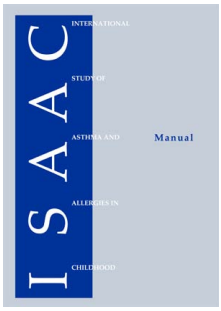
The ISAAC Story

ISAAC Resources

Phase One Manual
Phase One Data Manual
Video Questionnaire
Phase Two Modules
Phase Two Data Manual
Phase Two Skin Exam Manual
Phase Three Manual
Phase Three EQ Data Manual
Phase Three Environmental Questionnaire 6-7
Phase Three Environmental Questionnaire 13-14
Phase Four Website

All of the above resources are available on the ISAAC website at http://isaac.auckland.ac.nz/resources/tools.php



Phase One methods

Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, Mitchell EA, Pearce N, Sibbald B, Stewart AW, Strachan D, Weiland SK, Williams HC. *International study of asthma and allergies in childhood (ISAAC): rationale and methods*. Eur Respir J 1995; 8: 483-91.

ISAAC Methodology

ISAAC Phase One was an international multi-centre cross-sectional study involving two age groups of school children, 13-14 year olds (adolescents) and 6-7 year olds (children). Schools were randomly selected from a defined geographical area. Written questionnaires on asthma, rhinitis and eczema symptoms (translated from English) were completed by the adolescents at school, and at home by the parents of the children. An asthma symptoms video questionnaire for the adolescents was optional.

ISAAC Phase Two involved more intensive studies in a smaller number of selected centres. Children aged 9-11 years were examined for flexural dermatitis, underwent skin prick tests for atopy, bronchial responsiveness to hypertonic saline, blood sampling and storage for serum IgE and genetic analyses, and additional questionnaires were completed by their parents.

ISAAC Phase Three, a repeat of Phase One after at least five years, examined variations in time trends of childhood asthma, rhinoconjunctivitis and eczema around the world, and expanded the world maps of these conditions. Additional questions on risk factors were included in an “environmental questionnaire”.

ISAAC Phase Four is the development and expansion of the scope of the ISAAC website as a resource for ISAAC collaborators. It includes the addition of management plans that are useful for managing asthma, eczema, and rhinitis.

ISAAC methods and field manuals are freely available for use in other surveys, provided they adhere to the ISAAC publication policy on the ISAAC website (http://isaac.auckland.ac.nz/publications/publicationspolicy.html) and reference the use of the ISAAC tools appropriately.

Phase One Methodology

ISAAC Phase One was a multi-centre multi-country cross sectional study involving 2 age groups of school children, 13-14 year old (adolescents) and 6-7 year old.(children) Schools were randomly selected from a defined geographical area. Written questionnaires on asthma, rhinitis and eczema symptoms (translated from English) were completed by the adolescents at school, and at home by the parents of the children. An asthma symptoms video questionnaire for the adolescents was optional. A sample size of 3000 per age group was used to give sufficient power (90% at a 1% significance level), and a high participation rate was a requirement. In Phase One over 700,000 children were involved. Field work was conducted in the majority of centres between 1994 and 1995. Data was then sent to the International Data Centre in Auckland, New Zealand, where the methodology was checked and the data analysed.

Phase One used simple core written questionnaires for two age groups, and was completed in 156 collaborating centres in 56 countries with a total of 721,601 children participating. In the 13-14 year age group 155 centres from 56 countries participated, of which 99 centres completed a video questionnaire. For the 6-7 year age group there were 91 collaborating centres in 38 countries. ISAAC Phase One demonstrated a large variation in the prevalence of asthma symptoms in children throughout the world including hitherto unstudied populations. It is likely that environmental factors were responsible for the major differences between countries. The results provided a framework for studies between populations in contrasting environments to pursue new clues about the aetiology of asthma. Ecological studies were undertaken using the Phase One data to develop hypotheses about environmental factors.

Fuller details of Phase One are published in thePhase One Manual and in a paper in the European Respiratory Journal.

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Phase Two Methodology

ISAAC Phase Two involved more intensive studies in a smaller number of selected centres. It began in 1998 and involved 30 centres in 22 countries with 53,383 children participating. Phase Two was designed to investigate the relative importance of hypotheses of interest that arose from the Phase One results. Phase Two enabled internationally standardised comparisons of disease and relevant risk factors using the modules developed by ISAAC collaborators. The sample sizes were smaller than those recommended for Phase One to reflect the more intensive sampling procedures. A sample size of 1000 children per centre was recommended, and the more expensive and invasive tests could optionally be restricted to a stratified sample, comprising a sample of 100 wheezy children and 100 non-wheezy children.

Phase Two measured features of asthma, rhinoconjunctivitis and eczema which were not measured in Phase One. Additional standardised questions about cough, and the medical care of asthma, rhinitis and eczema were also developed. In addition there was a management and a "risk factor" questionnaire. Standardised protocols were also developed for child contact instruments including physical examination of the skin for flexural dermatitis and airway responsiveness testing using hypertonic saline aerosol challenge, skin prick tests for atopy, total and specific serum IgE, and storage of blood samples for genetic analyses and gene-environment interactions and endotoxin and house dust mite antigen measurement in the homes. The bronchial hyperresponsiveness measurement and skin examination were used to see whether these measures showed the same distribution internationally as the questionnaire results for wheeze and atopic eczema. Measures of atopy (using allergen skin tests and IgE measurements) were used to investigate whether variations in symptoms of asthma, rhinoconjunctivitis and eczema are reflected in variations in atopy. Some Phase Two centres also contributed DNA samples which were analysed for both within ISAAC, and as part of a larger asthma genetics consortium, GABRIEL.

ISAAC Phase Two was undertaken in 19 centres from 13 European countries: Albania, Estonia, France, Germany (2 centres), Greece (2 centres), Iceland, Italy, Latvia, Netherlands, Norway, Spain (4 centres), Sweden (2 centres) and the United Kingdom. The 11 centres outside Europe are in 9 countries: Brazil, China (3 centres), Ecuador, Georgia, Ghana, India, New Zealand, Turkey and Palestine.

Fuller details of Phase Two are published in the Phase Two Manual and in a paper in the European Respiratory Journal.

Phase Three Methodology

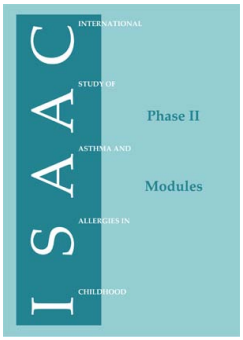
ISAAC Phase Three, a repeat of Phase One after at least five years, examined variations in time trends of childhood asthma, rhinoconjunctivitis and eczema around the world, and expanded the world maps of these conditions. New centres which did not do Phase One were included in the enlarged worldwide prevalence maps, and a risk factor questionnaire was added, permitting analysis of associations between the three diseases and a range of biomedical, environmental and lifestyle factors.

Phase Three was completed in 237 collaborating centres in 98 countries with a total of 1,187,496 children participating. In the 13-14 year age group 233 centres from 97 countries participated. For the 6-7 year age group there were 144 collaborating centres in 61 countries. The design of Phase Three corresponded to the Phase One study design. The same sampling frame, method of selecting schools and method of selecting children within schools was used.

The Phase Three field work was conducted during 2001-2. The time period between Phase One and Phase Three data collection was designed to be at least five years. This was chosen to be short enough to detect changes in centres where environmental changes may occur rapidly, as in low prevalence countries such as Greece and China, but not too short for centres where environmental changes may occur more slowly, as in high prevalence countries such as New Zealand and USA. 85% of centres conducted Phase Three 6-8 years after Phase One.

The risk factor questionnaire asked questions about diet, height, weight, heating and cooking fuels, exercise, pets, family size and birth order, socioeconomic status, immigration and tobacco smoke exposure. It was an optional component of the study design, so it was not completed in all centres.

Fuller details of Phase Three are published in the Phase Three Manual and in a paper in the International Journal of Tuberculosis and Lung Disease.

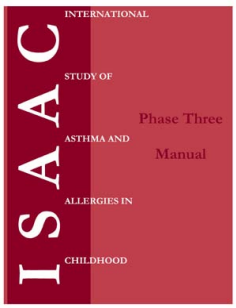


Phase Two methods

Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP, and the ISAAC Phase Two Study Group. *Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods.* Eur Respir J 2004; 24(3): 406-12.

Weiland SK, von Mutius E, Keil U, on behalf of the ISAAC Steering Committee. *The International Study of Asthma and Allergies in Childhood (ISAAC): rational methods and outlook.* Allergologie 1999; 22(5):275-282.

von Mutius E, Weiland SK, Keil U and the ISAAC Steering Committee. *The International Study of Asthma and Allergies in Childhood (ISAAC): study design and methods of phase II.* Allergologie 1999; 22(5):283-288.

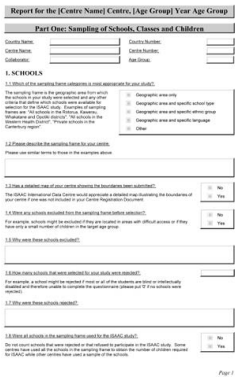


Phase Three methods

Ellwood P, Asher MI, Beasley R, Clayton TO, Stewart AW, and the ISAAC Steering Committee. *The International Study of Asthma and Allergies in Childhood (ISAAC): Phase Three rationale and methods.* Int J Tuberc Lung Dis 2005; 9(1): 10-6.

The ISAAC Story

Centre Reports


Report for the [Centre Name] Centre, [Age Group] Year Age Group

Part One: Sampling of Schools, Classes and Children

The Centre Report Documents can be viewed at http://isaac.auckland.ac.nz/phases/phasethree/centre report/centrereport.html

Quality Assurance

In ISAAC Phases One and Three, tools were developed to assist the ISAAC International Data Centre (IIDC) Research Manager to undertake quality assurance processes.

In ISAAC Phase One, to enable centre methodology to be checked, the Steering Committee developed a five page centre report . This was sent to the Principal Investigators (PI's) when they submitted their centre data to the IIDC which they completed and sent back. This documented aspects of the fieldwork and centre methodology, which were considered important to record and enabled checks to be made against aspects of the data. Close communication with the PI's was vital whilst undertaking the checks.

When the ISAAC Phase One data and methodology checks had been completed, the centre report was evaluated by several Steering Committee members to ensure it was suitable for use in Phase Three, particularly for those with English as a second language. The evaluation identified that some areas of the report were difficult to interpret. Subsequently the report was redesigned for use in Phase Three. The Phase Three centre report retained the same information but simplified the questions and in some cases a single question was changed and became several questions to ensure its meaning would be understood. Collaborators found this new Phase Three centre report an easier document to complete .

In addition, this report was sent to the PI's at the time they registered, so that they could complete it when the fieldwork was being undertaken rather than completing it retrospectively as in Phase One. For the centres that were new to Phase Three, the centre report enabled checks to be made against the data as in Phase One. For the Phase Three centres that had also completed Phase One, the Phase Three centre report was checked against the Phase One centre report to ensure PI's had used the same methodology as in Phase One. All deviations between Phase One and Three were documented and these were categorised: major deviations (centres excluded from the analyses); minor deviations (deviations identified by the use of footnotes in the published tables) and; very minor deviations (deviations accepted and not identified in the publication tables).

This information has been collated and a manuscript on "The challenge in replicating the methodology between Phase One and Three of ISAAC" will be submitted for publication in April 2011. From the 112 centre reports for the adolescent group (13-14 year olds) and 70 for the children (6-7 year olds) that were submitted, six centres for the adolescent group and four for the children had major deviations and were excluded. There were 35 minor deviations for the adolescents and 20 for the children which were identified in the publications by the use of a footnote and there were 92 very minor deviation for the adolescents and 51 for the children that were accepted and not identified. We also found that a change in PI between phases did not adversely affect the methodology (odds ratios 0.80 [95% CI 0.36, 1.81] for adolescents and 0.91 [95% CI 0.32, 2.62] for children).

We concluded that with attention to detail and careful recording of methodology, repeated, cross-sectional, epidemiological multicentre studies using the same methodology such as Phases One and Three in ISAAC are feasible and can be achieved throughout the world by people with diverse cultural backgrounds and research experience. The IIDC is very appreciative of the commitment of the ISAAC collaboration to their attention to detail which has produced such a high standard of methodology in Phase One and Phase Three.

Consent & Confidentiality

At the outset of ISAAC Phase One, a great deal of importance was placed on protecting the identity of the participants and deciding on the most appropriate method of obtaining consent. As well as maintaining confidentiality of the information given by the participants a high response rate was expected (= 80% for adolescents and =70% for children). In Phase One most centres had an ethics committee that viewed and approved the protocol prior to starting the study. Those centres that did not have an ethics committee used some other authorisation, such as the Ministry of Education to approve the study.

Although identifying information was obtained from the participants, this demographic information was only used to ensure participant details were correct and was checked against the school records for accuracy. The questions asked for the participant's name and school name, their age, date of birth, gender, home address, ethnicity and the date the questionnaire was completed. When these details had been certified correct the participant became identified by a unique ID number by centre number, school number, and participant number. These numbers were entered into the computer with the answers to the core questions on the symptom prevalence of asthma, rhinitis and eczema, providing total anonymity of participants.

Because of this anonymity and due to the innocuous nature of the questions asking about the symptom prevalence of asthma, rhinitis and eczema, most ethics committees approved the use of passive consent. This approach was also the recommended approach by the ISAAC Steering Committee. This involved, for the adolescent group, sending an information letter home to the parents informing them about the study and requesting they contact the

Consent & Confidentiality cont.

researcher/s if they or the adolescent did not wish to participate. If they did not contact the researcher it was assumed they would take part in the study. For the children, the questionnaire was sent home to parents/guardians with the information letter requesting them to complete it and return it to school. Some ethics committees requested active consent from parents/guardians which involved getting parents/guardians to give written consent prior to the study taking place in the schools for the adolescents and for the children, prior to sending the questionnaire home for completion.

In Phase Three we found that some ethics committees had made a huge shift in their approach to how consent was obtained in research and developed new policies for using active consent for all types of research, whether it was clinical trials, or epidemiological surveys. This had an adverse effect on the response rates in some schools and participants, resulting in exclusions from Phase Three. This has been documented in a publication [Ellwood 2010](above right). We found that a higher response rate in questionnaire-based epidemiological studies is more likely if parents are not required to give active consent. This was more evident in the English language centres that had been used to the passive consent approach for this type of study. It also raises questions about the ethics of using active consent when it is not strictly necessary, which can lead to low response rates and exclusion, thus wasting valuable research funding and denying the involvement of those parents/adolescents that wish to participate.

Data Management

(Tadd Clayton)

ISAAC is a unique international study which has been extremely fortunate to receive enthusiastic support from many researchers (and their research teams) throughout the world. Use of the same research design and tools (e.g. questionnaires) by all participating centres has been essential so that the results from the centres can be compared and any differences can be considered to reflect true differences in prevalence, rather than be attributed to differences in methodology. The ISAAC Phase One Manual, Phase One Coding and Data Transfer Manual, Phase Three Manual and Phase Three Environmental Questionnaire Coding and Data Transfer Document provided detailed instructions regarding how to carry out an ISAAC study, and how to prepare the data for transfer to the ISAAC International Data Centre (IIDC).

However, as ISAAC Phase One and Phase Three data has been contributed by many researchers who naturally have very varied training and research experience, it was important for the IIDC to carry out quality assurance checks on the data and assess how well each centre had followed the ISAAC protocol. My role at the IIDC was to receive the Phase One and Phase Three data from the participating centres, carry out a range of quality assurance checks on the data and communicate with the researchers with the aim of achieving the best quality possible final data set for each centre. For most centres there was at least one revised version of the data and in some cases several revisions were necessary. The checks carried out on the data included checks for consistency of date of birth, age and date of interview, checks for invalid values, and checks for unexpected patterns of results.

Checks for consistency

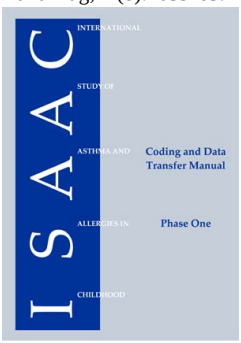
The ISAAC Phase One and Phase Three questionnaires included questions about the date the questionnaire was completed (date of interview), date of birth and current age of the child or adolescent. It was thus possible to generate a calculated age (using the date of birth and date of interview) and compare this with the age provided by the parent or adolescent. In many cases where there were differences between the age and the calculated age, the researchers were able to consult school records to identify appropriate corrections.

Checks for invalid values

The Phase One Coding and Data Transfer Manual (hyperlink), Phase Three Manual (hyperlink) and Phase Three Environmental Questionnaire Coding and Data Transfer Document (hyperlink) provide detailed information concerning what codes or values are valid for each question. In cases where unexpected values were present, the researcher was asked to review the original questionnaire and identify the appropriate correction.

Phase Three Consent

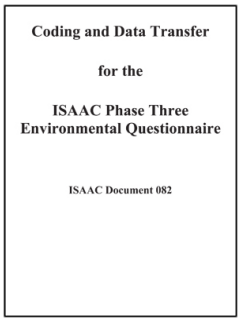
Ellwood P, Asher MI, Stewart AW and the ISAAC Phase III Study Group. *The impact of the method of consent on response rates in the ISAAC time trends study.* Int J Tuberc Lung Dis. 2010 Aug;14(8):1059-65.




ISAAC Phase II

Coding and Data Transfer Manual

ISAAC Phase II Coordinating and Data Centre (I2-CDC)
Muenster/Ulm, Germany
October 2000
written by Dr. Peter Rzehak


Coding and Data Transfer

for the

ISAAC Phase Three Environmental Questionnaire

ISAAC Document 082

Checks for unexpected patterns

The ISAAC Phase One and Phase Three core questionnaires use a "stem" and "branch" structure where it is intended that the participant would only answer some questions if they provided a positive response to the previous questions. An example of this is the first two questions of the asthma symptoms questionnaire:

1. Has your child / Have you ever had wheezing or whistling in the chest at any time in the past? Yes/No
   IF YOU HAVE ANSWERED "NO" PLEASE SKIP TO QUESTION 6
2. Has your child / Have you had wheezing or whistling in the chest in the past 12 months? Yes/No

If all parents or adolescents correctly followed the instruction between these questions, there would be no respondents who answered "No" for question 1 and "Yes" for question 2. After all, how can someone have wheezing in the last 12 months but not have wheezing at any time in their life? However, in practice we found that the data sets from nearly all centres have some children or adolescents where there are responses which appear to be inconsistent. For example, in Auckland, New Zealand for Phase Three there are approximately 5% of children and 10% of adolescents who have at least one case of responses which appear to be inconsistent.

Given that some parents and adolescents will provide responses which appear to be inconsistent, we had to decide what (if anything) to do about these cases. It is very easy to manipulate data using modern statistical analysis software and we could easily recode the data so that question 2 is set to missing. In other words, we would assume that the answer to question 1 ("No") is correct and that the response to question 2 should be blank as suggested by the instruction between the questions. However, in this example there are two questions and it is easily possible (perhaps equally as likely) that it is question 2 which is correct and question 1 which is incorrect. The ISAAC Steering Committee decided that there is not enough information to accurately decide which response is incorrect and that to recode the data based on the assumption that the first response is correct would run the risk of introducing bias into the data. The data was therefore left unchanged and cases where the responses appear to be inconsistent were accepted. This did not cause any problems for ISAAC analyses where the focus was on the prevalence of individual symptoms and the common denominator for prevalence calculations was the total number of participants.

However some of the data sent to the IIDC did not include any cases of response which appeared to be inconsistent. This suggested that the data may have been modified to remove the inconsistencies between responses before it was sent to the IIDC. For these centres we asked the researcher whether the data had been modified and whether it was possible for them to submit a copy of the data without the modification. Some centres were able to provide unmodified data while others were not, usually because the changes had been made during the data entry process. Several centres were identified as having modified the data to remove apparent inconsistencies in the data tables for Phase One and Phase Three publications.

Transfer of data

The IIDC has been receiving data files and other electronic files from researchers and colleagues since 1993 and there have been many changes in technology during that time. Most Phase One data files were sent to the IIDC by post on 3½ inch diskette although a few centres did use CD-ROMs and some even used 5¼ inch floppy disks. Email was not in common use at the time and it was very rare to receive data files as attachments to messages. By the time of Phase Three, email was available for nearly all of the researchers and it was much more common for to receive data by email although I did still receive some data by post on CD-ROM.

The Phase One Coding and Data Transfer Manual, Phase Three Manual and Phase Three Environmental Questionnaire Coding and Data Transfer Document provided very clear, detailed instructions regarding how ISAAC data should be prepared for transfer to the IIDC. The time and effort put into these documents proved to be very worthwhile and I would particularly like to acknowledge the efforts of Alistair Stewart who lead the development of the Phase One Coding and Data Transfer Manual which was the model for the subsequent documents. Nearly all the data files received by the IIDC used the structure and codes we specified. In only a few cases was it necessary to ask the researcher to send a further copy of the data, generally because there had been some damage to the files in transit. While most data used the expected structure there were occasionally some challenges in reading the data. Perhaps the most interesting challenge I encountered was to identify a way to convert dates from the Persian calendar to the Gregorian calendar.

For Phase One, most data was sent to the IIDC as text format data files as specified in the Coding and Data Transfer Manual although a few researchers did choose to use other formats such as Excel spreadsheet files or DBASE database files. For Phase Three, Excel files were much more common, and other formats such as SPSS and Access were also used on occasion. We were fortunate that the software resources available to us through The University of Auckland were sufficient to read all file formats we received throughout Phase One and Phase Three.

Statistical Analyses

Statistical methods used in ISAAC: Phase One

The two age groups (6 & 7 years and 13 & 14 years) were analysed separately. Symptom prevalences in each centre were calculated by dividing the number of positive responses to each question by the number of completed questionnaires for the written and video questionnaires separately. Thus, apparent inconsistencies between responses to the stem and branch questions were accepted and not recoded. Country and regional level prevalence estimates were calculated in the same manner. All the positive responses within the country (or region) were divided by the number of completed questionnaires from the same geographical area.

The main variables reported are defined as:

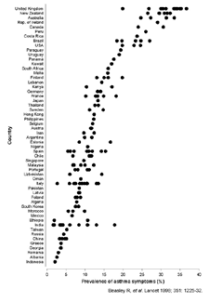
- Wheeze: “Have you/your child had wheezing or whistling in the chest in the last 12 months?”
- Severe wheeze: “Have you/your child had wheezing or whistling in the chest in the last 12 months?” and one of “4 or more attacks of wheeze” or “sleep been disturbed due to wheezing on average once or more per week” or “had wheezing severe enough to limit speech to only one or two words at a time between breaths”.
- Reported asthma: “Have you/your child ever had asthma?”
- Rhinoconjunctivitis: “In the past 12 months, have you had a problem with sneezing, or a runny, or a blocked nose when you DID NOT have a cold or the flu? If yes: in the past 12 months, has this nose problem been accompanied by itchy-watery eyes?”
- Hay Fever ever: “Have you/your child ever had hayfever?”
- Eczema: “Have you ever had an itchy rash which was coming and going for at least 6 months? If yes: Have you had this itchy rash at any time in the last 12 months? 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?”
- Reported eczema: “Have you/your child ever had eczema?”

In centres where a random sample of schools was taken, the effect of cluster sampling by schools was examined calculating the design effects [Rao 1992]. The effects of cluster sampling were generally small but have been incorporated in analyses involving tests of significance.

Basic descriptive summaries of the data were compiled by centre and country, in both age groups, along with Spearman correlations between variables. These summaries have often been displayed as ranked plots (see example right). A variety of analytic methods have been used in papers, some are described below.

The within-country and between-country variances were estimated using a generalised linear mixed model in which country, and centre within country, are random effects [Wolfinger 1993]. With this model, the ratio of the 95% CI of prevalences (between country to within country) were calculated.

Ranked Plot



Statistical methods used in ISAAC: Phase Two

Definitions for the key outcome variables in Phase Two followed the conventions set in Phase One. Sample sizes in most of the Phase Two centres were smaller than in Phase One, typically in the region of 1000 children, so clustering at the level of school within centres was not considered in the analysis.

An important feature of the Phase Two design was the restriction of more expensive or invasive measurements to a subsample of children within each centre, selected according to history of wheezing in the last year. This stratified sampling design required statistical analyses for many of the variables to be weighted (using “survey weights” inversely proportional to the sampling fractions for wheezers and non-wheezers). The SAS procedures SURVEYREG and SURVEYLOGISTIC were used for this purpose (in Stata, svy: commands perform the same survey-weighted analysis).

The general approach adopted for Phase Two data analysis was to fit separate models for each centre and then pool the resulting regression coefficients in a random-effects meta-analysis. The random-effects pooling allowed for possible heterogeneity of risk factor associations between centres. In many analyses, a separate pooling within two groups of centres (more affluent, and less affluent, defined by national GNI per capita) proved to be informative.

This two-step approach to analysis of risk factor associations in Phase Two contrasts with the single-step approach adopted in Phase Three, where a fixed-effect pooling of regression coefficients was implemented along with random centre-level intercepts, using PROC GLIMMIX in SAS. Such a single-step approach could not be implemented for many of the outcomes in Phase Two, since the necessary survey-weighted regression cannot be combined

with the multi-level model structure within PROC GLIMMIX.

However, for Phase Two outcomes which were ascertained on all subjects, multi-level models were developed in SAS (PROC GLIMMIX) and Stata (xtmelogit) to explore random effects both for intercepts (ie. centre-level prevalences) and slopes (ie. risk factor associations).

Statistical methods used in ISAAC: Phase Three prevalence maps and time trend analyses

The approaches used for global comparisons of prevalence in Phase Three followed those adopted in Phase One. However, for analysis of time trends between Phase One and Phase Three a number of additional statistical issues arose:

- Whether to use absolute or relative change in prevalence: the former was chosen.
- Calculation of change per year to address the variable time period between studies.
- Use of mean prevalence (average of Phase One and Phase Three), rather than Phase One prevalence, to assess change in relation to prevalence. This followed the approach of Bland and Altman which avoids the problem of "regression to the mean" leading to a spurious correlation between initial level of a measurement and change over time.
- Adjustment for the cluster sample design by adjustment to the effective sample size of the prevalence estimates. Since most centres selected a sample of schools and then studied all children of the eligible age within those schools, there is a theoretical "design effect" due to the greater correlation of asthma and allergy prevalence within schools than between schools. This "design effect" was accounted for in analyses which involved significance tests by decreasing the sample size of each prevalence estimate by a factor derived for each outcome, centre, age-group and ISAAC phase, representing the effective sample size, relative to the actual sample size, adjusting for clustering at the school level. In most centres, the effect of this adjustment was small.
- Tolerance of minor differences in fieldwork procedures between Phase One and Phase Three. This is discussed in greater detail under "Quality Assurance"

Statistical methods used in ISAAC: Phase Three risk factor analyses

Outcome definition and assessment of within-centre clustering followed the conventions set in the prevalence comparisons. For each outcome, centre and age-group, a single design-effect-adjustment variable was generated, representing the effective sample size for that age-group, centre and outcome. This set of design-effect adjustment factors was derived before merging in the risk factor (EQ) data, so it is a common set for all Phase Three risk factor analyses.

Centres with fewer than 500 children (except for centres representing a complete census of the population), and centres with more than 30% missing data for the risk factor and covariates of interest, were excluded from the analysis. Frequency tabulations of the outcome, risk factor of interest, and specified individual-level covariates were prepared for each centre and combined into a single dataset for each outcome and age group. The frequency counts were then adjusted downwards in proportion to the design-effect adjustment factors for the outcome in question, for each centre and age group.

These design-effect-adjusted frequency tabulations provided the input for SAS DATA/PROC... (conversion procedure to individual-level data? – equivalent procedure in Stata is "expand") and were analysed in PROC GLIMMIX specifying random intercepts at the centre level, but common slopes for the individual-level risk factors and covariates. Region, language and GNI per capita were included as standard centre-level covariates. Sex was always included as an individual-level covariate. Analyses were performed for all centres combined, for subgroups of centres defined by region, language and GNI, and for boys and girls separately. Additional individual-level covariates and interactions were included in the models, as appropriate for specific risk factor analyses.

Statistical methods used in ISAAC: Centre-level differences adjusted for individual-level risk factors

Two approaches have been used for investigating between-centre differences in prevalence, adjusting for individual-level risk factors. The first approach is analogous to direct standardisation of routine statistics such as national mortality rates. The second applies multi-level modelling techniques to evaluate simultaneously the associations at the individual and the centre level.

Direct standardisation:

1. Separate regression models are fitted for each study centre, to obtain centre-specific slopes for each explanatory (x-)variable. Since the main outcomes of interest are dichotomous, our outcome (y-)variable is logit(p) where p is the proportion of "cases" (affected individuals). Thus, the parameter estimates from these centre-specific models are in the form of log-odds-ratios and the linear predictions derived from them ("xb" in SAS/Stata terminology) are in the form of log-prevalence-odds: ln[p/(1-p)].
2. For each centre, a prediction (xb) and its standard error (stdp) is derived at the level of each explanatory variable which correponds to its mean in the global (all-centres) dataset. (This is analogous to directly standardising centre-specific death rates for each age-sex group by applying them to a global distribution of age and sex).
3. The standardised (risk-factor-adjusted) prevalence logodds for each centre, and their corresponding variances, can then be considered as units in a conventional meta-analysis, deriving measures of heterogeneity including Cochran's Q and Higgins I^2. They can also be used as the outcome variable in ecological analyses of disease prevalence at the centre level.

Multi-level modelling:

1. All centres are modelled in a single dataset with an categorical indicator variable for each centre and centre-level covariates (such as language, or GNI per capita) match-merged by centre.
2. Multi-level modelling procedures such as PROC GLIMMIX in SAS, and xtmelogit in Stata, offer options for analysing either the centre-level intercepts, or the centre-specific risk factor associations (regression slopes), or both, as “random effects” (ie. drawn from a hypothetical distribution of intercepts or slopes, with the usual assumption being that this distribution is Gaussian).
3. The approach used in Phase Three risk factor analyses specified random intercepts and common slopes. This is equivalent to a fixed-effect (inverse-variance-weighted) pooling of the risk factor associations across study centres.
4. The approach used in exploratory Phase Two analyses specifies random intercepts and random slopes.
5. The two-step meta-analytical approach used in standard Phase Two publications is broadly equivalent to fixed centre-level intercepts and random slopes.

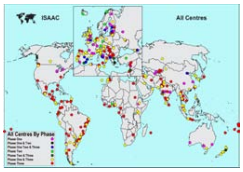
Statistical methods used in ISAAC: Ecological analyses at the centre level

A series of ISAAC papers were based on ecological data (data gleaned from external sources). These papers correlated the prevalence rates observed in ISAAC centres or countries with information available elsewhere. An example was the relationship of the prevalence levels to the per capita gross national product (GNP) for each of the countries. The GNP information came from the World Bank website. We assumed a linear relationship between the prevalence of the various symptom measures in each country and the GNP of that country. The data were modelled using a generalised linear mixed model that allowed each centre to be considered as if randomly selected from within its country (not a very good assumption in some cases). The model used a binomial error but assumed the identity link so there was a simple linear association between the outcome measure and the ecological variable. All ecological analyses (subsequent to the one in which GNP was the focus) included GNP in the model as a potential confounder.

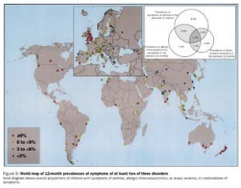
References

Rao JNK, Scott AJ. A simple method for the analysis of clustered binary data. Biometrics 1992; 48: 577-585.
Wolfinger R, O'Connell M. Generalized linear mixed models: a pseudo-likelihood approach. J Statist Comput Simul 1993; 48: 233-243.

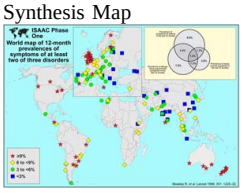
Map of all ISAAC Centres



Original Phase One Synthesis Map



Standardised Phase One Synthesis Map



Graphs & Maps

(Tadd Clayton)

Maps

Beginning in 1993, the ISAAC International Data Centre (IIDC) received data from 156 Phase One centres which were located throughout the world. By 1996 the ISAAC Steering Committee was beginning to prepare publications presenting the large amount of Phase One data from these centres and was considering how the data from so many centres could be presented in a way which provided a useful illustration of global patterns. After some discussion, the Steering Committee chose to use maps of the world with each centre represented by a symbol to indicate prevalence of symptoms.

Once the decision to use maps was made, it was my task as IIDC Data Manager to develop the style of the maps and prepare each map based on the data we had received. My early attempts to prepare maps used SAS which is a very comprehensive statistical analysis package which also includes a component for graphical presentation of data (SAS/Graph). The main advantages of SAS were that it was licensed by the University of Auckland and was thus free for us to use, and that it already included a library of maps. In theory, once I had generated coordinates for each ISAAC centre, I would have been able to use SAS programs to quickly generate each map in an automated manner. However, in practice I found that SAS was difficult to use as there was no way to manually edit the maps.

We decided to instead use a manual method of preparing the maps and purchased Corel Draw 7, a drawing program which would allow fine editing of the maps, and a collection of electronic maps in Adobe Illustrator format (the MapArt collection from Cartesia Software). The main drawback of this approach is that each symbol for the ISAAC centres had to be located manually, although this task did only have to be carried out once as subsequent maps could be based on the first one.

The base map we used is a Mercator projection with Europe and Africa occupying the central part of the map. We certainly cannot be accused of any favouritism towards our own country – this projection places a distorted New Zealand at the extreme lower right of the maps! The base map was modified to remove unnecessary grid lines and names, and to include an enlarged inset section for Europe where there were a large number of centres to plot in a comparatively small area. The location of each centre on the map was identified with the invaluable assistance of the Times Comprehensive Atlas of the World which not only includes many wonderful maps, but also an extremely comprehensive index of towns, cities and regions.

The Steering Committee agreed on a colour scheme for the maps, appropriate colours and shapes for the symbols, and appropriate cut-off values to define prevalence categories. We chose to use strong colours (blue, green, yellow and red illustrating low to high prevalence) and distinctive shapes (square, circle, diamond and star) for the symbols so that the maps would be readable when reproduced in both colour and monochrome (black and white). Each centre was assigned to a prevalence category based on their Phase One results and the appropriate symbol was placed into position on the map.

The maps presented in the ISAAC Phase One worldwide papers were well received and the Steering Committee chose to continue the use of maps in the Phase Three publications. The only major change for Phase Three was to use different shapes for the symbols (triangle, square and inverted triangle) to illustrate changes for the time trends maps.

While the overall layout and colours used for the maps have remained generally consistent, there have been some changes over time. The Phase One maps prepared for the papers used comparatively small symbols which were appropriate for the printed page but were difficult to see when the maps were used in PowerPoint presentations. Additional versions of those maps were prepared with symbols doubled in size to address this problem (see examples right). The larger symbols were exclusively used in all the Phase Three maps. The Phase One and Phase Three maps also used a subtly different colour scheme for the ocean and land which can be attributed to a change in software between the phases (a change from Corel Draw 7 to Adobe Illustrator CS2). The maps presented on this page have been standardised to use the same colours and symbol sizes.

Please see the appendices for the full selection of maps and graphs. Full size versions are available at http://isaac.auckland.ac nz/story/methods/methods/maps.php