

Capitolo 17

SIDRIA in the international context SIDRIA nel contesto internazionale

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ISAAC

The International Study of Asthma and Allergies in Childhood (ISAAC) was founded to maximise the value of epidemiological research into asthma, allergic rhinoconjunctivitis and atopic eczema through facilitating international collaboration.^{1,2} Although epidemiological research has the potential to add to our understanding of these conditions, previous studies have lacked standardisation in case-definition and methodology, thus limiting the value of spatial and temporal comparisons of the prevalence of these disorders. The ISAAC programme, comprising three phases, was designed to allow comparisons of the prevalence of these disorders between populations in different countries, thereby forming the basis for studies investigating the role of possible modifiable environmental factors that may ultimately lead to a reduction in the personal burden of these diseases.

In **Phase I**, children in the 13-14 year old age-group were studied in 155 centres in 56 countries (n. 463,801), and the 6-7 year old age-group were studied in 91 centres in 38 countries.³⁻⁶ Up to 20-fold variations in the prevalence of self-reported asthma symptoms were observed between centres worldwide (range 1.8% to 36.7%), with a 7-fold variation observed between the 10th and 90th percentiles (4.4%, 30.9%). The highest 12-month period prevalences were from centres in the United Kingdom, Australia, New Zealand, and the Republic of Ireland, followed by some centres from North, Central and South America; the lowest prevalences were from centres in Eastern Europe, Greece, China, Taiwan, Uzbekistan, India, Indonesia and Ethiopia.

Phase II involved more intensive investigation of possible aetiological factors in 9-11 year old children in 30 centres in 22 countries.⁷

Phase III⁸ has involved repeating the Phase I survey to:

- examine time trends in the prevalence of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries which participated in Phase I;
- describe the prevalence and severity of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries which are of interest but did not participate in Phase I;
- examine hypotheses at an individual level which have been suggested by the findings of Phase I, subsequent ecological analyses and recent advances in knowledge.

Of the 155 centres that participated in Phase I, 99 centres in 51 countries completed the Phase III survey and met the requirements for analysis, with a total of 284,799 participating children

in the 13-14 year age-group; 52 centres in 31 countries (a total of 164,090 children) also completed the video questionnaires in 13-14 year old children; 63 centres in 34 countries (a total of 188,413 children) also completed the survey and met the requirements for analysis for the 6-7 year age-group. However, as noted above, Phase III also involved new centres that had not conducted the Phase I survey, and the overall Phase III study has involved more than one million children and adolescents in 280 centres in 100 countries. The global Phase III publications are currently in preparation.

SIDRIA

The SIDRIA studies adopted the standardised ISAAC methodology to investigate the prevalence and causes of symptoms of asthma, rhinitis and eczema in Italy. The first phase of SIDRIA was carried out between October 1994 and May 1995 in ten Italian areas;^{9,10} it included 18,737 6-7 year old children (response rate 96.3%) and 21,846 adolescents (response rate 96.2%). The second phase of SIDRIA (corresponding to Phase III of ISAAC) was carried out in 8 of the previous areas, and in five additional areas, between January and May 2002;¹¹ it included 20,016 children (response rate 89%) and 16,175 adolescents (response rate 93%).

The basic prevalence findings^{3,4} show that Italy has an intermediate level of symptom prevalence. For example, the prevalence of current asthma symptoms («wheezing in the last 12 months») in 13-14 year old children was 9.8% which places Italy in the third prevalence quartile internationally with a prevalence considerably lower than that in English speaking European countries (the United Kingdom, the Republic of Ireland and Malta), and also lower than Germany, France, Sweden, Belgium, Austria, Estonia, Spain and Portugal, but higher than Latvia, Poland, Russia, Greece, Georgia, Romania and Albania.

However, although asthma symptom prevalence is relatively low in Italy, the ISAAC study findings nevertheless show that asthma, rhinitis and eczema represent a considerable public health problem in Italy. This public health burden was previously unrecognised, since most cases of asthma are not diagnosed and treated. The increase in lifetime asthma between SIDRIA-1 and SIDRIA-2 may therefore reflect increased public and physician awareness of the condition, which may in part be due to the conduct of SIDRIA itself.¹¹

In addition to demonstrating the important public health burden of asthma, rhinitis and eczema in Italy, the SIDRIA findings

are of considerable scientific importance both in Italy and internationally. SIDRIA-1 involved 10 centres, which was the greatest number of centres in a single country with the exception of the United Kingdom and India.^{3,4} It showed that there was considerable regional variation in symptom prevalence within Italy, a finding which is of importance internationally because regional comparisons within Italy are less likely to be affected by differences in language than are the international comparisons. This finding therefore requires further research into the causes of these regional differences.

A further, and perhaps more important, reason for the scientific importance of the SIDRIA findings is that SIDRIA represents the instance where risk factors information was collected in both Phases of the study. When the ISAAC study was created, it was decided that the Phase I would involve simple prevalence comparisons, using standard symptom questionnaires, in order that the methodology could be standardised on a global basis, and the study conducted in as many regions and countries as possible. Although it was considered desirable to also collect information on environmental exposures in ISAAC Phase I, it was considered to be too difficult to collect such information in a standardised manner on a global basis. It was therefore decided to leave the collection of risk factor information to Phases II and III. However, the ISAAC methodology was deliberately made as flexible and simple as possible, not only to ensure that the study was conducted in as many countries as possible, but also to encourage regions and centres to collect additional information that was not included in the core questionnaires.

The largest example of this approach is the SIDRIA study where, in addition to the information in basic ISAAC core questionnaires, a large amount of additional information on asthma symptoms and asthma risk factors was collected in a standardised manner across the Italian centres in both SIDRIA-1 (i.e. ISAAC Phase I) and SIDRIA-2 (i.e. ISAAC Phase III). It thus represents the largest example, in terms of both the number of centres and the numbers of children and adolescents, where it has been possible to collect both symptom prevalence information and risk factor information in both phases of the study. This means that not only can changes in symptom prevalence be assessed over time; changes in risk factors can also be assessed over time. The SIDRIA findings are therefore of considerable interest internationally, as well as being of major importance for investigating the prevalence and causes of symptoms of asthma, rhinitis and eczema in Italy. The findings are of interest not only for what they show, but also for what they do not show. For example, there has been little change in the prevalence of asthma symptoms, but a marked increase in diagnosed asthma, and in symptoms of allergic rhinitis and atopic eczema.¹¹ The disjunction between the trends for symptom prevalence for asthma, rhinitis and eczema, is consistent with other evidence that asthma is not simply 'an atopic disease' and that a substantial proportion of asthma cases involve non-allergic mechanisms.¹²⁻¹⁴

A number of risk factors have been investigated in the SIDRIA

study, and the findings are generally consistent with those from studies in other countries. For example, the findings of a lower prevalence of asthma associated with being born outside of Italy, having siblings, attending day care early in life, and having a cat have all been reported in previous studies in other countries.^{15,16} Similarly the findings of a greater prevalence in children with an increased Body Mass Index (BMI), or exposed to parental smoking, or indoor moulds have also been reported from other countries.^{15,16} The consistency of these findings with those of other studies therefore supports the validity of the SIDRIA study findings. However, the SIDRIA study was also able to assess time trends in these risk factors and has shown rapid changes in the socio-demographic characteristics of Italian society, including increases in the percentage of children born abroad, parental educational level, maternal age at pregnancy, maternal employment, breast feeding, child day care use, and exposure to car traffic, while there have been decreases in parental smoking. Despite these substantial social changes, the increase in asthma symptom changes has «levelled off» while the prevalence of symptoms of allergic rhinitis and atopic eczema has continued to increase.¹¹

Conclusions

What do these findings tell us? As with the global ISAAC findings, perhaps they tell us more about what we do not know, than what we do know. Ten years ago we 'knew' what caused asthma, and we knew how to prevent it. At least in Anglophone countries, asthma was an atopic disease caused by allergen exposure. The fundamental aetiological mechanism was that allergen exposure, particularly in infancy, produced atopic sensitization and continued exposure resulted in asthma through the development of eosinophilic airways inflammation, bronchial hyper-responsiveness and reversible airflow obstruction. Asthma prevalence was increasing around the world because of changes in lifestyle and domestic building design that were increasing allergen exposure. In recent years it has become increasingly evident that this picture is, at best, too simplistic and does not explain the international patterns of asthma prevalence revealed by the ISAAC study.¹⁶ The striking increases in asthma prevalence globally cannot be primarily due to genetic factors, since they are occurring too rapidly, and therefore they must be occurring due to changes in environmental exposures. It seems that as a result of this «package» of changes in the intrauterine and infant environment, we are seeing an increased susceptibility to the development of asthma and/or allergy. There are a number of elements of this «package» including changes in maternal diet, increased fetal growth, smaller family size, reduced infant infections and increased use of antibiotics and immunization. All of these have been (inconsistently) associated with an increased risk of childhood asthma, but as the SIDRIA findings show, none of these factors can alone explain the increases in prevalence.¹⁶ It is likely that the «package» is more than the sum of its parts, and that these social and environmental changes are all pushing infants' immune systems in the same direction. To know what that direction is, and which components

of the «package» are responsible, requires that better etiologic theories of asthma are developed. Furthermore, it requires that epidemiologists rigorously test these new theories systematically in population-based studies, rather than the *ad hoc* and anecdotal approach that has been adopted in the past with respect to studies of the allergen hypothesis. Epidemiology has played a major role in calling the established theory of asthma causation into question. It also has a major role to play in developing and testing new etiologic theories of asthma causation. The SIDRIA study is making a major contribution in this respect, because of the large number of centres involved within Italy, the considerable regional variation, and the large amount of information that has been collected on the prevalence of various asthma risk factors, the changes in their prevalence over time, and their relation to changes in the prevalence of symptoms of asthma, rhinitis and eczema.

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