09 (1.00,1.18)<br>1.00 | 1.67 (1.49,1.87)<br>1.37 (1.23,1.52)<br>1.10 (0.99,1.21)<br>1.00 | 1.51 (1.38,1.65)<br>1.29 (1.19,1.40)<br>1.08 (1.00,1.16)<br>1.00 | Sex, region, language, GNI |
| | Truck Traffic – All day<br>Frequently<br>Seldom<br>Never[R] | Common | 1.35 (1.23,1.49)<br>1.24 (1.13,1.35)<br>1.07 (0.98,1.16)<br>1.00 | 1.54 (1.37,1.73)<br>1.30 (1.17,1.45)<br>1.08 (0.97,1.19)<br>1.00 | 1.39 (1.27,1.52)<br>1.21 (1.12,1.32)<br>1.06 (0.98,1.14)<br>1.00 | Sex, region, language, GNI, mother's education, cooking fuel, mother currently smokes, father currently smokes, TV viewing, exercise, any older siblings, any younger siblings, fast food, current paracetamol use |

| | | | | | | |
|---|---|---|---|---|---|---|
| Cats and Dogs[43] | Has a Cat currently | Maximum | 1.14 (1.09,1.18) | 1.22 (1.16,1.28) | 1.16 (1.12,1.21) | Sex, region, language, GNI |
| | | Common A | 1.11 (1.05,1.18) | 1.27 (1.19,1.36) | 1.11 (1.05,1.18) | Sex, region, language, GNI |
| | | Common A | 1.09 (1.02,1.15) | 1.23 (1.15,1.32) | 1.08 (1.02,1.15) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |
| | Has a Dog currently | Maximum | 1.15 (1.11,1.20) | 1.21 (1.16,1.27) | 1.16 (1.12,1.20) | Sex, region, language, GNI |
| | | Common B | 1.16 (1.09,1.23) | 1.22 (1.14,1.30) | 1.13 (1.07,1.19) | Sex, region, language, GNI |
| | | Common B | 1.10 (1.04,1.16) | 1.16 (1.08,1.24) | 1.07 (1.01,1.13) | Sex, region, language, GNI, cooking fuel, mother's education, mother currently smokes, father currently smokes, exercise, TV viewing, fast food, current paracetamol use, any older siblings, any younger siblings, level of truck traffic |
| Tobacco[44] | Father currently smokes | Maximum | 1.20 (1.15,1.24) | 1.19 (1.14,1.25) | 1.15 (1.11,1.19) | Sex, region, language, GNI |
| | Mother currently smokes | Maximum | 1.32 (1.26,1.37) | 1.22 (1.16,1.28) | 1.20 (1.15,1.25) | Sex, region, language, GNI |
| | Neither parent smokes currently[R] | Maximum | 1.00 | 1.00 | 1.00 | Sex, region, language, GNI |
| | Only mother currently smokes | | 1.27 (1.19,1.36) | 1.20 (1.10,1.30) | 1.15 (1.08,1.23) | |
| | Only father currently smokes | | 1.13 (1.07,1.18) | 1.17 (1.10,1.23) | 1.12 (1.07,1.17) | |
| | Both parents currently smoke | | 1.43 (1.36,1.51) | 1.33 (1.24,1.42) | 1.27 (1.21,1.34) | |
| BMI, Exercise and TV[45] | BMI - Underweight | Common | 0.94 (0.88,1.01) | 0.89 (0.82,0.97) | 0.99 (0.93,1.05) | Sex, region, language, GNI, exercise, TV viewing, BMI measurement type |
| | Normal[R] | | 1.00 | 1.00 | 1.00 | |
| | Overweight | | 1.15 (1.08,1.22) | 1.16 (1.07,1.24) | 1.03 (0.97,1.09) | |
| | Obese | | 1.29 (1.14,1.46) | 1.42 (1.23,1.64) | 0.97 (0.86,1.09) | |
| | Exercise - never or occasionally[R] | Common | 1.00 | 1.00 | 1.00 | Sex, region, language, GNI, BMI, TV viewing, BMI measurement type |
| | 1 or 2 times a week | | 1.26 (1.18,1.33) | 1.18 (1.11,1.26) | 1.21 (1.15,1.28) | |
| | 3 or more times a week | | 1.27 (1.19,1.36) | 1.24 (1.15,1.34) | 1.25 (1.18,1.32) | |
| | TV - less than 1 hr per day[R] | Common | 1.00 | 1.00 | 1.00 | Sex, region, language, GNI, exercise, BMI, BMI measurement type |
| | 1hr but less than 3hrs per day | | 0.92 (0.85,0.99) | 0.94 (0.86,1.02) | 0.94 (0.88,1.01) | |
| | 3hrs but less than 5hrs per day | | 0.99 (0.92,1.07) | 0.99 (0.90,1.08) | 1.00 (0.94,1.08) | |
| | 5hrs or more per day | | 1.08 (1.00,1.17) | 1.16 (1.06,1.28) | 1.17 (1.09,1.26) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Diet[46] | Butter - never or occasionally[R])<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>1.05 (1.00,1.10)<br>1.06 (1.01,1.12) | 1.00<br>0.99 (0.93,1.05)<br>1.10 (1.03,1.17) | 1.00<br>1.01 (0.96,1.05)<br>1.10 (1.05,1.16) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Cereals - never or occasionally[R]<br>1or2×wk<br>≥3×wk | Maximum | 1.00<br>1.01 (0.94-1.09)<br>1.02 (0.95-1.09) | 1.00<br>0.98 (0.90-1.07)<br>1.02 (0.94-1.10) | 1.00<br>0.98 (0.91-1.05)<br>1.02 (0.96-1.09) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Eggs - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>0.98 (0.93-1.04)<br>1.05 (0.99-1.12) | 1.00<br>0.97 (0.91-1.03)<br>1.11 (1.04-1.20) | 1.00<br>0.92 (0.87-0.97)<br>1.02 (0.96-1.08) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Fast food - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.08 (1.03-1.13)<br>1.25 (1.18-1.33) | 1.00<br>1.04 (0.99-1.10)<br>1.20 (1.11-1.28) | 1.00<br>1.05 (1.01-1.10)<br>1.21 (1.14-1.28) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Fruit - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>0.90 (0.83-0.97)<br>0.87 (0.81-0.94) | 1.00<br>0.97 (0.89-1.06)<br>0.99 (0.91-1.08) | 1.00<br>0.84 (0.78-0.91)<br>0.85 (0.80-0.91) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Margarine - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.06 (1.01-1.11)<br>1.11 (1.05-1.18) | 1.00<br>1.04 (0.98-1.11)<br>1.17 (1.10-1.26) | 1.00<br>1.00 (0.95-1.05)<br>1.15 (1.09-1.22) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Meat - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.02 (0.94-1.09)<br>1.13 (1.05-1.22) | 1.00<br>0.91 (0.83-0.99)<br>1.07 (0.99-1.17) | 1.00<br>0.94 (0.87-1.01)<br>1.11 (1.03-1.20) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Milk - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>0.93 (0.87-0.99)<br>0.94 (0.89-1.00) | 1.00<br>0.90 (0.83-0.97)<br>0.89 (0.83-0.96) | 1.00<br>0.92 (0.87-0.98)<br>0.95 (0.89-1.00) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Nuts - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.04 (1.00-1.09)<br>1.10 (1.02-1.18) | 1.00<br>1.09 (1.03-1.15)<br>1.21 (1.12-1.31) | 1.00<br>1.01 (0.96-1.05)<br>1.10 (1.03-1.18) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Pasta - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.07 (1.01-1.13)<br>1.15 (1.07-1.22) | 1.00<br>0.99 (0.93-1.06)<br>1.13 (1.05-1.22) | 1.00<br>1.03 (0.97-1.08)<br>1.15 (1.08-1.22) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Potato - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.00 (0.94-1.06)<br>1.03 (0.97-1.11) | 1.00<br>1.02 (0.94-1.10)<br>1.12 (1.03-1.22) | 1.00<br>0.97 (0.91-1.03)<br>1.07 (1.00-1.14) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Pulses - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.01 (0.96-1.06)<br>1.02 (0.96-1.09) | 1.00<br>1.03 (0.97-1.10)<br>1.17 (1.09-1.26) | 1.00<br>0.99 (0.94-1.04)<br>1.09 (1.03-1.16) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Rice - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>0.97 (0.91-1.04)<br>1.06 (0.98-1.13) | 1.00<br>1.00 (0.93-1.08)<br>1.13 (1.04-1.23) | 1.00<br>1.02 (0.96-1.09)<br>1.13 (1.06-1.21) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Seafood - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>1.02 (0.98-1.07)<br>1.06 (0.99-1.14) | 1.00<br>1.08 (1.03-1.14)<br>1.21 (1.11-1.31) | 1.00<br>1.01 (0.97-1.06)<br>1.07 (1.00-1.15) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| | Vegetables - never or occasionally[R]<br>1 or 2 times a week<br>3 or more times a week | Maximum | 1.00<br>0.95 (0.89-1.01)<br>0.93 (0.87-0.99) | 1.00<br>0.94 (0.88-1.02)<br>1.02 (0.95-1.10) | 1.00<br>0.94 (0.88-1.00)<br>0.99 (0.93-1.05) | Sex, region, language, GNI, exercise, TV viewing, mother's education, mother currently smokes |
| Cooking Fuels[47] | Any use of open fire for cooking | Common A | 1.20 (1.06–1.37) | 1.35 (1.17-1.56) | 1.09 (0.96-1.24) | Sex, region, language, GNI |
| | | Common A | 1.19 (1.05–1.35) | 1.29 (1.13-1.49) | 1.07 (0.95-1.21) | Sex, region, language, GNI, mother's education, mother currently smokes, father currently smokes, TV viewing, exercise, any older siblings, any younger siblings, fast food, truck traffic, current paracetamol use |
| | Cooking on open fire only | Common B | 1.35 (1.15–1.58) | 1.37 (1.13-1.66) | 1.08 (0.91-1.28) | Sex, region, language, GNI |
| | | Common B | 1.35 (1.11–1.64) | 1.33 (1.07-1.66) | 1.02 (0.83-1.26) | Sex, region, language, GNI, mother's education, mother currently smokes, father currently smokes, TV viewing, exercise, any older siblings, any younger siblings, fast food, truck traffic, current paracetamol use |
| Migration[49] | Migration | Maximum | 0.86 (0.80–0.94) | 0.99 (0.91–1.09) | 0.88 (0.82–0.95) | Sex, region, language, GNI |
| | | Maximum | 0.88 (0.79–0.99) | 1.00 (0.88–1.13) | 0.90 (0.82–0.99) | Sex, region, language, GNI, eggs, fruit, meat, milk, vegetables, nuts, pulses, seafood, potato, current paracetamol use, mother's education, mother currently smokes |

| | | | | | | |
|---|---|---|---|---|---|---|
| Siblings[50] | Siblings – None[R]<br>One<br>Two<br>Three or more | Maximum | 1.00<br>0.96 (0.90-1.03)<br>0.98 (0.92-1.05)<br>0.97 (0.91-1.04) | 1.00<br>0.91 (0.85-0.98)<br>0.96 (0.88-1.03)<br>1.05 (0.97-1.13) | 1.00<br>0.97 (0.91-1.03)<br>0.96 (0.90-1.02)<br>1.03 (0.96-1.09) | Sex, region, language, GNI |
| | Older siblings (each extra sibling) | Common | 0.99 (0.97-1.01) | 1.03 (1.01-1.05) | 1.00 (0.99-1.02) | Sex, region, language, GNI, younger sibling |
| | Younger siblings (each extra sibling) | Common | 1.01** (0.99-1.03) | 1.03 (1.01-1.06) | 1.03 (1.01-1.05) | Sex, region, language, GNI, older siblings |

*Common (or common X) is the same sample within paper. [R]Reference category. **Misprint fixed from paper

# D Paper V: Worldwide time trends in prevalence of symptoms of rhinoconjunctivitis in children: Global Asthma Network Phase I

**Article submitted**

**SECTION A – Student Details**

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300807 | **Title** | Mrs |
| **First Name(s)** | Charlotte Emma | | |
| **Surname/Family Name** | Rutter | | |
| **Thesis Title** | Multi-level modelling of international variations and time trends in asthma and allergic diseases in children. | | |
| **Primary Supervisor** | Neil Pearce | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

**SECTION B – Paper already published**

| | | | |
|---|---|---|---|
| Where was the work published? | Pediatric Allergy and Immunology | | |
| When was the work published? | 28th August 2021 | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | **Yes** | Was the work subject to academic peer review? | **Yes** |

*If yes, please attach evidence of retention. If no, or if the work is being included in its published format, please attach evidence of permission from the copyright holder (publisher or other author) to include this work.

**SECTION C – Prepared for publication, but not yet published**

| | |
|---|---|
| Where is the work intended to be published? | |
| Please list the paper's authors in the intended authorship order: | |
| Stage of publication | |

**SECTION D – Multi-authored work**

| | |
|---|---|
| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role was on the paper was as CR below.<br><br>The following individual contributions were made: conceptualisation IA, KB, C-YC, AES, PE, LG-M, GM, NP, DS; data curation EE, PE, LG-M, EM, VP-F, CR, SR, RS; formal analysis NP, CR, DS; investigation IA; methodology IA, C-YC, PE, LG-M, NP, CR, DS, RS; project administration, IA, EE; PE; resources IA; supervision LG-M, NP, DS, RS; validation PE; visualisation EE, PE, CR; writing – original draft DS, CR, RS; writing – review/editing IA, KB, C-YC, AES, EE, PE, LG-M, EM, KM, VP-F, NP and the Global Asthma Network Phase I Study Group; the latter contributed original data to the analyses. Verification of the underlying data was undertaken by CR, NP, VP-F and DS. |

**SECTION E**

| | |
|---|---|
| **Student Signature** | [redacted] |
| **Date** | 21/03/2022 |

| | |
|---|---|
| **Supervisor Signature** | [redacted] |
| **Date** | 23/03/2022 |

## Abstract

**Background**

The Global Asthma Network (GAN), by using the International Study of Asthma and Allergies in Childhood (ISAAC) methodology, has updated trends in prevalence of symptoms of childhood allergic diseases, including non-infective rhinitis and conjunctivitis ('rhinoconjunctivitis'), which is reported here.

**Methods**

Prevalence and severity of rhinoconjunctivitis were assessed by questionnaire among schoolchildren in GAN Phase I and ISAAC Phase I and III surveys 15-23 years apart. Absolute rates of change in prevalence were estimated for each centre and modelled by multi-level linear regression to compare trends by age group, time period and per capita national income.

**Results**

Twenty-seven GAN centres in 14 countries surveyed 74,361 13- to 14-year-olds ('adolescents') and 45,434 6- to 7-year-olds ('children'), with average response proportions of 90% and 79% respectively. Many centres showed highly significant ($p < .001$) changes in prevalence of rhinoconjunctivitis in the past year ('current rhinoconjunctivitis') compared with ISAAC. The direction and magnitude of centre-level trends varied significantly ($p < .001$) both within and between countries. Overall, current rhinoconjunctivitis prevalence decreased slightly from ISAAC Phase III to GAN: -1.32% per 10 years, 95% CI [-2.93%, +0.30%] among adolescents; and -0.44% [-1.29%, +0.42%] among children. Together, these differed significantly ($p < .001$) from the upward trend within ISAAC. Among adolescents, centre-level trends in current rhinoconjunctivitis were highly correlated with those for eczema symptoms (rho = 0.72, $p < .0001$) but not with centre-level trends in asthma symptoms (rho = 0.15, $p = .48$). Among children, these correlations were positive but not significant.

**Conclusion**

Symptoms of non-infective rhinoconjunctivitis among schoolchildren may no longer be on the increase globally, although trends vary substantially within and between countries.

## Introduction

Non-infective rhinitis and conjunctivitis ('rhinoconjunctivitis') are common manifestations of allergic disease among children, and their prevalence varied substantially around the world during the 1990s, as documented by the International Study of Asthma and Allergies in Childhood (ISAAC) Phase I.[25] Approximately seven years later, a comparison of ISAAC Phase III with ISAAC Phase I assessed time trends in annual period prevalence of rhinoconjunctivitis symptoms among almost half a million children from 106 centres in 56 countries.[56] Although no consistent global pattern emerged, the average prevalence of rhinoconjunctivitis symptoms increased among both 6- to 7-year-olds and 13- to 14-year-olds. Greater increases were evident in centres from low- and middle-income countries, but prevalence decreased in many centres with the highest rates in ISAAC Phase I, suggesting that rhinoconjunctivitis symptoms may have peaked in those generally more affluent countries.[56]

In this paper, we extend those earlier ISAAC time trend comparisons to include more recent surveys using identical methodology, which were conducted by the Global Asthma Network[104] in 27 centres that had previously participated in ISAAC. This offers the opportunity to assess time trends over a longer period in both higher and lower income countries. We sought to evaluate whether the prevalence of symptoms of rhinoconjunctivitis among children has continued to rise, or has plateaued, or indeed started to decline, during the first two decades of the 21st century. We also compared this trend to those for symptoms of asthma (wheeze) and eczema (flexural itchy rash).

## Methods

The Global Asthma Network (GAN) was established in 2012 as a successor to ISAAC, in collaboration with the International Union Against Tuberculosis and Lung Disease. GAN Phase I, adapting the ISAAC approach and methods, focuses upon global surveillance of prevalence and severity of asthma symptoms, but has also included ISAAC questionnaires on symptoms of rhinoconjunctivitis and eczema.

Elsewhere, we have published the rationale and study design for GAN Phase I,[4, 104] the scope of completed fieldwork and its geographical overlap with ISAAC[21] and the results for time trends in prevalence of asthma symptoms, among GAN Phase I centres that previously participated in ISAAC.[146]

GAN Phase I surveys followed the standardised and validated ISAAC methodology,[2, 3, 103, 105, 106] and a specified protocol.[104] Cluster sampling was employed, selecting from a geographically defined sampling frame (the 'study centre') at least 10 schools at random (or all schools if <10),

from which all children of the relevant age (or class or grade) were surveyed. All centres studied 13- to 14-year-olds ('adolescents'), who self-completed written questionnaires at school. Additional inclusion of 6- to 7-year-olds ('children') was optional, and their questionnaires were completed at home by their parents. Sample sizes of at least 1000 and preferably 3000 were sought for each age group.

The symptom definitions used for comparisons in this paper were identical to those used in previous ISAAC rhinitis-related publications[25, 56]:

- 'rhinitis ever': a positive answer to the question '*Have you [has your child] ever had a problem with sneezing or a runny or blocked nose, when you [he or she] DID NOT have a cold or the 'flu?'*

- 'current rhinitis': a positive answer to '*In the past 12 months, have you [has your child] had a problem with sneezing or a runny or blocked nose, when you [he or she] DID NOT have a cold or the 'flu?'*

- 'current rhinoconjunctivitis': 'current rhinitis' plus a positive answer to '*In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?'*

- 'severe rhinoconjunctivitis': 'current rhinoconjunctivitis' plus an answer of 'a lot' to '*In the past 12 months, how much did this nose problem interfere with your [child's] daily activities – not at all / a little / a moderate amount / a lot.'*

- 'hay fever ever': a positive answer to the question '*Have you [has this child] ever had hay fever?'*

Country income category was obtained from the World Bank 2001 dataset with countries categorised into low-, lower-middle-, upper-middle- and high-income countries.[107]

Statistical analysis used Stata version 15.[85] We derived estimates of the absolute ten-yearly rate of change in prevalence of rhinitis ever, current rhinitis, current rhinoconjunctivitis, severe rhinoconjunctivitis and hay fever ever for each centre. The standard error (SE) of this change was calculated, allowing for school-level clustering. Random effects meta-analysis investigated heterogeneity of centre-level trends within and between countries and age groups.

Additional meta-analyses compared trend estimates from the 'earlier period' (ISAAC Phase I to ISAAC Phase III) and the 'later period' (ISAAC Phase III to GAN Phase I) for the subgroup of centres that had participated in all three surveys.

Mixed-effects linear regression models were used to compare prevalence trends from ISAAC Phase III to GAN Phase I with those from ISAAC Phase I to Phase III (including non-GAN centres) as previously published.[56] These models were fitted for each of the five symptom definitions separately. We included country- and centre-level random intercepts to model within-centre absolute changes in percentage point prevalence per 10-year interval. Data from both age groups were combined to improve model efficiency but we included age group, region and country income group as confounders and tested for these as effect modifiers.

The relationships between observed centre-level time trends in rhinoconjunctivitis, asthma and eczema symptoms were assessed by rank correlation. For comparison between trends in the three allergic diseases, we used the sentinel symptoms highlighted in previous ISAAC publications of time trends[102] and risk factors[121]: 'current rhinoconjunctivitis' (for rhinitis symptoms), wheeze in the past year (for asthma symptoms) and itchy rash in the past year with flexural involvement (for eczema symptoms).

## Results

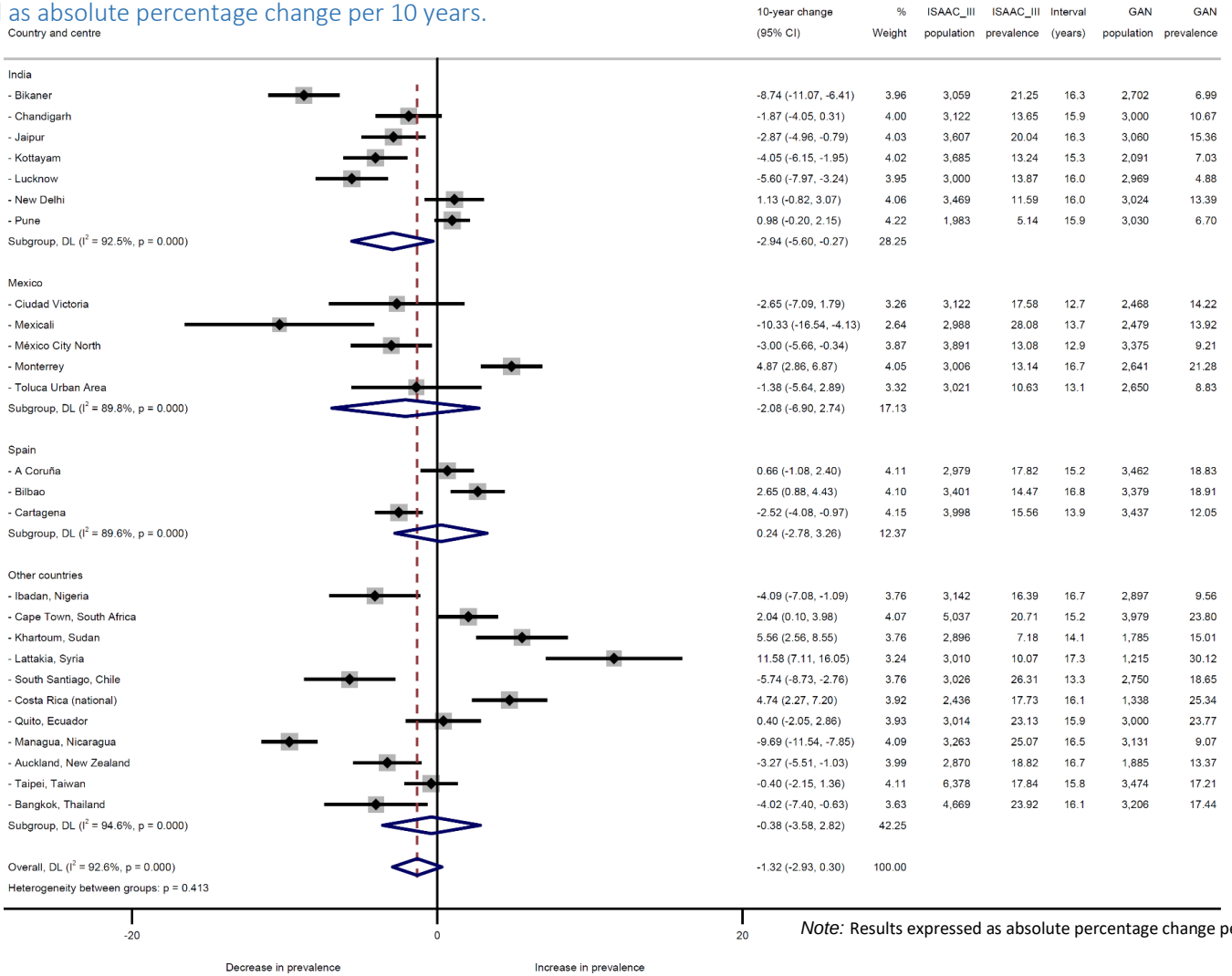
**Prevalence results and trends within GAN Phase I centres**

GAN survey data, locally checked and centrally collated by January 2021, were available for 119,795 GAN participants from 27 centres in 14 countries that had previously participated in ISAAC Phase I and/or Phase III. These included 74,361 adolescents in 27 centres (13 participating in both ISAAC Phases, 13 in Phase III only and one (Athens) in Phase I only) and 45,434 children in 19 centres (9 participating in both ISAAC Phases, 9 in Phase III only and one (Chandigarh) in Phase I only). Details are shown in Supplementary Tables available online at https://onlinelibrary.wiley.com/doi/10.1111/pai.13656. On average, GAN fieldwork (March 2015 to February 2020) took place 15.4 years after ISAAC Phase III (April 2001 to October 2003) and 22.7 years after ISAAC Phase I (March 1993 to October 1995). Details of dates of collection and response rates have been published elsewhere.[21]

Figure D.1 shows the trends in prevalence of current rhinoconjunctivitis for each of the 27 GAN-ISAAC centres, and (superimposed in black) the average trend in prevalence for ISAAC centres participating in both Phases I and III, but not in GAN. Earlier prevalence data for the non-GAN centres have been published previously.[56]

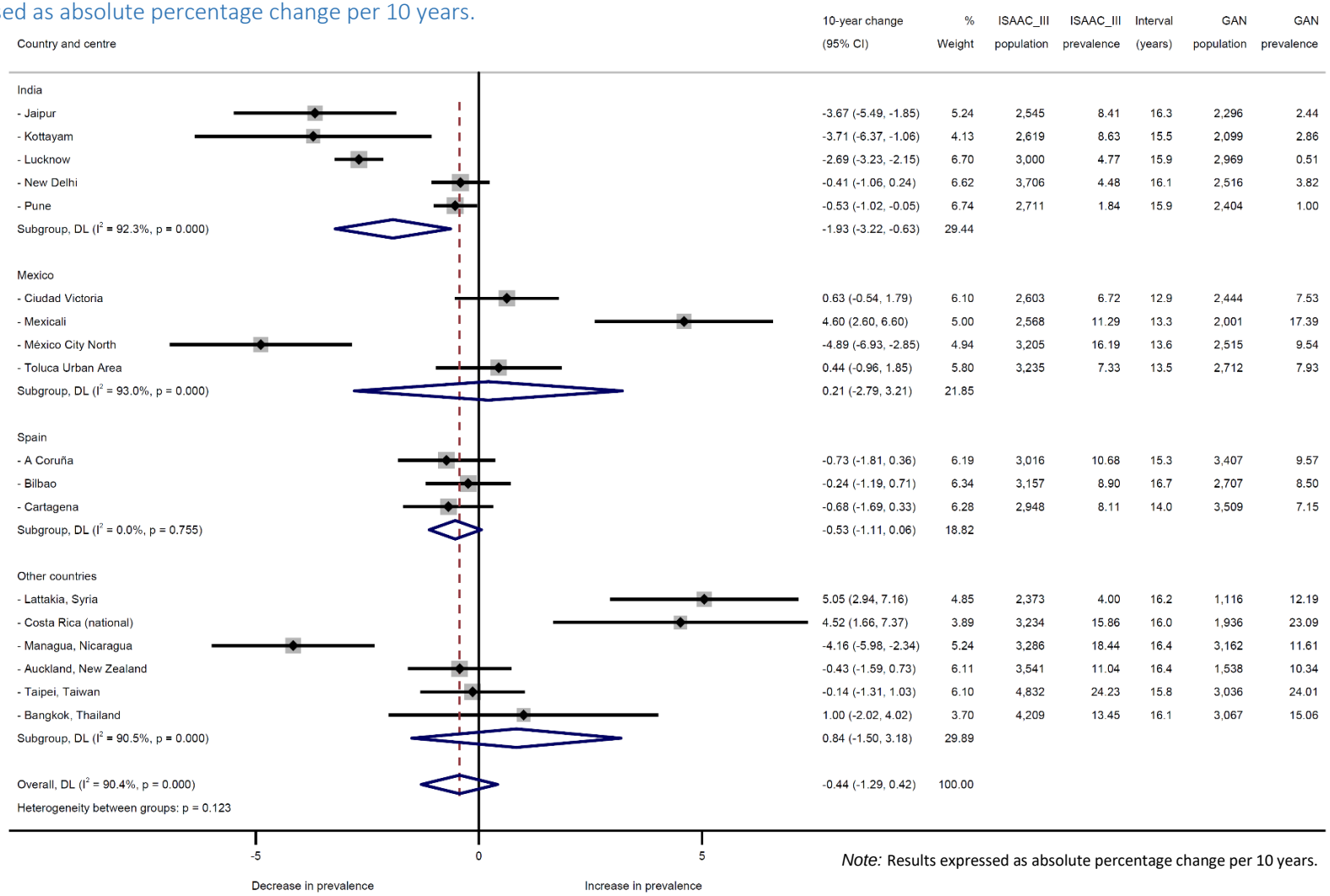
Within-centre trends in current rhinoconjunctivitis varied widely and significantly ($p < .001$) both within and between countries (Tables D.1 and D.2, Figures D.2 and D.3). On average (pooled random-effects estimates), current rhinoconjunctivitis prevalence decreased

Table D.1 Prevalence trends for current rhinoconjunctivitis from ISAAC Phase III to GAN Phase I among the 13- to 14-year-old age group, by country and centre. Results expressed as absolute percentage change per 10 years.



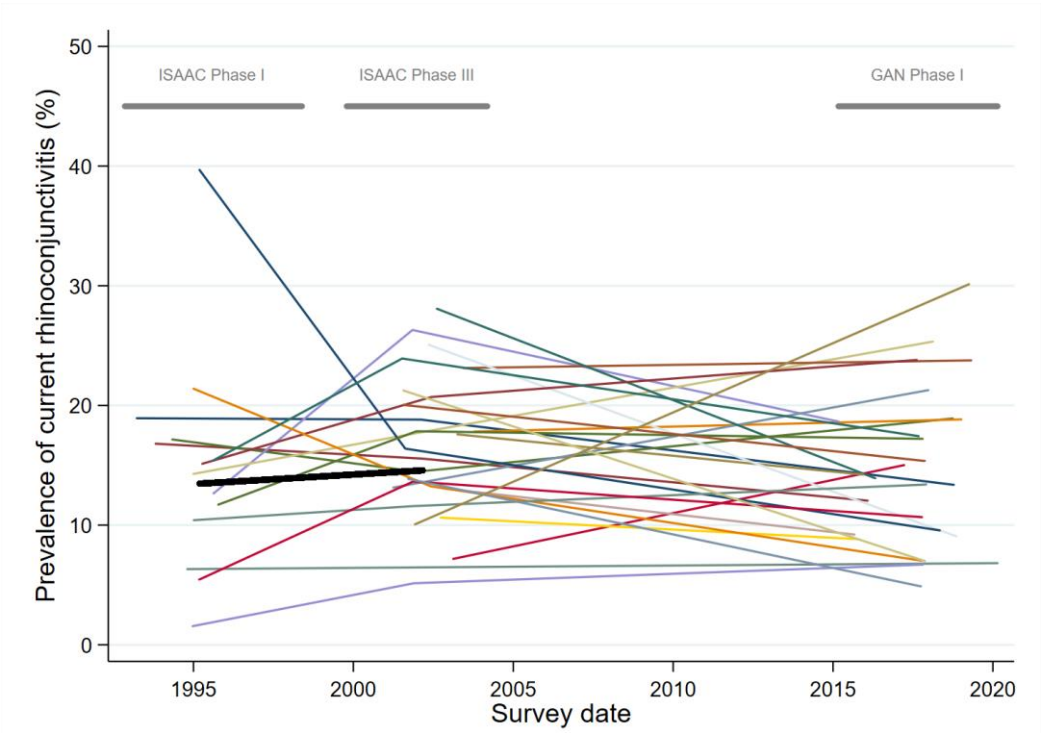

*Note:* Results expressed as absolute percentage change per 10 years.

Table D.2 Prevalence trends for current rhinoconjunctivitis from ISAAC Phase III to GAN Phase I among the 6- to 7-year-old age group, by country and centre. Results expressed as absolute percentage change per 10 years.




*Note:* Results expressed as absolute percentage change per 10 years.

**a**




**b**

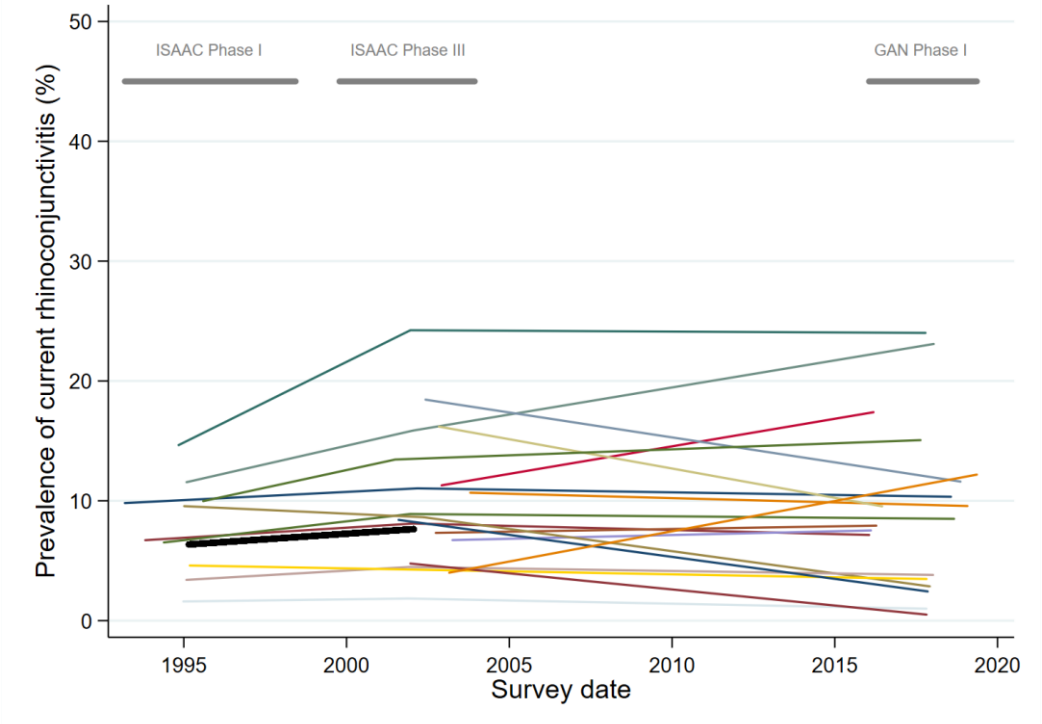



Figure D.1 Absolute changes over time in prevalence of current rhinoconjunctivitis (RC) symptoms by mean survey date for (a) 13- to 14-year-olds and (b) 6- to 7-year-olds.

Footnote for both subfigures a, b: Each coloured thin line represents one GAN Phase I centre. The thick black line shows the average absolute change from ISAAC Phase I to Phase III for those centres which did not participate in GAN Phase I. The span of the years of data collection for ISAAC Phase I, ISAAC Phase III and GAN Phase I is shown.

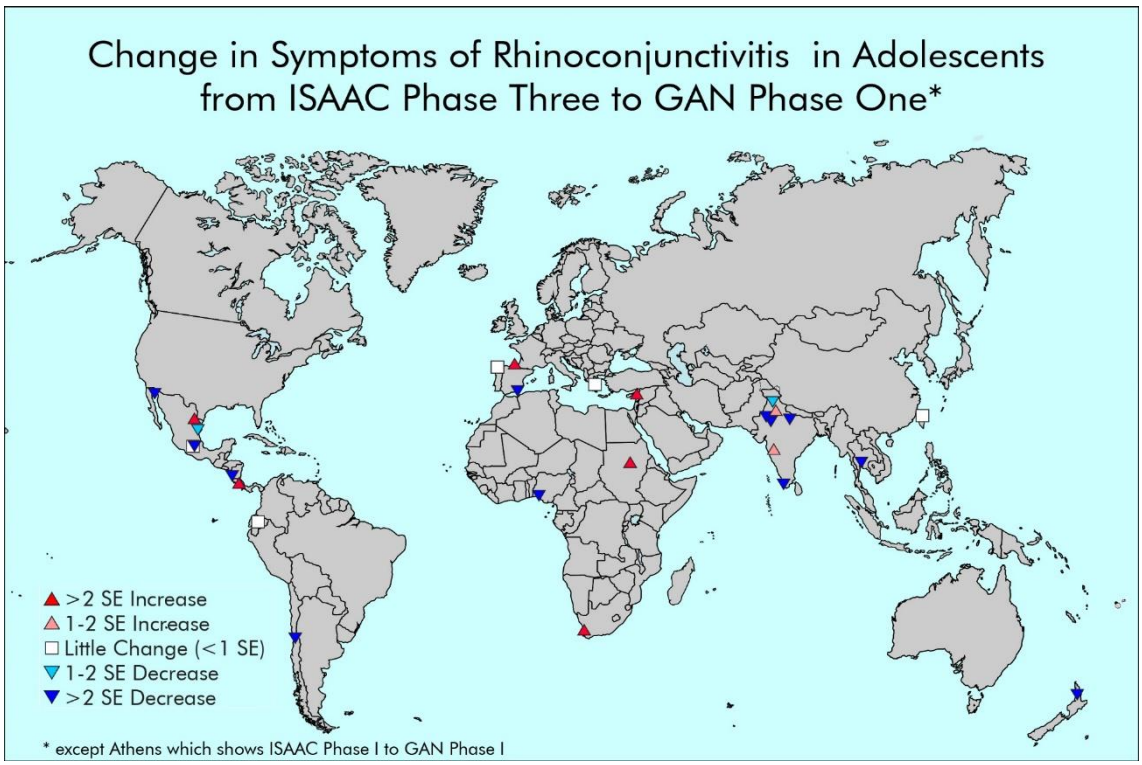



Figure D.2 Map of changes in prevalence of current rhinoconjunctivitis from ISAAC Phase III to GAN Phase I, for 13- to 14-year-olds

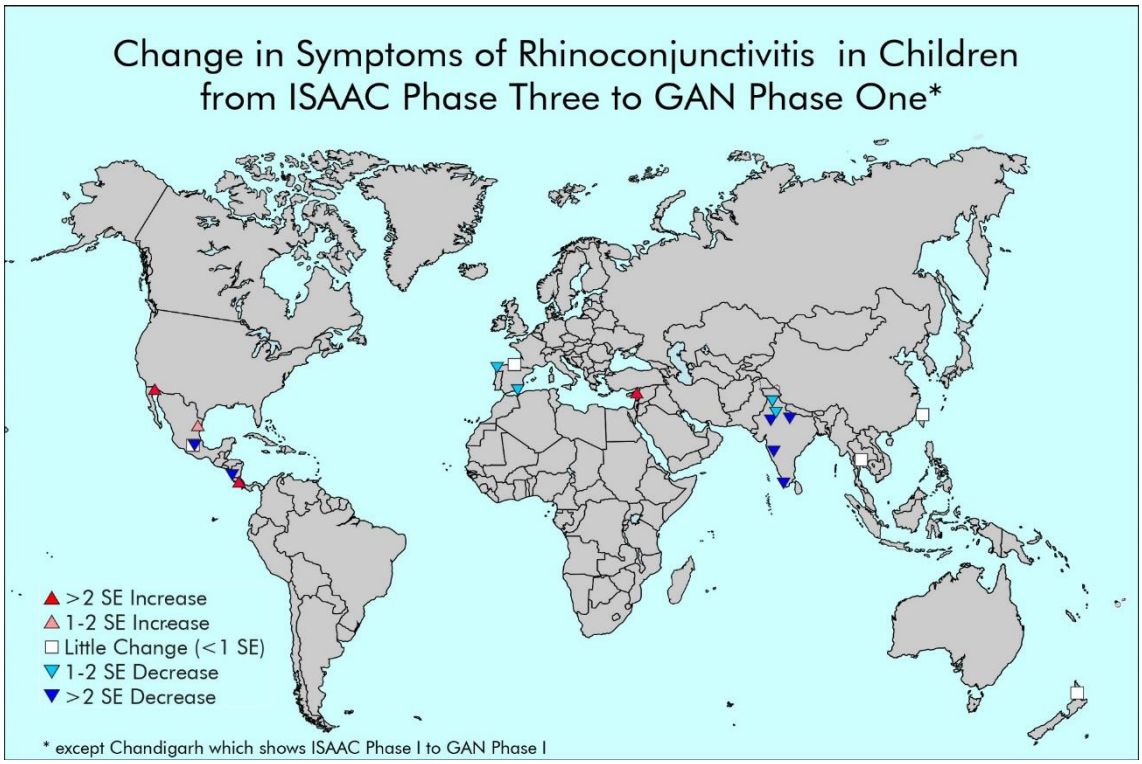



Figure D.3 Map of changes in prevalence of current rhinoconjunctivitis from ISAAC Phase III to GAN Phase I, for 6- to 7-year-olds

slightly but non-significantly from ISAAC Phase III to GAN: -1.32% per 10 years, 95% CI [-2.93%, +0.30%] among adolescents; -0.44% [-1.29%, +0.42%] among children.

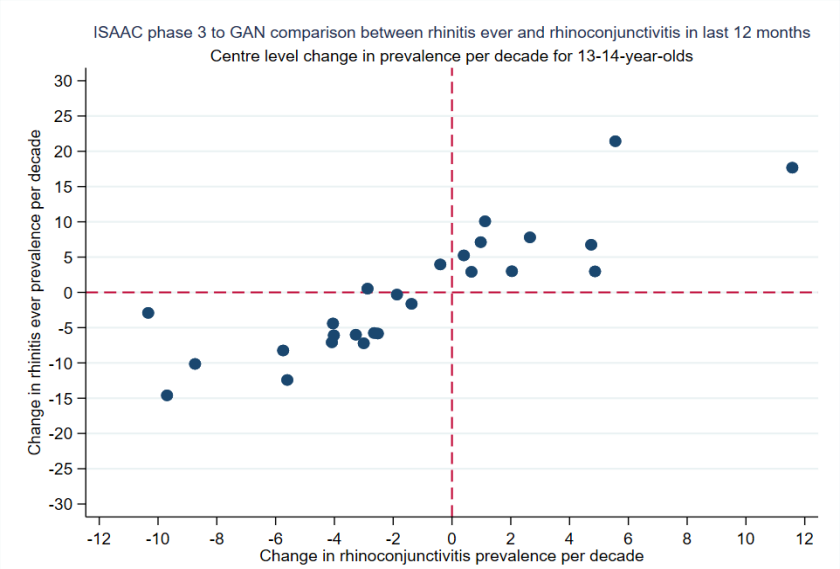
Many centre-specific changes in rhinoconjunctivitis prevalence differed from zero at conventional levels of statistical significance. Substantial and statistically significant diversity was also seen for other common outcomes (rhinitis ever, current rhinitis and hay fever). Even severe rhinoconjunctivitis, with much lower prevalence, changed significantly in several centres in both age groups (Supplementary Tables available online at https://onlinelibrary.wiley.com/doi/10.1111/pai.13656).

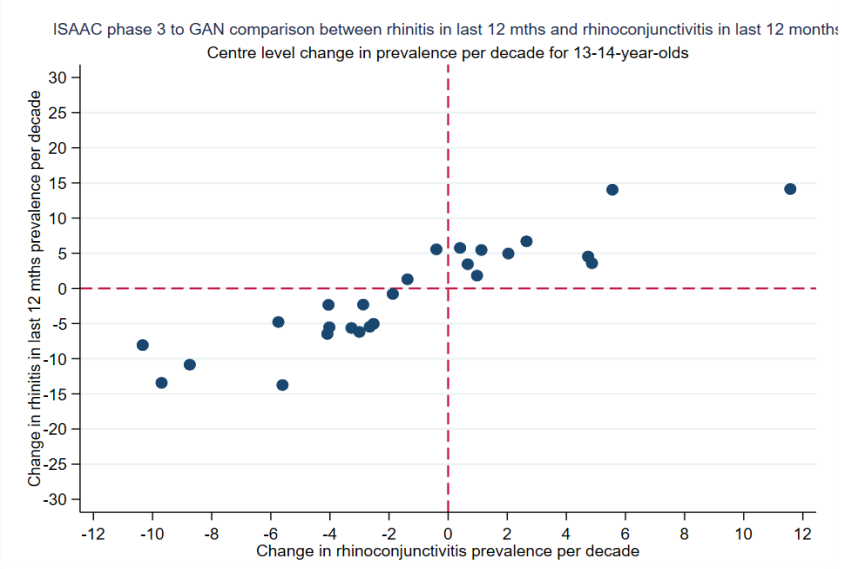
**Comparison of within-centre trends across symptoms, age groups and diseases**

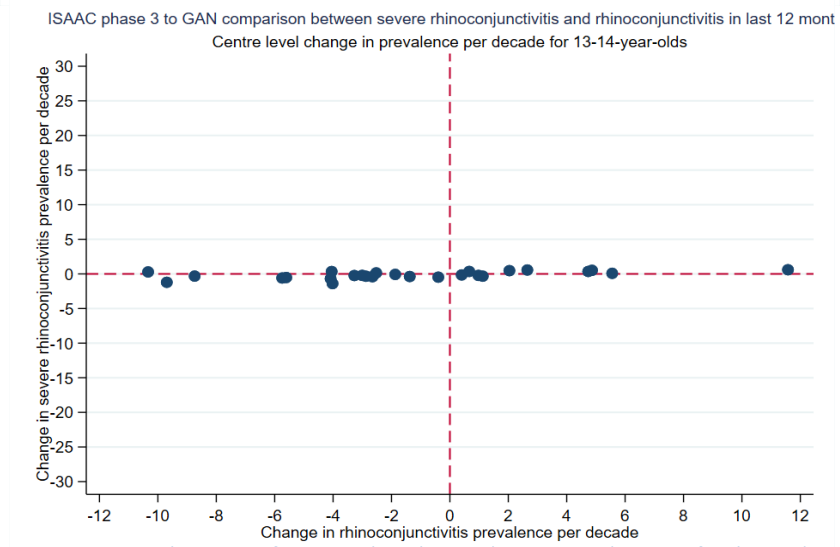
Among adolescents, centre-specific trends in current rhinoconjunctivitis from ISAAC Phase III to GAN correlated very closely with those for rhinitis ever and current rhinitis (both rho = 0.90, $p < .0001$, N = 26 centres) and to a moderate but significant degree with trends in severe rhinoconjunctivitis (rho = 0.64, $p = .0005$) and lifetime hay fever (rho = 0.54, $p = .005$). Among children, the corresponding correlations of trends in rhinoconjunctivitis with trends in rhinitis ever, current rhinitis and hay fever were significant but of intermediate strength (rho = 0.5-0.7, $p < .01$, N = 18 centres), whereas trends in severe rhinoconjunctivitis were only weakly correlated with those in current rhinoconjunctivitis (rho = 0.27, $p = .28$) (Figures D.4 and D.5).

From ISAAC Phase III to GAN, there was no substantial or significant rank correlation between trends in current rhinoconjunctivitis and the average prevalence of this outcome among adolescents (rho = 0.07, $p = .73$, N = 26) nor among children (rho = 0.27, $p = .27$, N = 18) (Figure D.6). When current rhinoconjunctivitis trends were compared between the two age groups, the correlation was weak and non-significant (rho = 0.38, $p = .11$, N = 18).

Figure D.7 compares within-centre trends in current rhinoconjunctivitis symptoms with the corresponding trends in symptoms of asthma (wheeze) and eczema (flexural itchy rash), by age group, from ISAAC Phase III to GAN. Although all correlations were positive, only two were statistically significant, both in the adolescent age-group (based on 26 centres): rhinoconjunctivitis v eczema (rho = 0.72, $p < .001$) and asthma v eczema (rho = 0.43, $p = .027$). There was only a weak rank correlation between trends in asthma symptoms and current rhinoconjunctivitis among adolescents (rho = 0.15, $p = .48$), and none of the cross-disease correlations in the younger age-group were significant. The correlation between rhinoconjunctivitis trends and eczema trends among adolescents was evident within each of four groups of countries defined by GNI.



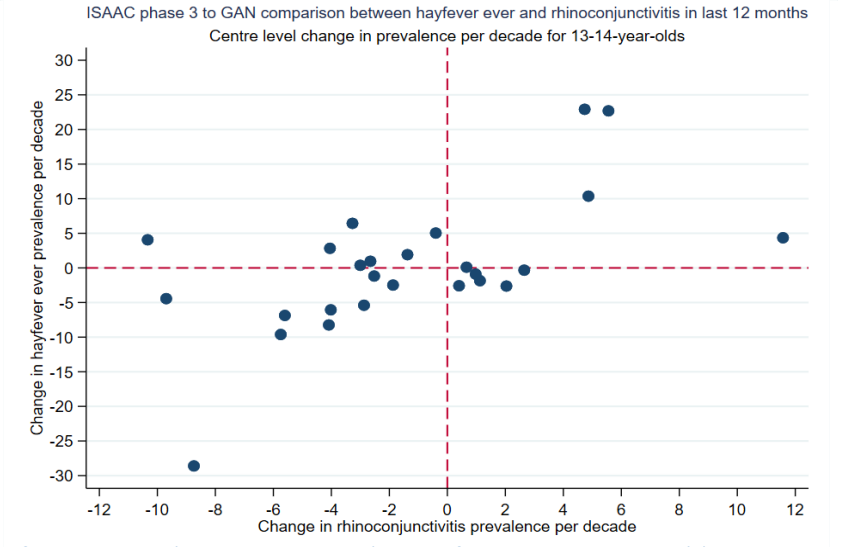




Figure D.4 Correlations of centre-level trends in prevalence of selected symptoms from ISAAC Phase III to GAN Phase I, for 13- to 14-year-olds

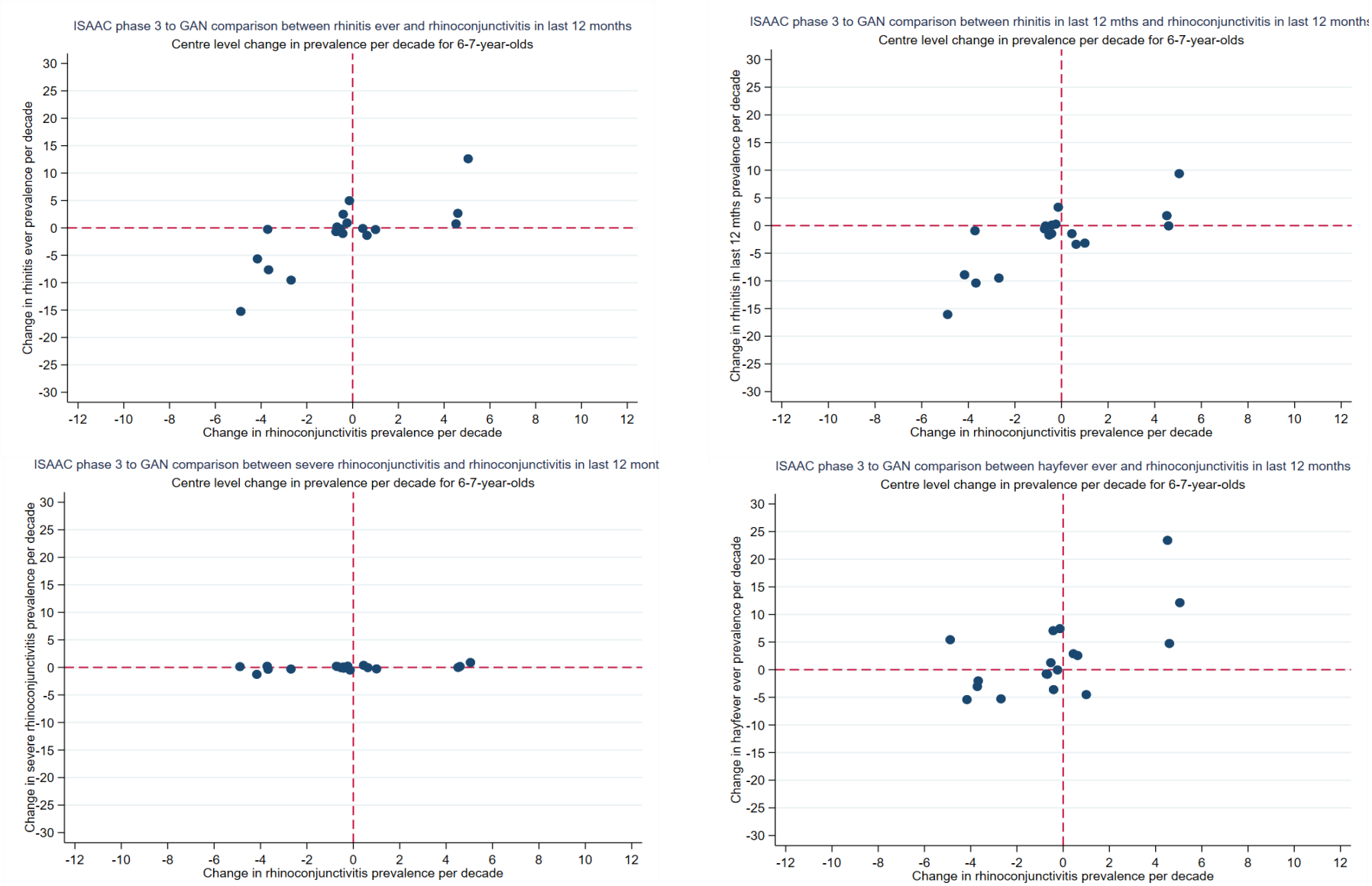
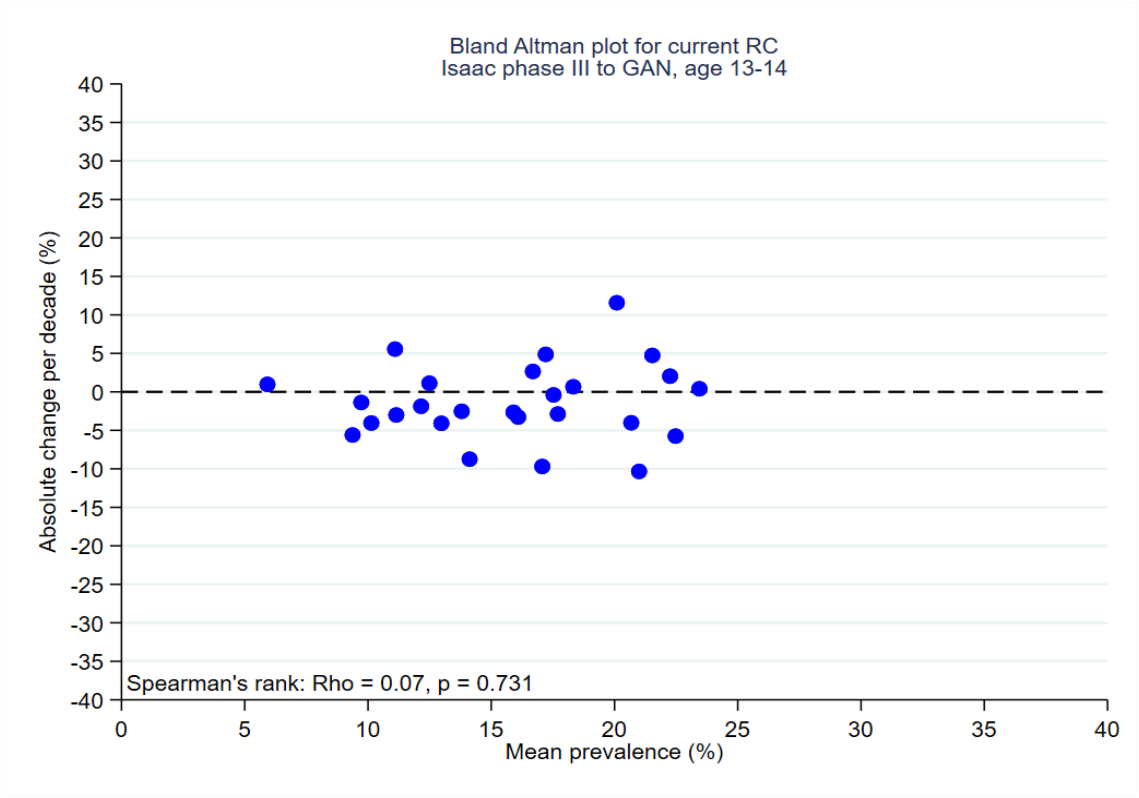



Figure D.5 Correlations of centre-level trends in prevalence of selected symptoms from ISAAC Phase III to GAN Phase I, for 6- to 7-year-olds



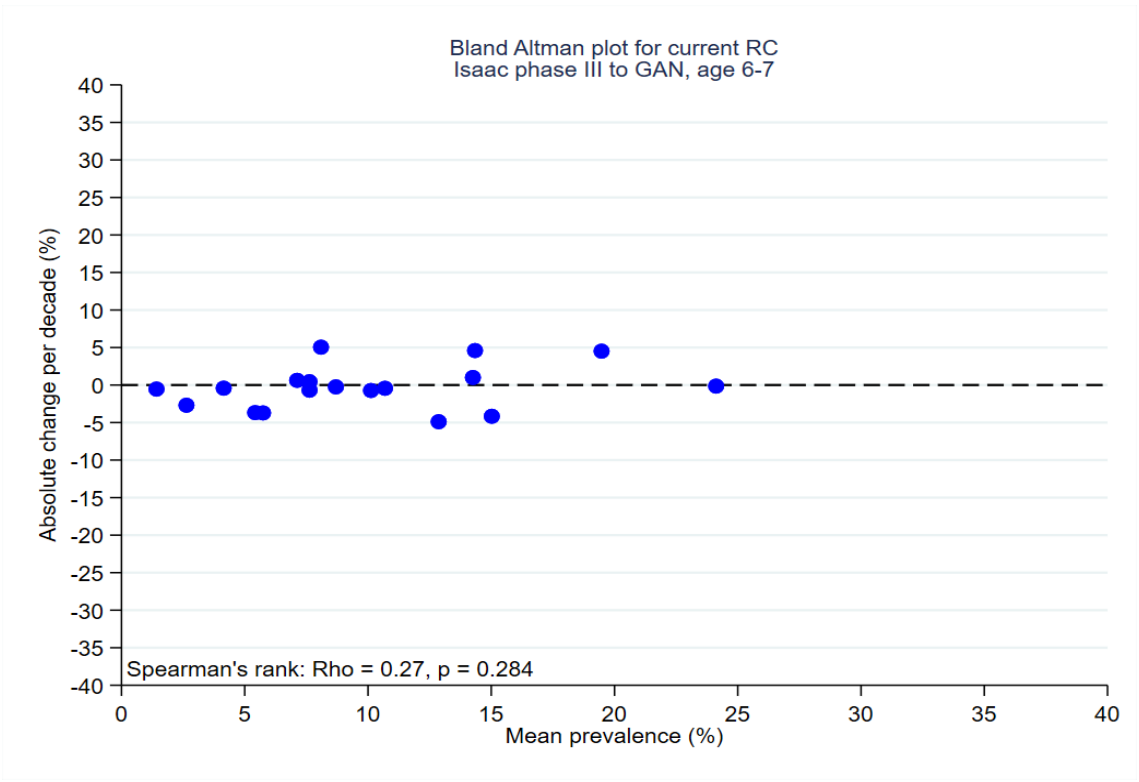




Figure D.6 Bland-Altman plots of change in prevalence versus average prevalence of rhinoconjunctivitis, by age group

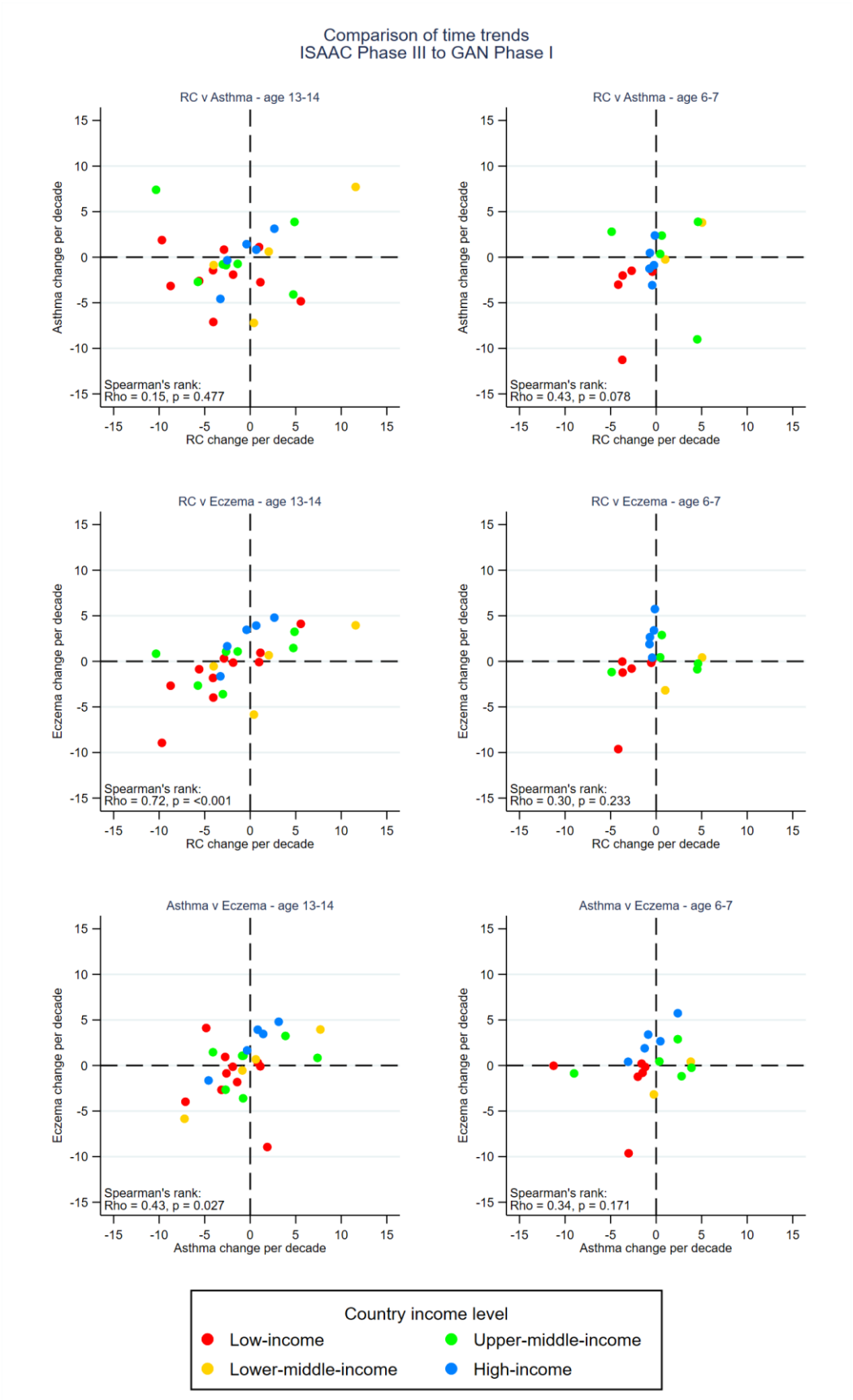



Figure D.7 Correlation of centre-level time trends (absolute percentage change per decade) in prevalence of symptoms of current rhinoconjunctivitis (RC), asthma and eczema from ISAAC Phase III to GAN Phase I, for 13- to 14-year-olds (left column) and 6- to 7-year-olds (right column), countries grouped by GNI per capita.

**Comparison of time trends by period in centres with data at three time points**

When the analysis was restricted to centres participating in all three surveys (13 contributing results for adolescents and 9 contributing results for children), the rate of change in prevalence of current rhinoconjunctivitis (pooled across age groups) was significantly ($p < .001$) lower after ISAAC Phase III than before. The inversion in slope (from positive to negative) was similar in both age groups (Table D.3). This is consistent with the pattern shown for current rhinoconjunctivitis in Table D.4 below.

**Modelling of time trends combining GAN and ISAAC data**

Multi-level modelling compared trends in 26 GAN and ISAAC centres (the 'later period') with results from 110 ISAAC centres participating in both Phases I and III (the 'earlier period'). Within each of these two periods, a single centre could contribute data for one or both age groups surveyed at two time points.

Modelling of the combined results for current rhinoconjunctivitis found no significant difference between the age groups (interaction $p = .28$), nor was there effect modification by grouped WHO region ($p = .31$). However, there was significant heterogeneity across country-level income group (interaction, $p < .001$) and evidence of non-linearity of the trend across the time period ($p = .02$ for quadratic term).

When earlier and later periods were considered separately (Table D.4), the increases for each symptom were greater in the earlier period in each age group, and none of the age-specific trends from ISAAC Phase III to GAN were significant. The upward trend in current rhinoconjunctivitis in the earlier period was more pronounced and statistically significant in lower-middle- and upper-middle-income countries, as previously reported,[56] and this pattern was similar for other symptoms. During the later period, only lower-middle-income countries sustained an increase in symptom prevalence from ISAAC Phase III to GAN although this was statistically significant only for rhinitis ever, not for current rhinoconjunctivitis. In contrast, the lifetime prevalence of hay fever increased significantly among upper-middle-income countries, despite little change in prevalence of the other outcomes (Table D.4).

Table D.3 Differences in rate of change of prevalence of current rhinoconjunctivitis, comparing trends after ISAAC Phase III with those before ISAAC Phase III among centres with data at three time points, by age group and centre. Results expressed as absolute percentage change per 10 years.

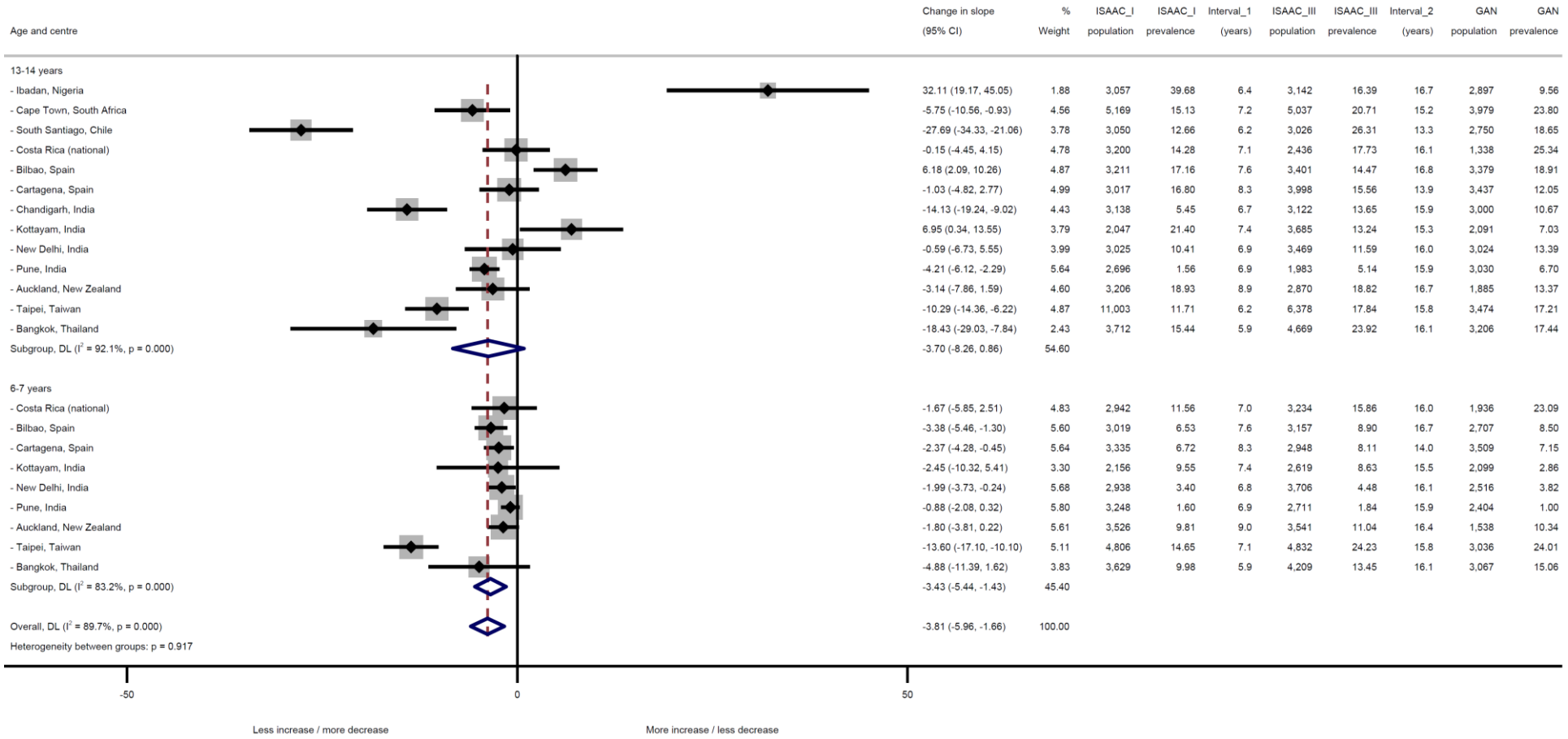


Table D.4 Modelled estimates of trends in each rhinitis-related outcome, expressed as absolute percentage change over 10 years.

Results from mixed models with random intercepts for country and centre, by age group and country-level income group, separately for two time periods.

| Strata | Absolute percentage change over 10 years (95% CI) by outcome: | | | | | Number of surveys |
|---|---|---|---|---|---|---|
| | Rhinitis (no cold or 'flu) ever | Rhinitis (no cold or 'flu) past year | **Rhinoconjunctivitis past year** | Severe rhinoconjunctivitis past year | Hay fever ever | |
| | | | | | | |
| ISAAC Phases I to III, Age 6-7[a] | 3.82 (0.30, 7.35) | 4.07 (1.31, 6.82) | **2.32 (0.59, 4.04)** | 0.12 (-0.08, 0.32) | 4.81 (1.84, 7.77) | 132 |
| ISAAC Phases I to III, Age 13-14[a] | 2.29 (-0.47, 5.06) | 3.03 (0.87, 5.19) | **1.28 (-0.08, 2.63)** | 0.18 (0.03, 0.34) | 4.81 (2.48, 7.14) | 214 |
| | | | | | | |
| ISAAC Phase III to GAN, Age 6-7[a] | -0.91 (-4.25, 2.42) | -2.31 (-5.27, 0.64) | **-0.41 (-2.34, 1.52)** | -0.04 (-0.25, 0.17) | 2.17 (-1.61, 5.95) | 36 |
| ISAAC Phase III to GAN, Age 13-14[a] | 0.17 (-2.59, 2.93) | -0.53 (-2.97, 1.92) | **-1.15 (-2.75, 0.45)** | -0.14 (-0.32, 0.03) | -0.14 (-3.27, 2.99) | 52 |
| | | | | | | |
| ISAAC I to III, Low-income countries[b] | 1.65 (-3.99, 7.28) | 1.53 (-2.86, 5.91) | **-0.03 (-2.82, 2.76)** | -0.04 (-0.35, 0.28) | 8.32 (3.51, 13.12) | 52 |
| ISAAC I to III, Lower-middle-income[b] | 13.96 (7.19, 20.74) | 12.04 (6.77, 17.31) | **4.90 (1.54, 8.25)** | 0.93 (0.55, 1.31) | 2.56 (-3.21, 8.34) | 46 |
| ISAAC I to III, Upper-middle-income[b] | 3.59 (-0.87, 8.06) | 5.36 (1.89, 8.83) | **3.20 (0.99, 5.41)** | 0.30 (0.05, 0.55) | 7.23 (3.43, 11.03) | 84 |
| ISAAC I to III, High-income countries[b] | 0.84 (-2.09, 3.76) | 1.50 (-0.78, 3.78) | **0.87 (-0.58, 2.32)** | 0.01 (-0.15, 0.17) | 3.24 (0.75, 5.74) | 164 |
| | | | | | | |
| ISAAC III to GAN, Low-income countries[b] | -2.34 (-5.59, 0.90) | -4.10 (-6.91, -1.30) | **-2.94 (-4.76, -1.12)** | -0.34 (-0.54, -0.13) | -3.73 (-7.21, -0.24) | 32 |
| ISAAC III to GAN, Lower-middle-income[b] | 5.35 (0.12, 10.57) | 4.17 (-0.35, 8.69) | **2.75 (-0.19, 5.68)** | 0.02 (-0.31, 0.35) | -0.02 (-5.64, 5.59) | 12 |
| ISAAC III to GAN, Upper-middle-income[b] | -1.70 (-5.96, 2.56) | -2.10 (-5.78, 1.58) | **-0.09 (-2.48, 2.30)** | 0.06 (-0.21, 0.33) | 7.33 (2.75, 11.90) | 24 |
| ISAAC III to GAN, High-income countries[b] | 0.95 (-3.22, 5.12) | 0.83 (-2.78, 4.43) | **-0.42 (-2.76, 1.92)** | 0.06 (-0.21, 0.32) | 2.55 (-1.93, 7.02) | 20 |

[a] Adjusted for income group

[b] Adjusted for age group

Estimates for the sentinel symptom 'current rhinoconjunctivitis' are shown in bold.

## Discussion

This is the most comprehensive analysis hitherto of time trends in symptoms related to allergic rhinitis among schoolchildren, across diverse study centres around the world using a standardised methodology. We followed ISAAC conventions by focusing on non-infective rhinitis symptoms accompanied by itchy-watery eyes, a symptom combination closely related to allergic sensitisation, particularly to seasonal allergens, among adults[147, 148] and children[149, 32] in Europe. Even in high-income countries, atopy appears less relevant to rhinitis without conjunctivitis, and in less affluent settings, the symptom associations with allergic sensitisation are much weaker.[32] Therefore, a global perspective on trends in these symptoms requires cautious interpretation.

Studies in Nordic countries suggest a marked increase in prevalence of allergic rhinitis among children[20] and older teenagers[150, 151] from the 1980s to mid-2000s. Elsewhere in Europe, serial prevalence studies of children show a mixed picture: in Switzerland,[152] the Netherlands[153] and Poland,[154] prevalence of rhinoconjunctivitis reached a plateau after the millennium, whereas it continued to increase in Greece.[155] Outside Europe, prevalence of doctor-diagnosed allergic rhinitis among children increased progressively in Turkey from 1994 to 2014,[156] while a series of 15 large studies of Japanese schoolchildren from 1975 to 2006 showed a continuing increase in the prevalence of seasonal rhinitis and associated itchy eyes.[157]

Our study provides further insight into these long-term trends in centres mostly outside Europe. Although Brazilian ISAAC centres did not contribute to GAN Phase I, the investigators repeated their 2003 ISAAC fieldwork in 2012 among nine Brazilian centres, which provides time trend data comparable to ours, but over a shorter time period.[158] A rising prevalence of rhinitis and rhinoconjunctivitis was reported.

Strengths of our study include sample sizes, typically around 3000 per age group, which were large enough to estimate within-centre trends with adequate precision, allowing for the cluster sampling design. With wide geographical coverage and diverse levels of affluence, we can comment on the patterns of trends internationally, but our most striking observation was of heterogeneity of trends within countries with multiple centres (India, Mexico, Spain) as well as between countries. This limits the extent to which results can be generalised and reduces the statistical power for contrasts such as those between richer and poorer countries.

Despite the smaller number of GAN centres compared with ISAAC and the incomplete overlap between these two lists, sufficient GAN centres had participated in both ISAAC Phases to allow a three-point within-centre analysis. This clearly demonstrates a slowing or reversal of the rate

of increase in prevalence of rhinoconjunctivitis previously seen within ISAAC.[56] This conclusion is robust to inclusion or exclusion of Ibadan, which was a notable outlier in the ISAAC Phase I prevalence data.[25] Furthermore, it is consistent with the broader comparison of trends in the earlier and later periods, using all available centres irrespective of overlap (Table D.4).

Our analysis focused on current rhinoconjunctivitis, but the conclusions generally apply to other rhinitis-related symptoms, whereas the patterns for trends in lifetime prevalence of hay fever were somewhat different. Hay fever is a label for seasonal allergic rhinitis and/or conjunctivitis in temperate climates but is a less familiar concept in subtropical and tropical regions, where many of our centres are located.

A potential limitation is our reliance upon symptoms reported by adolescents themselves or by parents on behalf of the younger children. No objective tests for allergic sensitisation were carried out, nor are any planned. However, the close correlation between within-centre trends in rhinoconjunctivitis and eczema symptoms (flexural itchy rash) in the adolescent group suggests a common underlying influence. This could be non-causal (related, for instance, to local awareness or reporting of the two conditions, or to ecological confounding at the centre level) or due to common causal mechanisms. Interestingly, the correlation between rhinoconjunctivitis trends and trends in itchy flexural rash is not limited to the higher-income countries. Given the weaker association between atopy and rhinoconjunctivitis symptoms outside of high-income settings,[32] it is important that non-allergic linking mechanisms are sought. The correlations between diseases shown in Figure D.7 extend our previous comparisons of trends[159] and risk factors[121] for these three related diseases.

## Conclusion

The trends we observed varied substantially and significantly both within and between countries, limiting the internal and external generalisability of conclusions. Local investigation is therefore important for understanding local trends and their implications for healthcare decision-making. Nevertheless, our wide international coverage, including many centres in low- or middle-income countries, provides a global perspective, which suggests that the prevalence of symptoms of non-infective rhinoconjunctivitis may no longer be increasing among children, as it was previously.

# E Paper VI: Is the prevalence of eczema in school age children still increasing globally? A Global Asthma Network Phase One Study

**Article submitted**

**SECTION A – Student Details**

| | | | |
|---|---|---|---|
| **Student ID Number** | 1300807 | **Title** | Mrs |
| **First Name(s)** | Charlotte Emma | | |
| **Surname/Family Name** | Rutter | | |
| **Thesis Title** | Multi-level modelling of international variations and time trends in asthma and allergic diseases in children. | | |
| **Primary Supervisor** | Neil Pearce | | |

**If the Research Paper has previously been published please complete Section B, if not please move to Section C.**

**SECTION B – Paper already published**

| | | | |
|---|---|---|---|
| Where was the work published? | | | |
| When was the work published? | | | |
| If the work was published prior to registration for your research degree, give a brief rationale for its inclusion | | | |
| Have you retained the copyright for the work?* | **Yes** | Was the work subject to academic peer review? | **Yes** |

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**SECTION C – Prepared for publication, but not yet published**

| | |
|---|---|
| Where is the work intended to be published? | Allergy |

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| Stage of publication | Submitted – under review |

**SECTION D – Multi-authored work**

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| For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary) | My role was on the paper was as CR in the following: conceptualisation SL, AM, IA, KB, C-YC, AES, PE, GM, NP, DS; data curation EE, PE, LG-M, EM, VP-F, CR, SR, RS, AM-T; formal analysis SL, AM, NP, RS, DS, CR; investigation SL; methodology SL, AR, NP, CR, DS, RS; project administration, IA, EE; PE; resources IA; supervision SL, NP, DS, RS; validation PE; visualisation EE, PE, CR; writing – original draft SL, AM; writing – review/editing NP, DS, RS, CR and the Global Asthma Network Phase I Study Group; the latter contributed original data to the analyses. Verification of the underlying data was undertaken by CR, NP, VP-F and DS. |

**SECTION E**

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| **Date** | 30/05/2022 |

## Abstract

**Background**

Eczema (atopic dermatitis) is a major public health issue globally due to its high prevalence and associated morbidity. Previous studies have shown eczema is increasing; our goal was to see whether eczema prevalence had stopped increasing or continued to increase, and if so, where, using an internationally accepted standardised methodology.

**Methods**

The Global Asthma Network (GAN) Phase I study is an international collaborative study arising from the International Study of Asthma and Allergies in Children (ISAAC). Using surveys, we assessed eczema symptom prevalence, as well as severity and lifetime prevalence of eczema, in a range of global centres that participated in GAN Phase I (2015-2020) and one or both of ISAAC Phase I (1993-1995) and Phase III (2001-3). With the addition of extra ISAAC-only centres, we fitted linear mixed models to estimate the ten yearly trend in prevalence across the whole time period, stratified by age group, income level and region.

**Results**

We analysed GAN Phase I data from 27 centres in 14 countries involving 74,361 adolescents aged 13-14 and 47,907 children aged 6-7 (response rate 90% and 79% respectively). Over 27 years, after adjusting for the effects of world region and income, we estimated small overall 10-year increases in current eczema symptom prevalence (adolescents: 0.98%, 95% CI 0.04%-1.92%; children: 1.21%, 95% CI 0.18%-2.24%), and in severe eczema symptoms (adolescents: 0.26%, 95% CI 0.06%-0.46%; children: 0.23%, 95% CI 0.02%-0.45%) with larger increases in lifetime prevalence (adolescents: 2.71%, 95% CI 1.10%-4.32%; children: 3.91%, 95% CI 2.07%-5.75%). There was substantial heterogeneity in 10-year change between centres (standard deviations 2.40, 0.58 and 3.04%). There was strong evidence that some of this heterogeneity was explained by world region and by income level, and evidence that eczema symptom prevalence in (mainly South) America has started to decrease following an earlier increase. There was weak evidence that prevalence in high-income settings has increased in adolescents following an earlier stabilisation, and for a continued increase in children.

**Interpretation**

Although the burden of eczema shows a small increase overall, there is substantial variation in changes in prevalence and severity over time by income and geographical region. Understanding why the burden of eczema is increasing in some regions and decreasing in others is a priority to help identify aetiological factors to inform prevention.

## Introduction

Eczema (also known as atopic eczema or atopic dermatitis) is an important condition that affects about 20% of children and up to 10% of adults and is associated with a high burden of morbidity and costs to individuals and health services.[7,160-162] Gaining insight into global time trends over time is a major priority, as it might provide insight into risk factors amenable to public health manipulation.[55] These changes in eczema prevalence over time are important, not only from a health services perspective, but also in terms of understanding eczema aetiology, which is critical if we want to intervene to reduce the global burden. Previous studies including the Global Burden of Disease project have assessed the global burden of eczema. However, these estimates are difficult to interpret due to wide variation in approaches to defining eczema, such that estimates may vary based on misclassification of eczema leading to comparison of the prevalence of different conditions.[161, 163, 164] Using a standardised validated case definition is essential to facilitate valid comparisons across geographies and over time.

The International Study of Asthma and Allergies in Childhood (ISAAC) was a unique global study which focused on understanding international trends in the prevalence of asthma, allergic rhinitis and eczema using harmonised methodologies.[2,7,50] The ISAAC study has provided unique insights into the burden of eczema at a global scale over its two decades (and we have used the term "eczema" for consistency with previous ISAAC papers and international guidance), enabling insights into the risk factors for and burden associated with eczema, with a key advantage being the use of standardised validated measurements to facilitate meaningful comparisons.[160] The Global Asthma Network (GAN) developed from the ISAAC study and provides prevalence estimates comparable to those from ISAAC Phases I and III.[4] A previous ISAAC study comparing eczema prevalence in Phases I and III reported that eczema prevalence appeared to be plateauing or reducing in settings that previously had high eczema prevalence, while in settings where eczema prevalence was previously low, substantial increases were seen particularly amongst younger children.[55] There remain unanswered questions about whether previous reducing prevalence was maintained, countries previously on the increase continued to increase or whether there are new settings with increased prevalence.

The goal of the current study was to understand trends in the presence of eczema symptoms globally from 1993 to 2020, using the same methods as the ISAAC study, now incorporated into GAN. Our hypothesis was that the prevalence of eczema would continue to increase in many countries as they become more westernised, while in high income countries, the prevalence of eczema would be stable or reduced.

## Methods

GAN Phase I is a cross-sectional study in multiple centres worldwide, involving a written questionnaire on symptoms of asthma, eczema and rhinitis using standardised methodology.[2,3] Data were collected between 2015-2020 and followed the same protocol and methodology as the earlier ISAAC studies (Phase I from 1992-1995[165] and phase III from 2001-2003[102]) in order to facilitate comparison of the prevalence of symptoms across different time points.[4]

All participating centres obtained ethical approval from their local ethics committees before commencing the study. Each centre was based on a defined geographical area from which a minimum of 10 schools were randomly selected (or all schools if there were 10 or fewer schools in the area). There were two age groups included in the study; adolescents aged 13-14 (compulsory) and children aged 6-7 (optional). Each centre could elect for students to be selected by grade/level/year or by chronological age. High levels of participation were required for inclusion as absent school pupils may be away from school due to symptoms: response rate at least 80% for adolescents and 70% for children.[3,102] All students meeting the age criteria were invited to complete the questionnaire, with adolescent questionnaires being self-completed at school and child questionnaires being completed at home by parents/carers. Most questionnaires were completed on paper and inputted with double entry checks although some were completed online and some were scanned using optical recognition marks. Questionnaires for other languages were translated from the English version and then translated back to English to ensure accuracy of the translations.[105]

We provide details of GAN centres that also took part in at least one ISAAC study phase (known as "GAN time trends centres").[21] Also included in the modelling are centres that did not take part in GAN but that took part in both ISAAC studies (ISAAC only time trends centres). Details of these centres are not shown here but have been previously reported.[102]

**Data handling and analyses**

Each centre submitted data to the GAN Global Centre in Auckland, New Zealand. After initial checks, the data, along with a centre report, were forwarded to either the Murcia GAN Data Centre (Spain) for Spanish and Portuguese speaking countries or to the London GAN Data Centre (United Kingdom) for all other countries, for thorough data checking and cleaning. Both data centres used the same suite of Stata programs to perform checks, liaising with centre principal investigators or their delegate for any queries/amendments in data coding or data entry checks. Centres with serious deviations from protocol, e.g. response rates <50%, were

excluded from analyses. Less serious deviations from protocol are identified with footnotes in the results tables.[36,166]

All centre prevalences were calculated, as in ISAAC, as a proportion of the total number of questionnaires returned with at least some symptom data. The numerator for the prevalence of current eczema symptoms (as an estimator of eczema prevalence) was the number of questionnaires with positive responses to both questions of "Have you (has this child) had this itchy rash at any time in the past 12 months?" and "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?". The numerator for the prevalence of current severe eczema symptoms required an additional response of "One or more nights per week" to the question of "In the past 12 months, how often on average, have you (has this child) been kept awake at night by this itchy rash?". (Options for other responses were "Never in the past 12 months" or "Less than one night per week".) The numerator for the prevalence of eczema ever was the number of positive responses to the question of "Have you (has this child) ever had eczema?".

The survey date for each centre was calculated as the mean date of questionnaire completion.[102,54] This is slightly different to the survey year method used in ISAAC publications and has resulted in very small differences in results when comparing to the previous paper.[55,102]

Countries were allocated to four regions based on WHO regions of the world. The WHO regions of Africa and Eastern Mediterranean were combined and South-East Asia and Western Pacific were combined, because of the smaller number of centres that completed GAN Phase I compared to ISAAC. These four groups also correspond to the nine ISAAC regions with North America and Latin America combined, Western Europe and Northern and Eastern Europe combined, Africa and Eastern Mediterranean combined, and Asia-Pacific, Indian sub-continent and Oceania combined.

Country income group was obtained from the World Bank which identifies countries as low-, lower middle-, upper middle- and high-income.[167] The 2001 classification was used as a mid-point for the ISAAC-GAN studies.

**Time trends**

Time trends of the prevalence of symptoms were calculated as the absolute change over 10 years by subtracting the prevalence at ISAAC Phase I or III from the prevalence in GAN Phase I and dividing the results by the number of decades between those two survey dates. The standard error (SE) of this time trend was calculated to take account of school level clustering in the study design. The 10-yearly change in SE units was derived to show broad patterns of change around the world and not to indicate particular statistical significance.

To model time trends of different types of countries and centres across the whole time period of ISAAC Phase I to GAN Phase I, for each age group (adolescents [aged 13-14] and children [aged 6-7]) we included data from ISAAC/GAN centres with at least two time points.[102] We fitted mixed effect linear regression models, with prevalence as the outcome, time (in decades) as the exposure of interest, and random intercepts and slopes, with independent covariance, for the country and centre. The resulting estimated coefficient for the time parameter (the "time trend") can be interpreted as the average within-centre, absolute change in percentage point prevalence per decade. To improve model efficiency, we included both age groups within the same model but we considered age group to be an *a priori* confounder and effect modifier of the time trend as we are interested in the results in each age group separately.

Further confounders and effect modifiers for consideration were world region and the country level income group. We also tested for evidence against a linear time trend through introduction of a quadratic term and again by fitting separate models for the two time periods, ISAAC Phase I to III and ISAAC Phase III to GAN Phase I. We explored whether the patterns of time trends across income group and geographic region varied by age group by fitting a three-way interaction term between age group, time and (separately) income group and geographic region.

We explored non-linearity and additional interactions in the current eczema symptoms model only and then applied the resultant model to the other secondary outcomes. All data checking and analyses were performed using Stata versions 13-15.[85]

**Role of the funding source**

The funding sources had no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

## Results

We analysed GAN Phase I data from 122,268 participants from 27 centres in 14 countries in four world regions where we also had available data from either ISAAC Phase I or III (see Figure E.1). Participants comprised 74,361 adolescents from 27 centres (response rate 90%) and 47,907 children from 19 centres (response rate 79%). Amongst the 27 centres contributing data for 13-14 year olds, 13 participated in both ISAAC Phases I and III, 13 in ISAAC Phase III only, and one centre in ISAAC Phase I only, while amongst the 19 centres contributing data for 6-7 years old, 9 contributed to both ISAAC Phases I and III, 9 to ISAAC Phase III only, and one to ISAAC Phase I only (Figure E.1). The mean time period between ISAAC Phase III (2001-3) and GAN Phase I (2015-2020) for adolescents was 15.4 years (range 12.7-17.3) while between ISAAC Phase I (1993-1995) and GAN Phase I the mean interval was 22.7 years (range 19.5-25.5). The mean times between assessments were similar in children (15.3 (range 12.9-16.7) and 23.0 (range 22.0-25.4) years, respectively) (Tables E.1 and E.2).

**Eczema prevalence in GAN Phase I centres and changes in prevalence from ISAAC to GAN**

Amongst adolescents the median prevalence of current eczema symptoms (27 centres) was 6.2%, ranging from 1.9% in Lucknow, India to 18.5% in South Santiago, Chile. The prevalence of severe rash which disturbed sleep ranged from 0% in Bikaner, India to 4.7% in Cape Town, South Africa, with a median prevalence of 1.1%. Amongst children the median prevalence of current eczema symptoms (19 centres) was 6.0%, ranging from 1.3% in Lucknow, India to 15.7% in Taipei, Taiwan. The prevalence of severe rash which disturbs sleep in this age group ranged from 0.1% in Kottayam, India to 2.1% in Taipei, Taiwan, with median prevalence of 0.6%.

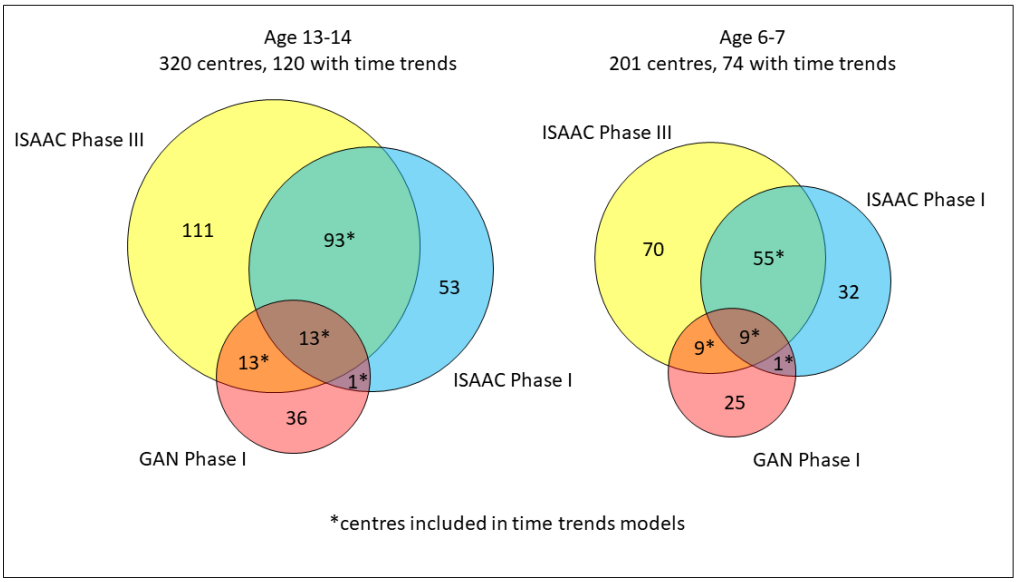


*Figure E.1 Centre participation in ISAAC Phase I, ISAAC Phase III and GAN Phase I.*

*Table E.1 Absolute changes in eczema current prevalence, severity and lifetime prevalence in adolescents for centres participating in GAN Phase I.*

| | | | | | | | | Flexural rash in last 12 months | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Region | Country | Centre | PI | GAN Phase I response rate | Country income level | GAN Phase I survey date | GAN Phase I sample size | GAN Phase I prevalence | Change per decade from ISAAC Phase III* | Number of SEs change |
| Africa and Eastern Mediterranean | Nigeria | Ibadan | *A Falade* | 85.0 | L | May-18 | 2,897 | 4.7% | -1.8% | -2.0 |
| | South Africa | Cape Town | *HJ Zar* | 84.4 | LM | Aug-17 | 3,979 | 14.3% | 0.7% | 0.7 |
| | Sudan | Khartoum | *M Nour* | 99.9 | L | Mar-17 | 1,785 | 10.5% | 4.1% | 3.3 |
| | Syrian Arab Republic | Lattakia | *G Dib* | 99.6 | LM | Apr-19 | 1,215 | 10.2% | 4.0% | 2.4 |
| America | Chile | South Santiago | *J Mallol* | 81.9 | UM | Mar-15 | 2,750 | 18.5% | -2.7% | -1.9 |
| | Costa Rica | Costa Rica | *ME Soto-Quirós* | 67.5 | UM | Feb-18 | 1,338 | 8.7% | 1.5% | 2.9 |
| | Ecuador | Quito | *A Cabrera Aguilar* | 100 | LM | Apr-19 | 3,000 | 10.6% | -5.8% | -5.0 |
| | México | Ciudad Victoria | *R García-Almaráz* | 82.3 | UM | Dec-15 | 2,468 | 6.5% | 1.1% | 0.5 |
| | México | Mexicali | *JV Mérida-Palacio* | 83.7 | UM | Apr-16 | 2,479 | 4.0% | 0.8% | 2.0 |
| | México | México City (North Area) | *BE Del Río Navarro* | 93.8 | UM | Sep-15 | 3,375 | 3.9% | -3.6% | -5.3 |
| | México | Monterrey | *SN González-Díaz* | 88.0 | UM | Dec-17 | 2,641 | 9.4% | 3.2% | 4.0 |
| | México | Toluca Urban Area | *EM Navarrete-Rodriguez* | 98.1 | UM | Oct-15 | 2,650 | 4.5% | 1.1% | 1.9 |
| | Nicaragua | Managua | *JF Sánchez* | 90.5 | L | Nov-18 | 3,131 | 5.7% | -8.9% | -10.0 |
| Europe | Greece | Athens* | *K Douros* | 75.5 | H | Feb-20 | 1,934 | 5.7% | 1.0% | 4.2 |
| | Spain | A Coruña | *A López-Silvarrey Varela* | 92.1 | H | Jan-19 | 3,462 | 10.9% | 3.9% | 7.9 |
| | Spain | Bilbao | *C González Díaz* | 91.1 | H | Sep-18 | 3,379 | 12.1% | 4.8% | 10.2 |
| | Spain | Cartagena | *L García-Marcos* | 73.8 | H | Jan-16 | 3,437 | 6.3% | 1.7% | 3.6 |
| South-East Asia and Western Pacific | India | Bikaner | *M Sabir* | 90.1 | L | Nov-17 | 2,702 | 4.2% | -2.7% | -3.6 |
| | India | Chandigarh | *M Singh* | 100 | L | Oct-17 | 3,000 | 3.4% | -0.1% | -0.3 |
| | India | Jaipur | *V Singh* | 98.7 | L | Nov-17 | 3,060 | 4.9% | 0.3% | 0.6 |
| | India | Kottayam | *TU Sukumaran* | 85.3 | L | Oct-17 | 2,091 | 3.2% | -4.0% | -3.6 |
| | India | Lucknow | *S Awasthi* | 94.0 | L | Oct-17 | 2,969 | 1.9% | -0.9% | -1.4 |
| | India | New Delhi (7) | *SK Kabra* | 100 | L | Nov-17 | 3,024 | 5.0% | 0.9% | 1.6 |
| | India | Pune | *S Salvi* | 99.6 | L | Oct-17 | 3,030 | 2.0% | -0.1% | -0.2 |
| | New Zealand | Auckland | *MI Asher* | 85.5 | H | Oct-18 | 1,885 | 6.2% | -1.6% | -2.1 |
| | Taiwan | Taipei | *J-L Huang* | 93.0 | H | Oct-17 | 3,474 | 9.6% | 3.5% | 10.3 |
| | Thailand | Bangkok | *S Chinratanapisit* | 97.9 | LM | Sep-17 | 3,206 | 9.5% | -0.5% | -0.7 |
| Total | | | | | | Sep-17 | 74,361 | | | |

*except Athens which uses change from ISAAC Phase I

Table E.1 continued

| Severe flexural rash (disturbing sleep) in last 12 months | | | Ever had eczema | | |
|---|---|---|---|---|---|
| GAN Phase I prevalence | Change per decade from ISAAC Phase III* | Number of SEs change | GAN Phase I prevalence | Change per decade from ISAAC Phase III* | Number of SEs change |
| 1.1% | -0.1% | -0.5 | 1.7% | 23.7% | 4.0% |
| 4.7% | 0.6% | 1.1 | 1.2% | 32.8% | 2.7% |
| 2.8% | 2.0% | 3.5 | 2.9% | 26.6% | 18.9% |
| 2.6% | 1.1% | 2.0 | 1.0% | 25.8% | 3.5% |
| 1.5% | -1.1% | -3.9 | 2.1% | 8.3% | -4.2% |
| 1.8% | 0.3% | 1.3 | 1.1% | 20.7% | -0.1% |
| 1.5% | -0.4% | -1.4 | 0.9% | 14.5% | 2.1% |
| 1.1% | 0.0% | 0.0 | 0.4% | 16.9% | -3.4% |
| 0.6% | 0.3% | 3.1 | 0.3% | 14.1% | 7.7% |
| 0.7% | -0.2% | -0.8 | 0.5% | 16.9% | 4.7% |
| 1.3% | 0.3% | 1.8 | 0.8% | 14.1% | -3.1% |
| 0.5% | 0.0% | -0.4 | 1.1% | 10.0% | -4.6% |
| 1.6% | -0.9% | -3.1 | 0.7% | 27.5% | 7.7% |
| 0.3% | 0.0% | -0.1 | 0.4% | 4.5% | -1.7% |
| 1.2% | 0.6% | 3.7 | 0.9% | 10.8% | 3.1% |
| 1.4% | 0.6% | 4.3 | 0.8% | 11.8% | 1.8% |
| 0.6% | -0.1% | -0.4 | 0.8% | 8.8% | -4.9% |
| 0.0% | -0.6% | -6.7 | 1.9% | 0.0% | -7.5% |
| 0.4% | 0.2% | 2.2 | 0.7% | 10.8% | 5.1% |
| 0.5% | -0.1% | -0.4 | 0.9% | 10.6% | -2.0% |
| 0.4% | 0.3% | 3.3 | 1.0% | 13.6% | 8.9% |
| 0.3% | -0.1% | -0.7 | 1.5% | 14.0% | 1.8% |
| 1.4% | 0.6% | 2.6 | 0.6% | 27.6% | 9.1% |
| 0.4% | 0.1% | 1.3 | 0.8% | 20.0% | 6.6% |
| 1.1% | -0.5% | -1.9 | 0.8% | 18.1% | -2.1% |
| 1.2% | 0.4% | 3.6 | 0.9% | 12.0% | 0.1% |
| 0.6% | -0.4% | -1.7 | 1.2% | 6.2% | -3.7% |

*except Athens which uses change from ISAAC Phase I

*Table E.2 Absolute changes in eczema current prevalence, severity and lifetime prevalence in children for centres participating in GAN Phase I.*

| | | | | | | | | Flexural rash in last 12 months | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Region | Country | Centre | PI | GAN Phase I response rate | Country income level | GAN Phase I survey date | GAN Phase I sample size | GAN Phase I prevalence | Change per decade from ISAAC Phase III* | Number of SEs change |
| Africa and Eastern Mediterranean | Syrian Arab Republic | Lattakia | *Y Mohammad* | 93.0 | LM | May-19 | 1,116 | 3.0% | 0.4% | 0.9 |
| America | Costa Rica | Costa Rica | *ME Soto-Quirós* | 64.5 | UM | Jan-18 | 1,936 | 7.5% | -0.9% | -1.3 |
| | México | Ciudad Victoria | *R García-Almaráz* | 81.5 | UM | Feb-16 | 2,444 | 6.1% | 2.9% | 6.6 |
| | México | Mexicali | JV Mérida-Palacio | 77.0 | UM | Mar-16 | 2,001 | 5.0% | -0.2% | -0.5 |
| | México | México City (North Area) | *BE Del Río Navarro* | 86.7 | UM | Jun-16 | 2,515 | 7.1% | -1.2% | -1.9 |
| | México | Toluca Urban Area | *EM Navarrete-Rodriguez* | 95.7 | UM | Apr-16 | 2,712 | 6.0% | 0.4% | 0.6 |
| | Nicaragua | Managua | *JF Sánchez* | 87.9 | L | Nov-18 | 3,162 | 4.2% | -9.6% | -9.5 |
| Europe | Spain | A Coruña | *A López-Silvarrey Varela* | 71.0 | H | Jan-19 | 3,407 | 10.2% | 1.9% | 4.3 |
| | Spain | Bilbao | *C González Díaz* | 55.2 | H | Aug-18 | 2,707 | 12.4% | 3.4% | 7.9 |
| | Spain | Cartagena | *L García-Marcos* | 65.9 | H | Jan-16 | 3,509 | 8.3% | 2.7% | 6.0 |
| South-East Asia and Western Pacific | India | Chandigarh* | M Singh | 100 | L | Oct-17 | 2,473 | 3.8% | 0.2% | 0.5 |
| | India | Jaipur | V Singh | 75.8 | L | Nov-17 | 2,296 | 4.2% | -1.2% | -1.1 |
| | India | Kottayam | *TU Sukumaran* | 68.4 | L | Dec-17 | 2,099 | 2.3% | 0.0% | -0.1 |
| | India | Lucknow | *S Awasthi* | 91.3 | L | Oct-17 | 2,969 | 1.3% | -0.8% | -2.6 |
| | India | New Delhi (7) | *SK Kabra* | 80.9 | L | Jan-18 | 2,516 | 4.6% | 0.2% | 0.5 |
| | India | Pune | S Salvi | 79.8 | L | Oct-17 | 2,404 | 1.7% | -0.2% | -0.6 |
| | New Zealand | Auckland | *MI Asher* | 63.7 | H | Jul-18 | 1,538 | 15.0% | 0.4% | 0.6 |
| | Taiwan | Taipei | *J-L Huang* | 76.3 | H | Oct-17 | 3,036 | 15.7% | 5.7% | 11.6 |
| | Thailand | Bangkok | *S Chinratanapisit* | 86.3 | LM | Aug-17 | 3,067 | 11.8% | -3.2% | -3.9 |
| Total | | | | | | Aug-17 | 47,907 | | | |

*except Chandigarh which uses change from ISAAC Phase I

Table E.2 continued

| Severe flexural rash (disturbing sleep) in last 12 months | | | Ever had eczema | | |
|---|---|---|---|---|---|
| GAN I prevalence | Absolute change per decade ISAAC III to GAN* | Number of SEs change | GAN I prevalence | Absolute change per decade ISAAC III to GAN* | Number of SEs change |
| 1.2% | 0.6% | 2.0 | 8.5% | 4.0% | 4.6 |
| 1.5% | 0.0% | -0.1 | 15.9% | 4.5% | 6.2 |
| 1.1% | 0.7% | 3.4 | 3.7% | 1.3% | 2.8 |
| 0.3% | -0.4% | -1.7 | 4.4% | 0.6% | 0.9 |
| 0.6% | -0.1% | -0.5 | 11.4% | 5.4% | 8.5 |
| 0.4% | 0.1% | 0.4 | 7.7% | 3.2% | 4.6 |
| 0.8% | -1.3% | -4.7 | 8.7% | -5.3% | -5.9 |
| 0.6% | 0.0% | 0.1 | 47.3% | 7.7% | 9.3 |
| 0.9% | 0.3% | 1.9 | 46.9% | 9.0% | 10.6 |
| 1.2% | 0.4% | 2.6 | 37.4% | 6.8% | 4.4 |
| 0.5% | 0.0% | -0.3 | 4.2% | 0.8% | 2.2 |
| 0.3% | -0.5% | -2.6 | 7.4% | -8.7% | -6.8 |
| 0.1% | 0.1% | 1.7 | 2.0% | -5.3% | -7.6 |
| 0.3% | -0.1% | -0.4 | 8.3% | 4.1% | 2.7 |
| 0.6% | 0.1% | 0.8 | 5.4% | 0.1% | 0.3 |
| 0.3% | 0.1% | 0.8 | 2.2% | -0.8% | -2.5 |
| 1.8% | -0.4% | -1.4 | 31.4% | 3.1% | 3.0 |
| 2.1% | 0.6% | 2.9 | 22.9% | -2.2% | -3.4 |
| 1.0% | -0.4% | -3.0 | 28.6% | 2.4% | 1.5 |

*except Chandigarh which uses change from ISAAC Phase I

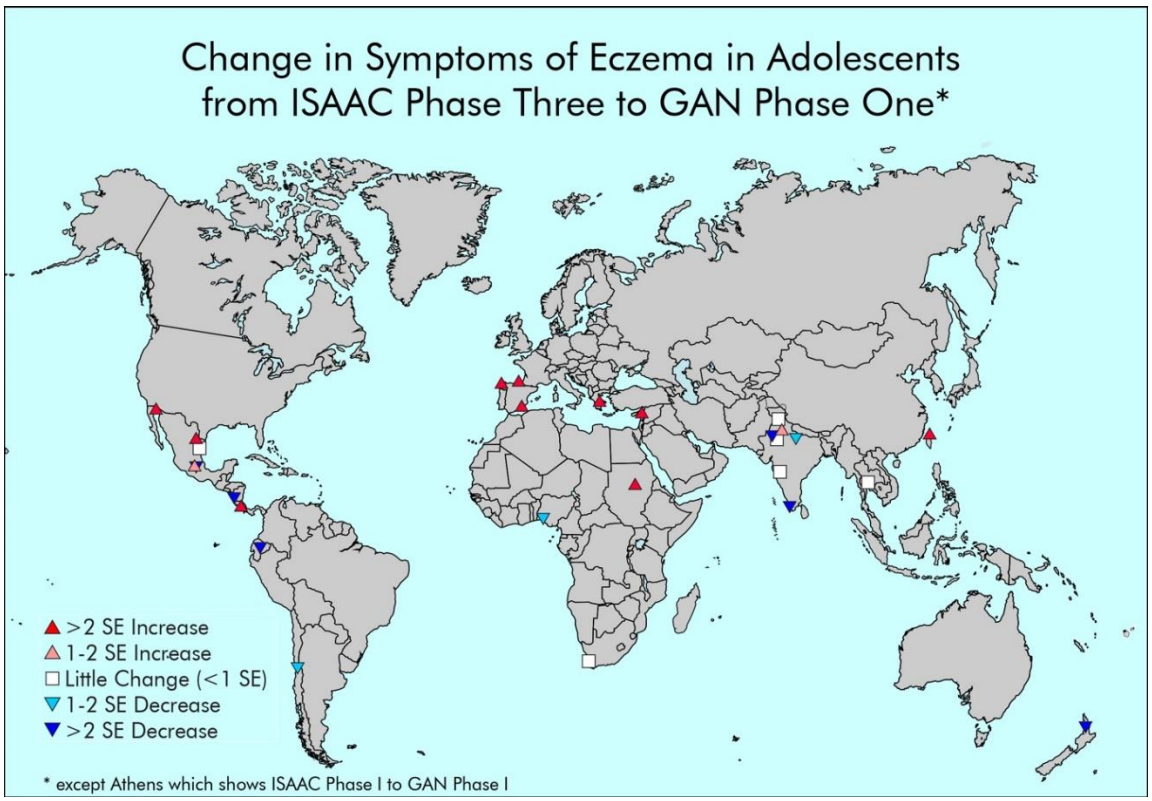


*Figure E.2 Changes in the centre prevalence of current eczema symptoms for adolescents reported between ISAAC Phase III and GAN Phase I, based on number of Standard Errors (SEs) of change.*

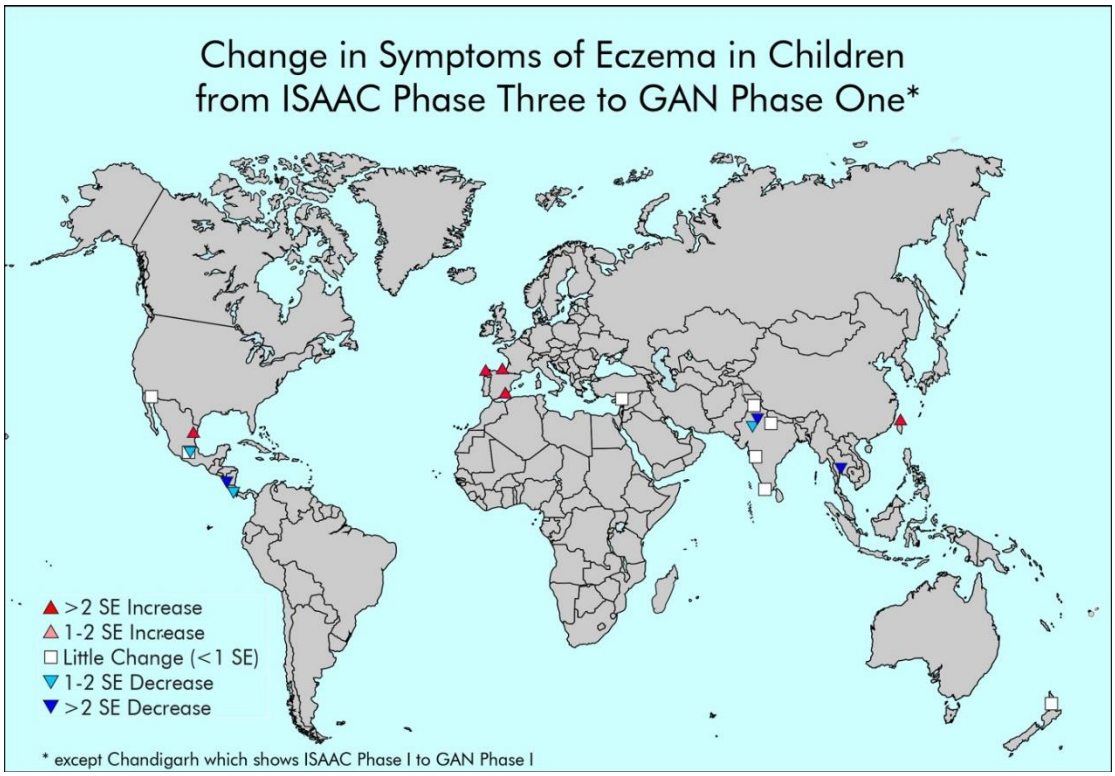


*Figure E.3 Changes in the centre prevalence of current eczema symptoms for children reported between ISAAC Phase III and GAN Phase I, based on number of Standard Errors (SEs) of change.*

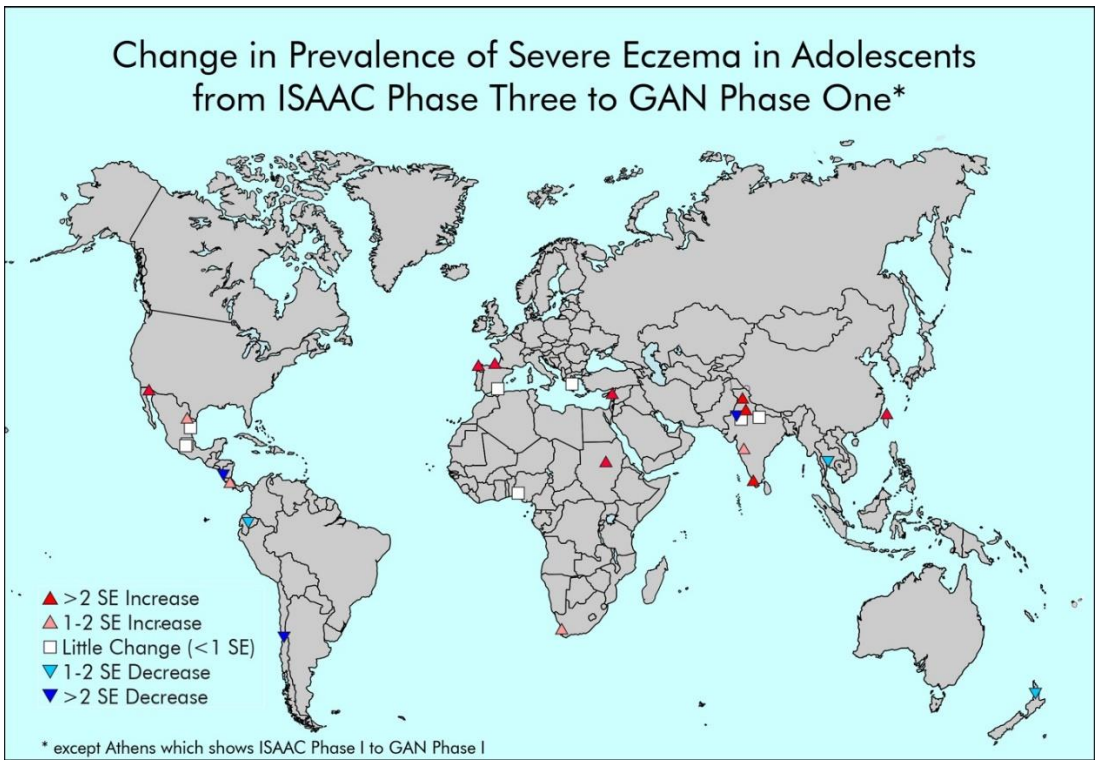


*Figure E.4 Changes in the centre prevalence of severe eczema symptoms for adolescents reported between ISAAC Phase III and GAN Phase I, based on number of Standard Errors (SEs) of change.*

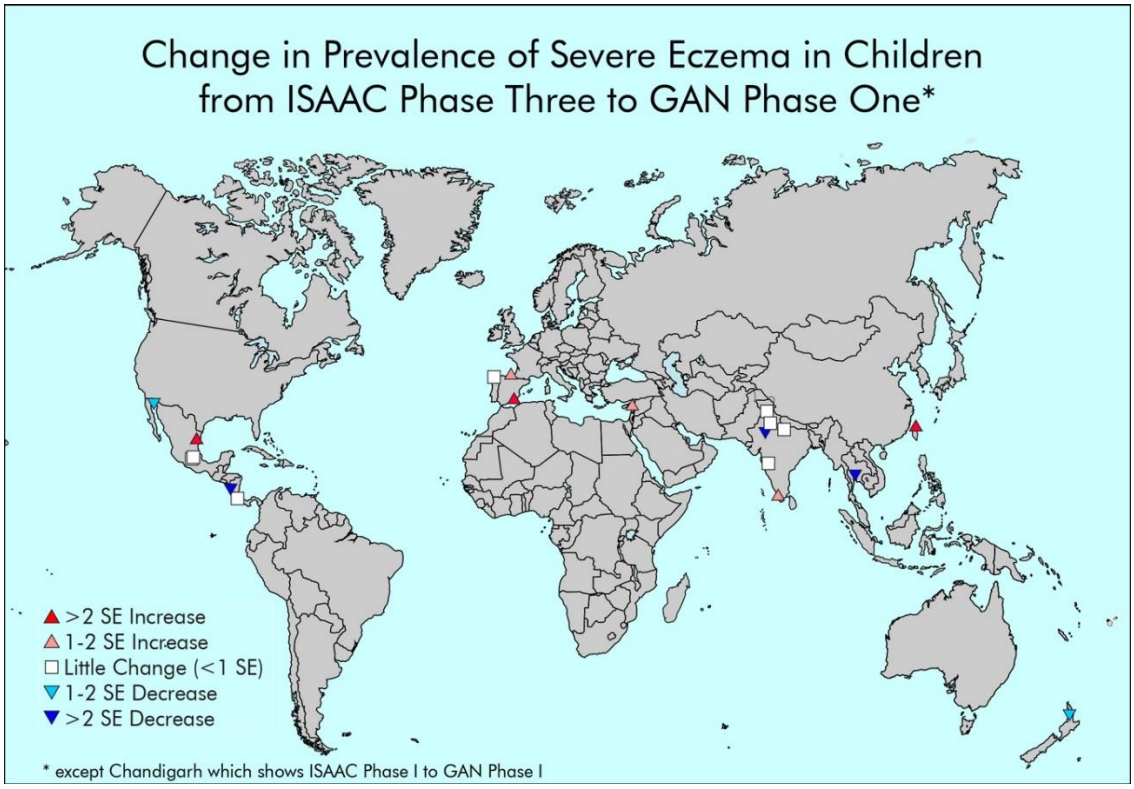


*Figure E.5 Changes in the centre prevalence of severe eczema symptoms for children reported between ISAAC Phase III and GAN Phase I, based on number of Standard Errors (SEs) of change.*

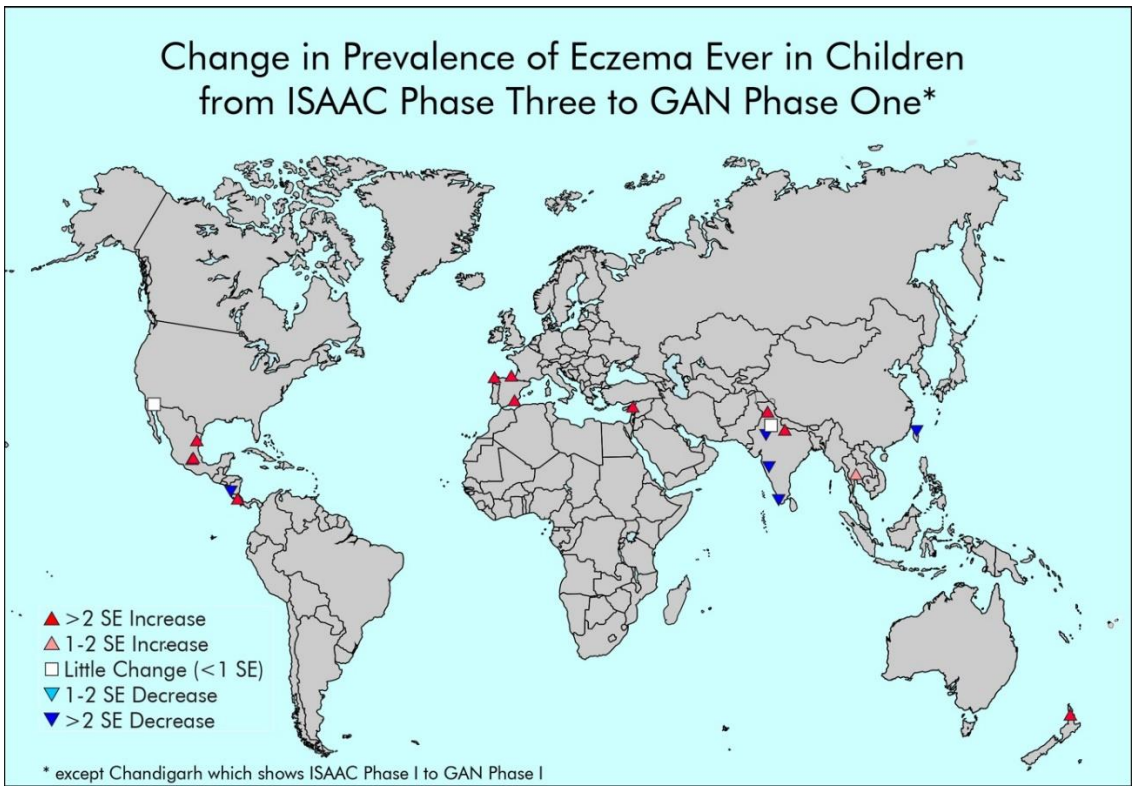


*Figure E.6 Changes in the centre prevalence of eczema ever for adolescents reported between ISAAC Phase III and GAN Phase I, based on number of Standard Errors (SEs) of change.*

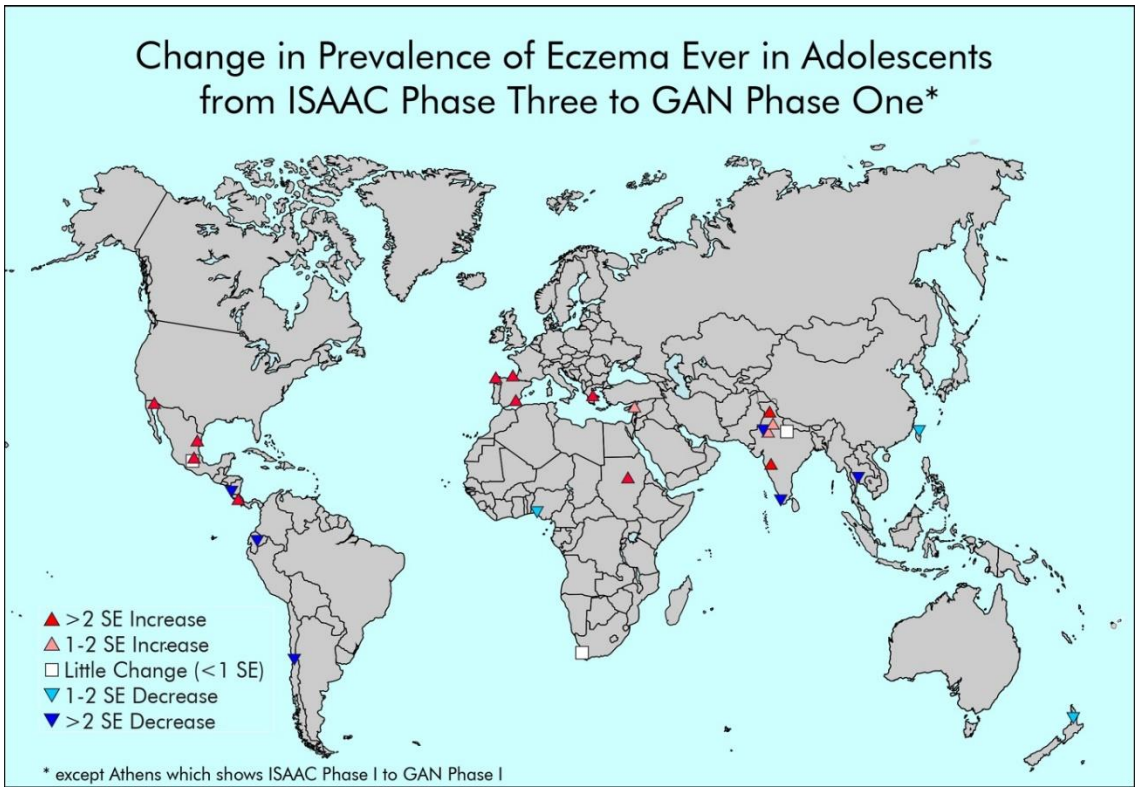


*Figure E.7 Changes in the centre prevalence of eczema ever for children reported between ISAAC Phase III and GAN Phase I, based on number of Standard Errors (SEs) of change.*

The absolute change in current eczema symptom prevalence in adolescents per decade from the latest available ISAAC data to GAN Phase I ranged from a reduction of 8.9% in Managua, Nicaragua to a rise of 4.8% in Bilbao, Spain. We observed a ≥2 SE decrease in current eczema symptom prevalence from the latest available ISAAC data to GAN Phase I in six centres, with a 1-2 SE decrease in three centres, minimal change in six centres, a 1-2 SE increase in two centres and with the remaining 10 centres showing a >2 SE increase (Figure E.2 and Table E.1). For children, the absolute change in current eczema symptoms prevalence per decade ranged from a reduction of 9.6% in Managua, Nicaragua to an increase of 5.7% in Taipei, Taiwan. We observed a ≥2 SE decrease from ISAAC Phase III to GAN Phase I in three centres, with a 1-2 SE decrease in three centres, minimal change in eight centres, and with increases in current eczema symptoms prevalence of >2 SE in the remaining five centres (Figure E.3 and Table E.2).

Changes in the secondary outcomes of severe eczema and lifetime prevalence can be seen in Figures E.4-E.7, and were similar to the primary outcome.

**Global and stratified estimates of change**

Our regression models showed no evidence that world region or income group explained the global effect of current eczema symptoms prevalence change over time. After adjusting for them, we estimated a global increase of 0.98% (95% CI 0.04%-1.92%) per decade in adolescents and 1.21% (95% CI 0.18%-2.24%) per decade in children. We also estimated increases in severe eczema symptoms (13-14: 0.26% (95% CI 0.06%-0.46%)); 6-7: 0.23% (95% CI 0.02%-0.45%) and lifetime eczema prevalence (13-14: 2.71% (95% CI 1.10%-4.32%); 6-7: 3.91% (95% CI 2.07%-5.75%)) (Table E.3). There was substantial heterogeneity between centres relative to 10-year changes (standard deviations of the random slope were 2.40, 0.58 and 2.87% for current eczema symptoms, severe eczema symptoms and lifetime prevalence over both age groups). The variability in trend of current eczema symptoms between centres can also been seen visually in Figures E.8 and E.9.

There was evidence that 10-year changes varied by world region and income group for most outcomes ($p<=0.0001$) except severe rash by income group ($p=0.10$). Despite this strong evidence for effect modification, there was little effect on between-centre heterogeneity in change over time, with estimated random slope SDs changing only marginally compared with

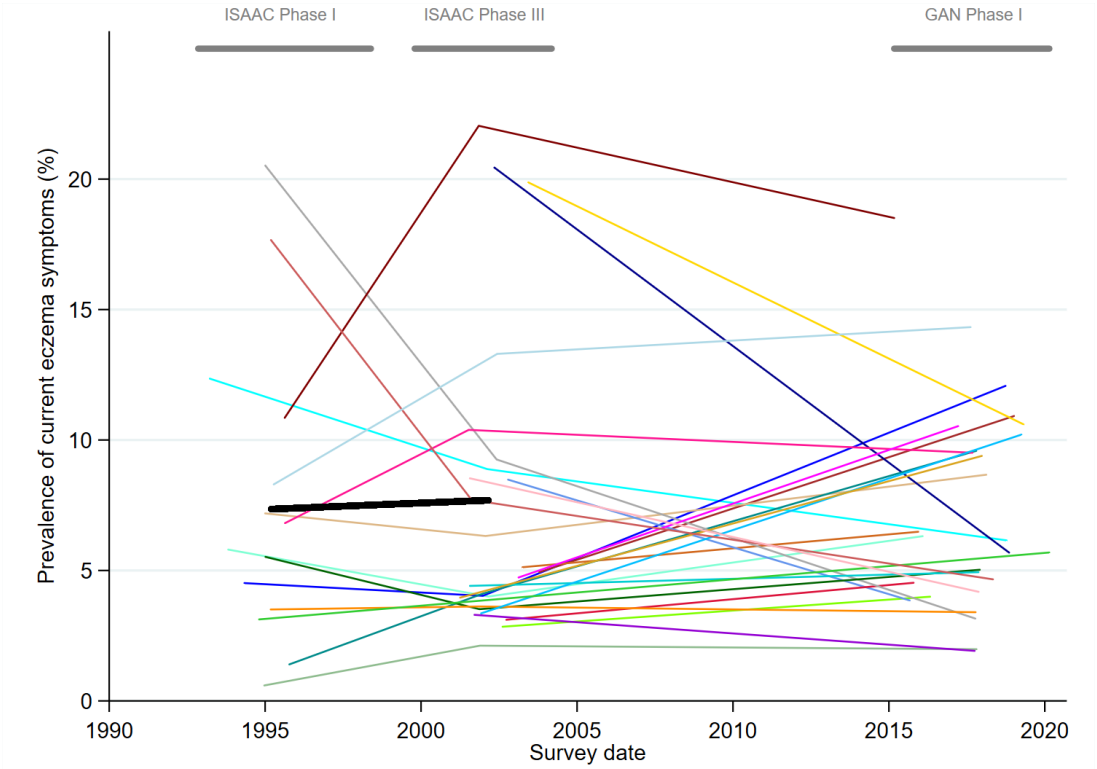


*Figure E.8 Prevalence of current eczema symptoms over time in adolescents for GAN Phase I centres participating in at least one of ISAAC Phase I and III (coloured lines) with additional mean trend of ISAAC-only centres participating in both Phases I and III (black line).*

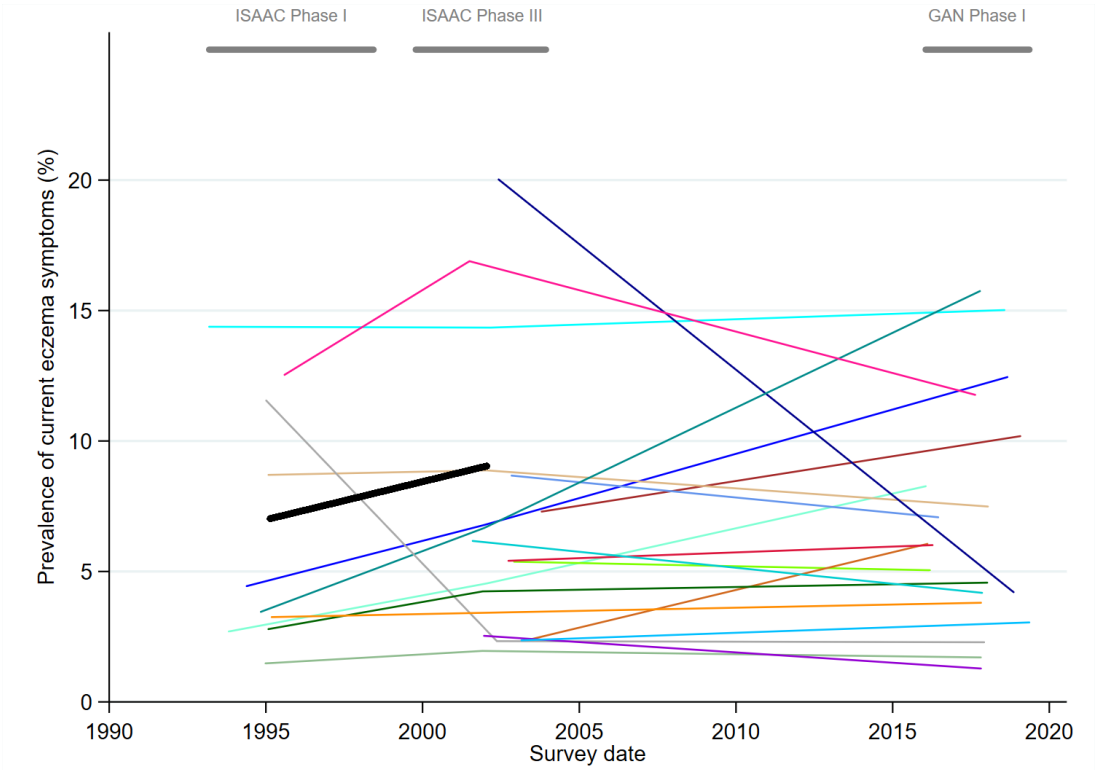


*Figure E.9 Prevalence of current eczema symptoms over time in children for GAN Phase I centres participating in at least one of ISAAC Phase I and III (coloured lines) with additional mean trend of ISAAC-only centres participating in both Phases I and III (black line).*

*Table E.3 Estimates of within centre, absolute percentage point change in eczema outcomes per decade. Changes come from mixed effect linear regression models of eczema outcomes on three-way interactions between time, age group and either world income group or geographic region, with random country and centre slopes and intercepts*.*

| Model | Strata | | N in strata | Outcome | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Current eczema symptoms | | Severe current eczema symptoms | | Lifetime eczema | |
| | | | | Estimate (95% CI) | Interaction test & AIC | Estimate (95% CI) | Interaction test & AIC | Estimate (95% CI) | Interaction test & AIC |
| Stratified by age group | Age 6-7 | | 157 | 1.21 (0.18, 2.24) | Age: p=0.53 AIC=2144 | 0.23 (0.02, 0.45) | Age: p=0.70 AIC=768 | 3.91 (2.07, 5.75) | Age: p=0.15 AIC=2743 |
| | Age 13-14 | | 253 | 0.98 (0.04, 1.92) | | 0.26 (0.06, 0.46) | | 2.71 (1.10, 4.32) | |
| | Random effects | | | Slope SD: 2.40 (1.68, 3.43) | | Slope SD: 0.58 (0.40, 0.83) | | Slope SD: 2.87 (1.68, 4.93) | |
| Stratified by age group and income group (test for addition of income) | Age 6-7 | Low income | 29 | -1.06 (-3.30, 1.18) | Income (3-way): P<0.0001 AIC=2118 | -0.03 (-0.52, 0.47) | Income (3-way): P=0.10 AIC=771 | 0.02 (-3.74, 3.78) | Income (3-way): P<0.0001 AIC=2677 |
| | | Low-middle income | 15 | 0.35 (-2.11, 2.80) | | 0.38 (-0.14, 0.91) | | 3.35 (-1.20, 7.91) | |
| | | Upper-middle income | 43 | 1.63 (-0.22, 3.47) | | 0.10 (-0.30, 0.51) | | 5.50 (2.22, 8.78) | |
| | | High income | 70 | 2.41 (0.87, 3.95) | | 0.32 (-0.02, 0.66) | | 7.46 (4.77, 10.14) | |
| | Age 13-14 | Low income | 47 | -1.48 (-3.56, 0.60) | | -0.02 (-0.49, 0.45) | | 0.03 (-3.36, 3.41) | |
| | | Low-middle income | 40 | 2.32 (0.40, 4.25) | | 0.71 (0.29, 1.14) | | 1.44 (-1.95, 4.82) | |
| | | Upper-middle income | 62 | 1.66 (-0.06, 3.37) | | 0.23 (-0.15, 0.61) | | 3.93 (0.96, 6.89) | |
| | | High income | 104 | 0.45 (-0.99, 1.88) | | 0.12 (-0.20, 0.44) | | 2.29 (-0.14, 4.72) | |
| | Random effects | | | Slope SD: 2.18 (1.45, 3.26) | | Slope SD: 0.54 (0.36, 0.80) | | Slope SD: 2.83 (1.58, 5.06) | |
| Stratified by age group and grouped region (test for addition of region) | Age 6-7 | Africa and Eastern Mediterranean | 10 | 1.59 (-1.50, 4.67) | Region (3-way): P=0.0001 AIC=2129 | 0.75 (0.14, 1.35) | Region (3-way): P<0.0001 AIC=741 | 4.57 (-1.37, 10.51) | Region (3-way): P<0.0001 AIC=2711 |
| | | America | 29 | -0.01 (-2.10, 2.08) | | -0.01 (-0.44, 0.42) | | 3.59 (0.14, 7.04) | |
| | | Europe | 64 | 1.21 (-0.59, 3.00) | | -0.01 (-0.37, 0.36) | | 8.45 (5.26, 11.65) | |
| | | South-East Asia and Western Pacific | 54 | 1.77 (-0.20, 3.73) | | 0.36 (-0.05, 0.78) | | 1.58 (-1.36, 4.52) | |
| | Age 13-14 | Africa and Eastern Mediterranean | 34 | 2.83 (0.67, 5.00) | | 0.82 (0.38, 1.27) | | 2.93 (-0.66, 6.53) | |
| | | America | 50 | 0.37 (-1.56, 2.31) | | 0.14 (-0.26, 0.55) | | 2.61 (-0.42, 5.63) | |
| | | Europe | 100 | 0.01 (-1.61, 1.63) | | 0.01 (-0.33, 0.34) | | 2.12 (-0.58, 4.82) | |
| | | South-East Asia and Western Pacific | 69 | 1.29 (-0.64, 3.22) | | 0.31 (-0.10, 0.72) | | 1.72 (-1.14, 4.57) | |
| | Random effects | | | Slope SD: 2.51 (1.82, 3.47) | | Slope SD: 0.57 (0.41, 0.80) | | Slope SD: 2.68 (1.26, 5.68) | |

*CI: confidence interval, AIC: Akaike Information Criterion, SD: Standard deviation

their estimates in the unstratified models (-0.22% to +0.11%), suggesting that other factors may be driving differences in change over time. With respect to world region, there were five statistically significant increases in the 24 estimated changes across all outcomes and both age groups, with Africa/Eastern Mediterranean driving most of the increase in period and severe rash prevalence, and Europe and America driving the much of the increase in lifetime prevalence in adolescents and children (Table E.3).

There were six statistically significant increases in the 24 estimated changes by income group. Children in high-income countries experienced 10-year increases in most outcomes (current eczema symptoms: 2.41% (0.87%, 3.95%); severe eczema: 0.32%, (-0.02%, 0.66%); lifetime eczema prevalence: 7.46%, (4.77%, 10.14%)), but there was little evidence for change in the other income groups apart from upper-middle lifetime prevalence: 5.50% (2.22%, 8.78%). There was evidence for change only in middle income adolescents, with lower-middle showing increases in eczema symptom prevalence (2.32% (0.40%, 4.25%)) and severe rash (0.71% (0.29%, 1.14%)) and upper-middle showing increases in lifetime eczema prevalence (3.93% (0.96%, 6.89%)) and weak evidence in eczema symptom prevalence (1.66 (-0.06, 3.37)).

**Changes in trend**

There was no evidence against a linear trend in current eczema symptom prevalence, across the whole time period (p=0.87), although this may be a consequence of the random slope model fitting perfectly interpolated fixed plus random effect slopes in the centres with only two time points. There was, however, a visual indication that rates of change may be different in some groups between ISAAC Phase I to III and ISAAC Phase III to GAN Phase I (Figures E.8 and E.9).

Table E.4 presents change estimates from models fitted separately for each time period to give an approximation (because a different set of centres were included in the main models) of the differences. Assuming both sets of centres can be fairly compared, many point estimates of change were different in the two periods. In high-income settings, eczema symptoms and severe symptoms were slightly decreasing or flat in adolescents in the first period, but rising again in the second.

*Table E.4 Estimates of within centre, absolute percentage point change in eczema outcomes per decade between ISAAC Phase I and III and between ISAAC Phase III and GAN Phase I. Changes come from two mixed effect linear regression models of eczema outcomes on three-way interactions between time, age group and either world income group or geographic region, with random country and centre slopes and intercepts.*

| Model | Strata | | Current eczema symptoms | | Severe current eczema symptoms | | Lifetime eczema | |
|---|---|---|---|---|---|---|---|---|
| | | | ISAAC I and III n=340 | ISAAC III and GAN I n=88 | ISAAC I and III n=340 | ISAAC III and GAN I n=88 | ISAAC I and III n=340 | ISAAC III and GAN I n=88 |
| | | | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) |
| Stratified by age group only | 6-7 years | n/a | 2.97 (1.54, 4.40) | -0.37 (-2.31, 1.57) | 0.41 (0.10, 0.72) | -0.02 (-0.38, 0.34) | 6.88 (4.03, 9.73) | 2.23 (-0.89, 5.35) |
| | 13-14 years | n/a | 0.62 (-0.58, 1.82) | -0.16 (-1.97, 1.65) | 0.23 (-0.03, 0.50) | 0.12 (-0.22, 0.45) | 3.52 (1.23, 5.82) | 0.74 (-1.90, 3.38) |
| | Random effects: Slope SD (95% CI) | | 2.76 (1.88, 4.04) | 3.01 (1.89, 4.81) | 0.74 (0.55, 0.99) | 0.57 (0.34, 0.95) | 3.54 (1.84, 6.80) | 2.07 (0.83, 5.18) |
| Stratified by age group and income group | 6-7 years | Low income | 0.23 (-3.41, 3.86) | -2.10 (-5.33, 1.14) | 0.11 (-0.70, 0.92) | -0.04 (-0.71, 0.62) | -1.75 (-8.88, 5.37) | -2.62 (-6.30, 1.06) |
| | | Lower-middle | 3.80 (-0.71, 8.31) | -3.09 (-6.83, 0.66)* | 0.84 (-0.12, 1.80) | -0.01 (-0.76, 0.74)* | 4.63 (-4.71, 13.97) | 2.71 (-3.59, 9.01)* |
| | | Upper-middle | 2.31 (-0.15, 4.77) | -0.12 (-3.83, 3.58) | 0.11 (-0.44, 0.67) | -0.21 (-0.97, 0.56) | 7.55 (2.61, 12.49) | 3.17 (-1.47, 7.82) |
| | | High income | 3.27 (1.41, 5.13) | 2.59 (-0.88, 6.06) | 0.38 (-0.05, 0.81) | 0.08 (-0.65, 0.80) | 9.21 (5.63, 12.78) | 4.99 (0.88, 9.10) |
| | 13-14 years | Low income | -1.10 (-4.04, 1.84) | -2.14 (-5.15, 0.86) | -0.33 (-1.00, 0.35) | 0.17 (-0.46, 0.79) | -0.61 (-6.23, 5.00) | -1.01 (-3.87, 1.86) |
| | | Lower-middle | 4.53 (1.92, 7.14) | -0.29 (-3.43, 2.84) | 1.11 (0.52, 1.69) | 0.24 (-0.40, 0.89) | 5.84 (0.57, 11.11) | -2.73 (-7.20, 1.74) |
| | | Upper-middle | 1.24 (-0.86, 3.34) | 0.34 (-3.15, 3.84) | 0.29 (-0.20, 0.77) | -0.16 (-0.89, 0.57) | 5.35 (1.25, 9.45) | 0.58 (-3.28, 4.44) |
| | | High income | -0.88 (-2.56, 0.80) | 2.23 (-1.23, 5.70) | 0.01 (-0.38, 0.41) | 0.17 (-0.55, 0.89) | 2.58 (-0.53, 5.70) | 4.56 (0.46, 8.66) |
| | Random effects: Slope SD (95% CI) | | 2.43 (1.60, 3.70) | 2.73 (1.68, 4.46) | 0.67 (0.49, 0.91) | 0.59 (0.36, 0.95) | 3.53 (1.94, 6.42) | 0.00 (n/a) |
| Stratified by age group and grouped region | 6-7 years | Africa and Eastern Mediterranean | 2.85 (-2.44, 8.13) | -0.42 (-5.06, 4.22)* | 1.08 (0.02, 2.15) | 0.55 (-0.20, 1.31)* | 2.66 (-8.60, 13.93) | 3.95 (-4.47, 12.38)* |
| | | America | 2.15 (-1.13, 5.42) | -3.25 (-6.05, -0.46) | 0.31 (-0.39, 1.00) | -0.49 (-0.94, -0.04) | 10.56 (3.79, 17.33) | 1.35 (-2.54, 5.23) |
| | | Europe | 2.30 (0.28, 4.32) | 2.75 (-2.40, 7.90) | 0.07 (-0.37, 0.51) | 0.21 (-0.60, 1.03) | 7.33 (3.26, 11.40) | 8.14 (3.03, 13.24) |
| | | South-East Asia and Western Pacific | 3.25 (0.81, 5.69) | 0.63 (-2.09, 3.35) | 0.61 (0.06, 1.16) | -0.11 (-0.54, 0.32) | 4.76 (-0.03, 9.54) | -0.84 (-3.86, 2.17) |
| | 13-14 years | Africa and Eastern Mediterranean | 3.78 (0.85, 6.72) | 1.70 (-1.23, 4.64) | 0.72 (0.08, 1.35) | 0.87 (0.40, 1.34) | 3.40 (-2.69, 9.49) | 3.32 (-0.98, 7.62) |
| | | America | 2.58 (-0.08, 5.24) | -2.68 (-5.20, -0.16) | 0.46 (-0.13, 1.04) | -0.36 (-0.76, 0.05) | 7.11 (1.74, 12.47) | -0.96 (-4.06, 2.15) |
| | | Europe | -0.96 (-2.70, 0.78) | 3.72 (-1.43, 8.87) | -0.06 (-0.45, 0.34) | 0.44 (-0.38, 1.25) | 1.98 (-1.39, 5.35) | 8.75 (3.63, 13.86) |
| | | South-East Asia and Western Pacific | 0.24 (-2.00, 2.48) | 0.10 (-2.60, 2.79) | 0.26 (-0.26, 0.77) | -0.07 (-0.49, 0.36) | 3.88 (-0.42, 8.18) | -2.63 (-5.32, 0.06) |
| | Random effects: Slope SD (95% CI) | | 2.57 (1.76, 3.75) | 2.41 (1.48, 3.91) | 0.71 (0.52, 0.95) | 0.38 (0.21, 0.69) | 3.85 (2.19, 6.78) | 0.00 (n/a) |

CI: confidence interval SD: Standard deviation * Strata contains <5

*Table E.5 Estimates of within centre, absolute percentage point change in eczema outcomes per decade between ISAAC Phase I and III and between ISAAC Phase III and GAN Phase I for centres with data at all three time points. Changes come from two mixed effect linear regression models of eczema outcomes on three-way interactions between time, age group and either world income group or geographic region, with random country and centre slopes and intercepts.*

| Model | Strata | | Current eczema symptoms | | Severe current eczema symptoms | | Lifetime eczema | |
|---|---|---|---|---|---|---|---|---|
| | | | ISAAC I and III n=340 | ISAAC III and GAN I n=88 | ISAAC I and III n=340 | ISAAC III and GAN I n=88 | ISAAC I and III n=340 | ISAAC III and GAN I n=88 |
| | | | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) | estimate (95% CI) |
| Stratified by age group only | 6-7 years | n/a | 0.38 (-4.07, 4.83) | 0.95 (-0.74, 2.64) | 0.30 (-0.59, 1.19) | 0.02 (-0.25, 0.29) | 6.23 (-2.63, 15.10) | 2.00 (-1.90, 5.89) |
| | 13-14 years | n/a | -0.94 (-4.78, 2.90) | 0.28 (-1.16, 1.72) | 0.00 (-0.80, 0.81) | 0.05 (-0.18, 0.28) | 4.05 (-3.69, 11.79) | -0.69 (-3.96, 2.59) |
| | | | | | | | | |
| Stratified by age group and income group | 6-7 years | Low income | -3.77 (-9.69, 2.15) | -0.01 (-1.94, 1.91) | -0.31 (-1.30, 0.69) | -0.08 (-0.57, 0.41) | -6.49 (-19.18, 6.19) | -1.87 (-6.89, 3.15) |
| | | Lower-middle* | 7.38 (-4.86, 19.63) | -3.15 (-6.43, 0.13) | 0.54 (-1.52, 2.59) | -0.11 (-0.76, 0.54) | 0.68 (-19.05, 20.40) | 2.43 (-6.11, 10.97) |
| | | Upper-middle* | 0.25 (-10.13, 10.63) | -0.81 (-4.11, 2.50) | 0.85 (-0.90, 2.59) | -0.23 (-0.89, 0.42) | 7.48 (-9.96, 24.92) | 4.52 (-4.09, 13.13) |
| | | High income | 2.06 (-2.45, 6.56) | 3.11 (1.43, 4.79) | 0.19 (-0.57, 0.94) | 0.16 (-0.23, 0.55) | 10.19 (1.12, 19.26) | 4.27 (-0.09, 8.64) |
| | 13-14 years | Low income | -6.20 (-10.90, -1.50) | -0.97 (-2.45, 0.51) | -1.23 (-2.02, -0.44) | 0.12 (-0.31, 0.54) | -9.26 (-20.11, 1.60) | -1.41 (-5.26, 2.44) |
| | | Lower-middle* | 6.56 (-1.22, 14.35) | 0.03 (-2.35, 2.42) | 1.73 (0.42, 3.04) | 0.07 (-0.44, 0.58) | 10.32 (-3.12, 23.76) | -4.27 (-10.48, 1.95) |
| | | Upper-middle* | 7.28 (-0.39, 14.96) | -0.40 (-2.93, 2.13) | 0.95 (-0.33, 2.24) | -0.34 (-0.86, 0.19) | 20.82 (7.55, 34.10) | -3.47 (-10.04, 3.10) |
| | | High income | -1.45 (-6.04, 3.14) | 2.04 (0.38, 3.71) | -0.19 (-0.96, 0.58) | 0.12 (-0.27, 0.50) | 1.52 (-7.69, 10.73) | 3.36 (-0.98, 7.71) |
| | | | | | | | | |
| Stratified by age group and grouped region | 6-7 years | Africa and Eastern Mediterranean** | -1.61 (-13.77, 10.56) | 0.06 (-4.00, 4.12) | -1.04 (-3.02, 0.94) | 0.14 (-0.48, 0.76) | -7.55 (-24.12, 9.01) | 0.74 (-6.59, 8.08) |
| | | America* | 0.25 (-13.25, 13.74) | -0.87 (-5.37, 3.64) | 1.56 (-0.65, 3.77) | -0.06 (-0.77, 0.64) | 0.67 (-17.71, 19.05) | 4.52 (-3.62, 12.66) |
| | | Europe* | 2.68 (-5.70, 11.07) | 3.16 (-0.15, 6.46) | 0.19 (-2.02, 2.40) | 0.32 (-0.23, 0.88) | 18.03 (6.61, 29.45) | 8.40 (2.45, 14.36) |
| | | South-East Asia and Western Pacific | -0.52 (-5.80, 4.75) | 0.48 (-1.36, 2.32) | 0.22 (-0.96, 1.40) | -0.05 (-0.36, 0.26) | 0.71 (-6.48, 7.89) | -0.31 (-3.63, 3.02) |
| | 13-14 years | Africa and Eastern Mediterranean* | -3.28 (-13.02, 6.47) | -0.69 (-3.89, 2.50) | -1.09 (-2.89, 0.71) | 0.21 (-0.29, 0.72) | -8.26 (-21.54, 5.02) | -1.12 (-6.89, 4.65) |
| | | America* | 7.35 (-2.62, 17.32) | -0.74 (-4.18, 2.71) | 1.03 (-0.79, 2.84) | -0.32 (-0.86, 0.23) | 20.08 (6.49, 33.66) | -3.33 (-9.55, 2.89) |
| | | Europe* | -1.49 (-9.79, 6.81) | 3.56 (0.26, 6.86) | -0.38 (-2.58, 1.83) | 0.37 (-0.19, 0.92) | 5.26 (-6.04, 16.56) | 8.00 (2.04, 13.95) |
| | | South-East Asia and Western Pacific | -2.20 (-7.22, 2.83) | -0.27 (-1.98, 1.43) | 0.17 (-1.01, 1.35) | 0.03 (-0.27, 0.32) | 0.00 (-6.85, 6.85) | -2.17 (-5.25, 0.91) |
| | | | | | | | | |

CI: confidence interval *Strata contains <5 ** Strata empty

This was contrary to our initial hypothesis that high income countries would continue to stabilise. Indeed, for children there showed an increase across both time periods for this group. Middle income countries showed a decrease or at least a slowing of increase in eczema symptom prevalence.

Conversely, current eczema symptoms and severe eczema symptoms in American (mainly South American) children and adolescents were estimated to be increasing during the first period and decreasing during the second, perhaps explaining the very small estimated linear changes reported in Table E.3. Most confidence intervals for the two sets of estimates were wide, owing to small numbers in each strata, and overlapping. Restricting this analysis to centres participating in all three studies showed similar findings, but even more strata were very small (<5 centres) with uncertain estimates, limiting our ability to investigate these data in any depth (Table E.5).

## Discussion

We have established worldwide prevalence estimates for eczema and severe eczema symptoms in adolescents and children using standardised methodology, allowing us to determine trends in eczema prevalence over three decades and to study the magnitude of these trends. We included GAN Phase I populations from 27 centres and 14 countries, using identical methodology to the ISAAC study.[2,3]

### Main findings

These findings suggest that the burden related to eczema is substantial in most settings, with a median of 6% of both children and adolescents having prevalent symptoms of current eczema. The largest absolute increase in prevalence in adolescents per decade from ISAAC Phase III to GAN Phase I was 4.8% in Bilbao, Spain with the largest absolute increase in children being 5.7% in Taipei, Taiwan, equating to 10.2 and 11.6 SEs change respectively. The largest absolute decrease in prevalence was in Managua, Nicaragua for both age groups, with 8.9% decrease in adolescents and 9.6% decrease in children.

Globally we estimated an average increase in the prevalence of current eczema symptoms of 0.98% per decade in adolescents and 1.21% per decade in children, and of 0.26% and 0.23% per decade in severe eczema symptoms. However, there was substantial heterogeneity in these change estimates that was not largely explained by stratifying on World Bank income group, although there was strong evidence that the average change differed by income group,

with evidence of increases in some outcomes in high-income children and middle-income adolescents. In similar models stratifying by geographic region, little of the between-centre heterogeneity was explained. We found that the average global increased prevalence of current eczema symptoms and severe rash in both age groups was being driven mostly by increases in Africa/Eastern Mediterranean, but increases in lifetime eczema prevalence were driven by increases in European and American children. There was some suggestion that prevalence estimates followed non-linear patterns that are not fully captured in linear estimates, e.g. in high-income countries they appear to be rising in the past decade after having plateaued in the previous decade.[55]

**Findings in context**

Evidence of changes in eczema prevalence over 10 or 20 years support a role for environmental factors, as rapid changes cannot be attributed to genetics, but the patterns are complex. For example, we found increased severe eczema in low income settings without an accompanying increase in overall prevalence. Environmental factors and gene-environmental factors are frequently discussed, but poorly understood in the aetiology of eczema.[168] Recent research has identified skin barrier changes in infancy preceding the later onset of eczema,[169] leading to a focus on the role of hygiene practices and food allergy in eczema aetiology.[170] Efforts to target the skin barrier with emollients to prevent the onset of eczema have thus far been disappointing, despite promising pilot data, with a lack of evidence from well conducted large randomised trials.[171] More understanding of why the prevalence of eczema is increasing in some settings is a major priority. From a health services and disease burden perspective, there is a need to focus research efforts on understanding why the prevalence of severe eczema symptoms is particularly high in specific geographical locations, specifically in adolescents in Cape Town, South Africa and younger children in Taipei, Taiwan.

Recent data from GBD 2017 reported that eczema ranked 59$^{th}$ among all diseases based on disability adjusted life years (DALYS) and 15$^{th}$ amongst non-fatal disorders.[163] The ISAAC group reported that, while global DALYs were stable over three decades, there was substantial variation between countries, from 85.14 to 326.91 DALYs per 100,000. The age-standardised prevalence ranged from 1.8 to 5.0 % with the highest reported prevalence in Andean Latin America in 2017. Concerns were also raised by authors about misclassification contributing to high burdens attributed to eczema in Andean Latin America, with a recommendation that future iterations use harmonised definitions and highlighting a need for more and higher quality data on eczema prevalence from settings outside Europe and North America.

Previous research from ISAAC identified that symptoms had plateaued or reduced from the early-1990s to early-2000s in countries that previously had high eczema prevalence, but that many countries had an increase of ≥2 SE in eczema symptoms over the previous decade, particularly in younger children.[55] In this study, we found that current eczema symptoms, severe eczema symptoms and lifetime prevalence of eczema were increasing in high-income countries, but appeared to be plateauing in children and increasing in adolescents. In low-income countries these outcomes were stably decreasing or the decrease was accelerating in both children and adolescents, but data availability meant that we were unable to consistently include the same centres across the two time periods (ISAAC Phase I to III and ISAAC Phase III to GAN Phase I), somewhat limiting our conclusions.

**Strengths and limitations**

We have used standardised validated tools used to determine eczema prevalence in centres across the world.[102] Throughout decades, we have maintained tight quality control and continued working with the same central personnel. Response rates have been high and we have representation from wide ranges of settings from low to high income involving countries with differing levels of eczema prevalence. GAN Phase I involved fewer centres than the ISAAC study.[21] Centres were self-selecting and hence may not be representative of the general population, and there is an over-representation of urban settings with few rural centres, hence findings may not apply to such settings. There were many challenges affecting GAN Phase I, including COVID-19 pandemic-related disruption and revised approaches to ethical approval, specifically the need for active rather than passive consent.[106]

**Implications for research**

We identified a substantial burden of eczema globally. Our data support an overall increase in the prevalence of eczema and severe eczema globally, but with substantial variation by geographical location and income as well as other factors unexplained by our modelling. Future studies on risk factors for eczema are planned for GAN phase I to determine if changes observed relate to changing risk factors, following on from previous analyses in ISAAC phase III.[81] Global focus is needed to address the global burden related to eczema with continued international efforts to identify strategies to prevent the onset of eczema and to better manage the burden to reduce the burden on individuals, their families and health services.

# F Stata code for frequentist prediction approach

**Stata version 15 do file[85] to create the point estimates of the predictions:**

```
*create skeleton dataset to use in bootstrap program
use cousens_modeldata, clear
tab agegp region2_who
tab agegp inc_2001
bysort agegp centre: gen first_cen=1 if _n==1
tab agegp inc_2001 if first_cen==1
tab agegp region2_who if first_cen==1

keep country_name country centre_name centre agegp inc_2001 region2_who
sort centre agegp
bysort centre: keep if _n == 1 //keep one record per centre
count
expand 2, gen(dupindicator) // double this to 2 for both age groups
replace agegp=6 if dupindicator==0
replace agegp=13 if dupindicator==1
drop dupindicator
save skeleton, replace

use cousens_modeldata, clear

**************************************************
* select model
**************************************************
*income 2way
        *mixed asthmapc i.region2_who c.decade##agegp c.decade##inc_2001 || country: || centre:
*income 3way
        *mixed asthmapc i.region2_who c.decade##agegp##inc_2001 || country: || centre:
*region 2way
        *mixed asthmapc i.inc_2001 c.decade##agegp c.decade##region2_who || country: || centre:
*region 3way
         mixed asthmapc i.inc_2001 c.decade##agegp##region2_who || country: || centre:

**************************************************
* select model name
**************************************************
*local model="inc2"
*local model="reg2"
*local model="inc3"
local model="reg3"
**************************************************

*get the blups for country and centre
capture drop blup1 blup2 // 1 is country, 2 is centre level intercept
predict blup1 blup2, reffects

* create skeleton file - both age groups for all centres
bysort centre: keep if _n == 1
expand 2, gen(dupindicator) // double this to 2 for both age groups
replace agegp=6 if dupindicator==0
replace agegp=13 if dupindicator==1
drop dupindicator

foreach year in 1992 2019 {
```

```
		*change covariate for new year
		replace decade=(`year'-1992)/10

		*pick up fitted values using parameters from model
		quietly mixed

		capture drop pred_asthhat
		predict pred_asthhat, xb
		gen pred_asthma_`year'=pred_asthhat+blup1+blup2
}
		drop pred_asthhat
gen pred_asthma_trend=(pred_asthma_2019-pred_asthma_1992)/2.7

tostring inc_2001, gen(inc_2001s)
tab inc_2001s
gen reg=substr(grouped_region,1,2)
tostring agegp, gen(age_s)
		*add on summarised variables
tempfile f g h i
save "`f'"
collapse (mean) pred_asthma_*, by(age_s inc_2001s)
gen type="c"+age_s+"_0i_"+inc_2001s
save "`g'"

use "`f'"
collapse (mean) pred_asthma_*, by(age_s reg)
gen type="c"+age_s+"_0r_"+reg
save "`h'"

use "`f'"
collapse (mean) pred_asthma_*, by(age_s)
gen type="c"+age_s+"_0"
save "`i'"

use "`f'"
collapse (mean) pred_asthma_*
gen type="c0_all"
append using "`g'"
append using "`h'"
append using "`i'"

foreach type2 in 2019 trend {
		gen result_`type2'=type+"_`type2'"
		sort result_`type2'
		mkmat pred_asthma_`type2', matrix(pred_asthma_`type2') rownames(result_`type2')
}

*join results matrices comb2
matrix obs_pred_asthma_`model'=pred_asthma_2019\pred_asthma_trend
matlist obs_pred_asthma_`model', format(%6.0g)
```

**Stata version 15 do file[85] to bootstrap results:**

```
use cousens_modeldata, replace
count

*************************************************
* Run all steps for each model
*************************************************
*Step 1
*create bootstraps and run repeatedly - as a program
capture program drop myboot
program define myboot, rclass
        preserve
        bsample

*************************************************
* select model
*************************************************
        *income 2way
        *mixed asthmapc i.region2_who c.decade##agegp c.decade##inc_2001 || country: || centre:
        *income 3way
        *mixed asthmapc i.region2_who c.decade##agegp##inc_2001 || country: || centre:
        *region 2way
        *mixed asthmapc i.inc_2001 c.decade##agegp c.decade##region2_who || country: || centre:
         *region 3way
        mixed asthmapc i.inc_2001 c.decade##agegp##region2_who || country: || centre:
*************************************************

        matrix define H = r(table)
        matrix list H

        *capture the model data
        capture drop blup1 // country
        capture drop blup2 // centre
        predict blup1 blup2, reffects

        * Centre predictions
        * create skeleton file - both age groups for all centres
        bysort centre agegp: keep if _n == 1 // start with one record per centre per age group
        sort centre agegp
        *merge with original skeleton to get all centres (some can't be estimated without blups)
        merge 1:1 centre agegp centre_name country country_name using skeleton
        sort centre agegp

*************************************************
* select correct BLUPS from regression output
*************************************************
        *local countrysd = exp(el(H,1,20)) // inc2 and reg2
        *local centresd = exp(el(H,1,21)) // inc2 and reg2
        local countrysd = exp(el(H,1,35)) // inc3 and reg3
        local centresd = exp(el(H,1,36)) // inc3 and reg3
*************************************************

        *if country blup is elsewhere then copy it to missing centre
        bysort country: egen blupcoun=min(blup1)
        replace blup1=blupcoun if blup1==.
        *if centre blup is elsewhere then copy it to missing centre
```

```
bysort country centre: egen blupcen=min(blup2)
replace blup2=blupcen if blup2==.
*generate random country blup to use for those with missing centre
gen randblup1 = rnormal(0,`countrysd')
bysort country: replace randblup1 = randblup1[1]
*generate random centre blup to use for those with missing age group
gen randblup2 = rnormal(0,`centresd')
bysort country centre: replace randblup2 = randblup2[1]
*randomly select blups otherwise for missing centres
replace blup1=randblup1 if blup1==.
replace blup2=randblup2 if blup2==.
drop randblup1 randblup2 blupcoun blupcen

keep country_name centre_name centre agegp blup1 blup2 inc_2001 region2_who decade

foreach year in 1992 2019 {
	*set decade for prediction
	replace decade=(`year'-1992)/10

	*pick up fitted values using parameters from model
	quietly mixed

	capture drop pred_asthhat
	predict pred_asthhat, xb
	gen pred_asthma_`year'=pred_asthhat+blup1+blup2

	*summarise to group level (both income and region)
	quietly sum pred_asthma_`year'
	return scalar c0_all_`year'=r(mean)

	foreach ag in 6 13 {

		quietly sum pred_asthma_`year' if agegp==`ag'
		return scalar c`ag'_0_`year'=r(mean)

		quietly sum pred_asthma_`year' if agegp==`ag' & inc_2001==1
		return scalar c`ag'_0i_1_`year'=r(mean)
		quietly sum pred_asthma_`year' if agegp==`ag' & inc_2001==2
		return scalar c`ag'_0i_2_`year'=r(mean)
		quietly sum pred_asthma_`year' if agegp==`ag' & inc_2001==3
		return scalar c`ag'_0i_3_`year'=r(mean)
		quietly sum pred_asthma_`year' if agegp==`ag' & inc_2001==4
		return scalar c`ag'_0i_4_`year'=r(mean)

		quietly sum pred_asthma_`year' if agegp==`ag' & region2_who==1
		return scalar c`ag'_0r_Af_`year'=r(mean)
		quietly sum pred_asthma_`year' if agegp==`ag' & region2_who==2
		return scalar c`ag'_0r_Am_`year'=r(mean)
		quietly sum pred_asthma_`year' if agegp==`ag' & region2_who==3
		return scalar c`ag'_0r_Eu_`year'=r(mean)
		quietly sum pred_asthma_`year' if agegp==`ag' & region2_who==4
		return scalar c`ag'_0r_So_`year'=r(mean)
	}
}

gen trend=(pred_asthma_2019-pred_asthma_1992)/2.7

quietly sum trend
return scalar c0_all_trend=r(mean)
```

```
	foreach ag in 6 13 {
		quietly sum trend if agegp==`ag'
		return scalar c`ag'_0_trend=r(mean)

		quietly sum trend if agegp==`ag' & inc_2001==1
		return scalar c`ag'_0i_1_trend=r(mean)
		quietly sum trend if agegp==`ag' & inc_2001==2
		return scalar c`ag'_0i_2_trend=r(mean)
		quietly sum trend if agegp==`ag' & inc_2001==3
		return scalar c`ag'_0i_3_trend=r(mean)
		quietly sum trend if agegp==`ag' & inc_2001==4
		return scalar c`ag'_0i_4_trend=r(mean)

		quietly sum trend if agegp==`ag' & region2_who==1
		return scalar c`ag'_0r_Af_trend=r(mean)
		quietly sum trend if agegp==`ag' & region2_who==2
		return scalar c`ag'_0r_Am_trend=r(mean)
		quietly sum trend if agegp==`ag' & region2_who==3
		return scalar c`ag'_0r_Eu_trend=r(mean)
		quietly sum trend if agegp==`ag' & region2_who==4
		return scalar c`ag'_0r_So_trend=r(mean)
	}

	restore
	end

**************************************************
*Step 2
*simulate bootstraps
**************************************************
* select model name
**************************************************
*local model="inc2"
*local model="reg2"
*local model="inc3"
local model="reg3"

use cousens_modeldata, replace
simulate c0_all_2019=r(c0_all_2019) c0_all_1992=r(c0_all_1992) ///
	c0_all_trend=r(c0_all_trend) ///
	c13_0_2019=r(c13_0_2019) ///
	c13_0i_1_2019=r(c13_0i_1_2019) c13_0i_2_2019=r(c13_0i_2_2019) ///
	c13_0i_3_2019=r(c13_0i_3_2019) c13_0i_4_2019=r(c13_0i_4_2019) ///
	c13_0r_Af_2019=r(c13_0r_Af_2019) c13_0r_Am_2019=r(c13_0r_Am_2019) ///
	c13_0r_Eu_2019=r(c13_0r_Eu_2019) c13_0r_So_2019=r(c13_0r_So_2019) ///
	c13_0_trend=r(c13_0_trend) ///
	c13_0i_1_trend=r(c13_0i_1_trend) c13_0i_2_trend=r(c13_0i_2_trend) ///
	c13_0i_3_trend=r(c13_0i_3_trend) c13_0i_4_trend=r(c13_0i_4_trend) ///
	c13_0r_Af_trend=r(c13_0r_Af_trend) c13_0r_Am_trend=r(c13_0r_Am_trend) ///
	c13_0r_Eu_trend=r(c13_0r_Eu_trend) c13_0r_So_trend=r(c13_0r_So_trend) ///
	c6_0_2019=r(c6_0_2019) ///
	c6_0i_1_2019=r(c6_0i_1_2019) c6_0i_2_2019=r(c6_0i_2_2019) ///
	c6_0i_3_2019=r(c6_0i_3_2019) c6_0i_4_2019=r(c6_0i_4_2019) ///
	c6_0r_Af_2019=r(c6_0r_Af_2019) c6_0r_Am_2019=r(c6_0r_Am_2019) ///
	c6_0r_Eu_2019=r(c6_0r_Eu_2019) c6_0r_So_2019=r(c6_0r_So_2019) ///
	c6_0_trend=r(c6_0_trend) ///
	c6_0i_1_trend=r(c6_0i_1_trend) c6_0i_2_trend=r(c6_0i_2_trend) ///
	c6_0i_3_trend=r(c6_0i_3_trend) c6_0i_4_trend=r(c6_0i_4_trend) ///
```

```
        c6_0r_Af_trend=r(c6_0r_Af_trend) c6_0r_Am_trend=r(c6_0r_Am_trend) ///
        c6_0r_Eu_trend=r(c6_0r_Eu_trend) c6_0r_So_trend=r(c6_0r_So_trend) ///
        , reps(10000) seed(83475) saving(bs_`model'_10000.dta, replace) : myboot

use bs_`model'_10000, clear


local name1 : rownames obs_pred_asthma_`model'
di "`name1'"
local dim `=rowsof(obs_pred_asthma_`model')'
di `dim'

postfile results str5 type str10 result nreps est se cill ciul using results_`model'.dta, replace

forvalues y=1/`dim' {
        tempname B C D E
        mat `B' = obs_pred_asthma_`model'[`y',1]
        local result : word `y' of `name1'
        use bs_`model'_10000, clear
        keep `result'

        quietly bstat, stat(`B') n(416)
        *extract results and save
        local nreps=e(N_reps)
        matrix define `C' = e(b)
        local est = el(`C',1,1)
        matrix define `D' = e(se)
        local se = el(`D',1,1)
        matrix define `E' = e(ci_normal)
        local cill = el(`E',1,1)
        local ciul = el(`E',2,1)
        post results ("`model'") ("`result'") (`nreps') (`est') (`se') (`cill') (`ciul')
}

postclose results

use results_`model', clear
```

# G Stata code for Bayesian prediction approach

**Stata version 17 do file[123] for Bayesian model and prediction:**

```
foreach vers in inc reg {

   use cousens_modeldata, clear
   sort agegp country_name centre_name

   if "`vers'"=="inc" {
         local vers="inc"
         bayesmh asthmapc decade i.agegp i.inc_2001 i.region2_who ///
         c.decade#i.agegp c.decade#i.inc_2001 ///
         U0[country] UU0[country>centre], ///
         likelihood(normal({var_0})) ///
         prior({asthmapc:}, normal(0, 10000)) ///
         prior({var_0 var_U0 var_UU0}, igamma(0.01, 0.01)) ///
         block(var_0 var_U0 var_UU0, split) ///
         rseed(16) mcmcsize(50000) burnin(25000) thin(5) dots saving(inc_mcmc, replace)

         bayesstats ess

         bayesstats summary (decL6:{asthmapc:decade}) ///
         (decLM6:({asthmapc:decade} + {asthmapc:2.inc_2001#c.decade})) ///
         (decUM6:({asthmapc:decade} + {asthmapc:3.inc_2001#c.decade})) ///
         (decH6:({asthmapc:decade} + {asthmapc:4.inc_2001#c.decade})) ///
         (decL13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade})) ///
         (decLM13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade} + ///
         {asthmapc:2.inc_2001#c.decade})) ///
         (decUM13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade} + ///
         (asthmapc:3.inc_2001#c.decade})) ///
         (decH13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade} + ///
         {asthmapc:4.inc_2001#c.decade}))
   }

   if "`vers'"=="reg" {
         bayesmh asthmapc decade i.agegp i.inc_2001 i.region2_who ///
         c.decade#i.agegp c.decade#i.region2_who ///
         U0[country] UU0[country>centre], ///
         likelihood(normal({var_0})) ///
         prior({asthmapc:}, normal(0, 10000)) ///
         prior({var_0 var_U0 var_UU0}, igamma(0.01, 0.01)) ///
         block(var_0 var_U0 var_UU0, split) ///
         rseed(16) mcmcsize(50000) burnin(25000) thin(5) dots saving(reg_mcmc, replace)

         bayesstats summary (decAf:{asthmapc:decade}) ///
         (decAm6:({asthmapc:decade} + {asthmapc:2.region2_who#c.decade})) ///
         (decEu6:({asthmapc:decade} + {asthmapc:3.region2_who#c.decade})) ///
         (decSo6:({asthmapc:decade} + {asthmapc:4.region2_who#c.decade})) ///
         (decAf13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade})) ///
         (decAm13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade} + ///
         {asthmapc:2.region2_who#c.decade})) ///
```

```
        (decEu13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade} + ///
        {asthmapc:3.region2_who#c.decade})) ///
        (decSo13:({asthmapc:decade} + {asthmapc:13.agegp#c.decade} + ///
        {asthmapc:4.region2_who#c.decade}))
    }

    bayesgraph diagnostics _all, histopts(normal) saving(diag_`vers', replace)
    bayesstats ess

    *create skeleton for prediction dataset
    *keep only last time point for each centre
    sort centre agegp
    by centre agegp (decade), sort: gen byte last_prev = (_n == _N)
    tab last_prev
    keep if last_prev==1
    count

    *ensure there is a record for both age group for all centres
    by centre: gen byte numrec = _N
    expand 1 if numrec==1, gen(dupindicator) // double this to 2
    replace agegp=13 if dupindicator==1 & agegp==6
    replace agegp=6 if dupindicator==1 & agegp==13
    drop dupindicator last_prev
    sort agegp centre

    *change decade to equivalent of 1/1/2019
    replace decade=2.7

    *make overall predictions based
    bayespredict {_ysim} (ymean: @mean({_ysim})), saving(predfile_`vers', replace) rseed(16)
    bayesstats summary {ymean} using predfile_`vers'
}
```

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