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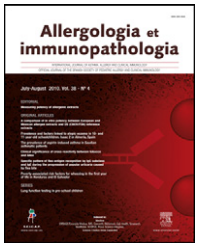

ORIGINAL ARTICLE

Changes over time in the relationship between symptoms of asthma, rhinoconjunctivitis and eczema: A global perspective from the International Study of Asthma and Allergies in Childhood (ISAAC)

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Abstract
Background: The International Study of Asthma and Allergies in Childhood (ISAAC) identified trends in the prevalence of symptoms of asthma, rhinoconjunctivitis and eczema over a seven-year period. We hypothesised that environmental influences on the three diseases are different and therefore investigated the correlation over time between trends in the prevalence of these diseases and their combinations at centre and individual level.
Methods: Centre level analyses were correlations between time trends in the prevalence of symptoms. At an individual level, odds ratios were calculated for associations between symptoms between Phases One and Three. We also investigated potential effect modification in the younger versus older age group; male versus female; and by average Gross National Income per capita (GNI).

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Results: Both phases were completed in 66 centres in 37 countries for the 6–7 year age group and in 106 centres in 56 countries for the 13–14 year age group. We found that the correlations in time trends were stronger for the older age group than the younger one. Between symptoms of diseases, correlations of time trends were the strongest for rhinoconjunctivitis with eczema and weakest for eczema with asthma. The relationship between the three diseases was generally consistent over the seven-year period, and there was little association found with average GNI.
Conclusions: Despite some increase in the proportion of children with symptoms of asthma, rhinoconjunctivitis and eczema, the pattern between the three diseases has not changed much, suggesting that similar factors may be affecting them at a global level.

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 world scale of the problem and the factors affecting prevalence.[1] ISAAC Phase One found large variations in the prevalence of symptoms of asthma,[2] rhinoconjunctivitis[3] and eczema.[4] In ISAAC Phase Three time trends in these diseases were examined a mean of seven years after Phase One.[5–7] Most centres showed a change $\geq$1 standard error (SE) in prevalence of at least one condition, with increases being twice as common as decreases, and increases more common in the 6–7 year olds than 13–14 year olds.[8]

We hypothesised that environmental influences on asthma, rhinoconjunctivitis and eczema are different and therefore the changes in prevalence over time would vary in an inconsistent manner for each of these diseases – the null hypothesis being that they would remain in the same relationship with each other. In this paper the relationship between trends in prevalence of symptoms of asthma, rhinoconjunctivitis and eczema and combinations of symptoms are examined at centre level, along with combinations of these symptoms at individual level to answer the question 'Do worldwide symptoms of asthma, rhinoconjunctivitis and eczema show the same time trends?' We also examined whether the relationship between the three diseases within individuals changed over time for the whole population.

Materials and methods

ISAAC Phase Three is a multi-centre multi-country cross-sectional study of two age groups of school children (13–14 year olds and 6–7 year olds) chosen from a sample of schools in a defined geographical area. The study instruments are simple standardised questionnaires with questions on symptoms of asthma, rhinitis and eczema. Each Phase Three centre conducted the study in the same way as Phase One to ensure comparable trend data. The details of the study design and methods are described elsewhere.[9] Centres obtained ethics approval. This paper reports on those centres which completed an ISAAC Phase Three study 5–10 years after completing Phase One in which the methodology met the ISAAC quality control standards. Only centres which completed both Phase One and Phase Three studies and submitted data for asthma, rhinitis and eczema are the subjects of this paper.

Answers to written questions were reported by parents of children (6–7 years) and self-reported by adolescents (13–14 years). In this paper current symptoms of asthma were estimated from positive answers to the written question ''Have you (Has your child) had wheezing or whistling in the chest in the past 12 months?''. Symptoms of severe asthma were defined as those with current wheeze who in the past 12 months have had >4 attacks of wheeze, or >1 night per week sleep disturbance from wheeze, or wheeze affecting speech. Current symptoms of rhinoconjunctivitis were estimated by 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?''. The answer ''a lot'' to this question: ''In the past 12 months, how much did this nose problem interfere with your (child's) daily activities?'' was used to assess the prevalence of severe rhinoconjunctivitis symptoms. Current symptoms of eczema were estimated by positive answers to these questions: ''Have you (Has your child) ever had this itchy rash at any time in the past 12 months?'' (this question was preceded by the question ''Have you (Has your child) ever had an itchy skin rash which was coming and going for at least 6 months?'') and if yes: ''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?''. Current eczema associated with sleep disturbance one or more nights per week was used as a surrogate of severe eczema.

The data analyses were of three types. Firstly correlations of time trends in each disease were examined at centre level. An estimate of the average absolute rate of change per year of prevalence of symptoms of asthma, rhinoconjunctivitis and eczema was derived for each centre. Weighted correlations of time trends for each condition with each other condition were calculated for each age group. The weights were the average of the inverse of the variance of rate of change in prevalence. Secondly, we examined the inter-relationship between the three diseases at an individual level, across all centres combined. This was illustrated by scaled rectangle diagrams of the prevalence of combinations of current symptoms in all the participating children for each age group for Phases One and Three. We also examined the relationship of each of the diseases with each other disease separately in Phase One (ORPh1) and in Phase Three (ORPh3) (shown in Web Tables 1 and 2). Each association was measured by the odds of symptoms of one disease given the symptom status of another disease. Thirdly to investigate potential changes in associations between the