Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood


In Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) time trends in the prevalence of rhinoconjunctivitis symptoms were analysed. Cross-sectional questionnaire surveys with identical protocols and questionnaires were completed a mean of 7 yr apart in two age groups comprising 498,083 children. In the 13- to 14-yr age group 106 centres in 56 countries participated, and in the 6- to 7-yr age group 66 centres in 37 countries participated. A slight worldwide increase in rhinoconjunctivitis prevalence was observed, but the variations were large among the centres and there was no consistent regional pattern. Prevalence increases in the older children exceeding 1% per year were recorded in 13 centres, including 3 of 9 centres in Africa, 2 of 15 in Asia-Pacific, 1 of 8 in India, 3 of 15 in Latin America, 3 of 9 in Eastern Europe and 1 of 34 in Western and Northern Europe. Decreasing rhinoconjunctivitis prevalence of similar magnitude was only seen in four centres. The changes were less pronounced in the 6- to 7-yr-old children and only in one centre did any change exceed 1% per year. The decrease in highest prevalence rates in ISAAC Phase I suggests that the prevalence has peaked in those regions. An increase was recorded in several centres, mostly in low and mid-income countries. The increases were more pronounced in the older age group, suggesting that environmental influences on the development of allergy may not be limited to early childhood.

The International Study of Asthma and Allergies in Childhood (ISAAC) was designed to allow comparisons of the prevalence of symptoms of asthma, rhinitis and eczema between populations in different countries (1, 2). In Phase I, children in the 13- to 14-yr age group were studied in 155 centres in 56 countries (n = 463,801), and 91 centres in 38 countries in the 6- to 7-yr age group (n = 257,601) (3–6). For the 13- to 14-yr age group, over 20-fold variations in the prevalence of self-reported rhinitis symptoms were observed between centres worldwide (range 3.2–66.6%), with a more than threefold variation observed between the 10th and 90th percentiles (13.3%, 41.5%) (5). The highest 12-month period symptom prevalence of rhinitis in 13- to 14-yr olds were from centres in Argentina (60%, 65%), Paraguay (67%), France (58%) and Brazil (55%), and the lowest from centres in Ethiopia (3%), India (3–9%) and countries in the former Soviet Union (9%, 10%). Phase II involved more intensive investigation of possible etiological factors in 9- to 11-yr-old children in 30 centres in 22 countries using
Table 1. Reported rhinitis, hay fever and rhinoconjunctivitis in 13- to 14-yr-old children for each centre by region participating both in ISAAC Phase I and Phase III. The change in reported symptoms per year is also shown.

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<th>Change per year (%)</th>
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<th>Change per year (%)</th>
<th>Hay fever ever</th>
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standardized child contact modules including examination of flexural dermatitis, skin prick testing, bronchial challenge, blood sampling and dust sampling (7).

In many of the countries participating in Phase I and Phase III, there has been little previous information on allergy prevalence and only a few, mostly industrialized affluent countries had undertaken time trends analyses. ISAAC Phase III aimed at examining time trends in the prevalence of symptoms of asthma, rhinoconjunctivitis and eczema in centres and countries which participated in Phase I (Phase III A) and at describing the prevalence and severity of these conditions in centres and countries which are of interest but did not participate in Phase I (Phase III B). Recently, worldwide trends in the prevalence of asthma, rhinoconjunctivitis and eczema were summarized (8). The present publication describes the detailed findings for time trends in the prevalence of rhinitis and conjunctivitis symptoms, as well as of perceived hay fever, in those centres that participated in both Phase I and Phase III.

Methods

The methods used in Phase III were the same as to those used in Phase I (9, 10). Briefly, two age groups of children (13- to 14-yr olds and 6- to 7-yr olds) were chosen from a randomly selected sample of schools from a defined geographic
Table 2. Reported rhinitis, hay fever and rhinoconjunctivitis in 6- to 7-yr-old children for each centre by region participating both in ISAAC Phase I and Phase III. The change in reported symptoms per year is also shown

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ISAAC global trends in rhinitis
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area. A simple questionnaire with questions related to symptoms of wheezing, rhinoconjunctivitis and eczema was completed by the older children and by parents of the younger children.

The Phase III A centres completed Phase III at least 5 yr after Phase I, and were required to conduct Phase III in the same way as Phase I (11). Questionnaires were translated if necessary from English into the local language for self-completion by the 13- to 14-yr olds and for completion by the parents of the 6- to 7-yr-old children. Respondents were asked:

1 Have you (has your child) ever had a problem with sneezing or a runny or blocked nose, when you (he or she) DID NOT have a cold or ‘the flu’?
2 In the past 12 months, have you (has your child) had a problem with sneezing or a runny or blocked nose, when you (he or she) DID NOT have a cold or ‘the flu’?
3 In the past 12 months, has this nose problem been accompanied by itchy-watery eyes?
4 In which of the past 12 months did this nose problem occur?

5 In the past 12 months, how much did this nose problem interfere with your (child’s) daily activities? (Not at all, a little, a moderate amount, a lot).
6 Have you (has your child) ever had hay fever?

This article will focus in particular on rhinitis with itchy eyes in the past year (rhinoconjunctivitis), i.e. affirmative responses to both questions 2 and 3. This combination of symptoms was selected as those which best predict allergic rhinitis (12), both in adults and children. Severe rhinoconjunctivitis was based on the combination of the two questions for rhinoconjunctivitis combined with the answer ‘a lot’ to question 5.

The data from the question concerning months of nose symptoms were excluded because of concerns regarding bias in the responses (17). Adequate documentation of the procedures for the study from each centre was a prerequisite for inclusion in publications of ISAAC worldwide results. Centres completed a Registration Document before starting the study and followed the published ISAAC Phase III Manual (10). Centres were expected to obtain ethics approval and

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parental consent according to the requirements of the country, and to fund their own study.

As in Phase I, the 13–14 yr and the 6–7 yr age groups were analyzed separately. The symptom prevalence of each condition in each centre was calculated by dividing the number of positive responses to each individual question by the number of completed questionnaires. Thus, apparent inconsistencies between responses to the stem and branch questions were accepted and not recoded. The annual change in prevalence was calculated by taking the difference between the Phase I and Phase III prevalence values and dividing by the number of years between the two surveys.

The data are presented in tabular form with the Phase I and Phase III prevalence and the annual change in prevalence for each question. For the national, regional and global summaries, the data for each centre were weighted by the number of participating children with the exception of the summary change per year values which were weighted by the inverse of the variance of the centre level change per year. The key findings are also presented as ranked change per year plots, with focus on the change in prevalence between Phase I and Phase III, rather than the absolute level of prevalence. Thus, the ranked change per year plot shows the change in prevalence of a symptom (e.g. rhinitis, current and severe rhinoconjunctivitis) for each centre by country, with countries ordered by their average prevalence (for all centres combined) across Phase I and Phase III. The average prevalence (rather than the Phase I prevalence) was used to order countries as this is statistically independent from the change in prevalence (between Phase I and Phase III) (14–16). The ranked change per year plots also show the confidence interval about zero change for a given number of participating children with the exception of the summary change per year values which were weighted by the inverse of the variance of the centre level change per year.

### Country (Prev. %)

<table>
<thead>
<tr>
<th>Country</th>
<th>Prev. %</th>
</tr>
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<tbody>
<tr>
<td>Paraguay</td>
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### Fig. 1. Ranking plot showing the change per year of symptoms of rhinitis in 13- to 14-yr-old children for each centre by country, with countries ordered by their average prevalence (for all centres combined) across Phase I and Phase III. The plot also shows the confidence interval about zero change for a given level of prevalence, given a sample size of at least 3000 and no cluster sampling effect.
level of prevalence (i.e. the average prevalence across Phase I and Phase III) given a sample size of 3000 and no cluster sampling effect.

Results

The details of the participating centres including years of data collection and response rates are listed in a separate Phase III overview paper (8). Of the centres that participated in Phase I, 106 centres from 56 countries completed the Phase III survey, thus allowing time trends analyses, with a total of 304,679 participating children in the 13- to 14-yr age group. In the 6- to 7-yr age group, 66 centres in 37 countries (a total of 193,404 children) also completed the survey and met the requirements for the time trends analyses. Data were collected within 1 yr for each centre within each Phase, but the year of study varied among centres between 1991 and 1998 (mostly 1994–95) for Phase I and between 1999 and 2004 (mostly 2002–03) for Phase III. The time period between Phase I and Phase III averaged 7 yr (range 5–10 yr).

The Phase I and Phase III prevalence rates and prevalence per year for symptoms of nose symptoms and rhinoconjunctivitis in 13- to 14-yr olds are presented by centre and country in Table 1. The symptom prevalence of rhinoconjunctivitis increased among the 13- to 14-yr-old children in 62 centres and decreased in 44 centres. The changes were mostly small and there was no consistent pattern in any of the regions. Increases exceeding 1% per year were recorded in three of nine African centres while a decrease of similar magnitude was observed in two centres. The corresponding figures for Asia-Pacific were 2 of 15 centres and no centre, respectively. In the Eastern Mediterranean region one centre showed...
a decrease of more than 1% per year. In the Indian sub-continent one of eight centres showed an increase and one a decrease. In Latin America an increase was recorded in 3 of 15 centres. In Northern and Eastern Europe, 3 of 12 centres showed an increase and no centres showed a decrease, while in Western Europe 1 of 34 centres showed a more than 1% increase and four centres, all in the UK or the Channel Islands, a decrease. No changes of this magnitude were recorded in North America or Oceania.

The findings in the 6- to 7-yr age group largely corroborated the findings in the older children, although the changes generally were smaller, with mostly small increases reported in 51 centres and small decreases reported in 15 centres (Table 2). An increase exceeding 1% per year was only observed in Taipei (Taiwan) which also reported a similar increase among the 13- to 14-yr olds (Table 1).

Figs 1 and 2 give the ranked prevalence plots for the two age groups, showing the change in prevalence of rhinitis in the last 12 months for each centre by country, with countries ordered by their average prevalence (for all centres combined) across Phase I and Phase III (c.f. Fig. 1).
However, there were a number of countries, mainly in Eastern Europe, which had a very low prevalence in Phase I and showed little evidence of an increase in Phase III. The prevalence of severe rhinoconjunctivitis in the past year increased in several centres with high prevalence in Phase I, particularly among older children.

There was a correlation (Pearson correlation coefficient $r = 0.43$, $p = 0.0005$) between changes in prevalence in the two age groups, although increases were usually more pronounced in the older children (Fig. 5). Ibadan in Nigeria was an exception with a 3.9% decrease per year in 13- to 14-yr olds and no change in the younger children.

We also analyzed possible gender differences in trends in prevalence of rhinoconjunctivitis among the 13- to 14-yr-old children. In no centre did one gender increase by 0.5% per year while the other gender decreased by this amount. In 66 (62%) of the centres girls and boys showed the same direction of change, 17 being increases by at least 0.5% per year and five being decreases of the same magnitude. There were 23 (22%) centres in which girls had increases by at least 0.5% per year or no change, while the boys had no change or a decrease respectively, and there were 17 (16%) centres in which boys increased or remained the same, while girls showed no change or decreased respectively.

Discussion

There was a slight worldwide increase in the prevalence of rhinoconjunctivitis, both in 13- to
14-yr old and 6- to 7-yr-old children, but the variations were large among the centres and there was no consistent regional pattern. Prevalence increases in the older children exceeding 1% per year were recorded in 13 centres, including 3 of 9 centres in Africa, 2 of 15 in Asia-Pacific, 1 of 8 in India, 3 of 15 in Latin America, 3 of 12 in Northern and Eastern Europe and 1 of 34 in Western Europe. Decreasing prevalence of similar magnitude was seen in four centres. The changes were less pronounced in the 6- to 7-yr-old children and only in one centre did any change exceed 1% per year.

The highest average prevalence for rhinoconjunctivitis among the 13- to 14-yr-old children was recorded in Asunción (Paraguay), Sousse (Tunisia) and Ibadan (Nigeria), and among the younger children in Taipei (Taiwan), Hong Kong and Costa Rica. It should be noted though that only one African centre and rather few centres in Latin America provided data for the 6–7 yr age group. The higher prevalence in these centres when compared with centres in Western Europe and New Zealand raise questions about the specificity of the questionnaire to identify rhinoconjunctivitis. Seasonal rhinitis and rhinoconjunctivitis in the absence of other signs of respiratory infection are strong indicators of IgE-mediated allergy in schoolchildren living in affluent countries with a temperate climate. Much less is known regarding the relationship between respiratory allergy and these symptoms in developing countries and tropical countries. Rhinitis as a single symptom on the other hand is less specific than rhinoconjunctivitis, as it is often triggered by infections, air quality and physical stimuli. This may explain the divergent outcomes for rhinitis when compared with rhinoconjunctivitis. We considered comparing peak months of rhinoconjunctivitis in the centres under the assumption that symptoms reported primarily during the pollen season would suggest allergy, while similar symptoms during the winter months would indicate infectious origin. Such comparisons between countries are reasonable and interesting in a temperate climate, as shown in a previous ISAAC study from Northern and Eastern Europe (17). This approach was not feasible, however, in a global comparison, in which many areas do not have clearly defined pollen seasons.

Over the past 40 yr, there has been a pronounced increase in the prevalence of childhood allergies in industrialized countries. This increase may not yet have peaked, not even in countries with a high prevalence, as indicated by an increase in severe rhinoconjunctivitis among 13- to 14-yr-old children in some centres which already had a high prevalence in ISAAC Phase I.

Several recent studies suggest that environmental factors encountered during the first few years of life may have a major impact on subsequently developing allergic manifestations (18). This hypothesis would have been supported by a more pronounced increase in the younger age group than among the 13–14 yr olds. That was not the case. On the contrary, in centres showing an increasing prevalence of rhinoconjunctivitis, the increasing prevalence was most
obvious in the older children. In particular, in those 13–14 yr olds in countries undergoing a rapid socio-economic transition where changes in environmental factors have been more recent. For example, the children in the older age group in the centres in Eastern Europe were born before the collapse of the socialist system, while the younger children were all born into societies with a different lifestyle, more similar to that in Western Europe. It is reasonable to suggest that the environmental impact on allergy development and induction of tolerance are not limited to the first few years of life.

In contrast to the prevalence of wheezing, English-speaking centres did not show particularly high prevalence figures for rhinitis or rhinoconjunctivitis. The high prevalence of reported wheezing may be explained by the fact that many languages lack a distinct word for ‘wheeze’. The fact that English-speaking centres did not demonstrate a correspondingly high prevalence of rhinoconjunctivitis indicates that allergies are not necessarily more common in these centres than in countries with similar environmental conditions.

In conclusion, no consistent global time trends in the prevalence of childhood rhinoconjunctivitis could be identified. A decrease was recorded in most centres with the highest prevalence rates in ISAAC Phase I, suggesting that the prevalence has peaked in those regions. In many countries undergoing rapid socio-economic development an increase was recorded. This was not more pronounced in the young age group, suggesting that environmental influences may not be limited to early childhood.

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We are grateful to the children and parents who willingly cooperated and participated in ISAAC Phases One and Three and the coordination and assistance by the school staff is sincerely appreciated. We thank the Phase One Principal Investigators and the Phase Three Principal Investigators and their colleagues, who helped make ISAAC Phase Three such a success. We would like to acknowledge and thank the many funding bodies throughout the world that supported the individual ISAAC centres and collaborators and their meetings. In particular, we wish to thank the New Zealand funding bodies, the Health Research Council of New Zealand, the Asthma and Respiratory Foundation of New Zealand, the Child Health Research Foundation, the Hawke’s Bay Medical Research Foundation, the Waikato Medical Research Foundation, Glaxo Wellcome New Zealand, the NZ Lottery Board and Astra Zeneca New Zealand. Glaxo Wellcome International Medical Affairs, supported the Regional Coordination and the ISAAC International Data Centre. Without help from all of the above, ISAAC would not have given us all these results from so many countries.

References
Appendix

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The full list of members of the ISAAC International Data Centre, ISAAC Phase Three Principal Investigators and National Coordinators is given in reference #8.