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The International Study of Asthma and Allergies in Childhood (ISAAC): Phase Three rationale and methods

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SUMMARY

The International Study of Asthma and Allergies in Childhood (ISAAC) programme commenced in 1991 to study the aetiology of asthma, allergic rhinoconjunctivitis and atopic eczema in children in different populations using standardised methodology and facilitating international collaboration.

ISAAC Phase One (1992–1996) found marked differences in the prevalence of symptoms of asthma and allergic disease throughout the world which have not been explained by the current understanding of these diseases. ISAAC Phase Two (1998–2004) uses intensive investigations to further examine the potential role of risk and protective factors that may contribute to the international difference observed in Phase One. Phase Three (2000–2003) essentially represents a repeat of Phase One, in which more detailed standardised data are obtained to enable the time trends of symptom prevalence to be determined as well as the development of a more comprehensive 'world map'.

The ISAAC Phase Three rationale and methods are described in this paper. With over 280 centres in 106 countries, we anticipate that ISAAC Phase Three will comprehensively determine the prevalence of symptoms of asthma and allergic disease worldwide, explore recent time trends in the prevalence of these symptoms and cast new light on the aetiology of asthma and allergic disease.

KEY WORDS: asthma; allergic rhinoconjunctivitis; atopic eczema; epidemiology; ISAAC

THE International Study of Asthma and Allergies in Childhood (ISAAC)¶ was developed to investigate childhood asthma, allergic rhinoconjunctivitis and atopic eczema at the population level. ISAAC has attracted worldwide interest and large-scale participation, facilitating international collaboration.

ISAAC Phase One involved over 700 000 children of two age groups, 13–14 years and 6–7 years, from 156 centres in 56 countries. ISAAC Phase One aims were achieved by 1997 with four key worldwide publications.[1–4] The Phase One manual details the development, scientific background, aims and methods.[5]

ISAAC Phase One demonstrated that there are large variations in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema throughout the world (differences of between 20-fold and 60-fold between centres).[1–4] Perhaps more importantly, it showed that the international patterns of disease prevalence cannot be explained by the current understanding of the aetiology of these conditions. A consistent finding in Phase One was the marked differences in asthma prevalence in populations with similar genetic or ethnic backgrounds,[6] suggesting that environmental factors in the broadest sense are the major determinants of the prevalence of asthma in a community.

Ecological analyses using Phase One data found weak positive associations with economic development[7] and dietary *trans* fatty acids[8] for all three diseases, while negative associations were found for tuberculosis[9,10] and greater plant intake in the diet.[11] In contrast, no clear associations with pollen,[12] immunisations,[13] tobacco,[14] climate[15] or antibiotics[16] were shown. These findings suggest that the protective effects of dietary factors (consumption of cereals, starch and vegetables) and exposure to infection (tuberculosis) are worthy of further exploration.

ISAAC Phase Two, in progress in 36 centres in 22 countries, uses intensive investigations to further examine the potential role of protective and risk factors that may contribute to the international differences observed in Phase One. The rationale and methods of Phase Two are described elsewhere.[17]

ISAAC Phase Three was developed to use the potential of the ISAAC study design to learn more about the aetiology of asthma, allergic rhinoconjunctivitis

§ See Appendix

¶ http://isaac.auckland.ac.nz

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and atopic eczema. In Phase Three, standardised prevalence data are collected in a manner identical to Phase One, allowing the time trends of symptom prevalence to be determined as well as a more comprehensive 'world map'. This paper describes the methodology used for ISAAC Phase Three and will be the basis for the worldwide papers to follow.

ISAAC PHASE THREE AIMS

1 To examine time trends in the prevalence of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries that participated in ISAAC Phase One.
2 To describe the prevalence and severity of asthma, allergic rhinoconjunctivitis and atopic eczema in centres and countries that did and did not participate in ISAAC Phase One.
3 To examine hypotheses at an individual level which have been suggested by the findings of ISAAC Phase One, subsequent ecological analyses and recent advances in knowledge.

RESEARCH DESIGN AND METHODS

ISAAC Phase Three is a multicentre cross-sectional study of schoolchildren in defined geographical areas involving the same age groups as in Phase One: 13–14 year olds (adolescents) and 6–7 year olds (children). The design is the same as that used in Phase One[5,18] and is outlined, together with the methods, in the Phase Three manual.[19] Each centre has a Principal Investigator (PI) and a National Coordinator. The ISAAC Steering Committee (SC) is made up of Regional Coordinators from the 10 regions, a five-member executive and nine committee members. The SC communicates regularly with the PIs, National Coordinators and the ISAAC International Data Centre (IIDC) in Auckland, New Zealand.

Classification of Phase Three centres

Phase Three A centres completed Phase One by the end of 1997, and are participating in Phase Three. The Phase Three A centres will provide symptom prevalence data, for the three conditions, for the worldwide time trends analyses. There are 116 registered Phase Three A centres (Figure). Phase Three A centres undertake Phase Three the same way as they conducted Phase One, using the same sampling frame, age groups, target sample size, selection of children, questionnaire, translation from English (if applicable) and time of year for data collection. The methodological details for the Phase One centres are archived at the IIDC. Phase Three B centres are centres from around the world that did not participate in ISAAC Phase One but are participating in Phase Three. There are 168 registered Phase Three B centres. Phase Three B centres proceed as for Phase One, following the instructions in the Phase Three manual for all new participating centres. Both groups (Phase Three A and B centres) will provide symptom prevalence data, for the three conditions, for the worldwide publications, providing a more comprehensive Phase Three 'world map'.

Subjects and selection

The compulsory age group is the 13–14-year-old adolescents who self complete the questionnaire. The 6–7-year-old children's group is optional; they take the questionnaire home for parental/guardian completion. Schools are the sampling units with a minimum of 10 schools randomly selected per centre (or all schools used). Students are selected depending on the local situation, either by grade/level/year, where the classes with most children in the age group are selected, or by age group, where only the children in the age group (regardless of grade/level/year) are selected.

ISAAC Phase Three questionnaires

Demographic questions

The demographic questions on the front page collect data on the participant's name, age, birth date, school, sex and date of interview. These details are validated using school records. Questionnaires are coded using a unique number for centre, school and participant to ensure anonymity. Where comparisons between ethnic groups are planned, the census of populations ethnicity question for the country is used, if it exists.

Core written questionnaires

The same standardised core questionnaires developed for use in Phase One are used. Questions on symptoms of asthma, allergic rhinoconjunctivitis and atopic eczema include both sensitive and specific questions which are repeatable and have good content, construct and concurrent and predictive validity.[5]

Video asthma questionnaire

An international clinical asthma video questionnaire, recommended for the adolescents, was developed and used in Phase One in response to possible translation problems with the written questionnaires, and obviated the need to describe symptoms verbally. The written and video questions have been compared for their prediction of bronchial hyper-responsiveness in different ethnic groups.[20–25]

Environmental questionnaire

An environmental questionnaire (EQ) for each age group has been developed by the ISAAC SC for optional use in Phase Three. It includes questions about diet, height, weight, heating and cooking fuels, exercise, pets, family size and birth order, socio-economic status, immigration and tobacco smoke exposure. The children's EQ is more comprehensive, as questions

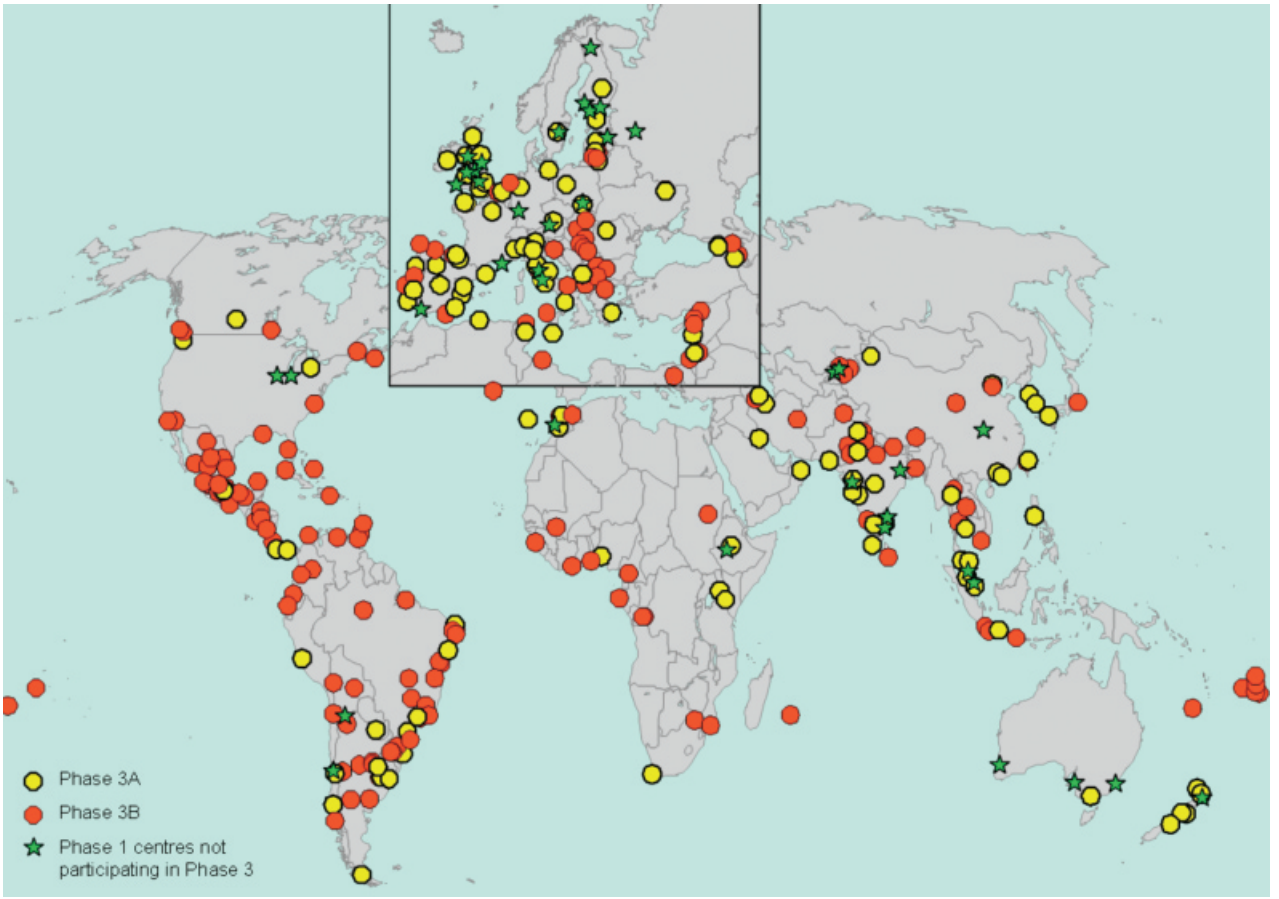

Figure World map of ISAAC centres, showing the participating Phase Three A centres (yellow circles), Phase Three B centres (red circles) and ISAAC Phase One centres not participating in Phase Three (green stars).

that concern early life events or other issues that adolescents could not reasonably be expected to know accurately have been omitted from the adolescents' EQ. Validated questions were sought in an extensive literature review and used where available. Because the ISAAC context is unique in studying children in a wide range of world environments, validated questions were not available for all factors or for all possible environments. The SC adapted questions or used questions from the ISAAC Phase Two risk factor questionnaire where necessary. The EQ was piloted in New Zealand, Latin America, French-speaking Africa and the Asia-Pacific regions, and appropriate modifications were made. The hypotheses and question source and the EQ for both age groups are available on the ISAAC website.*

Translation of written questionnaires

The translation of written questionnaires in non-English speaking countries is a key issue for the validity of comparisons. Translations were required to have the same structure and logic as the English language questionnaire, they had to be back translated into English by an independent translator and copies were archived at the IIDC. Translations must be able to be understood by adolescents and parents, using lay rather than medical language.[26] Translation guidelines have been developed and included in the Phase Three manual.[19]

Sample size and power considerations

A sample size of 3000 participants per age group was recommended. For the Phase Three A centre time trend analyses, this sample size enables detection of annual changes in prevalence in symptoms of ±0.3–0.7% at 5% levels of significance with a power of 90% over the range of prevalences in ISAAC centres. This calculation is based on previous time trend studies of asthma symptoms within countries which have reported a median annual change in prevalence of current wheeze of 0.76%[27–30] and of asthma of 0.45%.[28,30–44] For both Phase Three A and B centres this sample size enables detection of differences in prevalence of wheezing of 30% in one centre and 25% in another centre, with a study power to detect this difference of 99% at the 1% level of significance. If the true one-year prevalence of severe asthma is 5%

* http://isaac.auckland.ac.nz/Phasethr/EnvrQeust/EQFrame.html

in one centre and 3% in another centre with a sample size of 3000, the study power to detect this difference will be 90% at the 1% level of significance.[5] As sampling is done by school, while the information is gained from the school pupils, there is likely to be a cluster effect. The sample sizes given above are sufficiently large to allow good power in the presence of moderate intra-cluster correlations. Centres unable to obtain 3000 participants are included provided they fulfil the criteria described in the Phase Three manual.[19]

Time period

The time period between the Phase One and Phase Three data collection is at least 5 years, with 85% of Phase Three studies occurring 6–8 years after Phase One. This is short enough to detect changes in centres where environmental changes may be occurring rapidly, as in low prevalence countries such as China, but not too short for centres where environmental changes may be occurring more slowly, as in high prevalence countries such as New Zealand and the USA. In practice, the ISAAC Phase Three data collection took place in 2000–2003.

Season of data collection

Phase Three A centres collect the data at the same time of year as for the Phase One data. For Phase Three B centres, at least half of the study population is being investigated before the main pollen season of the study area. The season-of-response has been shown to affect questions on allergic rhinoconjunctivitis, but not asthma or atopic eczema.[45]

Non-participation

A participation rate of at least 90% among pupils is sought. The mean participation in ISAAC Phase One was 91% for adolescents and 87% for children, and it is anticipated that a similar level will be achieved in Phase Three. Because of concerns that pupils may be absent because of asthma or allergies, the questionnaire for the parents of the children is issued several times to encourage participation. If the participation rate is below 90% for the adolescents, a second visit is carried out to include those that were absent on the first visit.

Quality control

Copies of the Phase Three manual and the international version of the video were widely circulated. The manual includes a registration document; relevant sections of the Phase One manual; comprehensive instructions for the Phase Three A and B centres; the ISAAC questionnaires; translation guidelines for the written questionnaires; field worker guidelines for the written and video questionnaires; a coding and data transfer section; a draft Centre Report (CR), and instructions for completion.

Other resources prepared for PIs and available on the ISAAC website include the core questionnaires in Microsoft Word and PDF formats; the EQ in Microsoft Word and PDF; instructions for use of the EQ; field worker guidelines for the EQ; a coding and data transfer document for the EQ; a CR in Microsoft Word format; and Epi Info based data entry packages.

Centre report

Particular importance is attached to the quality of the data collection and procedures in ISAAC to ensure confidence in the results. Centres register with the IIDC, and a CR is generated and sent to each PI, who completes and returns it when the data are submitted. The CR provides a detailed account of the research methodology, especially focusing on quality indicators. The IIDC examines the CR for internal consistency and accuracy to confirm that the responses in the report are consistent with the data, and PIs are asked to explain any variations from protocol. Questions include the definition of the sampling frame; time of year of data collection; details of ethical approval; the method of sampling schools and children; response and participation rates; data entry; the method of translating questionnaires into other language(s) if appropriate; and questions regarding the video (for the adolescents). The Phase One CR form was evaluated in 1998 in four regions of the world, and a revised Phase Three CR was subsequently produced and circulated (P Ellwood, unpublished).

Data handling

Field workers are asked to check the questionnaires at the time of conducting the survey. Any obvious errors with the demographic data are corrected by obtaining the information from the schools, and any changes are documented. No alteration to the symptom and EQ data is allowed, and this information is entered on to the computer exactly as it is presented on the questionnaire, with anonymity of subjects preserved and unmodified data sent to the IIDC. A method of limiting data entry errors, such as double entry, is required. Each centre is responsible for its own data coding and entry. Once received by the IIDC, data are stored on a computer with the necessary statistical analysis capabilities, and a copy of the data is kept off site in a protected environment.

Data checking

Data are submitted to the IIDC as detailed in the Phase Three Manual.[19] Demographic data are checked for omissions, plausibility and inconsistencies. Symptom and EQ data are checked for consistency with the coding schedule, and collaborators are asked to explain any deviations from protocol. It is common for one or two revisions of the data to be submitted during the data checking process.

Footnotes

On completion of the centre data and methodology checking process, any deviations from protocol are examined carefully by the SC. Centre data are included in the analyses and subsequent publications provided the deviation from protocol is not severe enough for exclusion of the centre. Protocol violations in centres that are accepted for inclusion are footnoted in the tables of the publications. This follows the same principle as used in the Phase One publications.[1–4]

Ownership of data, ethics, dissemination of results and structure of ISAAC

Each centre owns their data. All publications and communications involving worldwide comparisons will have a writing group 'and the ISAAC Phase Three Study Group'. This group, comprising all SC members, Regional Coordinators, National Coordinators, PIs and the IIDC, will be consulted on the papers in preparation and acknowledged appropriately in the papers, as occurred in Phase One. Each centre is required to obtain approval from their local ethics committee before the start of the study.

CONCLUSION

We anticipate that ISAAC Phase Three will comprehensively determine the prevalence of symptoms of asthma and allergic disease worldwide, explore recent time trends in these symptoms and cast new light on the aetiology of asthma and allergic disease. It is anticipated that 1.2 million children and adolescents from 286 centres in 106 countries will participate in Phase Three.

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APPENDIX

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RÉSUMÉ

Le programme de l'Etude Internationale de l'Asthme et des Allergies chez l'Enfant (ISAAC) a commencé en 1991 et a visé à étudier l'étiologie de l'asthme, de la rhinoconjonctivite allergique et de l'eczéma atopique chez les enfants dans diverses populations en utilisant une méthodologie standardisée et facilitant une collaboration internationale.

La Phase Un ISAAC (1992–1996) a mis en évidence des différences marquées dans la prévalence des symptômes d'asthme et de maladie allergique dans le monde, différences qui n'ont pas été expliquées par nos connaissances actuelles de ces maladies. La Phase Deux ISAAC (1998–2004) recourt à des investigations intensives pour examiner davantage le rôle potentiel de facteurs de risque ou de protection qui pourraient contribuer aux différences internationales observées dans la Phase Un. La Phase Trois (2000–2003) représente essentiellement une répétition de la Phase Un, dans laquelle des données standardisées plus détaillées ont été obtenues pour permettre de déterminer les tendances évolutives de la prévalence des symptômes ainsi que l'élaboration d'une carte mondiale plus complète.

Les justifications et les méthodes de la Phase Trois ISAAC sont décrites dans cet article. Nous nous attendons à ce que la Phase Trois ISAAC puisse déterminer de façon complète, grâce à plus de 280 centres dans 106 pays, la prévalence des symptômes d'asthme et de maladie allergique au niveau mondial et explorer les tendances évolutives récentes de la prévalence de ces symptômes et à ce qu'elle apporte des éclaircissements sur l'étiologie de l'asthme et de la maladie allergique.

RESUMEN

En 1991, el Estudio Internacional de Asma y Alergias en la Infancia (ISAAC) comenzó el análisis de la etiología del asma, de la rinoconjuntivitis alérgica y del eccema atópico en niños en diferentes poblaciones, utilizando métodos estandarizados y promoviendo la colaboración internacional.

En la Fase Uno del ISAAC (1992–1996) se encontraron diferencias significativas en la prevalencia de los síntomas del asma y de la enfermedad alérgica en diferentes partes del mundo, las cuales no podían explicarse con los conocimientos existentes sobre estas enfermedades. En la Fase Dos del ISAAC (1998–2004) se llevaron a cabo investigaciones exhaustivas para analizar mejor el papel posible de los factores de riesgo y de los factores protectores que podrían contribuir a las diferencias observadas entre los diferentes países en la Fase Uno. La Fase Tres (2000–2003) consiste esencialmente en una repetición de la Fase Uno, en la cual se obtienen datos normalizados más detallados con el fin de determinar la tendencia temporal de la prevalencia de los síntomas y la elaboración de un 'mapa mundial' más completo.

En el presente artículo se describen el fundamento y los métodos de la Fase Tres del ISAAC. Para la Fase Tres del ISAAC se cuenta con más de 280 centros en 106 países y se espera determinar en forma pormenorizada la prevalencia mundial de los síntomas del asma y de la enfermedad alérgica, analizar las recientes tendencias temporales en la prevalencia de estos síntomas y arrojar nuevas luces sobre la etiología del asma y de la enfermedad alérgica.