

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



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Summary

Background Data for trends in prevalence of asthma, allergic rhinoconjunctivitis, and eczema over time are scarce. We repeated the International Study of Asthma and Allergies in Childhood (ISAAC) at least 5 years after Phase One, to examine changes in the prevalence of symptoms of these disorders.

Methods For the ISAAC Phase Three study, between 2002 and 2003, we did a cross-sectional questionnaire survey of 193 404 children aged 6–7 years from 66 centres in 37 countries, and 304 679 children aged 13–14 years from 106 centres in 56 countries, chosen from a random sample of schools in a defined geographical area.

Findings Phase Three was completed a mean of 7 years after Phase One. Most centres showed a change in prevalence of 1 or more SE for at least one disorder, with increases being twice as common as decreases, and increases being more common in the 6–7 year age-group than in the 13–14 year age-group, and at most levels of mean prevalence. An exception was asthma symptoms in the older age-group, in which decreases were more common at high prevalence. For both age-groups, more centres showed increases in all three disorders more often than showing decreases, but most centres had mixed changes.

Interpretation The rise in prevalence of symptoms in many centres is concerning, but the absence of increases in prevalence of asthma symptoms for centres with existing high prevalence in the older age-group is reassuring. The divergent trends in prevalence of symptoms of allergic diseases form the basis for further research into the causes of such disorders.

Introduction

The International Study of Asthma and Allergies in Childhood (ISAAC) epidemiological research programme was established in 1991 because of concern that asthma and allergies were increasing in prevalence and severity, but little was known about the scale of the problem worldwide or the factors affecting prevalence.¹ Until the 1990s, most studies of the prevalence of asthma and allergies had been undertaken in the UK, Australia, and New Zealand. The ISAAC investigators believed that new information would be contributed by the participation of other countries, including developing countries, with comparisons between, rather than within populations, helped by standardised methods.

The enormous participation in ISAAC Phase One, in which 700 000 children from 156 centres in 56 countries were included, demonstrated the worldwide concern about asthma and allergies. The participatory ISAAC approach with simple questionnaires enabled the collection of comparable data from children throughout the world.² The large variations in the worldwide prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema that were recorded, even in genetically similar groups,^{3–6} suggested that environmental factors underlie the variations. Many aspects of environments have been examined in ecological analyses of data from ISAAC Phase

One,^{7–14} and have provided some support for hypotheses that economic development,¹⁵ dietary factors,^{7,8} climate,⁹ infections,¹⁰ and pollens,¹¹ might influence some of this variation.

In ISAAC Phase Two, causes are studied in more detail in 30 study centres in 22 countries, with detailed questionnaires and objective measurements of physiological variables and indoor exposure.¹⁶ From the outset, ISAAC Phase Three was planned to assess time trends in the prevalence of symptoms by repeating the original cross-sectional study after at least 5 years. Our aim was to examine the hypothesis that the prevalence of asthma, allergic rhinoconjunctivitis, and eczema is increasing in some, but not all, regions of the world. The findings might give further clues about the causes of these conditions by revealing information about geographical variation in the rate of change in symptom prevalence for the three disorders.

Methods

ISAAC Phase Three is a repetition of a multicountry cross-sectional survey of two age-groups of school children—6–7 years and 13–14 years—undertaken at least 5 years after the baseline survey, ISAAC Phase One. Phase One study participants were identified through random samples of schools in defined geographical areas, or by

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including all schools where the area had less than 3000 children of the age-group. In ISAAC Phase Three, the study centres chose the children either by new random samples of schools in that area or by going back to the same schools chosen at random in Phase One. All centres aimed to complete the study for the older age-group. Inclusion of the younger age-group was optional, since it was more resource intensive because of the greater involvement of parents, and thus was not completed in every centre. The study instruments are straightforward standardised questionnaires with questions about symptoms of asthma, allergic rhinoconjunctivitis, and eczema. Each centre did Phase Three in the same way as Phase One to ensure the data obtained were comparable. Details of the study design and methods are described elsewhere.¹⁷ Centres were expected to obtain ethics approval and parental consent according to the requirements of the country, and to fund their own study. This study reports data for centres that completed both ISAAC Phase One and Phase Three, and achieved ISAAC quality-control standards for both phases.¹⁷ More detailed information regarding the trends for each disease, including the asthma video questionnaire used with the 13–14 year age-group, will be presented in separate reports. Answers to written questions were reported by parents for children and were self-reported for adolescents. In this study, we estimated asthma symptoms on the basis of positive answers to the written question: “Have you (has your child) had wheezing or whistling in the chest in the past 12 months?” Current allergic rhinoconjunctivitis symptoms were estimated on the basis of positive answers to both these questions: “In the past 12 months, have you (has your child) had a problem with sneezing or a runny or blocked nose when you (he/she) did not have a cold or the flu?” and if yes, “In the past 12 months, has this nose problem been accompanied by itchy watery eyes?” Current eczema symptoms were estimated on the basis of positive answers to two questions: “Have you (has your child) had this itchy rash at any time in the past 12 months?” and, “Has this itchy rash at any time affected any of the following places: the folds of the elbows; behind the knees; in front of the ankles; under the buttocks; or around the neck, ears, or eyes.” These questions were preceded by the question “Have you (has your child) ever had a skin rash which was coming and going for at least 6 months?” In Phase One, eczema defined in this way was called atopic eczema, but is now referred to as eczema, as recommended by the World Allergy Organisation.¹⁸

The written questionnaire was translated from English according to ISAAC guidelines,⁴ into one local language in 72% centres, and into more than one in 7% centres. In Phase Three, the written questionnaires were used in 39 languages. English was the most common language (31% of centres), followed by Spanish (16%), Italian and Portuguese (8%), Arabic and Chinese (6%), Malay (4%), German, Hindi, and Russian (3%), and 29 other languages made up the remainder.

We assessed centres for adherence to the protocol, and similarity between methods in Phases One and Three. Centres that had deficiencies in their methods or differences between the phases that could potentially seriously affect comparability of the estimates (such as low response rates) were excluded. Others with less serious deviations from the protocol were included, but their deviations were noted.

We derived an estimate of the absolute yearly rate of change in symptoms of asthma, allergic rhinoconjunctivitis, and eczema for each centre and an SE adjusted for the effect of cluster sampling.¹⁹ Increases or decreases of more than 1 SE could then be derived from these estimates. The level of 1 SE rather than 2 SE was chosen to show broad patterns of change rather than statistical significance. We used Bland-Altman plots to illustrate the yearly change versus mean prevalence of Phases One and Three for each centre. This mode of presentation was chosen to remove the influence of sampling error (regression to the mean)²⁰ when comparing the trends in higher or lower prevalence areas. We assessed heterogeneity of the centre-specific estimates of change in prevalence for the three disorders.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The ISAAC Phase Three studies were completed to the ISAAC standards in 172 data sets: 66 centres in 37 countries in the 6–7 year age-group (summarised in table 1 with full information in webtable 1) and in 106 centres from 56 countries in the 13–14 year age-group (summarised in table 1 with full information in webtable 2). Altogether, 190 data sets were received for both age-groups and 12 were excluded because of low response rates, four because of different sampling frames, and two because there were fewer than 1000 participants. 193 404 children participated from the younger age-group, and 304 679 from the 13–14 year age-group with mean response rates of 85% and 91% respectively. Both age-groups were studied in most centres, but in 44 centres in 28 countries, data were available for 13–14 year age-group only (these centres were most of the centres in English-speaking Africa, all those in French-speaking Africa and China, and some centres in Latin America, northern and eastern Europe, eastern Mediterranean, and western Europe). One centre provided data for 6–7 year age-group only. Of centres that provided data for both age-groups, data from two centres were excluded for the 13–14 year age-group because of low response rates and one because of a change of sampling frame (footnoted in webtable 2). The seven centres that did not have an ethics committee available to review the study design and the

See Online for
webtables 1 and 2

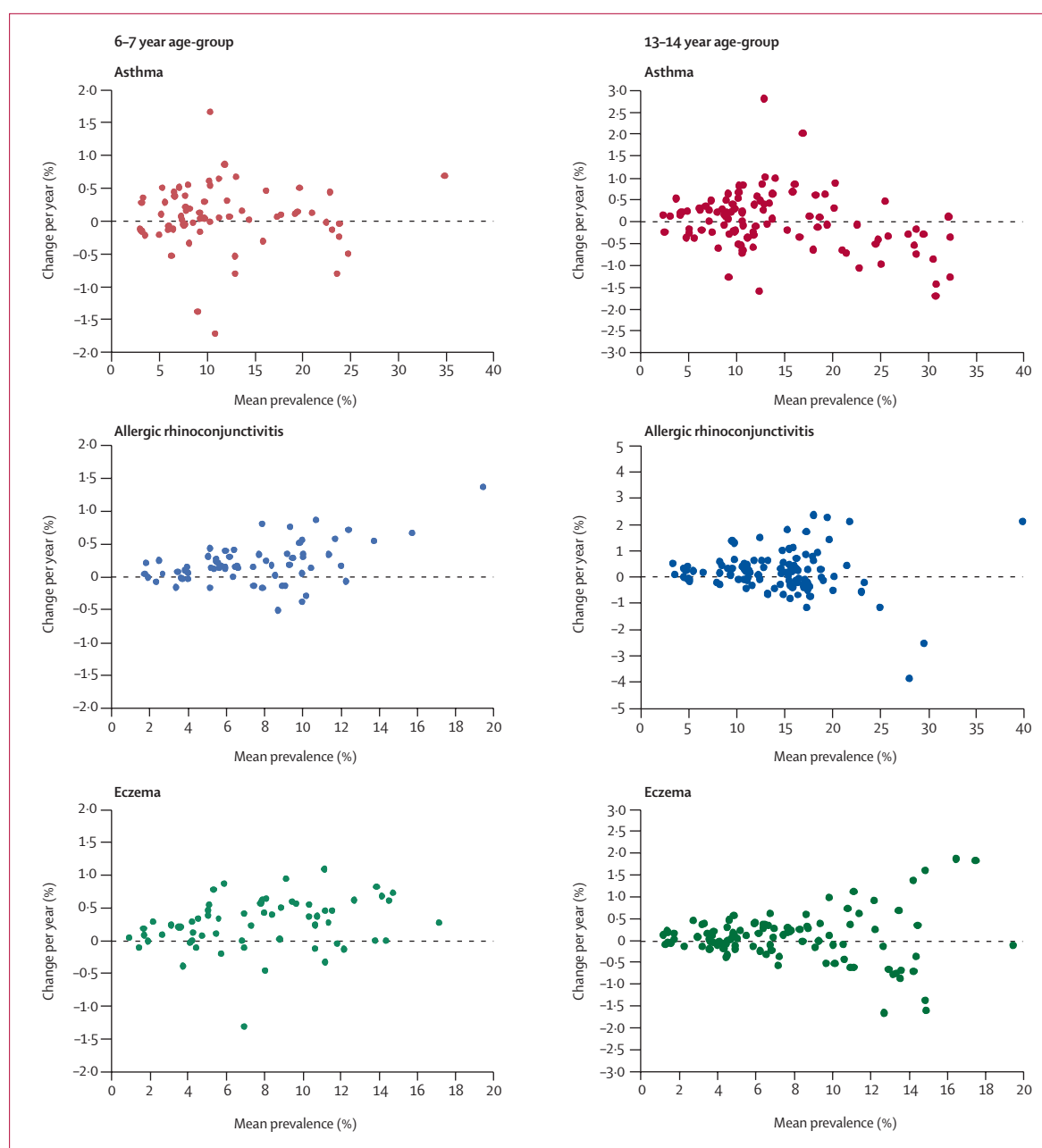


Figure 1: Bland-Altman plots showing mean change in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema per year for 6-7 year age-group and 13-14 year age-group versus mean prevalence of Phases One and Three for each centre

four centres that did not seek ethical approval are also shown in the footnote for webtables 1 and 2.

We recorded data within a year for each centre for Phases One and Three. The Phase One study took place between 1992 and 1998 (mostly 1994-95) and the Phase Three study between 1999 and 2004 (mostly 2002-03) (webtables 1 and 2). The time between Phases One and Three averaged 7 years (range 5-10 years, SD 1.2 years).

Although the mean prevalence for centres increased slightly for each of the three disorders in both age-groups,

there was wide variation between centres that could not be explained by random sampling variation (test for heterogeneity $p < 0.0001$, figure 1). Webtables 1 and 2 show the details of the time trends (summary data in table 1) and their pattern is shown in figures 2-4. For both age-groups, whereas most centres showed divergent changes of more than 1 SE in prevalence of the three disorders, more than a quarter of centres showed changes in the same direction (table 2). For the younger age-group, the centres that showed increases in all three disorders more frequently

than centres with decreases in all three disorders were Asia-Pacific, Indian subcontinent (India), North America, eastern Mediterranean, and western Europe, whereas in

the older age-group they were Africa, Asia-Pacific, India, Latin America, and northern and eastern Europe. For both age-groups, most centres reported a change of 1 SE or

	Years between Phases	Phase Three		Asthma symptoms				Allergic rhinoconjunctivitis symptoms				Eczema symptoms			
		Number of children	Response rate (%)	Phase One	Phase Three	Change per year	SE	Phase One	Phase Three	Change per year	SE	Phase One	Phase Three	Change per year	SE
6-7 year age-group															
Africa (English-speaking)															
Nigeria	7.0	2396	86.2	4.8	5.6	0.10	0.19	3.7	3.6	-0.01	0.17	4.5	5.0	0.07	0.13
Asia-Pacific															
Hong Kong	6.0	4448	96.0	9.1	9.4	0.03	0.16	13.7	17.7	0.67	0.23	3.9	4.6	0.12	0.09
Indonesia	6.0	2503	88.1	4.1	2.8	-0.21	0.11	3.8	3.6	-0.03	0.12	..	..	..	..
Japan	8.0	2958	90.7	17.4	18.2	0.10	0.13	7.8	10.6	0.35	0.11	..	..	..	..
Malaysia (3)	6.3	9940	84.1	6.5	5.8	-0.12	0.07	4.1	4.8	0.11	0.06	9.5	12.6	0.49	0.10
Singapore	7.0	5389	92.0	15.7	10.2	-0.80	0.25	8.5	8.7	0.02	0.15	2.8	8.9	0.87	0.18
South Korea (2)	5.0	6018	94.7	13.3	5.8	-1.45	0.28	9.8	8.7	-0.18	0.12	8.8	11.3	0.52	0.13
Taiwan	7.0	4832	96.8	9.6	9.8	0.04	0.13	14.6	24.2	1.37	0.17	3.5	6.7	0.46	0.08
Thailand (2)	6.0	7315	77.2	8.2	11.9	0.47	0.23	7.3	10.4	0.30	0.25	11.9	16.7	0.79	0.13
Eastern Mediterranean															
Iran (2)	6.0	6065	88.4	5.4	12.0	1.14	0.11	1.5	2.2	0.12	0.05	1.1	2.0	0.13	0.05
Malta	7.0	3795	79.7	8.8	14.9	0.86	0.16	7.2	8.9	0.24	0.11	4.2	4.0	-0.03	0.07
Sultanate of Oman	6.0	4130	97.5	7.1	8.4	0.21	0.12	6.2	7.0	0.13	0.10	4.2	4.2	0.00	0.08
Indian subcontinent															
India (6)	7.5	18 877	89.4	6.2	6.8	0.06	0.17	3.2	3.9	0.05	0.08	3.0	2.4	0.00	0.07
Latin America															
Brazil	7.0	3047	68.2	21.3	24.4	0.44	0.20	12.5	12.0	-0.07	0.14	6.8	6.8	0.00	0.12
Chile (3)	7.0	9310	88.9	18.2	17.9	-0.06	0.12	8.2	12.3	0.56	0.08	10.9	12.9	0.26	0.08
Costa Rica	8.0	3234	80.9	32.1	37.6	0.69	0.20	11.6	15.9	0.54	0.14	8.7	8.9	0.02	0.09
Mexico	8.0	2579	84.3	8.6	8.4	-0.03	0.11	8.6	7.2	-0.17	0.10	4.9	4.0	-0.11	0.08
Panama	6.0	2942	92.5	23.5	22.7	-0.13	0.20	7.1	11.7	0.77	0.18	7.9	14.4	1.09	0.17
North America															
Barbados	6.0	2759	85.9	18.9	19.5	0.11	0.18	5.5	6.4	0.15	0.10	6.7	9.2	0.42	0.12
Canada	9.0	1255	63.3	14.1	18.2	0.47	0.15	8.2	10.8	0.29	0.12	8.7	12.0	0.36	0.12
Northern and eastern Europe															
Albania	5.0	2896	87.6	7.6	5.0	-0.53	0.15	4.1	3.9	-0.03	0.13	2.5	3.7	0.24	0.10
Estonia	7.0	2385	85.6	9.3	9.6	0.05	0.11	3.5	4.2	0.11	0.08	9.8	11.5	0.24	0.12
Georgia	7.0	2666	92.9	9.3	6.9	-0.34	0.14	3.9	2.8	-0.16	0.11	5.1	2.4	-0.39	0.16
Lithuania	7.0	2772	92.0	4.6	6.6	0.28	0.10	3.2	3.8	0.08	0.08	2.3	3.0	0.09	0.08
Poland (2)	7.0	4496	81.9	10.9	13.6	0.38	0.13	7.2	13.0	0.78	0.11	6.3	11.5	0.77	0.08
Russia	6.0	2730	95.2	11.1	11.4	0.05	0.17	5.6	4.7	-0.16	0.09	9.4	6.6	-0.46	0.12
Sweden	8.0	2089	63.8	10.3	10.2	-0.01	0.13	8.0	6.9	-0.14	0.12	19.5	22.3	0.35	0.18
Ukraine	4.0	1950	99.1	12.2	12.5	0.07	0.36	9.7	7.7	-0.51	0.28	6.2	5.3	-0.21	0.17
Oceania															
Australia	9.0	2968	81.9	27.2	20.0	-0.80	0.16	9.8	12.9	0.34	0.11	11.1	17.1	0.67	0.11
New Zealand (4)	9.5	10 873	85.2	23.6	22.2	-0.11	0.07	9.5	11.4	0.19	0.05	14.3	15.0	0.08	0.06
Western Europe															
Austria (2)	7.0	6876	87.8	7.8	7.4	-0.05	0.07	5.1	6.1	0.15	0.06	5.7	6.1	0.05	0.06
Belgium	7.0	5645	77.8	7.3	7.5	0.02	0.08	4.9	5.8	0.13	0.06	7.7	11.6	0.56	0.09
Germany	5.0	3830	82.4	9.6	12.8	0.65	0.17	5.4	6.9	0.30	0.12	6.7	7.9	0.23	0.12
Italy (6)	8.0	11 287	92.5	7.5	7.9	0.07	0.05	5.4	6.5	0.15	0.04	5.8	10.1	0.53	0.04
Portugal (3)	7.0	5365	65.1	13.2	12.9	-0.07	0.10	8.7	9.3	0.16	0.10	9.6	9.7	0.09	0.12
Spain (6)	7.3	18 941	77.2	6.2	9.5	0.44	0.05	5.4	7.9	0.33	0.04	3.4	5.9	0.31	0.03
UK	5.0	1843	91.9	18.4	20.9	0.50	0.30	9.8	10.1	0.05	0.24	13.0	16.0	0.60	0.28
13-14 year age-group															
Africa (English-speaking)															
Ethiopia	8.0	3195	96.8	10.7	9.1	-0.20	0.19	10.6	9.9	-0.09	0.15	19.9	19.0	-0.12	0.18
Kenya (2)	6.0	6312	99.8	13.9	15.8	0.35	0.23	14.2	21.2	0.94	0.25	10.4	15.2	0.83	0.21
Nigeria	6.0	3142	99.7	10.7	13.0	0.38	0.33	39.7	16.4	-3.88	0.69	17.7	7.7	-1.66	0.49
South Africa	7.0	5037	83.4	16.1	20.3	0.60	0.30	15.1	20.7	0.80	0.23	8.3	13.3	0.71	0.18
Africa (French-speaking)															
Algeria	6.0	4203	89.6	5.9	8.7	0.48	0.20	9.9	20.7	1.80	0.40	3.2	6.5	0.56	0.13
Morocco (2)	6.5	3466	100.0	7.8	10.4	0.00	0.31	13.1	21.6	1.12	0.41	10.7	21.8	1.72	0.26
Tunisia	5.0	3042	99.9	8.5	11.9	0.67	1.62	35.8	23.2	-2.52	0.83	8.0	9.4	0.28	0.42
Asia-Pacific															
China (2)	7.0	7044	96.7	4.3	6.0	0.24	0.10	8.1	10.4	0.33	0.10	1.2	1.4	0.05	0.03
Hong Kong	7.0	3321	99.5	12.4	8.6	-0.55	0.11	24.0	22.6	-0.21	0.32	2.7	3.3	0.08	0.07
Indonesia	6.0	2826	99.6	2.1	5.2	0.52	0.19	5.3	4.8	-0.08	0.17	1.2	2.2	0.16	0.08
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Japan	8.0	2520	94.6	13.4	13.0	-0.05	0.21	14.9	17.6	0.34	0.16	..	..	..	..
Malaysia (3)	6.3	8955	91.5	10.1	8.9	-0.13	0.15	13.9	16.2	0.53	0.20	8.9	9.9	0.19	0.17
Philippines	7.0	3658	77.5	12.3	8.4	-0.55	0.24	15.3	11.0	-0.61	0.33	5.2	7.8	0.37	0.13
Singapore	7.0	4217	93.9	9.8	11.4	0.24	0.21	15.1	16.5	0.20	0.22	7.4	9.2	0.25	0.09
South Korea (2)	5.0	10263	96.4	7.7	8.7	0.20	0.11	10.2	11.6	0.28	0.12	3.8	5.7	0.39	0.08
Taiwan	6.0	6378	95.9	5.4	7.0	0.26	0.07	11.7	17.8	1.02	0.19	1.4	4.1	0.45	0.05
Thailand (2)	6.0	8207	94.6	13.1	11.6	-0.21	0.22	15.5	21.0	0.84	0.37	8.2	9.6	0.39	0.17
Eastern Mediterranean															
Iran (2)	6.5	6123	99.8	10.9	13.2	0.17	0.21	7.5	9.8	0.31	0.16	2.6	4.4	0.30	0.09
Kuwait	6.0	2882	91.6	17.1	7.6	-1.59	0.47	12.6	10.7	-0.32	0.31	8.4	6.1	-0.38	0.26
Malta	7.0	4136	90.0	16.0	14.6	-0.20	0.18	29.0	20.9	-1.15	0.39	7.7	5.4	-0.33	0.14
Pakistan	6.0	2999	96.0	8.5	11.7	0.53	0.49	18.1	16.8	-0.22	0.51	9.6	13.2	0.61	0.37
Sultanate of Oman	6.0	3747	97.2	8.9	8.4	-0.08	0.21	11.4	15.2	0.63	0.23	4.7	7.1	0.39	0.14
Indian subcontinent															
India (8)	7.1	20767	90.6	6.7	6.4	0.02	0.14	6.3	10.0	0.43	0.14	4.3	3.7	-0.03	0.12
Latin America															
Argentina	5.0	3445	99.4	11.2	13.6	0.48	0.24	17.4	16.9	-0.09	0.36	7.4	6.3	-0.23	0.22
Brazil (5)	7.4	15681	91.5	22.7	19.9	-0.42	0.17	16.2	15.8	-0.05	0.19	5.3	4.2	-0.08	0.05
Chile (3)	6.7	9175	89.3	10.2	15.5	0.84	0.13	10.7	22.2	1.12	0.19	9.6	16.1	0.86	0.16
Costa Rica	8.0	2436	69.6	23.7	27.3	0.46	0.24	14.3	17.7	0.43	0.16	7.2	6.3	-0.11	0.11
Mexico	8.0	1431	85.9	6.6	11.6	0.63	0.13	9.4	7.1	-0.28	0.13	4.4	2.8	-0.20	0.09
Panama	6.0	3183	92.9	17.6	22.9	0.88	0.19	9.4	11.7	0.40	0.18	7.8	14.5	1.11	0.17
Paraguay	5.0	3000	99.3	19.4	20.9	0.31	0.32	34.5	45.1	2.12	0.62	10.8	17.7	1.38	0.35
Peru	6.0	3022	99.2	26.0	19.6	-1.06	0.57	19.4	18.7	-0.12	0.34	8.2	10.5	0.38	0.21
Uruguay	8.0	3177	90.8	19.0	17.9	-0.13	0.20	16.0	10.6	-0.67	0.18	7.2	5.2	-0.25	0.14
North America															
Barbados	5.0	2498	70.6	17.7	20.8	0.62	0.44	11.0	11.8	0.16	0.25	5.0	7.0	0.40	0.19
USA	8.0	2422	86.6	22.9	22.3	-0.07	0.27	13.4	19.1	0.71	0.28	8.5	8.3	-0.03	0.11
Northern and eastern Europe															
Albania	6.0	2983	86.6	2.6	3.4	0.12	0.09	4.0	5.5	0.24	0.15	0.8	2.0	0.19	0.06
Estonia	7.0	3603	93.3	8.6	9.3	0.09	0.13	4.7	6.3	0.22	0.09	6.6	8.7	0.29	0.13
Finland	7.0	3051	98.8	13.1	19.0	0.84	0.19	15.3	15.5	0.04	0.17	13.2	15.6	0.34	0.17
Georgia	7.0	2650	88.9	3.6	5.1	0.21	0.13	4.5	4.5	-0.01	0.11	2.8	1.8	-0.14	0.08
Latvia	10.0	1283	94.8	8.3	10.5	0.22	0.14	5.3	4.5	-0.08	0.07	5.2	3.4	-0.19	0.09
Lithuania	6.0	2723	90.5	8.2	6.7	-0.24	0.22	5.6	4.6	-0.17	0.15	1.7	1.8	0.02	0.07
Poland (2)	7.5	4420	90.4	7.8	10.2	0.35	0.11	8.8	18.9	1.35	0.12	5.0	8.5	0.44	0.08
Romania	7.0	3019	92.8	3.0	22.7	2.81	0.23	5.2	14.3	1.29	0.17	6.3	5.4	-0.13	0.17
Russia	6.0	3769	97.2	9.9	11.2	0.22	0.21	7.8	11.7	0.65	0.15	4.9	3.8	-0.18	0.12
Sweden	8.0	2679	81.2	12.6	9.7	-0.36	0.13	11.1	10.4	-0.09	0.15	15.8	12.9	-0.37	0.13
Ukraine	4.0	2428	98.9	12.9	20.9	2.01	0.55	11.2	11.2	-0.01	0.53	5.3	5.7	0.11	0.23
Oceania															
New Zealand (5)	9.0	13317	89.2	29.7	26.7	-0.39	0.13	19.1	18.0	-0.13	0.10	12.9	8.8	-0.44	0.08
Western Europe															
Austria	8.0	1439	86.0	11.8	15.1	0.41	0.20	9.2	9.7	0.06	0.17	5.3	7.5	0.28	0.13
Belgium	7.0	3250	96.6	12.0	8.3	-0.52	0.17	14.5	16.9	0.34	0.18	6.7	7.2	0.07	0.11
Channel Islands (2)	5.5	2021	85.1	35.1	26.5	-1.62	0.44	17.3	15.0	-0.45	0.21	17.0	11.0	-1.04	0.23
Germany	5.0	4132	93.9	14.2	17.5	0.68	0.21	14.4	15.0	0.12	0.17	7.1	7.7	0.12	0.12
Isle of Man	6.0	1716	88.7	33.4	31.2	-0.36	0.30	20.1	20.2	0.02	0.28	15.6	11.1	-0.76	0.23
Italy (9)	7.9	11192	92.3	9.4	8.4	-0.22	0.07	14.3	15.5	0.07	0.10	6.2	7.7	0.16	0.05
Portugal (4)	7.8	10630	80.3	9.5	12.0	0.32	0.09	7.0	9.5	0.40	0.08	4.4	5.1	0.16	0.05
Republic of Ireland	8.0	3089	90.9	29.1	26.7	-0.30	0.19	19.3	15.5	-0.48	0.19	13.6	8.6	-0.62	0.11
Spain (8)	7.6	26149	86.1	9.3	9.6	0.04	0.05	13.9	15.0	0.10	0.07	4.1	4.0	-0.01	0.03
UK (6)	7.3	19226	88.4	31.0	24.7	-0.71	0.14	18.9	15.3	-0.57	0.09	14.7	10.6	-0.39	0.08

Numbers of centres is one for each country, unless otherwise indicated in brackets next to country name.

Table 1: Country totals for numbers of centres and children, response rate, 12-month prevalence of asthma, allergic rhinoconjunctivitis, and eczema symptoms in both phases, average change per year, and SE of the change by age-group (full information in webtables 1 and 2)

more in prevalence of at least one disorder. For the 6–7 year age-group, two of the 64 centres recorded reductions in all three disorders, 16 recorded increases, and 45 mixed changes (one centre reported no changes). For the 13–14 year age-group, 11 of 105 centres noted decreases in all three disorders, 20 showed increases, and 74 showed mixed changes.

In the 6–7 year age-group, the prevalence of asthma symptoms changed by 1 SE or more in most centres (59%). Of the 39 centres with changes, prevalence increased in 25

and decreased in 14 (table 2), and increases occurred more often than decreases for all levels of mean prevalence. In the 13–14 year age-group, the prevalence of asthma symptoms changed by 1 SE or more in most centres (77%). Of the 82 centres with changes, about equal numbers showed an increase (42) and a decrease (40) in prevalence (table 2). For lower mean prevalence values, more centres showed increases in prevalence of 1 SE or more, but for centres with higher mean prevalence, decreases in prevalence of 1 SE or more were more common (figure 1).

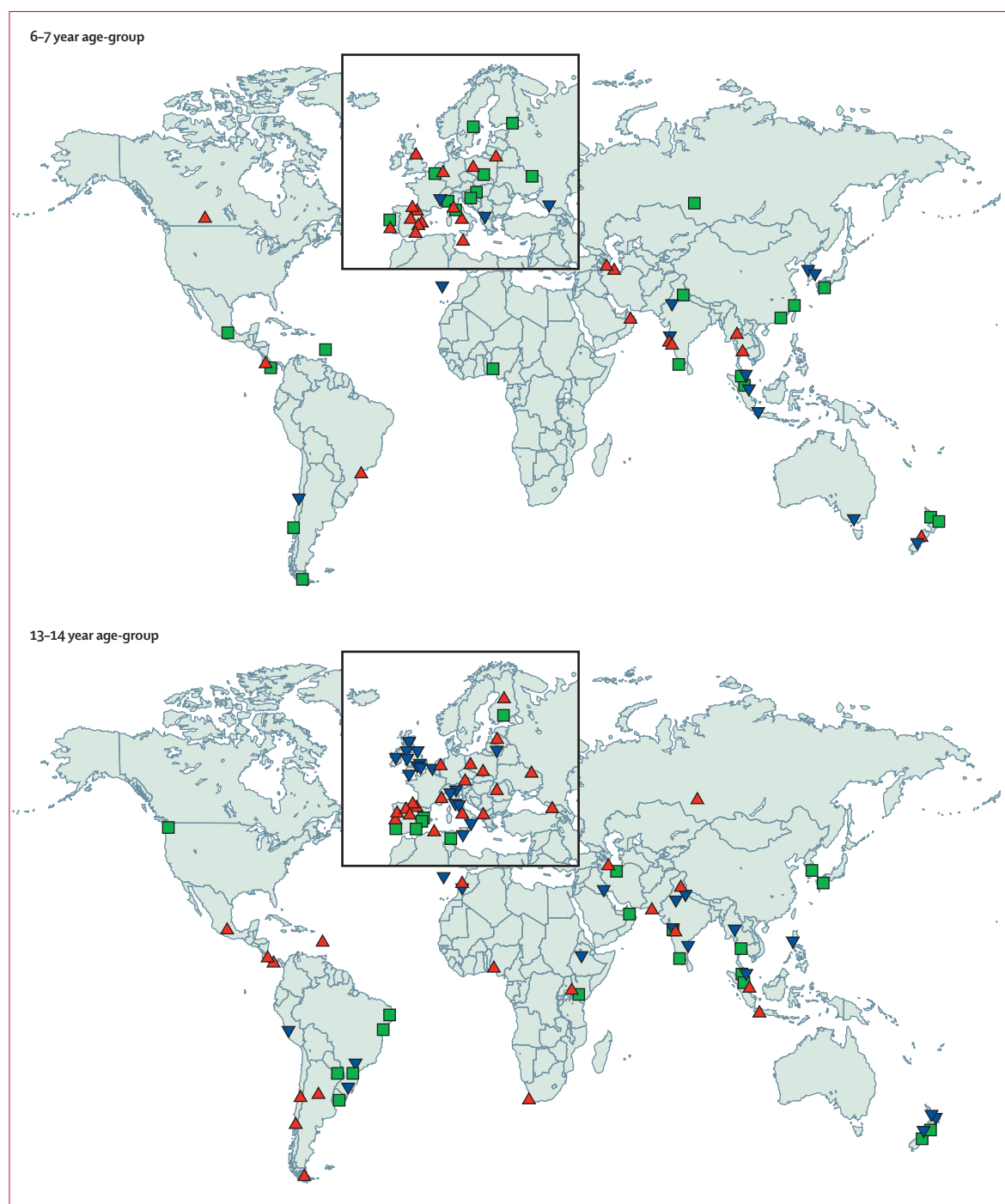


Figure 2: World map showing direction of change in prevalence of asthma symptoms for 6-7 year age-group and 13-14 year age-group
 Each symbol represents a centre. Blue triangle=prevalence reduced by ≥ 1 SE per year. Green square=little change (<1 SE). Red triangle=prevalence increased by ≥ 1 SE per year.

In the 6-7 year age-group, the prevalence of symptoms of allergic rhinoconjunctivitis changed by 1 SE or more in most centres (80%). Of the 53 centres with changes, 44 showed an increase and nine a decrease in prevalence (table 2). Prevalence increased more often than it decreased for all levels of mean prevalence. In the 13-14 year age-

group, the prevalence of allergic rhinoconjunctivitis changed by 1 SE or more in most centres (70%). Of the 74 centres with changes, 48 reported an increase and 26 a decrease in prevalence (table 2), and prevalence increased more often than it decreased for all levels of mean prevalence.

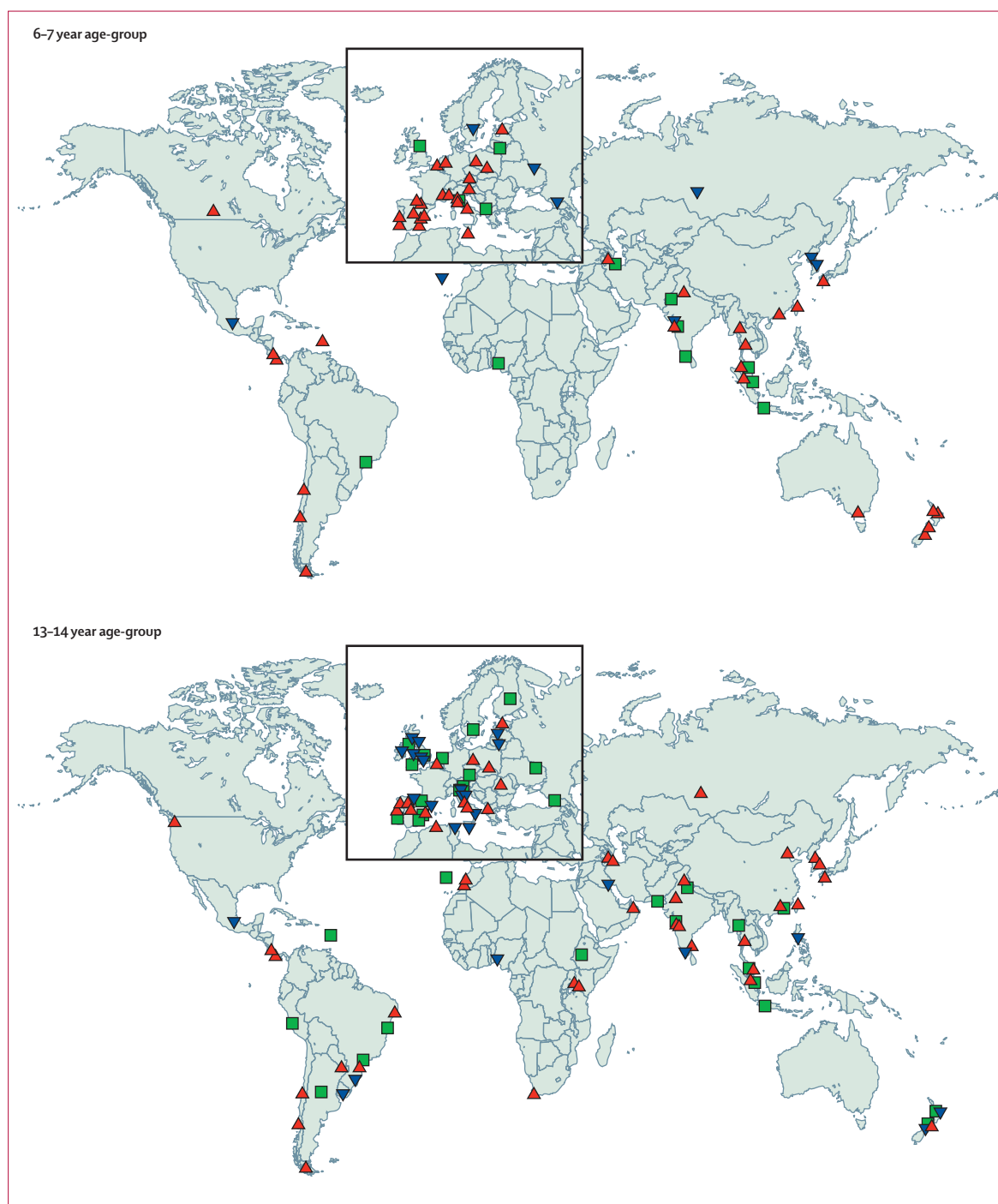


Figure 3: World map showing direction of change in prevalence of allergic rhinoconjunctivitis symptoms for 6–7 year age-group and 13–14 year age-group. Each symbol represents a centre. Blue triangle=prevalence reduced by ≥ 1 SE per year. Green square=little change (<1 SE). Red triangle=prevalence increased by ≥ 1 SE per year.

The prevalence of eczema symptoms in the 6–7 year age-group changed by 1 SE or more in most centres (81%). Of the 52 centres with changes, 44 recorded an increase and eight a decrease in prevalence (table 2), and prevalence increased more often than it decreased for all levels of mean prevalence. In the 13–14 year

age-group, prevalence of eczema symptoms changed by 1 SE or more in most centres (75%). Of the 79 centres with changes, 47 noted an increase and 32 a decrease in prevalence (table 2). For lower mean prevalence values, more centres showed increases in prevalence of 1 SE or more than showed decreases, but for centres with

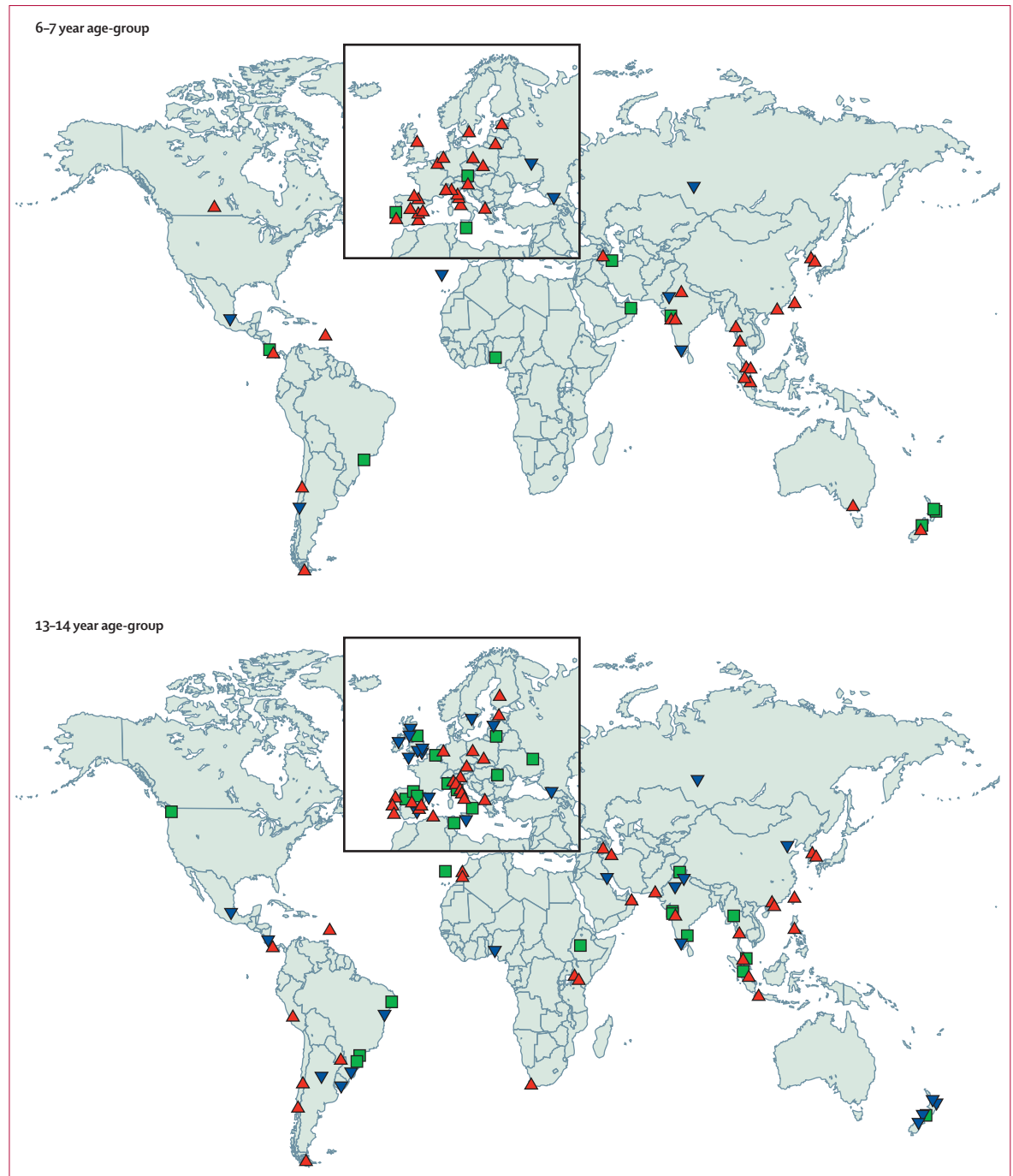


Figure 4: World map showing direction of change in prevalence of eczema symptoms for 6–7 year age-group and 13–14 year age-group
Each symbol represents a centre. Blue triangle=prevalence reduced by ≥ 1 SE per year. Green square=little change (< 1 SE). Red triangle=prevalence increased by ≥ 1 SE per year.

higher mean prevalence, there was no clear pattern (figure 1).

For all centres combined, the proportion of children with symptoms of more than one disorder rose slightly from Phase One to Phase Three. For those with all three disorders the proportion rose from 0.8 to 1.0% in the 6–7 year age-group and from 1.1 to 1.2% in the 13–14 year age-group; for

those with both asthma and allergic rhinoconjunctivitis, the proportion rose from 1.9 to 2.2% in the 6–7 year age-group and from 3.2 to 3.5% in the 13–14 year age-group; for those with both allergic rhinoconjunctivitis and eczema, the proportion rose from 0.7 to 1.1% in the 6–7 year age-group and from 1.3 to 1.5% in the 13–14 year age-group. For those with both asthma and eczema, the proportion

Region	Asthma symptoms			Allergic rhinoconjunctivitis symptoms			Eczema symptoms*			All disorders		
	Increase	Decrease	Little change	Increase	Decrease	Little change	Increase	Decrease	Little change	Increase	Decrease	Mixed or little change
6–7 year age-group												
English-speaking Africa	0	0	1	0	0	1	0	0	1	0	0	1
Asia-Pacific	2	5	5	7	2	3	10	0	0	2	0	8
Eastern Mediterranean	4	0	0	3	0	1	1	0	3	1	0	3
Indian sub continent	2	2	2	2	1	3	3	2	1	1	0	5
Latin America	2	1	4	5	1	1	3	2	2	0	0	7
North America	1	0	1	2	0	0	2	0	0	1	0	1
Northern and eastern Europe	2	2	5	3	4	2	6	3	0	1	1	7
Oceania	1	2	2	5	0	0	2	0	3	0	0	5
Western Europe	11	2	7	17	1	2	17	1	2	10	1	9
Total	25	14	27	44	9	13	44	8	12	16	2	46
13–14 year age-group												
Africa†	5	2	2	6	2	1	6	1	2	4	0	5
Asia-Pacific	6	4	5	9	1	5	10	1	3	3	0	11
Eastern Mediterranean	2	2	2	3	2	1	4	2	0	1	2	3
Indian Sub-Continent	2	4	2	5	1	2	1	3	4	1	0	7
Latin America	7	3	5	8	3	4	6	6	3	4	1	10
North America	1	0	1	1	0	1	1	0	1	0	0	2
Northern & Eastern Europe	9	2	1	6	2	4	5	4	3	3	0	9
Oceania	0	3	2	1	2	2	0	4	1	0	1	4
Western Europe	10	20	4	9	13	12	14	11	9	4	7	23
Total	42	40	24	48	26	32	47	32	26	20	11	74

Data are number. *Two centres for the 6–7 year age-group and one centre for the 13–14 year age-group were unable to provide valid eczema symptom data. †Includes English-speaking and French-speaking Africa.

Table 2: Number of centres with changes (increase ≥ 1 SE, decrease ≥ 1 SE and little change <1 SE) by region, disorder, and age-group

increased from 1.1 to 1.2% in the 6–7 year age-group, but did not change in the 13–14 year age-group (1.1%).

Discussion

We have obtained worldwide comparable population estimates of direction and size of change in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema, using identical instruments. For almost all centres, time trend data had not been previously recorded. This study included a large number of centres from around the world, and a large proportion of the centres participated in both Phase One and Phase Three, with about two-thirds of the original centres replicating the protocol and achieving high response rates. The simplicity of the study tools, design, and communication enhanced acceptability and participation.²

Clear patterns for the change in prevalence were noted. Most centres showed a change in prevalence of 1 SE or more for at least one disorder, with increases being more common than decreases, and occurring more commonly in the younger age-group than the older age-group. The changes were greatest for eczema in the younger age-group, and for allergic rhinoconjunctivitis in both age-groups. The only regions where increases in prevalence of all three disorders occurred more often in both age-groups than decreases were Asia Pacific and India. A pattern of more increases than decreases was noted for all levels of mean

prevalence, apart from in the older age-group at high prevalences, for which asthma symptoms more commonly decreased, and eczema symptoms, which showed no clear pattern.

These patterns might be a due to a greater effect of environmental change in younger people for allergic rhinoconjunctivitis and eczema, but not asthma, or a cohort effect, where an environmental change took place at a later date that affected the prevalence in the younger age-group, but not the older age-group. For example, in northern and eastern Europe, rapid environmental change took place in the 1990s (after the collapse of the communist systems) and is thus more likely to have affected the 6–7 year age-group in Phase Three than the 13–14 year age-group who were born before these changes occurred. In developing countries, wheezing seems to be less related to atopy than does allergic rhinoconjunctivitis and eczema.²¹

The variations in symptom prevalence in most regions suggests that the factors that affect these conditions vary in different locations. For example, in Latin America, several centres had high prevalence rates, similar to those in centres in some developed countries, despite large differences between socioeconomic status and living conditions in these countries,²² and showed little change over 7 years. Factors that affect asthma and allergies might act in different ways in developed countries than in developing countries, or their interaction with socio-

economic status might be important. If a single factor accounts for the changes in prevalence, it would need to have a strong effect and be prevalent worldwide,²³ but to date, such a factor has not been identified. The factors that cause variation in prevalence might differ from one location to another and from one age-group to another, and could be related to aspects of lifestyle, dietary habits, microbial exposure,²⁴ economic status, indoor or outdoor environment, climatic variation, awareness of disease, or management of symptoms. There is likely to be a constellation of environmental factors associated with the development process that relate to the worldwide changes, including loss of protective factors and addition of risk factors, and these might be different for each of the three disorders. These will be explored in the environmental analyses of ISAAC Phase Three.¹⁷

The strengths of this study include the large number of centres that participated worldwide, the use of standardised methods that were duplicated in repeat surveys and achieved high response rates, the use of disease symptoms rather than disease labels, and the completion of rigorous central methods and data checks. The time interval (mean 7 years) was probably adequate to detect changes in centres in which environmental changes might be occurring rapidly, such as in China, and to detect changes which might be occurring more slowly. We avoided the possibility of regression to the mean by using the mean prevalence when assessing the change between Phase One and Phase Three, rather than a simple plot of the difference between Phase Three and Phase One relative to the Phase One prevalence, which would give rise to correlations, even when there is no relation between the prevalences recorded in Phase One and Phase Three prevalences.²⁰ The pattern of changes in prevalence is more varied than expected on the basis of chance alone, and the heterogeneity indicates that there are many factors that influence change in disease prevalence. Apart from questionnaire responses, no objective measures of allergic diseases were obtained, but these will be examined in ISAAC Phase Two. Prevalence has been examined at two time points only, so calculation of mean yearly change cannot be interpreted with confidence as a consistent linear change during the study. The self-selection of centres, which were mainly urban, means that the centres included might not be representative of its country or region, especially for the younger age-group, for which fewer centres participated. Self-reporting of symptoms by the older children could have led to higher estimates in this group than for the younger children, whose parents' responses were recorded.

In addition to the ISAAC studies, we are aware of five other studies of trends in population prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in children and adolescents that have used similar methods. In the counties of Troms and Finnmark in Norway, divergent trends in symptom prevalence were recorded.²⁵ In centres in eastern and southwest Germany, investigators reported no change in prevalence of asthma,

hayfever, or IgE;^{21,26} whereas in another study in east Germany, prevalence of hayfever symptoms increased, but not asthma or eczema symptoms.²⁷ In Aberdeen, UK, the prevalence of asthma symptoms plateaued while the prevalence of eczema and hayfever symptoms increased.²⁸ In Ankara, Turkey, a significant fall in the cumulative prevalence of allergic rhinitis was noted, with a slight insignificant rise in asthma and eczema.²⁹ Tallinn in Estonia is the only centre included in the present study for which trends for asthma, allergic rhinoconjunctivitis, and eczema had been studied previously.³⁰ Little change was reported in prevalence of wheezing, rhinitis, and itching rash between cross-sectional studies completed in 1992–93 and 1996–97.

We have provided estimates of trends for symptoms of asthma, allergic rhinoconjunctivitis, and eczema. The data have direct relevance for health-service delivery in the countries included in the study as well as providing a basis for understanding these disorders. In almost all centres, there was a change in prevalence of one or more of the disorders over time. Although changes in mean annual prevalence to the order of 0.5% might sound small, such changes could have substantial public-health implications, especially since the increases took place most commonly in heavily populated countries. Urban centres in developing countries might have few resources to implement management programmes for these diseases in the face of overwhelming infectious diseases. However, interest from centres in developing countries in collaborating in this study shows that they are concerned that asthma and allergies in children are emerging as important public-health problems.

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All authors participated in the development, design, analysis, and interpretation of this work and in the writing of this paper.

Conflict of interest statement

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

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