The ISAAC Story

ISAAC Findings

In many areas of the world, ISAAC Phases One and Three provided the first population-based assessment of the prevalence and severity of asthma and allergic diseases among children. ISAAC Phase Three produced the first internationally comparable estimates of direction and magnitude of change in symptoms of asthma, rhinoconjunctivitis and atopic eczema.

In ISAAC Phases Two and Three, symptoms and objective measures of asthma and allergy have been related to individual exposure to environmental factors and to genetic markers. Ecological analyses have also been conducted, relating prevalence of these conditions to characteristics of the populations living in each of the study centres.

Details of all ISAAC publications can be found on the ISAAC website, (http://isaac.auckland.ac.nz) together with a search facility to identify publications by title, author, year, ISAAC phase or location. The location may be global, regional, national or local (single centre).

In this section we focus upon the findings of worldwide comparisons, and their global impact. Details of other publications may be found on the regional, national and centre pages under "Centres".

Overview of Global Findings

When ISAAC began two decades ago the understandings of asthma, rhinitis and eczema in populations were seriously limited by the small number of countries in which standardised research methods had been used. This was mainly confined to various English-speaking countries - mainly Australia, Canada, New Zealand, UK and USA - and although a great deal of research was also being done in continental European countries, the methods used were generally not standardised across countries, and there had been little comparable work in other parts of the world. At that time new work on asthma and allergies from Erika Von Mutius in East and West Germany demonstrated the value of asthma research going beyond English-language countries and including environments of greater contrast using standardised methods.

The research breakthroughs that ISAAC has made include:

- measuring for the first time the symptom prevalence and severity of asthma, rhinitis and eczema in very large numbers of centres and countries in the world; this in turn has led to new global research questions, and informed public health policy
- demonstrating that asthma, rhinitis and eczema symptoms have increased substantially over the last 15 years, especially in younger children
- illustrating that asthma, rhinitis and eczema are important non-communicable diseases in non-affluent (developing) as well as affluent (developed) countries in the world
- providing new information about environmental and genetic factors which could potentially affect the symptom prevalence of asthma, rhinitis and eczema
- demonstrating how weak the link is between atopy (allergy) and symptoms of asthma, rhinitis and eczema, especially in non-affluent countries
- engagement of a global network of researchers in collaboration

The extent of the new understandings from ISAAC are presented here by posing questions which are then answered by the ISAAC global findings

Question

Is it possible to perform standardised questionnaire-based studies of asthma, rhinitis and eczema and achieve high participation rates in large numbers of countries in all regions of the world in many different languages?

ISAAC findings

Yes, ISAAC has shown that it is possible. In ISAAC Phase One 156 centres in 56 countries completed the research to the required standard with high participation rates[Asher 1998], [Strachan 1997], [Williams 1999], [Beasley 1998]. The majority of these centres had never undertaken epidemiological research before. In Phase Three two thirds of those centres repeated the study [Asher 2006], [Pearce 2007], [Björkstén 2008], [Williams 2008]. and a further 128 centres in 64 countries (34 new ISAAC countries) completed ISAAC for the first time [Lai 2009], [Aït-Khaled 2009], [Odhiambo 2009]

Question

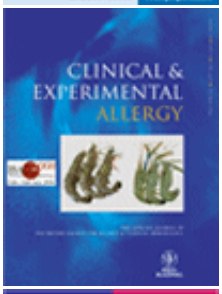
Were translations of written questionnaires valid?

ISAAC findings

In Phase One questionnaires were translated from English into another language in 81% of centres, and in Phase Three in 87% of centres. Most (86%) centres translated the questions correctly [Ellwood 2009]. When asthma symptom prevalence determined by written questionnaire was compared with a video asthma questionnaire [Asher 1998] the overall

Cumulative total of ISAAC publications

Year	Papers	Citations
1993	1	0
1994	5	0
1995	9	8
1996	17	16
1997	44	56
1998	71	164
1999	104	333
2000	128	561
2001	150	882
2002	179	1,231
2003	199	1,648
2004	240	2,048
2005	298	2,541
2006	329	3,183
2007	376	3,900
2008	418	4,782
2009	453	5,728
2010	500	6,538



pattern of international differences was similar. Thus it appears that ISAAC translations were valid.

Question

Does the method of consent matter for simple questionnaire surveys?

ISAAC findings

ISAAC has shown that it may do. We found that the requirement for active consent for population school-based questionnaire studies can impact negatively on response rates, particularly in English language centres, thus adversely affecting the validity of the data. Ethics committees need to consider this issue carefully [Ellwood 2010]

Question

Are asthma, rhinitis and eczema diseases of only high income 'developed' western countries?

ISAAC findings

ISAAC found that this is not true. ISAAC Phase One found that symptoms of asthma, rhinitis and eczema were more common in some high income western countries such as UK, New Zealand, Australia, but not as high in others such as Spain [Asher 1998], [Strachan 1997], [Williams 1999]. Moreover some low and middle income countries had prevalence values for symptoms of asthma, rhinitis and eczema which were at the same level as some high income western countries. There were striking variations in the prevalence of symptoms of asthma and allergic disease throughout the world (more than 20 fold between centres [Beasley 1998])

Question

Are asthma, rhinitis and eczema rare in developing countries?

ISAAC findings

Although ISAAC Phase One found that the prevalence of symptoms of asthma, rhinitis and eczema are on the whole lower in developing countries, some developing countries have particularly high levels of these conditions and proportionately more severe symptoms. [Asher 1998], [Strachan 1997], [Williams 1999], [Beasley 1998]. In the larger Phase Three study this finding was more obvious [Lai 2009], [Aït-Khaled 2009], [Odhiambo 2009] Asthma, rhinitis and eczema are thus not rare in developing countries.

Question

How do the ISAAC questionnaires perform compared with 'objective' markers of asthma and allergy?

ISAAC findings

ISAAC Phase Two found these relationships were variable. At the level of whole populations, prevalences of examined and reported flexural dermatitis matched well, offering reassurance that ISAAC questionnaire-derived prevalence data for eczema are sufficiently precise for comparisons between populations[Flohr 2009]. In contrast, high rates of bronchial responsiveness to inhaled hypertonic saline challenge were not confined to centres with high prevalences of asthma symptoms, nor to affluent countries, and did not parallel the worldwide variation of wheeze. [Buchele 2010]. Analysis of the inter-relationships of skin prick tests, total and allergen-specific IgE in Phase Two centres with diverse living conditions found no support for down regulation of local inflammatory responsiveness [Weinmayr 2010].

Question

Is it possible to study eczema by questionnaire, and is eczema important?

ISAAC findings

ISAAC studied eczema by questionnaire using core questions validated against skin examination to define the prevalence of symptoms of eczema in Phase One in 156 centres in 56 countries[Williams 1999]. In Phase Two, prevalences of examined and reported flexural dermatitis matched well, offering reassurance that ISAAC questionnaire-derived prevalence data for eczema are sufficiently precise for comparisons between populations [Flohr 2009]. Phase Three found that the prevalence of eczema symptoms was increasing in many centres[Williams 2008], was a common health problem for children throughout the world, and is a disease of developing as well as developed countries[Odhiambo 2009]. So it is possible to study eczema by questionnaire, and eczema is important.

Question

Is rhinitis common but unimportant?

ISAAC findings

Symptoms of rhinoconjunctivitis (rhinitis with itchy-watery eyes) were common in centres in several regions [Strachan 1997], [Aït-Khaled 2009]. Severe rhinoconjunctivitis symptoms were found mainly in the centres from middle and low income countries, particularly in Africa and Latin America. [Aït-Khaled 2009], illustrating that this condition is important, and can cause significant morbidity.

Question

Is asthma is becoming more and more common in western countries?

ISAAC findings

The Phase Three time trends analyses have helped to answer this question [Pearce 2007] While asthma has become more common in some high prevalence centres in western countries, in many cases the prevalence in Phase Three was similar to Phase One or even decreased. At the same time in many developing countries an increase in the prevalence of

symptoms was found more commonly than a decrease. The rise in prevalence of symptoms in many centres in countries with high populations suggests that the world burden is increasing. Paradoxically at the same time the global disparities are decreasing.

Question

Is asthma more severe in affluent than non-affluent countries?

ISAAC findings

In ISAAC Phase Three the most comprehensive examination of this question was undertaken in 237 centers from 98 countries. Symptoms of severe asthma were defined as those with current wheeze who, according to the written questionnaire, in the past 12 months, have had >4 attacks of wheeze, or >1 night per week sleep disturbance from wheeze, or wheeze affecting speech. The highest proportions of severe wheezers among current wheezers were found in non-affluent countries, not in affluent countries. [Lai 2009]. We have also established that there are consistently positive associations between asthma symptom prevalence, admissions and mortality [Anderson 2008].

Question

Will genetics explain differences in rates of asthma?

ISAAC findings

The large world wide variations in asthma prevalence found in ISAAC Phase One, including between people of similar genetic origin living in different environments, led us to believe that environmental factors rather than genetic factors were the cause of these large variations. [Asher 1998]. Genetic influences were explored directly in Phase Two with the analyses of 55 candidate single nucleotide proteins (SNPs) [Genuneit 2009]. Significant associations with wheeze were detected in only four genes, *and* variants of only two of thesewere also related to allergen-specific immunoglobin E (IgE). There were also highly significant associations between *SPINK5* variants and visible eczema and between *IL13* variants and total IgE. These findings suggest that, despite the biological plausibility of IgE-related mechanisms in asthma, genetic evidence for this pathway is sparse. This conclusion was borne out by the larger collaborative analysis conducted by the GABRIEL consortium [Moffatt 2010], of which ISAAC is a partner.

Question

Do asthma, rhinitis and eczema really have an allergic basis?

ISAAC findings

It has long been believed that allergies were the cause of asthma, rhinitis and eczema symptoms. However in ISAAC Phase Two a very weak relationship was found between allergy (atopy) and asthma[Weinmayr 2007], rhinoconjunctivitis [Weinmayr 2008], and eczema [Flohr 2008]. The association of atopy with each of these diseases was stronger in more affluent centres than in less affluent centres. In Phase One we also found that most children with one of these conditions had no symptoms of the other two [Beasley 1998]. There has been an increasing trend to separate allergic and non-allergic forms of these conditions [World Allergy Organisation 2003], and to avoid these qualifiers where the situation is unclear. Reflecting this change in thinking, the ISAAC worldwide papers have gradually dropped the term ‘allergic’ and ‘atopic’ in defining asthma, rhinitis, and eczema. In summary ISAAC has found that there is less commonly an allergic basis for asthma, rhinitis and eczema than previously thought, especially in non-affluent countries.

Question

If allergen exposure were prevented, then would asthma and rhinitis disappear?

ISAAC findings

The previous paragraph recounts how ISAAC identified that the association between allergy in populations and asthma and rhinitis is very weak. In our Phase One ecological study of pollens we found that the higher the pollen counts the less common were rhinitis symptoms [Burr 2003], and there was no effect on asthma symptoms. Thus preventing allergen exposure would not make asthma and rhinitis disappear.

Question

Does air pollution cause asthma?

ISAAC findings

There was no positive association between centre particulate air pollution and asthma shown in the Phase One ecological studies [Anderson 2010], with the relationship being slightly inverse. However in Phase Three high truck traffic exposure in the street where children lived was associated with more asthma symptoms[Brunekreef 2009]. This suggests that air pollution is not a causative factor for prevalence differences in asthma between populations, but may be for individuals within the populations. Further research is needed to explore this relationship further.

Question

Does diet influence asthma and allergies?

ISAAC findings

The Phase One ecological study found that populations who consume more plant based foods such as cereals, rice and vegetables have lower asthma, rhinitis and eczema symptom prevalence[Ellwood 2001] whereas in a European analysis dietary trans fatty acids were a risk factor for asthma, rhinitis and eczema [Weiland 1999]. In PhaseTwo potentially protective effects were found from fruit, vegetables, fish and a mediterranean diet, but children who ate burgers were more likely to have symptoms [Nagel 2010]. Breastfeeding was associated with protection against non-atopic wheeze, which was particularly evident in non-affluent countries [Nagel 2009]. A recent ecological analysis of Phase Three

suggested sugar consumption could be a risk factor [Thornley 2010]. Clearly further studies of diet, asthma, rhinitis andeczema are needed.

Question

What other environmental factors are important?

ISAAC findings

A number of other environmental factors were explored in the Phase One ecological analyses, suggesting hypotheses that are worthy of further exploration [Asher 2010]. There was a possible risk from higher country economic development (gross national product) [Stewart 2001].The ecological findings for smoking were mixed with women smoking being a risk, but a potential protective effect of men smoking [Mitchell 2001]. Subsequent analyses at the individual level showed that both maternal and paternal smoking was associated with increased risk of asthma symptoms (unpublished). The 2001 finding is an example of the "ecological fallacy". Good news for immunisation programmes was the finding of a possible protective effect from DTP & measles immunisation [Anderson 2001]. In support of the hygiene hypothesis TB notifications had a possible protective effect [Von Mutius 2000], [Shirtcliffe 2002], whereas the picture with antibiotic sales was not clear [Foliaki 2004], but in Phase Three at an individual level antibiotic use in the first year of life was found to be a risk factor [Foliaki 2009]. There were mixed associations of symptom prevalence with climate, but overall little effect [Weiland 2004]. Paracetamol sales were found to be associated with asthma in children and adults. [Newson 2000] This was explored further in the Phase Three at an individual level where paracetamol use was found to be a risk factor for wheezing in children and adolescents [Beasley 2008], [Beasley 2011] which needs to be explored further in a randomised controlled trial. In Phase Two asthma and current wheeze were more common in homes with lower endotoxin levels, and there was a less consistent inverse association of endotoxin levels with allergic sensitisation [Gehring 2008].

For a complete list of ISAAC publications see appendices or go to
http://isaac.auckland.ac nz/publications/publicationsintro html

World Wide Publications

ISAAC PhaseOne Publications (worldwide)

1.0 Preliminary Papers

1.1 ISAAC.*ISAAC Manual (2nd Edition).*Auckland/Münster.December 1993.

1.2 Pearce N, Weiland S, Keil U, Langridge P, Anderson HR, Strachan D, Bauman A, Young L, Gluyas P, Ruffin D, Crane J, Beasley R.*Self-reported prevalence of asthma symptoms in children in Australia, England, Germany and New Zealand an international comparison using the ISAAC protocol.*Eur Respir J 1993; 6: 1455-61.

1.3 Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW, Strachan D, Weiland SK, Williams HC.*International study of asthma and allergies in childhood (ISAAC) rationale and methods.*Eur Respir J 1995; 8: 483-91.

2.0 Main Findings

2.1 Strachan D, Sibbald B, Weiland S, Aït-Khaled N, Anabwani G, Anderson HR, Asher MI, Beasley R, Björkstén B, Burr M, Clayton T, Crane J, Ellwood P, Keil U, Lai C, Mallol J, Martinez F, Mitchell E, Montefort S, Pearce N, Robertson C, Shah J, Stewart A, von Mutius E, Williams H.*Worldwide Variations in prevalence of symptoms of allergic rhinoconjunctivitis in children the International Study of Asthma and Allergies in Childhood (ISAAC).*Pediatr Allergy Immunol 1997; 8(4): 161-76.

2.2 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee.*Worldwide variation in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema ISAAC.*Lancet 1998; 351(9111): 1225-32.

2.3 Williams H, Robertson C, Stewart A, Aït-Khaled N, Anabwani G, Anderson HR, Asher MI, Beasley R, Björkstén B, Burr M, Clayton T, Crane J, Ellwood P, Keil U, Lai C, Mallol J, Martinez F, Mitchell E, Montefort S, Pearce N, Shah J, Sibbald B, Strachan D, von Mutius E, Weiland S.*Worldwide variations in the prevalence of symptoms of atopic eczema in the international study of asthma and allergies in childhood.*J Allergy Clin Immunol 1999; 103(1 Pt 1): 125-38.

2.4 The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee.*Worldwide variations in the prevalence of asthma symptoms the International Study of Asthma and Allergies in Childhood (ISAAC).*Eur Respir J 1998; 12(2): 315-335.

3.0 Other Overview Papers

3.1 Asher MI, Weiland SK, on behalf of the ISAAC Steering Committee.*The International Study of Asthma and Allergies in Childhood (ISAAC).*Clin Exp Allergy 1998; 28 Suppl 5: 52-66.

3.2 Beasley R, Ellwood P, Asher I.*International patterns of the prevalence of pediatric asthma the ISAAC program.*Pediatr Clin North Am 2003; 50(3): 539-53.Copyright© Elsevier 2003.

3.3 Lai C, Pearce N.*The contribution of ISAAC to the understanding of asthma.*Leukotriene Res & Clin Rev 2001; 2: 1-4.

3.4 Mallol J, Asher MI, Williams H, Clayton T, Beasley R on behalf of the ISAAC Steering Committee.*ISAAC findings in children aged 14 years an overview.*Allergy Clin Immunol Int 1999; 11: 176-82.

3.5 von Mutius E.*Epidemiology of asthma ISAAC--International Study of Asthma and Allergies in Childhood.*Pediatr Allergy Immunol 1996; 7(9 Suppl): 54-6.

4.0 Ecological Analyses

4.1 Anderson HR, Gupta R, Kapetanakis V, Asher MI, Clayton T, Robertson CF, Strachan DP, and the ISAAC Steering Committee.*International correlations between indicators of prevalence, hospital admissions and mortality for asthma in children.*Int J Epidemiol 2008; 37(3):573-82.

4.2 Anderson HR, Poloniecki JD, Strachan DP, Beasley R, Björkstén B, Asher MI, and the ISAAC Phase One Study Group.*Immunization and symptoms of atopic disease in children Results from the International Study of Asthma and Allergies in Childhood.*Am J Publ Health 2001; 91(7): 1126-9.

4.3 Burr ML, Emberlin JC, Treu R, Cheng S, Pearce NE, and the ISAAC Phase One Study Group.*Pollen counts in relation to the prevalence of allergic rhinoconjunctivitis, asthma and atopic eczema in the International Study of Asthma and Allergies in Childhood (ISAAC).*Clin Exp Allergy 2003; 33(12): 1675-80.

4.4 Ellwood P, Asher MI, Björkstén B, Burr M, Pearce N, Robertson CF, and the ISAAC Phase One Study Group.*Diet and asthma, allergic rhinoconjunctivitis and atopic eczema symptom prevalence An ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data.*Eur Respir J 2001; 17(3): 436-443.

4.5 Foliaki S, Kildegaard Nielsen S, Björkstén B, von Mutius E, Cheng S, Pearce N, and the ISAAC Phase One Study Group.*Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema The International Study of Asthma and Allergies in Childhood (ISAAC).*Int J Epidemiol 2004; 33(3): 558-63.

4.6 Mitchell EA, Stewart AW, on behalf of the ISAAC Phase One Study Group.*The ecological relationship of tobacco smoking to the prevalence of symptoms of asthma and other atopic diseases in children The International Study of Asthma and Allergies in Childhood (ISAAC).*Eur J Epidemiol 2001; 17(7): 667-73.

4.7 Shirtcliffe P, Weatherall M, Beasley R, on behalf of the ISAAC Phase One Study Group.*An inverse correlation between estimated tuberculosis notification rates and asthma symptoms.*Respirology 2002; 7(2): 153-5.

4.8 Stewart AW, Mitchell EA, Pearce N, Strachan DP, Weiland SK, on behalf of the ISAAC Steering Committee.*The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC).*Int J Epidemiol 2001; 30: 173-9.

4.9 von Mutius E, Pearce N, Beasley R, Cheng S, von Ehrenstein O, Björkstén B, Weiland S, on behalf of the ISAAC Steering Committee.*International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis and eczema.*Thorax 2000; 55(6): 449-453.

4.1 Weiland SK, von Mutius E, Hüsing A, Asher MI, on behalf of the ISAAC Steering Committee.*Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe.*Lancet 1999; 353(9169): 2040-1.

4.11 Weiland SK, Hüsing A, Strachan D, Rzehak P, Pearce N, and the ISAAC Phase One Study Group.*Climate and the prevalence of symptoms of asthma, allergic rhinitis and atopic eczema in children.*Occup Environ Med 2004; 61(7): 609-15.

4.12 Anderson HR, Ruggles R, Pandey KD, Kapetenakis V, Brunekreef B, Lai CKW, Strachan DP, Weiland SK, and the ISAAC Phase One Study Group. *Ambient particulate pollution and the world-wide prevalence of asthma, rhinoconjunctivitis and eczema in children Phase One of the International Study of Asthma and Allergies in Childhood (ISAAC).*Occup Environ Med 2010; 67(5): 293-300. doi:10.1136/oem.2009.048785. epub: 9 October 2009.

4.13 Asher MI, Stewart AW, Mallol J, Montefort M, Lai CKW, Aït-Khaled N, Odhiambo J, and the ISAAC Phase One Study Group.*Which population level environmental factors are associated with asthma, rhinoconjunctivitis and eczema? A review of the ecological analyses of ISAAC Phase One.*Respiratory Research. 2010; 11(8):

5.0 Other Papers

5.1 Crane J, Mallol J, Beasley R, Stewart A, Asher MI, on behalf of the ISAAC Phase One Study Group.*Agreement between written and video questions for comparing asthma symptoms in ISAAC.*Eur Respir J 2003; 21(3): 455-61.

5.2 Pearce N, Sunyer J, Cheng S, Chinn S, Björkstén B, Burr M, Keil U, Anderson HR, Burney P, on behalf of the ISAAC Steering Committee and the European Community Respiratory Health Survey.*Comparison of asthma prevalence in the ISAAC and the ECRHS.*Eur Respir J 2000; 16(3): 420-6.

ISAAC PhaseTwo Publications (worldwide)

1.0 Preliminary Papers

1.1 ISAAC.*ISAAC Phase II Modules.*Münster, Germany.May 1998.

1.2 von Mutius E, Weiland SK, Keil U and the ISAAC Steering Committee.*The International Study of Asthma and Allergies in Childhood (ISAAC) study design and methods of phase II.*Allergologie 1999; 22(5):283-288.

1.3 Weiland SK, von Mutius E, Keil U, on behalf of the ISAAC Steering Committee.*The International Study of Asthma and Allergies in Childhood (ISAAC) rational methods and outlook.*Allergologie 1999; 22(5):275-282.

1.4 Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP, and the ISAAC Phase Two Study Group.*Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II) rationale and methods.*Eur Respir J 2004; 24(3): 406-12.

2.0 Main Findings

2.1 Weinmayr G, Weiland SK, Björkstén B, Brunekreef B, Büchele G, Cookson WO, García-Marcos L, Gotua M, Gratziou C, van Hage M, von Mutius E, Riikjärv MA, Rzehak P, Stein RT, Strachan DP, Tsanakas J, Wickens K, Wong GW, and the ISAAC Phase Two Study Group.*Atopic sensitization and the international variation of asthma symptom prevalence in children.*Am J Respir Crit Care Med 2007; 176(6): 565-74.

2.2 Flohr C, Weiland SK, Weinmayr G, Björkstén B, Bråbäck L, Brunekreef B, Büchele G, Clausen M, Cookson WOC, von Mutius E, Strachan DP, Williams HC, and the ISAAC Phase Two Study Group.*The role of atopic sensitization in flexural eczema Findings from the International Study of Asthma and Allergies in Childhood Phase Two.*J Allergy Clin Immunol 2008; 121(1): 141-7.

2.3 Weinmayr G, Forastiere F, Weiland SK, Rzehak P, Abramidze T, Annesi-Maesano I, Björkstén B, Brunekreef B, Büchele G, Cookson WO, von Mutius E, Pistelli R, Strachan DP, and the ISAAC Phase Two Study Group.*International variation in prevalence of rhinitis and its relation with sensitization to perennial and seasonal allergens.*Eur Respir J 2008; 32: 1250–1261.

2.4 Gehring U, Strikwold M, Schram-Bijkerk D, Weinmayr G, Genuneit J, Nagel G, Wickens K, Siebers R, Crane J, Doekes G, Di Domenicantonio R, Nilsson L, Priftanji A, Sandin A, El-Sharif N, Strachan D, van Hage M, von Mutius E, Brunekreef B, and the ISAAC Phase Two Study Group.*Asthma and allergic symptoms in relation to house dust endotoxin Phase Two of the International Study on Asthma and Allergies in Childhood (ISAAC II).*Clin Exp Allergy 2008; 38: 1911–1920.

2.5 Flohr C, Weinmayr G, Weiland SK (deceased), Addo-Yobo E, Annesi-Maesano I, Björkstén B, Bråbäck L, Büchele G, Chico M, Cooper P, Clausen M, El-Sharif N, Martínez Gimeno A, Mathur RS, von Mutius E, Morales Suárez-Varela MM, Pearce N, Svabe V, Wong GWK, Yu M, Zhong NS, Williams HC and the ISAAC Phase Two Study Group.*How well do questionnaires perform compared with physical examination in detecting flexural eczema? Findings from the International Study of Asthma and Allergies in Childhood (ISAAC) Phase Two.*Br J Dermatol 2009; 161(4): 846-853. Epub 27 May.

2.6 Nagel G, Büchele G, Weinmayr G, Björkstén B, Chen Y-Z, Wang H, Nystad W, Saraçlar Y, Bråbäck L, Batllés-Garrido J, García-Hernández G, Weiland SK, and the ISAAC Phase Two Study Group.*Effect of Breastfeeding on Asthma, Lung function, and Bronchial Hyperreactivity in ISAAC-Phase-Two.*Eur Respir J.2009; 33: 993–1002; Epub 2009 Jan22.

2.7 Genuneit J, Cantelmo JL, Weinmayr G, Wong GWK, Cooper PJ, Riikjärv MA, Gotua M, Kabesch M, von Mutius E, Forastiere F, Crane J, Nystad W, El Sharif N, Batllés-Garrido J, García-Marcos L, García-Hernández G, Morales Suárez-Varela MM, Nilsson L, Bråbäck L, Saraçlar Y, Weiland SK, Cookson WOC, Strachan DP, Moffatt MF, ISAAC Phase Two Study Group.*A multi-centre study of candidate genes for wheeze and allergy. The International Study of Asthma and Allergies in Childhood Phase Two.*Clin Exp Allergy 2009 Dec; 39(12): 1875-1888

2.8 Weinmayr G, Genuneit J, Nagel G, Björkstén B, van Hage M, Priftanji A, Cooper P, Rijkjärv M-A, von Mutius E, Tsanakas J, Forastiere F, Doekes G, Garrido JB, Morales Suárez-Varela MM, Bråbäck L, Strachan DP, the ISAAC Phase Two Study Group.*International variations in associations of allergic markers and diseases in children ISAAC Phase Two.*Allergy 2010; 65(6): 766–775. epub 21 Dec 2009. DOI:10.1111/j.1398-9995.2009.02283.x

2.9 Nagel G, Weinmayr G, Kleiner A, García-Marcos, Strachan DP, the ISAAC Phase Two Study Group.*Effect of diet on asthma and allergic sensitisation in the International Study on Allergies and Asthma in Childhood (ISAAC) Phase Two.*Thorax 2010; 65(6): 516-522 doi:10.1136/thx.2009.128256

2.1 Büchele G, Genuneit J, Weinmayr G, Björkstén B, Gehring U, von Mutius E, Priftanji A, Stein RT, Addo-Yobo EO, Priftis KN, Shah JR, Forastiere F, Svabe V, Crane J, Nystad W, García-Marcos L, Saraçlar Y, El-Sharif N, Strachan DP and the ISAAC Phase Two Study Group*International Variations in Bronchial Responsiveness in Children Findings From ISAAC Phase Two*Pediatr Pulmonol 2010; 45(8): 796–806

ISAAC PhaseThree Publications (worldwide)

1.0 Preliminary Papers

1.1 Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, on behalf of the ISAAC Steering Committee and the ISAAC Phase Three Study Group.*ISAAC Phase Three Manual.*Auckland.July 2000.ISBN 0-473-06910-5.

1.2 Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, and the ISAAC Steering Committee.*The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three rationale and methods.*Int J Tuberc Lung Dis 2005; 9(1): 10-6.

2.0 Main Findings

2.1 Asher MI, Montefort S, Björkstén B, Lai CKW, Strachan DP, Weiland SK, Williams H, and the ISAAC Phase Three Study Group.*Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood ISAAC Phases One and Three repeat multicountry cross-sectional surveys.*Lancet 2006; 368(9537): 733-743.

2.2 Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, Robertson C, and the ISAAC Phase Three Study Group.*Worldwide trends in the prevalence of asthma symptoms Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC).*Thorax 2007; 62(9): 758-66.

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2.7 Odhiambo J, Williams H, Clayton T, Robertson C, Asher MI, and the ISAAC Phase Three Study group.*Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three*J Allergy Clin Immunol. Dec 2009;124(6):1251-8.

3.0 Environmental Questionnaire Analyses

3.1 Beasley R, Clayton T, Crane J, von Mutius E, Lai CKW, Montefort S, Stewart A, for the ISAAC Phase Three Study Group.*Association between paracetamol use in infancy and childhood, and risk of asthma, rhinoconjunctivitis, and eczema in children aged 6-7 years analysis from Phase Three of the ISAAC programme.*Lancet 2008; 372(9643): 1039-48.

3.2 Brunekreef B, Stewart AW, Anderson HR, Lai CKW, Pearce NE, and the Phase Three Study Group.*Self Reported Truck Traffic on the Street of Residence and Symptoms of Asthma and Allergic Disease A Global Relationship in ISAAC Phase Three.*Environ Health Perspect 2009; 117(11): 1791-98. Epub July 2009.

3.3 Foliaki S, Pearce N, Björkstén B, Mallol J, Montefort S, von Mutius E and the ISAAC Phase Three Study Group.*Antibiotic use in infancy and risk of symptoms of asthma, rhinoconjunctivitis and eczema in 6 to 7 year old children ISAAC Phase Three.*J Allergy Clin Immunol 2009;124(5):982-9.

3.4 Beasley RW, Clayton TO, Crane J, Lai CKW, Montefort SR, von Mutius E, Stewart AW, and the ISAAC Phase Three Study Group.*Acetaminophen Use and Risk of Asthma, Rhinoconjunctivitis and Eczema in Adolescents ISAAC Phase Three*Am J Resp Crit Care Med. 2011; 183(2): 171-178. epub 13 August 2010

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4.1 Ellwood P, Williams H, Aït-Khaled N, Björkstén B, Robertson C, and the ISAAC Phase III Study Group.*Translation of questions The International Study of Asthma and Allergies in Childhood (ISAAC) experience.*Int J Tuberc Lung Dis.September 2009; 13(9): 1174-1182.

4.2 Ellwood P, Asher MI, Stewart AW and the ISAAC Phase III Study Group*The impact of the method of consent on response rates in the ISAAC time trends study.*Int J Tuberc Lung Dis. 2010 Aug;14(8):1059-65.

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Phase One Prevalence

At the time of ISAAC Phase One there were few countries in the world where anything was known about the prevalence of asthma, rhinitis and eczema, and even less about their severity. Little was known about the effects of gender. Almost all the studies to that date had been undertaken in affluent, high income, developed countries, mostly Australia, Canada, New Zealand, UK and USA.

The new key scientific findings from Phase One were the description of the prevalence and severity of asthma [Asher 1998], rhinitis [Strachan 1997] and eczema [Williams 1999] in two age groups (6-7 yr olds, 13-14 yr olds), in 156 centres from 56 countries, most of whom had never undertaken research of this nature before. There were striking variations in the prevalence of symptoms of asthma, rhinitis and eczema throughout the world (more than 20 fold between centres [Beasley 1998], both within and between countries inhabited by similar ethnic groups, suggesting that environmental factors may be critical in determining disease expression.

The relationship of the three conditions was examined. Most symptomatic children had symptoms of only one disorder in the last year, which indicates that risk factors different from atopic sensitisation may be important in the development of these three conditions [Beasley 1998].

Asthma

The prevalence of wheeze in the last 12 months ranged from 2.1-32.2% in the older age group and 4.1-32.1% in the younger age group and was particularly high in English speaking countries and Latin America. A video questionnaire completed in the older age group in 99 centres (42 countries) showed a similar pattern. While the high prevalence centres for asthma symptoms were mainly in developed countries, there were some (for example Costa Rica, Peru) which also had high rates. There were some large differences in prevalence between people of similar genetic origin living in different environments (for example Hong Kong and Guangzhou, China). The prevalence of asthma symptoms was greater in males in the younger age group and a mixed picture in the older age group, but on average females had slightly higher prevalence than males [Asher 1998]. We concluded that environmental factors were the cause of these large variations.

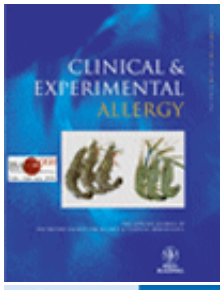
There are extensive data on the prevalence of childhood asthma world-wide but the relationships between asthma symptom prevalence, mortality and hospital admissions had not been investigated. This was done with Phase One written questionnaire, and Phase Three time trends centres - 12-month period prevalence of asthma symptoms by parental report in both age groups in 60 countries. The prevalence values of any wheeze and severe wheeze were correlated with national data on mortality and hospital admissions for asthma in 5–14 year olds. All correlations with prevalence were positive. Thus the prevalence of asthma symptoms in children obtained from local questionnaire studies may provide a guide to estimate the incidence of severe episodes of asthma in countries with incomplete data on hospital [Anderson 2008].

Rhinitis

While the initial ISAAC approach to nasal symptoms had been to use them to define allergic rhinitis, all the ISAAC papers focused in particular on rhinitis with itchy-watery eyes (rhinoconjunctivitis) as being the symptom combination most closely relating to objective indicators of allergic sensitisation in European children.[Strachan 1997]. The prevalence of rhinoconjunctivitis in the past year varied across centres from 0.8 to 14.9% in 6-7 yr olds, and from 1.4 to 39.7% in 13-14 year olds. In centres of higher prevalence there was great variation in the proportion of rhinoconjunctivitis labeled as hay fever. The lowest prevalences were found in parts of eastern Europe and south and central Asia.

Eczema

At the time of ISAAC Phase One there had been only one between country study comparing atopic dermatitis in three countries in Northern Europe. In ISAAC the prevalence range for symptoms of eczema was from less than 2% in Iran to over 16% in Japan and Sweden in the 6 to 7 year age range and less than 1% in Albania to over 17% in Nigeria for the 13 to 14 year age range. Higher prevalences of eczema symptoms were reported in Australasia and Northern Europe, and lower prevalences were reported in Eastern and Central Europe and Asia. Similar patterns were seen for symptoms of severe eczema [Williams 1999]. Thus eczema is a common health problem for children and adolescents throughout the world. Studies that include objective skin examinations have since been completed in ISAAC Phase Two[Flohr 2009] confirming these findings.



Phase One Ecological Analyses

Ecological analyses were undertaken with ISAAC Phase One data to explore factors that may have contributed to the large variations found in Phase One [Asher 2010]. Symptom prevalence of all three conditions was positively associated with GNP, trans fatty acids, paracetamol, and women smoking, and inversely associated with food of plant origin, pollen, immunisations, tuberculosis notifications, air pollution, and men smoking. The magnitude of these associations was small, but consistent in direction between conditions. There were mixed associations of climate and antibiotic sales with symptom prevalence. The potential causality of these associations warrant further investigation. Factors which prevent the development of these conditions, or where there is an absence of a positive correlation at a population level may be as important from the policy viewpoint as a focus on the positive risk factors.

Economic factors

Early reports of asthma prevalence found high prevalences in affluent countries, and there were anecdotal reports of low prevalences in non-affluent countries. This led us to explore the relationship between gross national product (GNP) and symptoms, and we found this was weakly positive [Stewart 2001]. However caution should be used in interpreting the findings because of the great inequalities in income distribution within almost all countries in developing regions of the world. GNP represents the total economic activity of the country, reflecting mean wealth rather than median wealth, not distribution of wealth within a country. All other ecological analyses were adjusted for GNP

Air pollution

There is extensive evidence from individual level studies that air pollution may aggravate existing asthma. However does air pollution influence the proportion of children in a population who have asthma symptoms? We found a weak inverse relationship between modelled city-level particulate air pollution (PM10) and symptoms of the three conditions, even after controlling for GNP which has a strong inverse association with air pollution [Anderson 2010]. Meta-analyses of data from countries with multiple centres found some evidence of weak positive associations. These findings are in line with other, more limited ecological evidence which suggest that community levels of particulate air pollution do not explain variations in prevalence between communities.

Antibiotics

The hygiene hypothesis postulates that growing up in a more hygienic environment with less microbial exposure may enhance atopic (TH2) immune responses, whereas microbial pressure would drive the response of the immune system—which is known to be skewed in an atopic TH2 direction during fetal and perinatal life—in a TH1 direction and away from its tendency to develop atopic immune responses. This would protect against atopy and allergic (but not nonallergic) asthma. A corollary of the hygiene hypothesis is that antibiotic use may increase the risk of asthma by reducing the protective effect of microbial exposure, for example, through disruption of the normal gut microbiota. This was explored in Phase One [Foliaki 2004] in 28 countries using country antibiotic sales. The relationships between symptom prevalence and antibiotic exposure was not clear cut: a mixture of weak inverse and positive effects were found between symptom prevalences and total antibiotic sales and broad spectrum antibiotic sales. This analysis suggested that even if there was a potential causal association of antibiotic use with asthma risk, it did not appear to explain the world wide differences between countries.

Climate

As climate affects whole populations, ecological studies are ideally suited to examine the relationship between prevalence of diseases and climatic conditions between populations. In the worldwide analyses few significant associations were seen [Weiland 2004]. As the world becomes more affected by climate change there may be some regions such as Western Europe where prevalence of disease is affected by potentially modifiable factors including humidity and temperature, but at a global level our ecological analyses showed little effect.

Diet

Dietary patterns have changed rapidly with modernisation or westernisation, and the associated move away from plant-based foods and addition of man-made fats might affect symptom prevalence. No associations were found for meat, and milk, but there was a pattern of inverse association between plant-based food and symptoms of the three conditions [Ellwood 2001]. The analysis in European countries of *trans* fatty acids found a positive association, suggesting that man-made fats may be a factor in the prevalence of the three conditions [Weiland 2000]. Thus dietary influences on the three conditions require further investigation.

Immunisation

There had been mixed reports about whether immunisation had no effect on these three diseases, or was potentially a risk factor related to the hygiene hypotheses. Country level analyses showed no associations [Anderson 2010]. The more powerful centre-level analyses showed small inverse relationships between DTP and measles in the older age group only,

with no associations with BCG. In view of earlier reports that immunisation might be a risk factor for asthma, this mainly null result is reassuring for population immunisation programmes, given their importance for child health.

Pollen

Pollen commonly triggers hay fever. On the other hand studies have found that the symptom prevalence of hay fever and asthma tends to be lower in rural than in urban areas, and lowest among people living on farms, where there is likely to be higher pollen exposure. In the Phase One ecological analysis exposure to allergenic pollen was assessed by exposures around the dates of early life [Burr 2003]. It did not appear to increase the risk of acquiring symptoms of respiratory allergy, and may even give some protection. but this has not been consistently found outside Europe and USA, and was not studied in our analyses. The degree of consistency in the inverse associations suggests the possibility of a protective effect of pollen on allergy.

Tobacco

Given the strong relationship between tobacco exposure and asthma symptoms at an individual level, we examined this at a centre and country level in Phase One. A mixed picture emerged for tobacco with no association observed between country tobacco consumption and symptoms [Mitchell 2001]. However there was generally a positive relationship between women smoking, yet an inverse association between men smoking and the three conditions. This analysis indicated that the well established individual level association between parental cigarette smoking and asthma did not account for the international differences in asthma prevalence.

Tuberculosis

There had been interest in whether the lack of exposure to infections such as tuberculosis increasing the risk of atopic disorders. We found inverse associations between asthma symptom prevalence and estimated TB incidence [Von Mutius 2000] and actual TB notifications rates [Shirtcliffe 2002], supporting other evidence that exposure to *Mycobacterium tuberculosis* may reduce the risk of developing asthma through induction of Th1 type immune responses. The implications of this relationship in the changing incidence of worldwide distributions of tuberculosis disease need further study.

Phase Two Findings

The inclusion of objective markers of allergic sensitisation, bronchial responsiveness and flexural dermatitis in ISAAC Phase Two enabled the description of international variations in disease prevalence beyond the level measured in Phase One by core questionnaires. Markers of disease have also been related to individual exposure to environmental factors and genetic markers.

The role of allergic sensitisation in disease

The first set of Phase Two publications investigated the role of atopy (as measured by positive allergen skin prick tests) in asthma [Weinmayr 2007], rhinoconjunctivitis [Weinmayr 2008] and eczema [Flohr 2008]. At the level of individual children, the association of atopy with each of these diseases was stronger in more affluent centres than in less affluent centres. At the level of whole populations (centres), however, the correlation between the prevalence of atopy and the prevalence of symptoms for each disease was weak or non-existent.

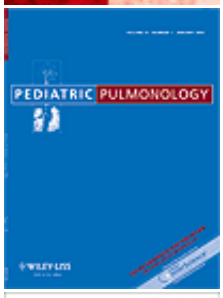
Thus, international variations in the prevalence of atopy did not explain much of the between-centre variations in disease prevalence, whereas within centres, a highly variable proportion of symptoms of asthma, rhinoconjunctivitis or eczema was statistically attributable to atopy: this proportion being greater in more affluent centres than in less affluent centres. These findings, across diverse study centres worldwide, suggest that much asthma, rhinoconjunctivitis and eczema has a non-allergic basis, especially in developing countries.

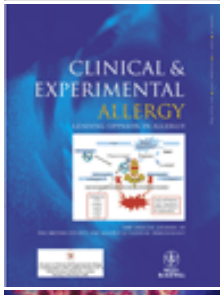
Objective markers v questionnaire measures

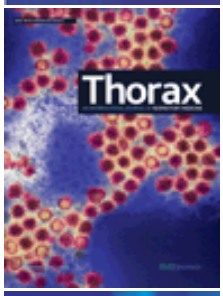
A second set of papers addressed the correlations between objective markers and the corresponding questionnaire measures of disease. At the level of whole populations, the correlation between prevalences of examined and reported flexural dermatitis was high, offering reassurance that ISAAC questionnaire-derived prevalence data for eczema are sufficiently precise for comparisons between populations [Flohr 2009].

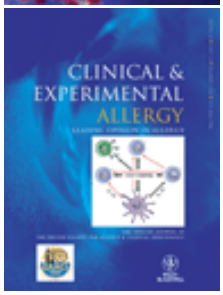
In contrast, high rates of bronchial responsiveness to inhaled hypertonic saline challenge were not confined to centres with high prevalences of asthma symptoms, nor to affluent countries. At the individual level, the association between wheeze and BHR differed across centres but this heterogeneity could be largely explained by a stronger association with wheeze in atopic children than in non-atopic children [Buchele 2010]. “Downregulation” of local inflammatory responsiveness had previously been proposed to explain a low prevalence of positive skin prick tests (SPTs) in less affluent countries. Analyses of the inter-relationships of SPTs, total and allergen-specific IgE in Phase Two centres with diverse living conditions found no support for this hypothesis [Weinmayr 2010].

The ISAAC Story









Environmental and lifestyle risk factors

A third set of papers investigated known or suspected risk factors for asthma or allergy. Endotoxin (bacterial products) has been suggested as both a trigger of asthma and a protective factor against allergic sensitisation. Living room floor dust was collected and analysed for endotoxin in six centres from Albania, Italy, New Zealand, Sweden and the United Kingdom. Asthma and current wheeze were more common in homes with lower endotoxin levels, and there was a less consistent inverse association of endotoxin levels with allergic sensitisation [Gehring 2008].

Breastfeeding was associated with less wheeze both in affluent and nonaffluent countries, but this relationship was mainly due to non-atopic wheeze. Breastfeeding was not associated with atopic wheeze or with objective measures of allergy [Nagel 2009].

More frequent consumption of fruit, vegetables and fish was associated with a lower prevalence of wheeze and asthma, whereas high burger consumption was associated with higher lifetime asthma prevalence. None of the food items studied was associated with allergic sensitisation. Except for fruit juice and fruit consumption, no associations were found with atopic wheeze. These results support previous suggestions that adherence to the 'Mediterranean diet' may provide some protection against wheeze and asthma in childhood [Nagel 2010].

Genetic risk factors

Early genetic studies within Phase Two focused on 55 candidate single nucleotide polymorphisms (SNPs) in 14 genes that had been associated with asthma or allergy in the published literature up to 2003 [Genuneit 2009]. Significant associations with wheeze were detected in only four genes *(IL4R, TLR4, MS4A2, TLR9)*. Variants in *IL4R* and *TLR4* were also related to allergen-specific IgE, while polymorphisms in *FCER1B* (*MS4A2*) and *TLR9* were not. There were also highly significant associations between *SPINK5* variants and visible eczema (but not IgE levels) and between *IL13* variants and total IgE. Heterogeneity of these genetic effects across centres was rare, despite differences in allele frequencies.

These findings suggest that, despite the biological plausibility of IgE-related mechanisms in asthma, genetic evidence of this pathway is sparse. This conclusion was borne out by the larger collaborative analysis conducted by the GABRIEL consortium [Moffatt 2010], of which ISAAC is a partner. Studies of possible interactions between genetic variants and non-genetic risk factors are currently being pursued as part of the GABRIEL work programme.

Phase Three Time Trends

Until ISAAC Phase Three, only 5 centres in the world had previously conducted collaborative time trends studies in all 3 conditions using standardised methods. While a number of other centres had used standardised methods to study asthma trends over time, different centres had used different methods so the findings were not comparable between centres. Most centres who undertook ISAAC Phase One repeated the study after at least five years, reflecting the large worldwide interest in time trends of prevalence. For most centres it was the first opportunity to obtain time trends information. The time trends results in 2 age groups from 104 centres in 55 countries provided very helpful new information on the direction and magnitude of change in [Asher 2006]. In many regions with developing countries, an increase in the prevalence of symptoms was found more commonly than a decrease in the prevalence of symptoms for all 3 conditions. In centres where symptom prevalence had previously been low, it mostly increased, and where it had been high it mostly decreased or did not change. The rise in prevalence of symptoms in many centres in countries with high populations suggests that the world burden is increasing. Paradoxically at the same time the global disparities are decreasing.

Asthma time trends

Following reports from English language countries in the 1990s of increases in asthma prevalence from the 1980s, continuing increases in prevalence had been expected. However ISAAC found that in most high prevalence countries, particularly the English language countries, the prevalence of asthma symptoms changed little between Phase One and Phase Three, and even declined in some cases [Pearce 2007]. In contrast, a number of countries that had high or intermediate levels of symptom prevalence in Phase One showed significant increases in prevalence in Phase Three. Examples include Latin American countries such as Costa Rica, Panama, Mexico, Argentina and Chile, and Eastern European countries such as the Ukraine and Romania. Other countries with significant increases in symptom prevalence included Barbados, Tunisia, Morocco and Algeria. With the exception of India, all of the countries with very low symptom prevalence rates in Phase One reported increases in prevalence in Phase Three. The overall percentage of children and adolescents reported to have ever had asthma increased significantly, possibly reflecting greater awareness of this condition and/or changes in diagnostic practice. The increases in asthma symptom prevalence in locations of high population density such as Africa, Latin America and parts of Asia indicate that the global burden of asthma is continuing to rise, and at the same time the global prevalence differences are lessening.

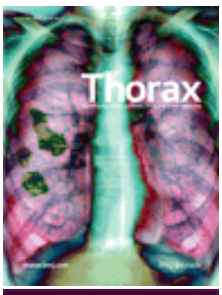
Rhinitis time trends

Before ISAAC Phase Three there had been little study of changes in rhinitis or hayfever over time. In the 13- to 14-yr age group 106 centres in 56 countries and in the 6- to 7-yr age group 66 centres in 37 countries studied, a slight worldwide increase in rhinoconjunctivitis prevalence was observed, but the variations were large among the centres and there was no consistent regional pattern [Björkstén 2008] . Prevalence increases in the older children exceeding 1% per year were recorded in 13 centres, including 3 of 9 centres in Africa, 2 of 15 in Asia-Pacific, 1 of 8 in India, 3 of 15 in Latin America, 3 of 9 in Eastern Europe and 1 of 34 in Western and Northern Europe. Decreasing rhinoconjunctivitis prevalence of similar magnitude was only seen in four centres. The changes were less pronounced in the 6- to 7-yr-old children and only in one centre did any change exceed 1% per year. The decrease in highest prevalence rates in ISAAC Phase I suggests that the prevalence has peaked in those regions. An increase was recorded in several centres, mostly in low and mid-income countries. The increases were more pronounced in the older age group, suggesting that environmental influences on the development of allergy may not be limited to early childhood rhinoconjunctivitis

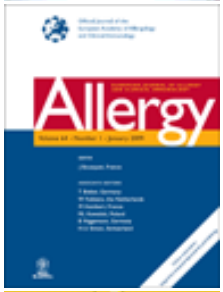
Eczema time trends

At the time of ISAAC Phase Three it was unclear whether eczema prevalence was truly increasing worldwide. In 13 to 14 year old children from 105 centres from 55 countries and 6 to 7 year old children in 64 centers from 35 countries annual prevalence changes in relation to average prevalence across Phase One and Three were generally small and differed in direction according to the age of the participants and world region [Williams 2008]. For 13 to 14 year olds, eczema symptom prevalence decreased in some previously high prevalence centress from the developed world, such as the United Kingdom and New Zealand, whereas centers with previously high prevalence rates from developing countries continued to increase. In the children 6 to 7 years old, most centers showed an increase in current eczema symptoms. Similar patterns to these were present for severe eczema at both ages. Thus the epidemic of eczema seems to be leveling or decreasing in some countries with previously high prevalence rates. The picture elsewhere is mixed, with many formerly low-prevalence developing countries experiencing substantial increases, especially in the younger age group.

Time Trend Publications



The ISAAC Story



Phase Three World Maps

In Phase Three ISAAC "mapped" the prevalence of asthma, rhinoconjunctivitis and eczema, conducted between 2000 and 2003.

Asthma

Further study of the global prevalence and severity of asthma symptoms was undertaken in ISAAC Phase Three, involving adolescents from 233 centres in 97 countries, and children from 144 centres in 61 countries [Lai 2009]. As in ISAAC Phase One, wide variations in prevalence were found around the world. The prevalence of wheeze in the past 12 months in adolescents varied from 32.6% in Wellington (New Zealand) to 0.8% in Tibet (China), and in children from 37.6% in Costa Rica to 2.4% in Jodhpur (India). The prevalence of symptoms of severe asthma (defined as =4 attacks of wheeze, or =1 night per week sleep disturbance from wheeze, or wheeze affecting speech in the past 12 months) varied from 16% in Costa Rica to 0.1% in Pune (India) in adolescents, and from 20.3% to 0% in the same two centres in children. Ecological economic analyses revealed a significant trend towards a higher prevalence of current wheeze in centres in higher income countries in both age groups, but this trend was reversed for the prevalence of severe symptoms among current wheezers, especially in the older age group. Thus wide variations exist in the symptom prevalence of childhood asthma worldwide. Although asthma symptoms tend to be more prevalent in more affluent countries, they appear to be more severe in less affluent countries.

Rhinitis

Further study of the global prevalence and severity of rhinitis symptoms was undertaken in ISAAC Phase Three, involving children from 236 centres in 98 countries [Aït-Khaled 2009]. The average overall prevalence of current rhinoconjunctivitis symptoms was 14.6% for the 13- to 14-year old children (range 1.0–45%). Variation in the prevalence of severe rhinoconjunctivitis symptoms was observed between centres (range 0.0–5.1%) and regions (range 0.4% in western Europe to 2.3% in Africa), with the highest prevalence being observed mainly in the centres from middle and low income countries, particularly in Africa and Latin America. Co-morbidity with asthma and eczema varied from 1.6% in the Indian sub-continent to 4.7% in North America. For 6- to 7-year old children, the average prevalence of rhinoconjunctivitis symptoms was 8.5%, and large variations in symptom prevalence were also observed between regions, countries and centres. Thus wide global variations exist in the prevalence of current rhinoconjunctivitis symptoms, being higher in high *vs* low income countries, but the prevalence of severe symptoms was greater in less affluent countries. Co-morbidity with asthma is high particularly in Africa, North America and Oceania. This global map of symptom prevalence is of clinical importance for health professionals.

Eczema

Further study of the global prevalence and severity of rhinitis symptoms was undertaken in ISAAC Phase Three, involving children from 236 centres in 98 countries [Odhiambo 2009]. Current eczema was defined as an itchy flexural rash in the past 12 months and was considered severe eczema if associated with 1 or more nights per week of sleep disturbance. For the age group 6 to 7 years, data on 385,853 participants from 143 centers in 60 countries showed that the prevalence of current eczema ranged from 0.9% in India to 22.5% in Ecuador, with new data showing high values in Asia and Latin America. For the age group 13 to 14 years, data on 663,256 participants from 230 centers in 96 countries showed prevalence values ranging from 0.2% in China to 24.6% in Columbia with the highest values in Africa and Latin America. Current eczema was lower for boys than girls (odds ratio, 0.94 and 0.72 at ages 6 to 7 years and 13 to 14 years, respectively). Thus ISAAC Phase Three provided comprehensive global data on the prevalence of eczema symptoms that is essential for public health planning. New data reveal that eczema is a disease of developing as well as developed countries

Phase Three Risk Factors

In Phase Three risk factors have been explored using the environmental questionnaire. Many themes have been explored. Those which have been published are summarised below.

Paracetamol (Acetaminophen)

Previous reports suggested that exposure to paracetamol during intrauterine life, childhood, and adult life may increase the risk of developing asthma. In ISAAC Phase Three in 6-7-year-old children from 73 centres in 31 countries[Beasley 2008] the use of paracetamol for fever in the first year of life was associated with an increased risk of asthma symptoms when aged 6 -7 years (OR 1.46 [95% CI 1.36 - 1.56]). Current use of paracetamol was associated with a dose-dependent increased risk of asthma symptoms (1.61 [1.46 - 1.77] and 3.23 [2.91 - 3.60] for medium and high use *vs* no use, respectively). Use of paracetamol was similarly associated with the risk of severe asthma symptoms, with population-attributable risks between 22% and 38%. Paracetamol use, both in the first year of life and in children aged 6 - 7 years, was also associated with an increased risk of symptoms of rhinoconjunctivitis and eczema. In the analysis of adolescents from 113 centers in 50 countries the recent use of paracetamol was associated with an exposure-dependent increased risk of current asthma symptoms (OR, 1.43 [95%CI 1.33 - 1.53] and 2.51 [95% CI 2.33 - 2.70] for medium and high versus no use, respectively). Paracetamol use was also associated with an exposure-dependent increased risk of current symptoms of rhinoconjunctivitis and eczema [Beasley 2011]. While these findings might indicate causation, they could be as a result of either reverse causation, for example if paracetamol were prescribed because of respiratory symptoms; or they could be a result of confounding by indication, for example if paracetamol were prescribed for chest infections, which were in turn associated with subsequent respiratory disease. Further research is needed, including randomised controlled trials, into the long-term effects of paracetamol in childhood.

Antibiotics

The hygiene hypothesis postulates that growing up in a more hygienic environment with less microbial exposure may enhance atopic (TH2) immune responses, whereas microbial pressure would drive the response of the immune system - which is known to be skewed in an atopic TH2 direction during fetal and perinatal life - in a TH1 direction and away from its tendency to develop atopic immune responses. This would protect against atopy and allergic (but not nonallergic) asthma. A corollary of the hygiene hypothesis is that antibiotic use may increase the risk of asthma by reducing the protective effect of microbial exposure, for example, through disruption of the normal gut microbiota This was explored in Phase Three [Foliaki 2009] in a total of 71 centers in 29 countries. Reported use of antibiotics in the first year of life was associated with an increased risk of current asthma symptoms (wheezing in the previous 12 months) with an OR adjusted for risk factors of 1.70 (95% CI, 1.60-1.80) when adjusted for other risk factors for asthma. Similar associations were observed for severe asthma symptoms (OR, 1.82; 95% CI, 1.67-1.98), and asthma ever (OR, 1.94; 95% CI, 1.83-2.06). Use of antibiotics in the first year of life was also associated, but less strongly, with increased risks of current symptoms of rhinoconjunctivitis (OR, 1.56; 95% CI, 1.46-1.66) and eczema (OR, 1.58; 95% CI, 1.33-1.51). This association between antibiotic use in the first year of life and current symptoms of asthma, rhinoconjunctivitis, and eczema in children 6 and 7 years old requires further research to determine whether the observed associations are causal or are a result of of reverse causation, for example if antibiotics were prescribed because of respiratory symptoms; or they could be a result of confounding by indication, for example if antibiotics were prescribed for chest infections, which were in turn associated with subsequent respiratory disease.

Truck traffic exposure

Associations between traffic pollution on the street of residence and a range of respiratory and allergic outcomes in children have been reported in developed countries, but little has been known about such associations in developing countries. In Phase Three frequency of truck traffic on the street of residence was positively associated with the prevalence of symptoms of asthma, rhinoconjunctivitis, and eczema with an exposure - response relationship[Brunekreef 2009]. Odds ratios for “current wheeze” and “almost the whole day” versus “never” truck traffic were 1.35 (95% CI, 1.23 - 1.49) for 13- to 14-year-olds and 1.35 (195% CI,.22 - 1.48) for 6- to 7-year-olds. These findings that higher exposure to self-reported truck traffic on the street of residence is associated with increased reports of symptoms of asthma, rhinitis, and eczema in many locations in the world require further investigation in view of increasing exposure of the world’s children to traffic.

The ISAAC Story

Ellwood P, Asher MI, Stewart AW and the ISAAC Phase III Study Group *The impact of the method of consent on response rates in the ISAAC time trends study.* Int J Tuberc Lung Dis. 2010 Aug;14(8):1059-65.

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Ellwood P, Williams H, Aït-Khaled N, Björkstén B, Robertson C, and the ISAAC Phase III Study Group. *Translation of questions The International Study of Asthma and Allergies in Childhood (ISAAC) experience.* Int J Tuberc Lung Dis.September 2009; 13(9): 1174-1182.

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Methodological Studies

Translations

As ISAAC has used many languages and translations, a systematic analysis of the ISAAC Phase Three translations was undertaken [Ellwood 2009]. In Phase Three 53 language translations were developed which followed standardised guidelines, including back-translating the questionnaires into English to check their accuracy and meaning. Serious deviations for one or more questions were found in seven translations for the adolescents (14%) and in three translations for the children (7%) resulting in exclusion of the data for those questions from the final data set. Thus translations of questionnaires should follow a consistent protocol in global epidemiological research. Cultural norms need to be considered when evaluating back translations into English, as disease labels are not available in every language, nor are they understood in the same way. Deviations from literal translations of English should be permitted if the intent of the original meaning is retained.

Consent

The relationships between achieved response rates and method of consent for 13–14 and 6–7-year-olds were examined between phases and between English and non-English language centres [Ellwood 2010]. We found that the requirement for active consent for population school-based questionnaire studies can impact negatively on response rates, particularly English language centres, thus adversely affecting the validity of the data. Ethics committees need to carefully consider the usefulness of the use of passive consent in epidemiological studies to obtain high response rates from participants.

Replication of Methodology

Centre reports were completed by Principal Investigators in Phases One and Three which enabled a detailed checking process to be undertaken on the methodology. For the Phase Three Time Trends centres all deviations between Phase One and Three were documented and were categorised: major deviations (centres excluded from the analyses); minor deviations (deviations identified by the use of footnotes in the published tables) and; very minor deviations (deviations accepted and not identified in the publication tables). This information has been collated and a manuscript on “The challenge in replicating the methodology between Phase One and Three of ISAAC” will be submitted for publication in April 2011.

We concluded that with attention to detail and careful recording of methodology, repeated, cross-sectional, epidemiological multicentre studies using the same methodology such as Phases One and Three in ISAAC are feasible and can be achieved throughout the world by people with diverse cultural backgrounds and research experience