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ORIGINAL ARTICLE

The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: A global synthesis

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Abstract This ISAAC Phase Three synthesis provides summarised information on the main findings of the study, regional tables and figures related to the prevalence and severity of current symptoms of asthma, rhinoconjunctivitis and eczema in the main regions of the world. The large number of surveyed children (≈1,200,000), the large number of centres (233) and countries (98) that participated in ISAAC Phase Three makes this study the most comprehensive survey of these diseases ever undertaken. Globally, the prevalence for current asthma, rhinoconjunctivitis and eczema in the 13–14-year age group was 14.1%, 14.6% and 7.3%, respectively. In the 6–7-year age group the prevalence for current asthma, rhinoconjunctivitis and eczema was 11.7%, 8.5% and 7.9%, respectively. The study shows a wide variability in the prevalence and severity of asthma, rhinoconjunctivitis and eczema which occurs not just between regions and countries but between centres in the same country and centres in the same city. This study definitively establishes that the prevalence of those diseases can be very high in non-affluent centres with low socioeconomic conditions. The large variability also suggests a crucial role of local environment characteristics to determine the differences in prevalence between one place and another. Thus, ISAAC Phase Three has provided a large body of epidemiological information on asthma, rhinoconjunctivitis and eczema in childhood from contrasting environments which is expected to yield new clues about the aetiology of those conditions and reasons for their marked global variability.
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Introduction

Asthma, rhinoconjunctivitis and eczema in childhood have become three of the more important public health problems worldwide. Although in the past it was thought that these diseases occurred more frequently in populations from developed countries, it has been evident since the first global report from the International Study of Asthma and Allergies in Childhood (ISAAC) that prevalence of those conditions in some low-resourced countries was similar or even higher than in developed ones and that a wide variability in their prevalence occurred at regional and even at country level.[1–4]

Since then, a large body of new national, regional and global information on the prevalence, severity, risk factors, trends and several other aspects related to asthma, rhinoconjunctivitis and eczema in childhood, has been reported by ISAAC.[5] The recently completed third ISAAC Phase included the largest number of centres from the main world regions ever studied in regard to these conditions, with about 1,200,000 schoolchildren surveyed; detailed information on the global prevalence and severity of asthma, rhinitis and eczema has been reported in the ISAAC world map journal articles.[6–8]

The well-known methodological consistency of the ISAAC programme, its originality and especially the inclusion of countries with different cultures, socioeconomic development and lifestyles, has led to its results being employed by several governmental and academic institutions at country and regional level. It has constituted the epidemiological basis for many of the well-known global initiatives on asthma, rhinitis and eczema management in childhood, and for guidelines and recommendations from international health organisations.

This article presents new information on disease overlap (asthma, rhinoconjunctivitis, eczema), socioeconomic and geospatial considerations from ISAAC Phase Three (written questionnaires) concerning the prevalence of asthma, rhinoconjunctivitis and eczema in children aged 6–7 and 13–14 years.

Methods

The detailed methodology employed by ISAAC to obtain and analyse data for Phase Three, has already been published in detail elsewhere.[5,9] Briefly, written questionnaires were self-completed at school by 13–14-year olds and completed at home by parents of 6–7-year olds. Samples of 3000 children for each age group (with a minimum of 1000) within each centre were selected by randomly sampling schools within the study area. Almost all centres studied the 13–14-year age group, but only some centres studied the optional 6–7-year age group. Data checks were undertaken by the ISAAC International Data Centre in Auckland, New Zealand which ensured adherence to the protocol. The English language questionnaire was translated where required, and a back translation to English was provided. In this paper, we focus on the current symptoms (past 12 months) of asthma, rhinoconjunctivitis and eczema; and reported asthma ever.

Associations between prevalence of current symptoms of asthma, rhinoconjunctivitis and eczema, and a range of geo-climatic factors were assessed using maps prepared in the ArcGIS geographic information system (version 9.3.1, ESRI Inc., Redlands, CA, USA). The factors presented are altitude,[10] air pollution as indicated by the predicted concentrations (micro grams per cubic metre) of particulate matter less than 10 μm in diameter (PM_{10}),[11] and Gross National Income per capita (GNI).[12] High altitude was

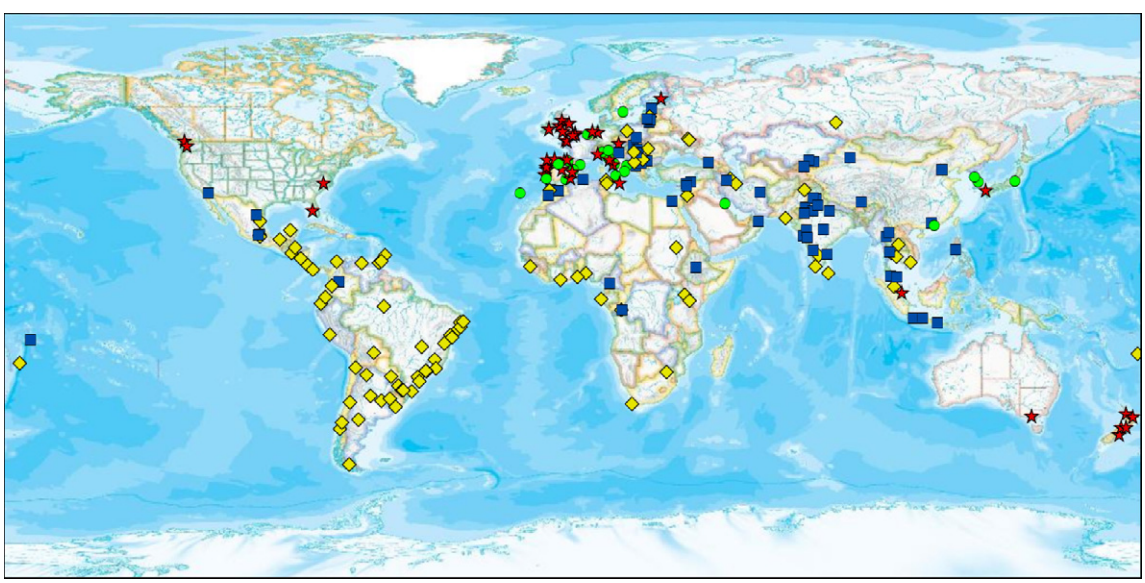

Figure 1 Geospatial distribution of prevalence of current symptoms of asthma and country income, 13–14-year age group. Each symbol represents a centre. The four symbols depict different levels of prevalence of symptoms combined with their categorisation as affluent or non-affluent. Red stars indicate high prevalence of current symptoms of asthma ($\geq$10%) and affluent (GNI > \$9265); yellow diamonds indicate high prevalence of current symptoms of asthma and non-affluent; green circles indicate low prevalence of current symptoms of asthma and affluent; and blue squares indicate low prevalence of current symptoms of asthma and non-affluent. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

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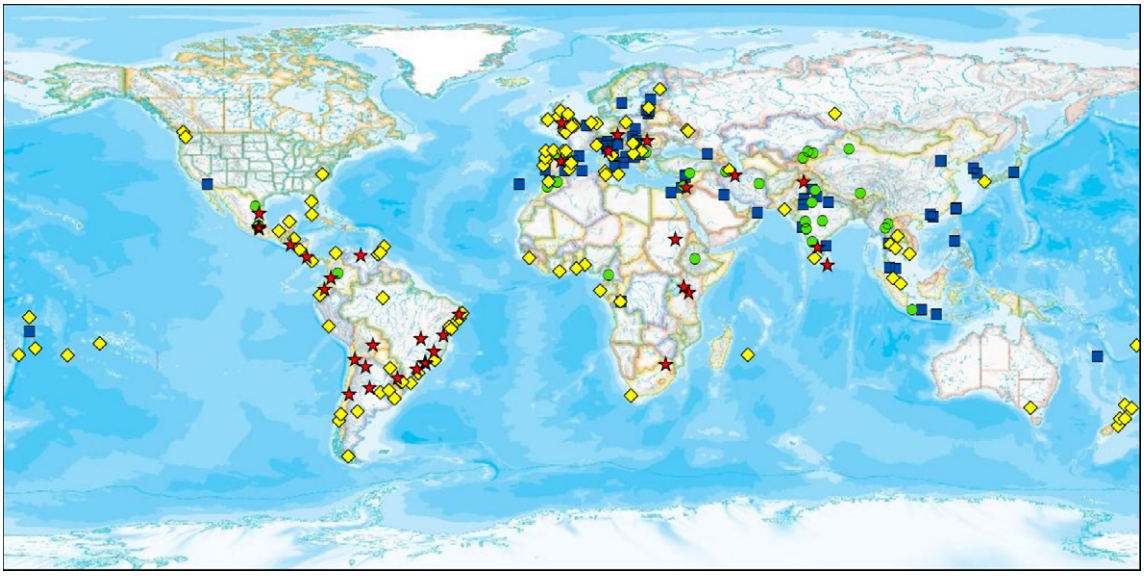

Figure 2 Geospatial distribution of prevalence of current symptoms of asthma and altitude, 13–14-year age group. Each symbol represents a centre. The four symbols depict different levels of prevalence of symptoms combined with their categorisation as low or high altitude. Red stars indicate high prevalence of current symptoms of asthma (≥10%) and high altitude (≥300 m); yellow diamonds indicate high prevalence of current symptoms of asthma and low altitude; green circles indicate low prevalence of current symptoms of asthma and high altitude; and blue squares indicate low prevalence of current symptoms of asthma and low altitude. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

defined as ≥300 m. High PM_{10} was defined as ≥50 μg/m^3. Data for altitude and air pollution were available at centre level whereas the GNI data were only available at country level. Non-affluent countries were those classified by the World Bank as low, lower middle, or upper middle income, and affluent countries are those classified as high income. The maps (Figs. 1–3) illustrate the distribution of low and high values of prevalence and GNI, altitude and PM_{10}. For current symptoms of asthma (current wheeze) and current symptoms of eczema, high prevalence centres were defined

Figure 3 Geospatial distribution of prevalence of current symptoms of asthma and particulate matter (PM_{10}), 13–14-year age group. Each symbol represents a centre. The four symbols depict different levels of prevalence of symptoms combined with their categorisation as low or high (PM_{10}). Red stars indicate high prevalence of current symptoms of asthma (≥10%) and high PM_{10} (≥50 μg/m^3); yellow diamonds indicate high prevalence of current symptoms of asthma and low PM_{10}; green circles indicate low prevalence of current symptoms of asthma and high PM_{10}; and blue squares indicate low prevalence of current symptoms of asthma and low PM_{10}. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)

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Table 1 Prevalence of current symptoms of asthma, rhinoconjunctivitis and eczema by world region and gender, 6–7-year age group.

Region	Gender	*N*	Asthma		Rhinoconjunctivitis		Eczema	
			N	%	*N*	%	*N*	%
Africa	Male	2979	321	10.8	223	7.5	283	9.5
	Female	2886	268	9.3	230	8.0	262	9.1
Asia-Pacific	Male	30,509	3296	10.8	3712	12.2	2962	10.2[b]
	Female	29,470	2423	8.2	2615	8.9	2796	10.0[b]
Eastern Mediterranean	Male	20,769	2146	10.3	1130	5.4	1001	4.8
	Female	19,804	1678	8.5	968	4.9	943	4.8
Indian Sub-Continent	Male	25,867	1909	7.4	1166	4.5	786	3.0
	Female	24,225	1483	6.1	917	3.8	735	3.0
Latin America	Male	45,926	8691	18.9	6017	13.1	4482	9.8
	Female	47,848	7565	15.8	5914	12.4	4873	10.2
North America	Male	2011	433	21.5	176	8.8	197	9.8
	Female	2001	334	16.7	136	6.8	207	10.3
Northern and Eastern Europe	Male	21,444	2132	9.9	1277	6.0	1286	6.0
	Female	21,104	1583	7.5	1064	5.0	1302	6.2
Oceania	Male	7028	1705	24.3	879	12.5	991	14.1
	Female	6860	1315	19.2	742	10.8	1163	17.0
Western Europe	Male	39,328	4296	10.9	3247	8.3	3018	7.7
	Female	38,394	3191	8.3	2491	6.5	3301	8.6
Male Total		195,861	24,929	12.7	17,827	9.1	15,006	7.7[b]
Female Total		192,592	19,840	10.3	15,077	7.8	15,582	8.2[b]
Global Total[a]		388,811	44,799	11.5	32,928	8.5	30,616	7.9[b]

[a] Includes participants with unknown gender (358).
[b] Percent values calculated using smaller denominators as not all centres included the eczema questionnaire.

as those with prevalence of 10% or greater. For current symptoms of rhinoconjunctivitis, high prevalence centres were defined as those with prevalence of 15% or greater for the 13–14-year age group and 7.5% or greater for the 6–7-year age group. These definitions are based on the levels used in the maps presented in the ISAAC prevalence papers.[1–4,6–8] Spearman correlation (rho) was used to study the association of altitude, latitude and longitude with the prevalence of current symptoms of asthma, rhinoconjunctivitis and eczema.

Spearman's correlation (rho) was employed to determine associations between current symptoms of asthma, rhinoconjunctivitis and eczema, with centre level altitude, latitude, longitude and PM_{10}, and with country level GNI, in 6–7-year and 13–14-year age groups.

Results

Participants

ISAAC Phase Three surveyed about 1,200,000 children from 233 centres in 98 countries, involving almost 800,000 children aged 13–14 years and almost 400,000 aged 6–7 years. For asthma the data sets comprised 1,187,496 schoolchildren from 233 centres in 98 countries, of whom 128 centres (689,413 participants) in 64 countries (34 countries new to ISAAC) had not undertaken ISAAC Phase One; 798,685 were aged 13–14 years and 388,811 were aged 6–7 years. The majority of the new ISAAC centres were from countries in Latin America, Eastern Europe and Africa, although there were also some from other regions.[7] In the case of rhinoconjunctivitis, the 13–14-year age group involved 670,242 children and 388,811 children aged 6–7 years. Regarding eczema, for the 13–14-year age group there were 663,256 children and 385,853 for the 6–7-year age group.[8] Of the 54 languages used in Phase Three, English was the most common (21% of centres) followed by Spanish (20%), Portuguese (11%), Arabic (7%), Italian (6%), French (5%) and Chinese (4%). The number of participating centres per region ranged from seven in North America to 56 in Latin America.

Symptoms by region and gender

The regional prevalences of current symptoms for the three conditions are shown in Tables 1 and 2 by gender.

There was large variability of prevalence between regions for symptoms of each of the three conditions and both age groups. For the younger age group the lowest prevalence values for asthma symptoms were found in the Indian Subcontinent, with intermediate values in Africa, Asia-Pacific, Eastern Mediterranean, Northern and

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Table 2 Prevalence of current symptoms of asthma, rhinoconjunctivitis and eczema by region and gender, 13–14-year age group.

Region	Gender	*N*	Asthma		Rhinoconjunctivitis		Eczema	
			N	%	*N*	%	*N*	%
Africa	Male	32,373	4521	14.0	5087	15.7	3822	11.8
	Female	33,935	4747	14.0	6850	20.2	4640	13.7
Asia-Pacific	Male	49,675	4428	8.9	6208	12.5	2174	4.7[b]
	Female	49,959	4303	8.6	7498	15.0	2692	5.8[b]
Eastern Mediterranean	Male	25,879	2748	10.6	3393	13.1	1627	6.3
	Female	25,826	2053	7.9	3361	13.0	1615	6.3
Indian Sub-Continent	Male	27,432	2362	8.6	3203	11.7	1218	4.4
	Female	28,351	1522	5.4	2762	9.7	916	3.2
Latin America	Male	80,715	11,753	14.6	11,193	13.9	5062	6.3
	Female	85,185	14,597	17.1	17,543	20.6	8631	10.1
North America	Male	69,739	13,793	19.8	906	13.8[b]	421	6.4[b]
	Female	71,270	16,634	23.3	1445	19.6[b]	693	9.4[b]
Northern and Eastern Europe	Male	35,455	3168	8.9	2721	7.7	1356	3.8
	Female	36,602	3841	10.5	3873	10.6	2308	6.3
Oceania	Male	17,837	3060	17.2	2620	14.7	1520	8.5
	Female	18,462	3241	17.6	3547	19.2	2028	11.0
Western Europe	Male	54,741	7545	13.8	6771	12.4	2968	5.4
	Female	52,932	7938	15.0	8835	16.7	4414	8.3
Male Total	Male	393,846	53,378	13.6	42,102	12.7[b]	20,168	6.2[b]
Female Total	Female	402,522	58,876	14.6	55,714	16.5[b]	27,937	8.3[b]
Global Total[a]		798,685	112,630	14.1	97,866	14.6[b]	48,131	7.3[b]

[a] Includes participants with unknown gender (2317).
[b] Percent values calculated using smaller denominators as not all centres included the rhinoconjunctivitis and eczema questionnaires.

Eastern Europe, Western Europe, and the highest levels in Latin America, North America, and Oceania. The lowest prevalence values for rhinoconjunctivitis symptoms were found in Eastern Mediterranean, Indian Subcontinent, and Northern and Eastern Europe, with intermediate values in Africa, Asia-Pacific, and, Western Europe, and the highest in Latin America, North America, and Oceania. The lowest prevalence values for symptoms of eczema were found in Eastern Mediterranean, Indian Subcontinent, with intermediate values in Africa, Asia-Pacific, and Northern and Eastern Europe, Western Europe, North America, and the highest values in Latin America, and Oceania.

For the older age group the lowest prevalence values for asthma symptoms were found in Asia-Pacific, Eastern Mediterranean, Indian Subcontinent, and Northern and Eastern Europe, with intermediate values in Africa and Oceania, Western Europe, and Latin America, and the highest in North America. The lowest prevalence values for rhinoconjunctivitis symptoms were found in Indian Subcontinent, and Northern and Eastern Europe, with intermediate values in Asia-Pacific, Eastern Mediterranean, Oceania and Western Europe, and the highest values in Africa, Latin America, and North America. The lowest prevalence values for symptoms of eczema were found in Asia-Pacific, Eastern Mediterranean, Indian Subcontinent, and Northern and Eastern Europe, with intermediate values in Latin America, Oceania, North America, and Western Europe, and the highest values in Africa.

The summaries by gender for symptoms of each of the three diseases and both age groups showed that in the younger age group there were more boys than girls with asthma and rhinoconjunctivitis symptoms, and this held true for all regions for asthma, and most for rhinoconjunctivitis symptoms, but eczema symptoms overall were more common in girls although this varied across the regions. In the older age group there were more girls than boys with symptoms of all three conditions, and this held true for most regions.

Concurrent prevalence of symptoms of current asthma, rhinoconjunctivitis and eczema

A low proportion of children simultaneously reported current symptoms of asthma, rhinoconjunctivitis and eczema. Amongst the world regions there was a large variability in the prevalence of the three diseases; for those with current symptoms of asthma the prevalence for the concurrence of the three conditions varied from 6.3% in Northern and Eastern Europe to 13.6% in Africa in the 13–14 years old group

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Table 3 Prevalence of current symptoms of asthma only with associated co-morbidities, 6–7-year age group.

	Current wheeze *N*	Asthma only %[a]	Asthma and rhinoconjunctivitis %[a]	Asthma and eczema %[a]	All 3 conditions %[a]
Africa	590	60.3	15.1	12.7	11.9
Asia-Pacific	5186	57.4	21.5	11.5	9.5
Eastern Mediterranean	3824	73.6	13.2	8.0	5.2
Indian Sub-Continent	3395	72.6	16.3	5.9	5.1
Latin America	16,266	59.8	21.6	9.4	9.1
North America	767	66.9	13.0	11.7	8.3
Northern and Eastern Europe	3717	68.7	15.3	9.6	6.4
Oceania	3020	56.9	16.1	15.6	11.4
Western Europe	7497	60.5	20.1	10.6	8.8

[a] Percentage of participants with current wheeze.

Table 4 Prevalence of current symptoms of asthma only with associated co-morbidities, 13–14-year age group.

	Current wheeze *N*	Asthma only %[a]	Asthma and rhinoconjunctivitis %[a]	Asthma and eczema %[a]	All 3 conditions %[a]
Africa	9275	51.0	24.5	10.9	13.6
Asia-Pacific	8037	60.4	26.6	6.4	6.6
Eastern Mediterranean	4801	60.9	23.5	7.1	8.5
Indian Sub-Continent	3894	61.5	23.1	5.2	10.1
Latin America	26,352	57.1	26.9	7.0	9.0
North America	2337	55.6	27.9	7.3	9.1
Northern and Eastern Europe	7012	64.7	21.6	7.3	6.3
Oceania	6306	58.6	23.7	8.7	9.0
Western Europe	15,503	58.3	25.6	8.1	7.9

[a] Percentage of participants with current wheeze.

and from 5.1% in the Indian Subcontinent to 11.9% in Africa in those aged 6–7 years. The relative proportions for the regional concurrent prevalence of the three diseases are presented in Tables 3–8.

The global prevalence of current symptoms of the three diseases reported simultaneously by children is shown in Fig. 4.

Prevalence in centres related to socioeconomic status of countries

In both, the 6–7 and 13–14-year age groups, GNI was positively correlated (Spearman's rho) with current symptoms of asthma, rhinoconjunctivitis and eczema (Table 9). The geospatial distribution of current symptoms of asthma and

Table 5 Prevalence of current symptoms of rhinoconjunctivitis with associated co-morbidities, 6–7-year age group.

	Rhinoconjunctivitis *N*	Rhinoconjunctivitis only %[a]	Rhinoconjunctivitis and asthma %[a]	Rhinoconjunctivitis and eczema %[a]	All 3 conditions %[a]
Africa	454	47.4	19.6	17.6	15.4
Asia-Pacific	6015	58.5	18.6	14.7	8.2
Eastern Mediterranean	2098	57.2	24.1	9.2	9.5
Indian Sub-Continent	2085	56.7	26.6	8.3	8.3
Latin America	11,940	45.4	29.5	12.7	12.4
North America	312	35.6	32.1	11.9	20.5
Northern and Eastern Europe	2343	54.0	24.3	11.5	10.2
Oceania	1621	35.0	30.0	13.8	21.2
Western Europe	5746	48.9	26.2	13.3	11.5

[a] Percentage of participants with current symptoms of rhinoconjunctivitis.

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Table 6 Prevalence of current symptoms of rhinoconjunctivitis with associated co-morbidities, 13–14-year age group.

	Rhinoconjunctivitis *N*	Rhinoconjunctivitis only %[a]	Rhinoconjunctivitis and asthma %[a]	Rhinoconjunctivitis and eczema %[a]	All 3 conditions %[a]
Africa	11,943	53.5	19.0	16.9	10.6
Asia-Pacific	12,310	69.7	17.3	8.6	4.3
Eastern Mediterranean	6754	66.1	16.7	11.2	6.0
Indian Sub-Continent	5968	70.0	15.1	8.3	6.6
Latin America	28,738	55.8	24.6	11.3	8.2
North America	2354	53.9	27.7	9.3	9.0
Northern and Eastern Europe	6599	61.5	23.0	8.8	6.7
Oceania	6179	53.7	24.2	12.9	9.2
Western Europe	15,619	58.7	25.4	8.0	7.9

[a] Percentage of participants with current symptoms of rhinoconjunctivitis.

Table 7 Prevalence of current symptoms of eczema with associated co-morbidities, 6–7-year age group.

	Current eczema *N*	Eczema only %[a]	Eczema and asthma %[a]	Eczema and rhinoconjunctivitis %[a]	All 3 conditions %[a]
Africa	546	58.8	13.7	14.7	12.8
Asia-Pacific	5762	65.7	10.4	15.3	8.6
Eastern Mediterranean	1944	64.1	15.7	10.0	10.2
Indian Sub-Continent	1521	63.8	13.3	11.4	11.4
Latin America	9363	51.7	16.3	16.2	15.8
North America	405	52.8	22.2	9.1	15.8
Northern and Eastern Europe	2595	66.7	13.7	10.4	9.2
Oceania	2154	51.9	21.9	10.4	15.9
Western Europe	6326	64.9	12.5	12.1	10.5

[a] Percentage of participants with current symptoms of eczema.

GNI is shown in Fig. 1. There are four patterns of centres shown: a high prevalence in affluent centres; a high prevalence in non-affluent centres; a low prevalence in affluent centres; and a low prevalence in non-affluent centres.

Geo-climatic factors and their relationship with current prevalence of asthma, rhinoconjunctivitis and eczema

Globally, it was found that lower latitudes and Eastern longitudes were slightly but significantly associated with higher prevalence of current symptoms of asthma, and rhinoconjunctivitis and eczema in both age groups (Table 9). However, this was not a consistent finding. For instance, in large regions including both hemispheres as Latin America, no significant association was found between latitude/longitude and prevalence of current symptoms. The mean prevalence of the three diseases was similar in centres located in tropical versus non-tropical areas. The distribution of prevalence of current symptoms by altitude in the group aged 13–14 years (Fig. 5) showed a weak but significant inverse correlation just for current asthma but not for rhinoconjunctivitis or eczema; in the 6–7-year age group there was a weak but significant inverse

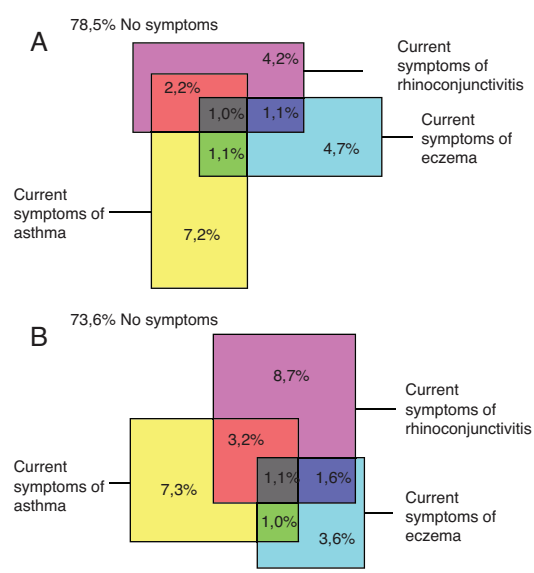

Figure 4 Overall proportions of children with current symptoms of asthma, rhinoconjunctivitis, or eczema, or combinations of symptoms, 6–7-year age group (A) and 13–14-year age group (B) for ISAAC Phase Three.

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Table 8 Prevalence of current symptoms of eczema with associated co-morbidities, 13–14-year age group.

	Current eczema *N*	Eczema only %[a]	Eczema and asthma %[a]	Eczema and rhinoconjunctivitis %[a]	All 3 conditions %[a]
Africa	8466	49.3	11.9	23.9	15.0
Asia-Pacific	4868	56.7	10.6	21.9	10.9
Eastern Mediterranean	3242	53.5	10.6	23.3	12.6
Indian Sub-Continent	2136	48.7	9.6	23.2	18.5
Latin America	13,694	45.4	13.5	23.8	17.3
North America	1117	46.0	15.3	19.6	19.1
Northern and Eastern Europe	3665	58.0	13.9	15.9	12.1
Oceania	3555	46.3	15.4	22.4	15.9
Western Europe	7388	49.4	17.1	16.9	16.6

[a] Percentage of participants with current symptoms of eczema.

Table 9 Associations (Spearman's rho) between current symptoms of asthma, rhinoconjunctivitis and eczema, with centre level altitude, latitude, longitude and PM_{10}, and with country level GNI, in 6–7-year (144 centres) and 13–14-year age groups (233 centres).

	Asthma		Rhinoconjunctivitis		Eczema	
	rho	*p*	rho	*p*	rho	*p*
6–7 year age group						
Altitude	−0.236	0.005	−0.045	0.593	−0.186	0.027
Latitude	−0.369	<0.001	−0.383	<0.001	−0.210	0.012
Longitude	−0.356	<0.001	−0.402	<0.001	−0.201	0.016
GNI	0.244	0.004	0.328	<0.001	0.464	<0.001
13–14-year age group						
Altitude	−0.130	0.047	−0.062	0.349	−0.113	0.087
Latitude	−0.274	<0.001	−0.249	<0.001	−0.188	0.004
Longitude	−0.380	<0.001	−0.265	<0.001	−0.262	<0.001
GNI	0.291	<0.001	0.206	0.002	0.203	0.003

relationship between altitude, asthma and eczema but not with rhinoconjunctivitis (Table 9).

Particulate matter less than or equal to 10 μm (PM_{10}) and the relationship with current prevalence of asthma, rhinoconjunctivitis and eczema

Overall, ISAAC Phase Three found that PM_{10} showed a trend to be inversely related with current symptoms of asthma, rhinoconjunctivitis and eczema at level centre; however, the relationship was inconsistent or null at within-country level.

Discussion

This is the largest study of asthma, rhinoconjunctivitis and eczema ever conducted, and the first time that the relationship between the three diseases, and various geospatial and geo-climatic phenomena has been examined. ISAAC Phase Three was performed in all WHO regions thus the main continents and ethnic areas of the world were represented in the study.

The large variability of prevalence between regions, continents, countries, centres in the same country, and even between centres in the same city (as in Mexico City) is probably the main and most consistent finding of ISAAC.[6–8] The marked difference of prevalence between centres in the same city, as occurred in Mexico City, has also been found amongst New York neighbourhoods, with a 3–19% difference in asthma prevalence across the city associated with variations in allergen exposures.[13] This highlights the heightened

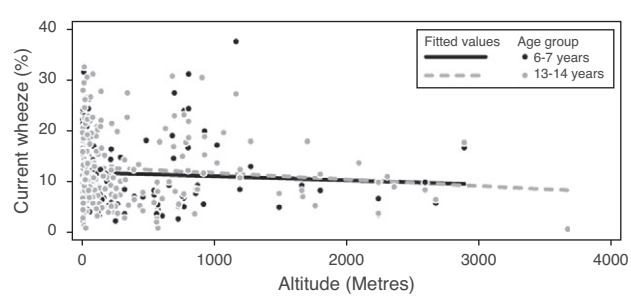

Figure 5 Associations between prevalence of current wheeze and altitude in ISAAC Phase Three, 6–7-year (rho −0.24, $p = 0.005$) and 13–14-year (rho −0.13 $p = 0.047$) age groups.

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impact of still undefined local environmental or ecologic factors present at each centre, which may determine varying epidemiological and clinical expressions of diseases in populations at similar settings.[14–16] The latter, i.e. the influence of local variation in exposures on prevalence, seems to be supported by the large variability found amongst centres in the prevalence of allergen sensitisation [17] and airway hyperresponsiveness.[18]

Although the whole study found a subtle relationship between GNI and overall symptom prevalence, in large regions such as Latin America (56 centres in 17 countries), which accounted for about 25% of all the children surveyed by ISAAC Phase Three in the world,[19] there was not a significant correlation between GNI and prevalence. Using the GNI or other country-average index to study the effect of socioeconomic status on the prevalence of current symptoms, especially when including centres from affluent and non-affluent countries, may be misleading, since the income distribution in developing countries is highly unequal. Therefore, assigning the GNI of a developing country to all centres in that country would be inadequate because the risk of losing the large differences in income distribution between centres in developing countries, and regions.[20] Until socioeconomic data at an individual level are available for all participating centres, the effect of socioeconomic development on the prevalence and severity of asthma, rhinoconjunctivitis and eczema will be bedevilled by this methodological issue. The results of studies looking at the relationship between socioeconomic status and prevalence of symptoms vary from an inverse association,[21–24] to no association[25] to a positive association[26]; apart from methodological considerations which may reflect the lack of proper and standardised instruments to assess such associations at centre or individual level.

Higher or lower prevalence of current symptoms of asthma, rhinoconjunctivitis and eczema occurred regardless of whether centres were located in developing or developed countries or regions,[1,2,5–8] and this was consistent with the findings of ISAAC Phase One.[2] For instance, in Africa the 13–14-year age group had the same mean prevalence of current wheezing as Western Europe (14%); similar prevalence of rhinoconjunctivitis and eczema also occurred between developing and developed countries, as shown in Tables 1 and 2. In general, most centres with a high or low prevalence in Phase Three tended to remain close to the level of prevalence they had in Phase One; although there were some centres showing important increases or decreases between the two phases. In areas sharing the same language but different socioeconomic development, the prevalence of current asthma symptoms was higher in developing than developed countries (i.e., Iberian Peninsula vs. Latin America).[19]

The inclusion of many more centres from developing countries in Phase Three than in Phase One is an important achievement of ISAAC as the proportion of the world population that lives in developing areas is about 80%. This is important because several theories on asthma causation are related to the protective effect of factors usually associated with low socioeconomic status. Considering that conditions of poverty have been persistently affecting populations in developing areas for a long time, without dramatic changes in the last 20 years, a lower prevalence of asthma, rhinoconjunctivitis, and eczema would have been expected in children and adolescents from those low-resourced countries. The participation of many more centres from developing countries certainly provides a more realistic representation of the world prevalence of asthma, rhinoconjunctivitis and eczema in childhood. At present, and thanks to the information gathered by ISAAC, the old statement that asthma was just a disease of industrialised and developed countries can be considered simply as an exclusion bias.

As in Phase One, most symptomatic children had symptoms of only one disorder in the previous year, which indicates that many different risk factors may be required for the clinical expression of these related disorders or may involve different time of occurrence, latency periods and time trends.

Although the proportion of subjects having the three diseases simultaneously was relatively low, those children probably represent a highly demanding group for specialised health care. Furthermore, it is likely that as seen in daily practice, coexistence of these diseases may be associated with greater functional impairment in terms of activity limitation and lower quality of life as compared to children who have one condition alone. Co-morbidities are important for clinicians treating asthma as they may be markers of patients at risk of poor outcomes, they may point to specific effective treatment options and they are important to researchers as possible confounding factors in clinical trials.

The effect of geo-climatic factors on the current symptom prevalence should be interpreted cautiously because of the dynamic nature of climatic factors that sometimes act independently of latitude and longitude, as is apparently occurring in this last decade. Consequently, geo-climatic factors should be considered as part of a much more complex model interacting with several other ecological conditions which also could be altered by seasonal or yearly changes. As other authors previously found,[27,28] ISAAC Phase Three found correlations between some geo-climatic factors and the prevalence of asthma, rhinoconjunctivitis and eczema; however, the interpretation and time-dependency of such effects remains difficult to understand.

The complex relationships between air pollution and symptoms of asthma, rhinoconjunctivitis and eczema probably cannot be elucidated from data as those obtained by ISAAC. Further information on the type, magnitude and temporality of exposures, which also consider variations caused by geo-climatic (i.e. seasonal) factors, should help to a better understanding of the true effects of air pollution on the prevalence of asthma, rhinoconjunctivitis and eczema in children.

Limitations

In some way, ISAAC shares the potential limitations of any large multicentre international cross-sectional study (differences in language, socioeconomic development, lifestyle, cultural standard, environmental aspects, educational level, medical practice and health concepts, amongst others). We acknowledge the limitations of international prevalence comparisons of this kind and also of interpretations on its findings. Another concern is that centre GNI was

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assumed to be the same as country GNI. Unfortunately, for most of the centres in developing countries or regions there is no official information available regarding socioeconomic status. At present, it is clear that in those countries or areas with huge inequities of income distribution [19] the wholesale application of a country level measure to all centres conceals more than it reveals.Nevertheless, the worldwide scope of ISAAC Phase Three including centres across the main world regions, the use of standardised and validated methodology, a meticulous translation of questionnaires to different languages,[29] strict data quality control and management, and a thorough repetition of the study after several years, has provided for the first time a unique and fundamental epidemiological analysis of the world distribution and trend of the prevalence and severity of asthma, rhinoconjunctivitis and eczema in children.[30] At the same time ISAAC has provided a stimulus for the development of new hypotheses and a challenge to identify modifiable protective and risk factors for asthma, and the other diseases studied. The worldwide time trends in the prevalence of current symptoms are not described in the present paper because they have been extensively detailed elsewhere.[31–33]

As found in ISAAC Phase One, there was a low degree of overlap between the three conditions[2] suggesting that asthma, rhinoconjunctivitis and eczema may have different aetiologies, time of occurrence and clinical course, probably related with particular enviromental exposures at each locality or area.The wide variability of the prevalence of the studied diseases, found by ISAAC in all its phases, strongly points to local ecological factors or exposures which are probably typical for each locality, as the main determinants for the observed variability of symptoms, allergic sensitisation and airways hyperresponsiveness reported by recent ISAAC studies. The latter is in accordance with current research on how and when exposures to environmental agents can induce epigenetic changes that will result in varying biological, clinical and epidemiological expressions of asthma and allergies.[14–16]

Another most successful task of ISAAC Phase Three was the consolidation of a world research force based on a huge scientific, trained and efficient network, throughout the continents and main regions of the planet and despite the marked differences in cultural and environmental aspects amongst participating countries and centres. Ellwood et al. have found that the majority of centres in this repeat multi-centre international research project undertaken by researchers with diverse cultural backgrounds were able to replicate the methodology between phases (data not shown).

The ISAAC programme has demonstrated that it is feasible to monitor the prevalence and severity of asthma, rhinoconjunctivitis, and eczema in children, globally. It is possible that prevalence of current symptoms of asthma rhinoconjunctivitis and eczema, as well as those factors that could induce changes on it, may behave accordingly to the important environmental and climatic changes presently occurring in the world. ISAAC Phase Three has extended, updated and disseminated valuable epidemiological information on asthma, rhinoconjunctivitis and eczema in childhood, proposing new hypotheses, contrasting old ones and modernising the basis for further aetiological research into the genetic, lifestyle, environmental, clinical and medical-care factors for those diseases.

Ethical disclosure

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation.
Right to privacy and informed consent. The authors declare that no patient data appears in this article.
Confidentiality of data. The authors declare that no patient data appears in this article.

Conflict of interest

The named authors declare that they have no conflict of interest.

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