ISAAC Findings In Children Aged 13–14 Years — An Overview

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The International Study of Asthma and Allergies in Childhood (ISAAC) is being undertaken in the main regions of the world in order to determine key aspects concerning the prevalence and severity of symptoms related to asthma, rhinitis, and eczema. Phase I showed large variations in the prevalence of these conditions among participating centers and countries. ISAAC has provided a worldwide basis for future studies on the influence of different factors on the observed variations in the prevalence and severity or the assessed diseases in children.

Introduction

Asthma, rhinitis, and eczema have affected human beings for millennia. Despite the high and ever-increasing number of patients around the world who have been consulting their physician due to these conditions over the past decades, there are still many etiological and modulating factors that remain to be clarified. Although a large body of clinical and epidemiological data has been obtained from research within populations, comparisons between populations are rare. In order to obtain data suitable for such comparisons, the same methods must be used by a range of participating centers in different countries that are representative of the global geographical and socioeconomic distribution. The lack of a global perspective has been an important limitation on previous attempts to compare the prevalence of asthma and other related diseases, and has meant that interpretation of the findings at a global level has been difficult, if not impossible. There is therefore a clear need for a worldwide, long-term, well-planned, systematic, and standardized international comparison of the prevalence of asthma and allergies in order to generate new hypotheses and to evaluate existing hypotheses. Such an approach is now being followed by the International Study of Asthma and Allergies in Childhood (ISAAC).

Phase I of ISAAC was designed to measure the prevalence of symptoms of asthma, rhinitis, and eczema in children, using simple methods which could be used in a wide range of countries with different languages, ethnic backgrounds, and degree of economic development [1]. Thus, the first task of the worldwide ISAAC Phase I was to determine the extent to which the prevalence of childhood asthma, rhinitis, and eczema symptoms vary between different parts of the world. The detailed results of ISAAC for each of these diseases have been recently published [2–5]. In this paper we summarize the method and results. Thus, the following discussion is based on some of the findings concerning the 12-month period prevalence (written questionnaires) of the core symptoms of asthma, rhinitis, and eczema in 13–14-year-olds, since this is the age group that was studied by all participating centers.

Methods

The methodology and rationale of the ISAAC have been described in detail elsewhere [1–5]. In summary, the study was based on samples of two age groups: 13–14 years (self-completion of questionnaires) and (optionally) 6–7 years (parental completion of questionnaires). In both age groups, simple one-page written core questionnaires were used for assessing symptoms of wheezing, rhinitis, and eczema; a video asthma questionnaire [6, 7] was also strongly recommended for use in the 13–14-year-olds. A sample size of 3000 per age group in each center was recommended in order to provide sufficient precision for estimates of symptom severity, but smaller sample sizes (minimum 1000) were permitted for prevalence comparisons. Guidelines for translating the questionnaire from English were provided in an attempt to reduce the problems associated with the administration of the questionnaires in many different languages [1]. Symptom prevalence in each center was calculated by dividing the number of positive responses to each question by the number of completed questionnaires. The questions used to define symptom prevalence (cumulative or current prevalence of symptoms related to asthma, rhinitis, and eczema), as well as the detailed findings on the symptom frequency and severity for the three

diseases in both 6–7 and 13–14-year-olds, and video-questionnaire results, are described in the main ISAAC papers [2–5]. ISAAC was open to any collaborator who agreed to adhere to the protocol, but countries where there was little or no existing information about asthma and allergies were particularly encouraged to participate. Each collaborating center was responsible for completing a registration document, as well as obtaining the necessary ethics committee approval prior to the start of the study.

Results

The participating centers and the prevalence of asthma, rhinitis, and eczema symptoms in the last 12 months are illustrated in Figures 1–3. The 13–14-year-old age group (n=461,801) was studied in 155 centers from 56 countries in Europe, Asia, Africa, Australia and New Zealand, and Latin and North America. There were marked variations in the prevalence of asthma symptoms between many centers, with up to 10-fold differences between countries being observed for the prevalence of wheeze in the last 12 months (3.0–32.8%). The highest prevalences of wheeze in the last 12 months were found in English-speaking countries and Latin America, and wheeze that disturbed sleep was also high in centers in Kenya, Kuwait and Lebanon, Nigeria, and South Africa. "Asthma ever" was reported in children from all countries, at prevalences ranging from 1.4 to 28.2%. Exercise-induced wheezing was more common than 12-month wheeze. Only small sex differences were found, with asthma symptoms more common in girls in this age group in most countries.

The current prevalence (last 12 months) of symptoms of allergic rhinoconjunctivitis had a 30-fold variation between centers (1.4–39.7%); eczema symptoms had a 60-fold variation in prevalence (0.3–20.5%). Although the patterns for the prevalences of eczema symptoms differed from those for asthma and allergic rhinoconjunctivitis, significant correlations were found between the prevalences of the mentioned diseases.

The mean prevalences of asthma, rhinitis, and eczema by region are presented in Table 1. Australia and New Zealand had the highest prevalence of asthma symptoms in the last 12 months (29.7%, range 24.7–33.5%) and Southeast Asia had the lowest (6.6%, range 1.6–17.8%). The region of Australia and New Zealand showed a slight but consistently higher prevalence of severe symptoms of asthma, of rhinitis, and of eczema than the other regions.

Table 1

Mean Prevalence of Asthma, Allergic Rhinoconjunctivitis, and Atopic Eczema Symptoms by Region, in Children Aged 13–14 Years (Range in Parentheses)

Region	Wheeze in last 12 months (%)		4 or more attacks of wheeze in last 12 months (%)		Sleep disturbed by wheeze, 1 or more nights per week (%)		Wheeze affecting speech in last 12 months (%)		Rhinoconjunctivitis symptoms in last 12 months (%)		Eczema symptoms in last 12 months (%)		N
Western Europe	16.9	(2.7–36.7)	4.6	(0.7–11.6)	1.7	(0.0–4.7)	4.3	(0.7–10.0)	14.8	(6.2–25.5)	8.7	(1.8–18.9)	135,559
Northern and Eastern Europe	9.7	(2.6–19.8)	1.9	(0.3–5.1)	0.7	(0.1–2.2)	2.0	(0.7–5.1)	8.9	(3.8–22.9)	7.5	(0.8–17.3)	60,819
Eastern Mediterranean	10.9	(5.6–17.0)	3.0	(1.5–6.3)	2.8	(1.0–5.7)	4.2	(2.2–10.6)	13.8	(5.9–28.9)	6.6	(2.1–12.0)	28,468
Latin America	17.0	(6.6–27.0)	3.4	(1.1–6.0)	2.6	(0.8–4.6)	4.6	(1.3–10.1)	16.2	(8.4–34.5)	7.2	(3.7–11.4)	52,549
Africa	10.7	(1.9–17.1)	3.2	(0.9–5.6)	2.9	(0.3–6.3)	5.1	(1.0–8.4)	16.2	(1.8–39.7)	10.7	(3.2–19.9)	21,648
Asia–Pacific	8.1	(2.1–13.5)	2.2	(0.4–4.4)	0.7	(0.2–2.0)	1.8	(0.4–4.1)	12.0	(4.9–24.0)	4.9	(0.8–10.5)	83,826
Australia and New Zealand	29.7	(24.7–33.5)	9.9	(7.5–12.8)	3.1	(2.3–4.6)	8.1	(7.1–8.7)	19.0	(15.4–22.6)	11.5	(8.5–13.8)	31,301
Southeast Asia	6.6	(1.6–17.8)	1.7	(0.5–3.5)	1.1	(0.4–2.0)	3.3	(1.0–13.5)	6.0	(1.4–21.4)	4.2	(0.3–20.5)	37,171
North America	24.4	(19.8–30.6)	7.8	(5.6–10.0)	3.1	(2.0–5.9)	8.4	(5.5–13.3)	18.1	(12.0–25.0)	5.4	(0.0–9.5)	12,460
Global Total	**14.3**	**(1.6–36.7)**	**3.8**	**(0.3–12.8)**	**1.7**	**(0.0–6.3)**	**4.0**	**(0.4–13.5)**	**13.4**	**(1.4–39.7)**	**7.5**	**(0.0–20.5)**	**463,801**

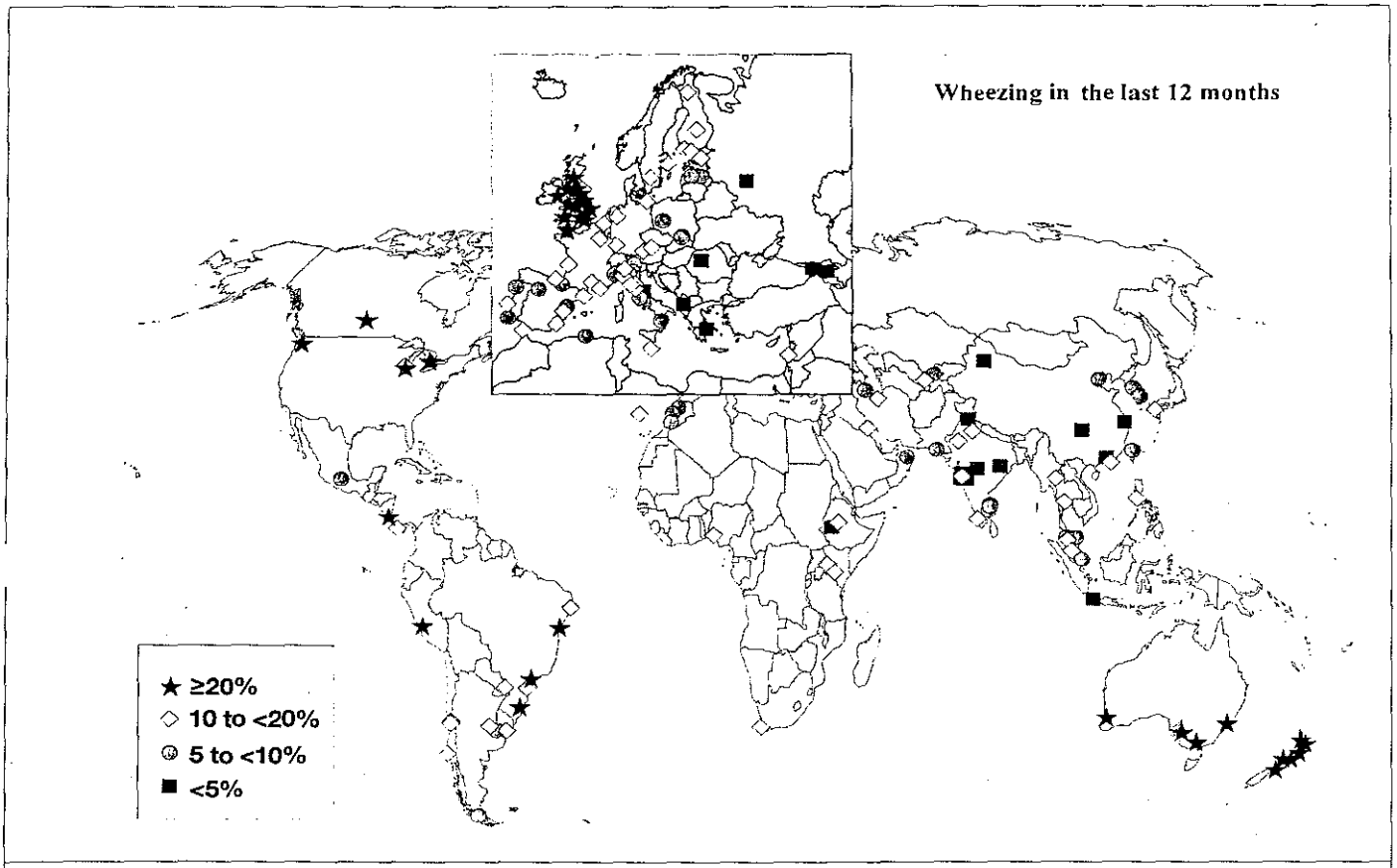

Figure 1. Prevalence of wheezing in the last 12 months in children aged 13–14 years (with permission from ref. [2]).

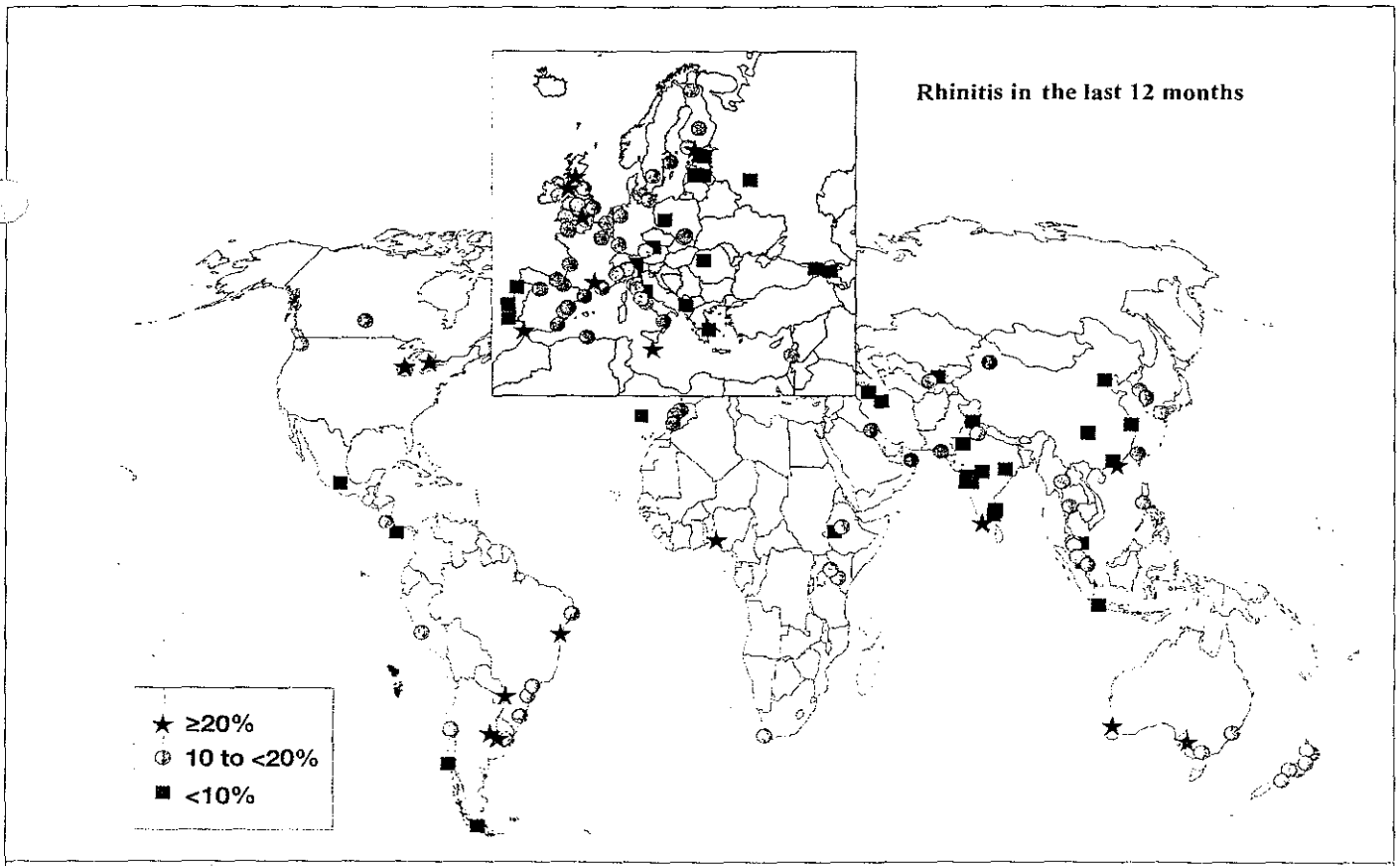

Figure 2. Prevalence of rhinitis in the last 12 months in children aged 13–14 years (with permission from ref. [4]).

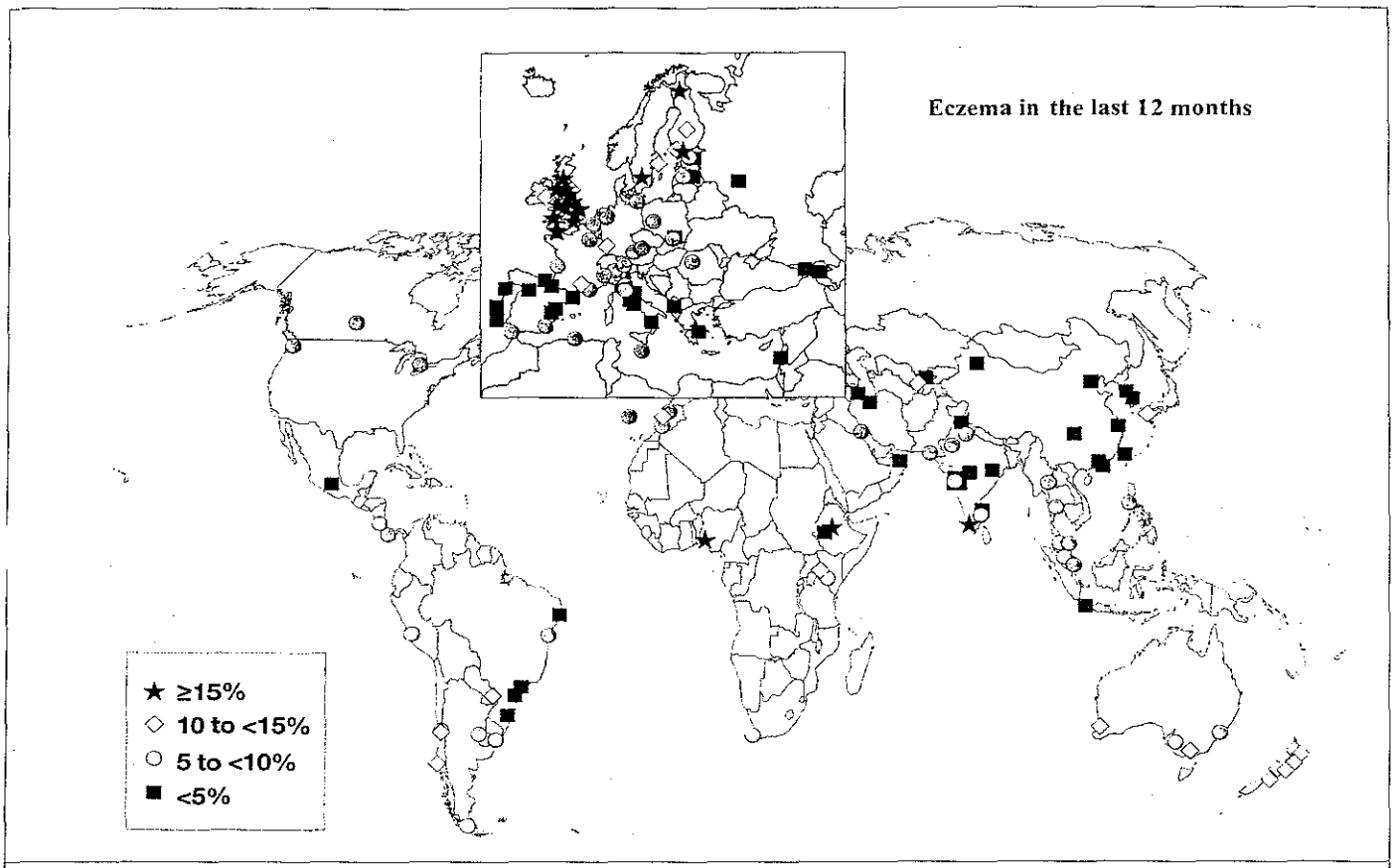

Figure 3. Prevalence of eczema in the last 12 months in children aged 13–14 years (with permission from ref. [5]).

Discussion

Certainly, the International Study of Asthma and Allergies Childhood (ISAAC) is the largest and most standardized study undertaken so far to determine and compare the prevalence and severity of symptoms related to asthma, rhinitis, and eczema in children from developed and developing regions. No other studies in the past have included children from so many countries, in a worldwide distribution, including participating centers from all the main regions of the world. ISAAC Phase I provides, for the first time, the unique possibility of looking at the variability of symptoms among participating centers from a new and global perspective, and of investigating the differential effect that genetic and environmental factors have on the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema.

The main finding of the ISAAC Phase I is the wide variation in the prevalence of symptoms related to asthma, rhinitis, and eczema. There were differences of between 20-fold and 60-fold between centers in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema [2–5]. This variation was found to occur among centers in the same country as well as in centers from different countries and continents. The pattern was not consistently related to latitude or longitude. Prevalence also varied, but not uniformly, according to language, racial, or ethnic characteristics or inheritance. When classifying centers as high, medium, and low prevalence, the trend was to a higher prevalence in English-speaking countries and a lower prevalence in Asian and African centers, with Latin America behaving as a mixture of high, medium, and low prevalences. This interesting variation in Latin America may reflect the influence of different, but coexisting, socioeconomic status, life-styles inherited from colonizers, climates, other environmental features, and genetic characteristics.

ISAAC has shown that lower or higher prevalences of asthma and other allergic symptoms do not seem to be related to industrialization, at least not in the way that was originally thought, with developing countries having prevalence figures as high (or as low) as some of those found in developed regions. In Latin America the prevalences showed a trend to be lower in centers located at the northern and southern extremes, with very high prevalences registered at centers in the semitropical or tropical latitudes [3]. However, this trend was not consistent and needs further analysis, with more objective measurements of atopy and airways responsiveness, as has been proposed for the ISAAC Phase II studies.

It should be considered that another important finding of ISAAC is the demonstration that studies involving a wide range of developing countries, with markedly different cultural backgrounds, languages, and environments, can be carried out successfully. The skills and experience in the use of epidemiological methods that the ISAAC study gives to centers in developing regions have a multiplicative effect and open

frontiers facilitating the future participation of these countries in large collaborative epidemiological studies. Furthermore, ISAAC has provided the means of learning for the first time about the prevalence of symptoms of asthma, rhinitis, and eczema, in regions such as Latin America, Asia, and Africa. These regions had been largely ignored in previous international prevalence studies. Closer analysis of data from these regions may provide new insights to generate or contrast hypotheses on several aspects of asthma and other allergic conditions.

The global information provided by ISAAC suggests that the marked differences observed cannot be explained merely by methodological, language, geographic, racial, or educational differences [2–5]. It is likely that the large differences found in the prevalence and severity of asthma between the ISAAC centers in developing and developed countries may be determined mainly by environmental and lifestyle differences, rather than genetic variation. The modulating effect of environment on important risk factors that could vary in magnitude, nature, and expression can be easily overlooked when globally representative information is not available. The many possible combinations of environmental characteristics and socioeconomic status seem to play a major role as determinants for the observed variability in the prevalence of asthma, rhinoconjunctivitis, and eczema. However, ethnic susceptibility to asthma and other allergic diseases might also be modulated by environmental characteristics, playing a role in the observed variations of prevalence between populations who share a similar ethnic background.

The large differences in the prevalence of asthma between populations living in Africa, or in the Iberian peninsula (Spain and Portugal) and in some localities of Latin America, who share a common racial pattern, would point to the influence of environment in determining the much higher prevalence of asthma among those living in Latin America.

When examining the prevalences of symptoms in populations that share the same language, the differences between indigenous and emigrant populations were striking (see Table 2). For all symptoms of asthma, rhinitis, and eczema, China had almost the half the prevalence of the other Chinese-speaking centers. A very similar pattern was observed for Portugal and the other Portuguese-speaking centers, and between Spain and the other Spanish-speaking centers. The United Kingdom (UK) and the other English-speaking centers were the exception, with the former having much higher prevalences for asthma, rhinitis, and eczema symptoms (see Table 2).

TABLE 2

MEAN PREVALENCE OF ASTHMA, ALLERGIC RHINOCONJUNCTIVITIS, AND ATOPIC ECZEMA SYMPTOMS BY LANGUAGE, IN CHILDREN AGED 13–14 YEARS (RANGE IN PARENTHESES)

Language	Wheeze in last 12 months (%)		4 or more attacks of wheeze in last 12 months (%)		Sleep disturbed by wheeze, 1 or more nights per week (%)		Wheeze affecting speech in last 12 months (%)		Rhinoconjunctivitis symptoms in last 12 months (%)		Eczema symptoms in last 12 months (%)		*N*
Chinese													
China	4.1	(3.3–5.1)	0.9	(0.4–1.5)	0.2	(0.2–0.3)	0.7	(0.4–0.9)	7.3	(4.9–10.1)	1.1	(0.8–1.6)	19008
Other Chinese	7.9	(5.2–12.4)	2.4	(1.6–4.4)	0.6	(0.4–1.0)	1.5	(0.8–2.4)	13.2	(8.0–24.0)	4.4	(1.4–7.1)	22012
Language Total	5.8	(3.3–12.4)	1.6	(0.4–4.4)	0.4	(0.2–1.0)	1.0	(0.4–2.4)	9.9	(4.9–24.0)	2.6	(0.8–7.1)	41020
English													
UK	32.0	(19.9–36.7)	9.2	(6.2–11.6)	3.4	(2.3–4.7)	8.3	(5.0–10.0)	18.4	(15.9–22.5)	15.6	(10.5–18.9)	35485
Other English	17.3	(1.6–33.5)	5.4	(0.5–12.8)	2.2	(0.4–6.3)	5.3	(1.0–8.9)	14.2	(1.4–39.7)	7.7	(0.0–17.7)	98324
Language Total	21.8	(1.6–36.7)	6.6	(0.5–12.8)	2.6	(0.4–6.3)	6.2	(1.0–10.0)	15.5	(1.4–39.7)	10.1	(0.0–18.9)	133809
Portuguese													
Portugal	9.3	(7.4–11.1)	2.3	(1.7–2.8)	1.4	(1.0–1.8)	2.2	(1.6–2.7)	7.3	(6.2–8.8)	3.9	(1.8–5.4)	10751
Other Portuguese	22.6	(18.4–27.0)	4.4	(3.5–6.0)	3.7	(2.7–4.6)	4.6	(2.7–5.7)	16.1	(11.3–25.0)	5.2	(3.7–9.2)	15454
Language Total	16.7	(7.4–27.0)	3.5	(1.7–6.0)	2.6	(1.0–4.6)	3.5	(1.6–5.7)	12.2	(6.2–25.0)	4.6	(1.8–9.2)	26205
Spanish													
Spain	10.2	(5.5–15.4)	2.7	(1.5–4.2)	1.2	(0.5–1.9)	2.4	(1.1–4.2)	15.0	(11.7–21.8)	4.4	(2.9–6.0)	25021
Other Spanish	15.0	(6.6–26.0)	3.2	(1.1–5.6)	2.4	(0.8–5.9)	5.2	(1.3–13.3)	16.7	(8.4–34.5)	7.3	(0.0–11.4)	40851
Language Total	13.2	(5.5–26.0)	3.0	(1.1–5.6)	1.9	(0.5–5.9)	4.1	(1.1–13.3)	16.1	(8.4–34.5)	6.2	(0.0–11.4)	65872

The prevalence of symptoms of asthma was relatively low in centers with well-known high levels of air pollution such as Santiago de Chile; conversely, centers with low air pollution such as those in New Zealand had comparatively high prevalences of respiratory symptoms related to asthma. The actual effect of the different types of atmospheric pollution on the prevalence and severity of asthma symptoms remains to be determined by future studies.

Questions can also be raised when looking at the prevalences in regions speaking Spanish when comparing them with prevalences observed in Spain, or in Chinese-speaking localities when comparing them with China. Is the trend to racial mixture in colonized regions (which were certainly different depending on whether the colonizers were English, Spanish, or Portuguese) playing some role? Does the mixture of black, local aborigines, and whites occurring in Latin America somehow determine the medium level of prevalence found in this region (between Africa and Europe)? Why has a similar pattern not occurred among the English-speaking localities, where the other centers have lower prevalences than the UK? Certainly, it does not appear that genetic factors are involved as major determinants for the variations observed. Instead, a strong and sustained environmental influence in which allergens, pathogenic agents, climate, feeding habits, lifestyles, and air, water, or food pollution are all significant factors, is likely to be playing a major role.

There are very few studies that allow for comparisons with ISAAC results. However, the European Community Respiratory Health Survey (ECRHS) [8, 9] has suggested regional risk factors for the development of asthma and rhinitis in Western Europe, and other standardized studies in children [10–13] have also found significant regional differences in the prevalence of respiratory symptoms.

The most important aim of ISAAC is to advance our understanding of the causes of asthma. Although genetic factors are important risk factors for individuals within populations, migrant studies indicate they are unlikely to be responsible for the large variations in asthma which exist between populations, and cannot be responsible for the recent upward trends within populations. There are also a number of theories concerning the provocation of asthma by various agents, including aeroallergens, diet, indoor, and outdoor pollution, and others, that have failed to demonstrate their universality. ISAAC is now using its prevalence data to conduct ecological studies to test these and other hypotheses.

The highest prevalence of rhinitis symptoms were reported from centers scattered throughout most regions of the world, including Western Europe, Africa, North America, Southeast Asia, Australia, and New Zealand. None of the 10 centers with the highest prevalence of rhinitis symptoms (including several centers in France) were represented amongst the highest 10 centers for asthma symptoms, suggesting that the major risk factors are different for these related disorders, or that they involve different latency periods and time trends. As with asthma symptoms, centers in Africa (Ethiopia), Eastern Europe, and the Mediterranean had the lowest reported prevalences of rhinitis symptoms [4].

The pattern of eczema symptom prevalences differed in some respects from that for asthma and rhinitis. The highest prevalences of eczema symptoms were generally in centers at high latitude, including Scandinavia, the United Kingdom, and New Zealand, although there were some notable exceptions, including some centers in Africa and Central America. It is worth mentioning that Central America has a large proportion of its population that is of black African origin. The centers with low prevalences of atopic eczema were generally the same as those with low prevalences of asthma and rhinoconjunctivitis symptoms [5].

Another finding from ISAAC Phase I is that the factors predicted to be theoretically protective for asthma do not seem to play that role in some developing regions. An attractive current theory is that improved hygiene in modern civilizations has altered the pattern of exposure to infection in early life in such a way as to predispose the immune system towards the atopic response. However, the information provided by ISAAC suggests that this may be a relatively "local" theory because very high prevalences of respiratory and other allergic symptoms also occur in populations that have much lower standards of hygiene, as in some centers from developing regions. In Latin America, gastrointestinal parasite infestation, a high number of children per family, and a high burden and severity of acute viral infection in infancy are common in many countries. However, these factors do not seem to play any protective role against asthma, since the prevalence of respiratory symptoms related to asthma is at least as high as those from UK or other centers in Europe, suggesting another kind of relationship between asthma symptoms and the mentioned factors. In fact, it has recently been demonstrated that IgE and respiratory symptoms of asthma significantly decrease after treating patients who are infested by *Ascaris lumbricoides* with antihelminthic medications [14].

In summary, Phase I of the ISAAC study has for the first time provided standardized international data on the prevalence of symptoms of asthma, rhinitis, and eczema in children. A wide variation in the prevalence of these disorders was observed throughout the world, with differing regional patterns for the different atopic disorders. It is likely that environmental factors were responsible for the major differences between centers. However, risk factors associated to socioeconomic status should be taken into account, particularly when they act together with environmental risk factor. Several factors advocated as protective for asthma in developed regions are not evident in some developing regions. While acknowledging the limitations of international prevalence comparisons of this kind, these and other ISAAC findings nevertheless provide a framework for further etiological research into the genetic, lifestyle, environmental, and medical care factors affecting these conditions, as planned for ISAAC Phase II.

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