The Global Asthma Network (GAN)
Rationale and Methods for Phase I Global Surveillance:
Prevalence, Severity, Management and Risk Factors

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ABSTRACT

The Global Asthma Network (GAN) was established commenced in 2012 to improve asthma care globally, with a focus on low- and middle-income countries, through enhanced surveillance, research collaboration, capacity building and access to quality-assured essential medicines. The Network was established following on from the long-term programme of work of the International Study of Asthma and Allergies in Childhood (ISAAC). GAN Phase I represents a continuation and development of the global asthma surveillance and research conducted under ISAAC, particularly ISAAC Phase One and ISAAC Phase Three. and the publication of the Global Asthma Report 2011 with the International Union against Tuberculosis and Lung Disease (The Union).

The Global Asthma Network will build on the findings from ISAAC, by collecting further information on asthma, rhinitis and eczema prevalence and severity, diagnoses, asthma emergency room visits and hospital admissions, management policies and access to quality assured essential medicines. As with the ISAAC study, GAN Phase I will is the first major global surveillance of asthma prevalence, severity, management and risk factors which includes two age groups of school children (6-7 and 13-14 year olds); it also includes, for the first time, and also adults/parents of each age group. ItThis will also include centres in "new" countries to provide new information about changes in risk factors to increase the current understanding of these conditions and monitor time trends. GAN will continue to promote the recognition of asthma as an important non-communicable disease to increase understanding and reduce worldwide suffering.

Word count 253

BACKGROUND

The Global Asthma Network (GAN) was established in 2012, 2012 to improve asthma care globally, with a focus on low- and middle-income countries, through enhanced surveillance, research collaboration, capacity building and access to quality-assured essential medicines. The Network was established following on from the 21 year programme of work (1991-2012) of the International Study of Asthma and Allergies (ISAAC) and the International Union Against Tuberculosis and Lung Disease (The Union). GAN is a new and independent organisation, but the GAN Steering Group is made up of several members from ISAAC and The Union.

These two organisations have been dedicated to helping countries worldwide identify and address the growing global problem of asthma ~~which has established itself as an important Non-communicable Disease (NCD) globally~~. In 2011, the Union and~~approached~~ ISAAC ~~to~~ prepared The Global Asthma Report 2011 which was launched in New York on 19th September 2011 coinciding with the United Nations High-Level meeting on NCDs in New York, 19-20 September 2011. Subsequently GAN produced The Global Asthma Report 2014 which was launched at the 45th Union World Conference on Lung Health, Barcelona, Spain, 28 October to 1 November 2014. ~~The GAN Steering Group is made up of some members from each of the founding organisations, ISAAC and The Union.~~

GAN aims to progress recommendations in the reports and engage Government's health ministers, policy-makers, health workers, those living with asthma, development partners, donors and media in efforts to improve asthma care globally. Core activities of GAN are: global surveillance; promotion and backing of standard case management of asthma; operational research; capacity building; engagement with policy makers; and access to affordable quality-assured medicines.

RATIONALE FOR GAN

GAN Phase I represents a continuation and development of the global asthma surveillance and research conducted under ISAAC, particularly ~~GAN will also build on the global findings from~~ ISAAC Phases One[1-5] ~~Two[6] [There is not one main overview paper there are around 12 Phase 2 papers should they all be referenced here?]~~ and Three[7-9], ~~the Phase Three time trends papers[10-13] and from the environmental questionnaire[what refs here? - all of them? or website publications address]~~.

ISAAC Phase One[14] (1994-1995), involv~~ed~~ing over 700,000 children of two age groups (13/14 and 6/7 year olds) from 156 centres in 56 countries. It identified large variations in the prevalence of symptoms of asthma, rhinitis and eczema throughout the world with differences of between 20 fold and 60 fold between centres. Phase One also showed that the international patterns of disease prevalence could not be explained by the current understanding, at the time, of the aetiology of asthma rhinitis and eczema. A consistent finding in Phase One was the marked differences in asthma prevalence in populations with similar genetic or ethnic backgrounds[15], suggesting that environmental factors in the broadest sense were the major determinants of the prevalence of asthma in a community. ~~Ecological analyses using Phase One data found no associations with pollen[16], immunisations[17], tobacco[18], climate[19] or antibiotics[20]. However negative associations were found with tuberculosis[21, 22] and higher dietary plant intake[23], and positive associations were found with economic development[24] and dietary trans fatty acids[25] suggesting those findings were worthy to be investigated in more depth.~~

ISAAC Phase Two[26] began in 1998 and was undertaken in 30 centres from 22 countries involving 53,383 children aged between 10 and 12 using child contact modules. This age group was chosen as they were more likely to understand the procedures than 6-7 year olds and to be more compliant that 13-14 year olds. Comparisons between populations (centres) were undertaken using objective measures of disease, and assessment of environment, lifestyle, and clinical management. Populations which were potentially informative were involved, such as those with contrasting prevalence of disease, environmental exposures, management or genetic factors. ISAAC Phase Two enabled the description of variation in disease prevalence beyond the level measured in Phase One by core questionnaires. Markers of disease were related to individual exposure to environmental factors and genetic markers. ISAAC Phase Two showed little evidence of genetic factors in asthma and that most asthma, rhinitis and eczema has a non-allergic basis, especially in developing countries.

ISAAC Phase Three[27] fieldwork was undertaken between 2001 and 2003. It involved over xxx,000 children of two age groups (13/14 and 6/7 year olds) from xxx centres in xx countries. The methodology involved and was a repeat of the Phase One core questions, using the same age groups, with the addition of an environmental questionnaire to explore in more depth the findings from the Phase One ecological analyses and other potential risk factors. Initially, Phase Three was designed to assess look at time trends in centres that had also participated in Phase One; however, but new centres were encouraged to participate to obtain a more comprehensive global map of the three conditions particularly in low and middle income countries. ISAAC Phase Three has been a crucial part of the process by which the extent, nature and causes of the global increases in the prevalence of these conditions are understood, particularly from the findings of the environmental data. Areas of interest include: paracetamol and antibiotic use particularly in the first year of life; breastfeeding; frequency of truck traffic in the street of residence; association with farm animals in pregnancy; exposure to cats and dogs in the first year of life; air pollution; tobacco use, body mass index; diet; use of cooking fuels, birthweight; migration; and siblings.

GOALS of GAN:

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(i) **Global surveillance.** Conduct asthma surveillance around the world and produce and disseminate surveillance data to achieve global recognition of the burden of asthma, especially the burden in low- and middle-income countries.

(ii) **Management**. Promote effective, efficient, appropriate, affordable and accessible asthma management and care to reduce the rates of death, disability and suffering caused by asthma.

(iii) **Research.** Research, develop and share evidence, success stories and practical tools that enable countries to improve and expand asthma management and prevention activities, organise the care of asthma patients to cover their whole populations.

(iv) **Capacity-building.** Stimulate capacity-building in surveillance, health education and asthma standard case management and research in asthma, especially in low- and middle-income countries.

(v) **Access to affordable quality-assured essential medicines.** Ensure quality-assured essential asthma medicines are available and affordable in all countries - promotes a quality improvement package for the diagnosis, treatment and management of asthma.

(vi) **Communication and advocacy on asthma and chronic airflow limitation.** Raise the profile of asthma and chronic airflow limitation on national multilateral and global agendas and empower other organisations to do the same.

RESEARCH DESIGN AND METHODS

Overview of the GAN Phase I study design

GAN Phase I is a cross-sectional, multi-centre, multi-country, epidemiological research methodology which will follow and expand on the ISAAC Phase Three methodology. In particular, it will ~~to~~ include additional~~more in depth~~ questions on ~~the~~ environment risk factors, and on and management of asthma. The manual containing the information required to undertake the fieldwork is available from the GAN website http://www.globalasthmanetwork.org/surveillance/manual/manual.php. Each centre has a defined geographical area and the centres that undertook ISAAC Phase Three and/or Phase One are expected to use the same sampling frame so that comparisons of data can be subsequently undertaken. Principal Investigators are identified at the registration stage which began in November 2015. The Phase I Co-ordinator is Professor Neil Pearce, London School of Hygiene & Tropical Medicine, London, UK who will lead the main data centre. Professor Luis Garcia-Marcos, IMIB Research Institute and University of Murcia, Spain will lead the data centre for Spanish and Portuguese language centres. The GAN Global Centre, will be led by Professor Innes Asher, the University of Auckland, Auckland, New Zealand, assisted by Philippa Ellwood as research manager.

Classification of GAN Phase I Centres

Centres that participated in ISAAC Phase Three have been encouraged to participate in GAN, however, as in ISAAC, new centres are encouraged to join to obtain wider global participation.

Expression of Interest and Registration forms

These forms are available from the GAN website. Formal registrations opened in November 2015. As of 1 December 2015 there have been expressions of interest from 338 centres in 131 countries, including ~~and we have received~~ formal registrations from 63 centres in 23 countries. The Registration form identifies the Principal Investigators (up to two can be appointed per centre) and a National Coordinator appointed if there is more than one~~1~~ centre in a country and if there is an identified need.

Subjects and Selection

School children

The same age groups used in ISAAC Phases One and Three will be used in GAN: 13/14 year olds (self-completed questionnaires) and 6/7 year olds (parental completed questionnaires). The sampling unit will be a school for each age group which will be selected using a table of random numbers. A minimum of 10 schools will be required, or all schools in the sampling frame if there are fewer than 10 schools. School children are the most accessible people of any age group and the 13/14 year age group, the compulsory age group, was chosen to reflect the period when mortality from asthma was thought to be more common. It is recommended that centres also include the 6/7 year age group which was chosen to give a reflection of the early childhood years when asthma is common and admission rates are particularly high. In addition, children in many countries do not start school until the age of 6. Students of both age groups are selected either by grade/level/year or by age group.

Adults

In addition to the 13/14 and 6/7 year age groups, GAN is recommending that the adults/parents of both age groups are also surveyed~~included~~ in order to obtain more in-depth environmental data, particularly from the parents of the 13/14 year age group that may not have been able to answer some questions relating to early life.

GAN Phase I Questionnaires
Demographic questions
The front page of the questionnaire will collect data on the participant's name, age, birth date, school, gender, and date of interview, although it is acknowledged that some centres will not include participants names. Questionnaires will be coded using a unique number for each centre, school and participant to ensure anonymity. Collection of data regarding participants ethnicity is optional and ethnicity categories from local census forms should be used.

Written questionnaires
The same standardised core questionnaires developed for ISAAC for use in Phases One and Three will be used in GAN with the addition of a question about Doctor diagnosed asthma, rhinitis and eczema. The core questions are both sensitive and specific, have good content, construct and concurrent and predictive validity[28]. Height and weight measurements will be taken by the fieldworkers. The environmental questionnaire, developed for ISAAC Phase Three has been expanded for use in GAN. Not all of these questions are compulsory as indicated in the GAN Manual. Some questions that were not considered appropriate for the 13/14 year age group to complete in ISAAC Phase Three have been included in the Adult questionnaire.

Video Asthma Questionnaire
The international version of the ISAAC video questionnaire used in Phase Three is strongly recommended for use in GAN. This 6 minute video shows clinical signs of asthma symptoms and was developed by the Wellington Asthma Research Group, to avoid problems of translation and comprehension of terms such as 'wheeze' or 'whistling' and their use in culturally heterogeneous populations[29]. The video has the advantage of obtaining data from a large number of students quickly and efficiently.

Translation of written questionnaires
The English language version of the questionnaire will be translated to the local language using guidelines that were developed in ISAAC Phase One[30]. Translations are required to have the same structure and logic as the English language questionnaire, back translated into English by an independent translator and a copy sent to the GAN global centre in Auckland, New Zealand.

Sample Size and Power Considerations

A sample size of 3000 participants per age group (therefore 3000 adults of each group) will be used, as in ISAAC. The sample size required to detect differences in severity of asthma is higher than that required to detect the same magnitude of differences in the prevalence of asthma because severe asthma is less common. ~~The sample size estimates are stringent because of the number of hypotheses being tested and the need to be certain of the results in such a major study.~~ The 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 on-year prevalence of severe asthma is 5% in one centre and 3% in another centre with a sample size of 3000, the study power to detect this difference with by 90% at the 1% level of significance[28]. 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 above are sufficiently large to allow good power in the presence of moderate intro-cluster correlations. If centres are unable to obtain 3000 participants, provided they have no less than 1000 and fulfil the criteria described in the GAN manual, they may be included.

Non-participation

The mean participation in ISAAC Phase One was 91% for adolescents and 87% for children; the corresponding rates for Phase Three were xx% and xx% respectively. A similarly high participation is sought for GAN Phase I (at least 80% for 13/14 year olds and 70% for 6/7 year olds and 70% for adults/parents) ~~due to concerns that pupils may be absent because of asthma or allergies~~. Marginally lower participation rates may be accepted on a centre by centre basis as long as they fulfil the criteria described in the GAN manual. For the 13/14 year age group a return visit to school can be made to capture the absentees and for the 6/7 year age group redistribution of questionnaires to the parents can be done once and maybe twice.

Quality control

~~On line~~On-line documents are now available from the GAN website. The expression of interest form has been available since 2012. This has enabled a data base of interested centres to be developed and information circulated such as a regular newsletter. The registration document became available from November 2015, which is a formal application to participate in the GAN Phase One Fieldwork. This form identifies which age groups will be studied, the name of the Principal Investigator [PI] (two can be appointed), contact details of the PIs, contact person if not the PI. The manual contains all the necessary information needed to undertake the fieldwork and describes the criteria required for inclusion in the worldwide data set.

Footnotes

On completion of the data checks and methodology checks from the centre report any deviations from protocol will be examined carefully by the GAN Steering Group. Provided the deviation from protocol is not severe enough for exclusion of the centre, the data will be included in the analyses and subsequent publications. Protocol variations that are accepted will be footnoted in the tables of the publications. This follows the same principles as adopted in ISAAC Phases One and Three.

Centre Report

Once registered centres are emailed a personal copy of the centre report for use during fieldwork. This centre report will be available to be completed ~~on line~~on-line shortly so that the information can be completed directly ~~on line~~on-line and submitted via the website to the GAN Global centre in Auckland, New Zealand.

Data Handling

At the time of conducting the survey, fieldworkers are requested to check the questionnaires for any obvious demographic entry errors so that this information can be corrected using school records. No alteration to the symptom and environmental questionnaire data is allowed. Data is entered onto the computer as it is presented on the questionnaire, preserving anonymity by coding. At least 10% of the data must be double entered so as to identify data entry errors. Each centre is responsible for its own data coding and entry. An epi info package will be made available on the GAN website for investigators use. Some centres may wish to use questionnaire scanning software such as OMR (Optical Mark Recognition) for data entry, however procedures to deal with data entry errors must be documented and sent to the GAN Global Centre. The software should have the ability to export the data set as a .CSV file.

Data Centres

Data will be submitted to the GAN Global Centre, Auckland, New Zealand, at the same time the centre report is submitted. The GAN Global Centre will acknowledge receipt of the data

and centre report, will undertake some quality control checks and will then send the data to one of two designated data centres.

Murcia, Spain. The data centre in Murcia, led by Professor Luis Garcia-Marcos will undertake the data checks on all Spanish and Portuguese speaking centres.

London, United Kingdom. The data centre in London, led by Professor Neil Pearce will undertake the data checks for centres using all other languages.

Ownership of data, ethics, dissemination of results and funding

Each centre owns its own data and is free to publish this data without prior approval of the GAN Steering Group (however the GAN Data Centres would appreciate being sent copies of any publications so that these can be uploaded to the GAN website). All worldwide publications will have a writing group 'and the Global Asthma Network Phase 1 Study Group'. This group, comprising all Steering Group members, National Coordinators (if one has been appointed) and Principal Investigators will be named at the end of each paper. They will be consulted on the paper in preparation prior to journal submission. Each centre is required to obtain ethics approval from their local ethics committee prior to the start of their study. Each centre is required to provide their own funding.

Significance of GAN

This will be the first major global surveillance of asthma prevalence, severity, management and risk factors which includes adults/parents in addition to two age groups of school children and the adults/parents of each age group. GAN will also It is anticipated that a large number of centres will adhere to the GAN fieldwork protocol to collect further information on the topics addressed in the Global Asthma Reports 2011 and 2014: including asthma prevalence and severity; diagnosis of asthma; unplanned visits including emergency room visits and hospital admissions; management policies; and access to quality assured essential medicines. In addition, GAN will expand on the ISAAC time trends Phase Three findings to explore in depth the negative and positive associations found with the environmental data. New centres from countries that had not previously undertaken ISAAC will provide rich new information and the data from centres that previously have undertaken ISAAC will allow trends to be analysed.

CONCLUSION

ISAAC Phase One involved over 700,000 children of two age groups (13/14 and 6/7 year olds) from 156 centres in 56 countries; it found marked variation in the prevalence of symptoms of asthma, rhinitis and eczema throughout the world which had not been explained by the current understanding at the time of these diseases. ISAAC Phase Three involved xxx,xxx children in xxx centres in xx countries; it found that the prevalence of asthma was increasing in many locations especially in low- and middle- income countries and identified several environmental factors that require further investigation. GAN Phase I will provide important further information with regards to both asthma surveillance (geographical patterns and time trends), and asthma risk factors. The findings from ISAAC have showed little evidence of genetic factors in asthma and that most asthma rhinitis and eczema has a non-allergic basis. ISAAC has also identified environmental factors that may have an important impact on the increasing prevalence and severity of these conditions in children and which need further exploration. By including the adults/parents of these two age groups of children we will provide new information about these conditions. We will work together as a team to increase the worldwide understanding of asthma, rhinitis and eczema, reduce suffering of

these conditions and continue to promote the recognition of asthma as an important non-communicable disease.

GAN Steering Group
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References

1. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Worldwide variation in prevalence of symptoms of asthma, allergic Rhinitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. Lancet. 1998;351(9111):1225-32.

2. ISAAC Steering Committee. Worldwide variations in the prevalence of asthma symptoms: the International Study of Asthma and Allergies in Childhood (ISAAC). European Respiratory Journal. 1998;12(2):315-35.

3. Strachan D, Sibbald B, Weiland S, Ait-Khaled N, Anabwani G, Anderson H, et al. Worldwide variations in prevalence of symptoms of allergic Rhinitis in children: the International Study of Asthma and Allergies in Childhood (ISAAC). Pediatric Allergy & Immunology. 1997;8(4):161-76.

4. Williams H, Robertson C, Stewart A, Ait-Khaled N, Anabwani G, Anderson R, et al. Worldwide variations in the prevalence of symptoms of atopic eczema in the International Study of Asthma and Allergies in Childhood. Journal of Allergy & Clinical Immunology. 1999;103(1 Pt 1):125-38.

5. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A, et al. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. Allergol Immunopathol (Madr). 2013 Mar-Apr;41(2):73-85.

6. Weinmayr G, Genuneit J, Nagel G, Bjorksten B, van Hage M, Priftanji A, et al. International variations in associations of allergic markers and diseases in children: ISAAC Phase Two. Allergy. 2010 Jun 1;65(6):766-75.

7. Lai K, Beasley R, Crane J, Foliaki S, Shah J, SK. W, et al. Global variation in the prevalence and severity of asthma symptoms: Phase Three of the International study of Asthma and allergies in Childhood (ISAAC). Thorax. 2009;64:476-83.

8. Aït-Khaled N, Pearce N, Anderson H, Ellwood P, Montefort S, Shah J, et al. Global map of the prevalence of symptoms of Rhinitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. Allergy. 2009;64:123-48.

9. Odhiambo J, Williams H, Clayton TO, Robertson C, Asher MI, and the ISAAC Phase Three Study group. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009 December;124(6):1251-8.

10. Asher MI, Stewart AW, Wong G, Strachan DP, Garcia-Marcos L, Anderson HR, et al. Changes over time in the relationship between symptoms of asthma, Rhinitis and eczema: a global perspective from the International Study of Asthma and Allergies in Childhood (ISAAC). Allergol Immunopathol (Madr). 2012 Sep-Oct;40(5):267-74.

11. Pearce N, Aït-Khaled N, Beasley R, Mallol J, Keil U, Mitchell E, et al. Worldwide trends in the prevalence of asthma symptoms: Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC). Thorax. 2007 Sep;62(9):758-66.

12. Björkstén B, Clayton TO, Ellwood P, Stewart AS, Strachan DP, ISAAC Phase III Study Group. Worldwide time trends for symptoms of rhinitis and conjunctivitis: Phase III of the International Study of Asthma and Allergies in Childhood. Pediatric Allergy & Immunology. 2008 Mar;19(2):110-24.

13. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR, International Study of A, et al. Is eczema really on the increase worldwide? Journal of Allergy & Clinical Immunology. 2008 Apr;121(4):947-54.

14. Asher MI, Keil U, Anderson HR, Beasley R, Crane J, Martinez F, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. European Respiratory Journal. 1995 Mar;8(3):483-91.

15. Beasley R, Ellwood P, Asher I. International patterns of the prevalence of pediatric asthma the ISAAC program. Pediatric Clinics of North America. 2003;50(3):539-53.

16. Burr M, Emberlin J, Treu R, Cheng S, Pearce N, and the ISAAC Phase One Study Group. Pollen counts in relation to the prevalence of allergic Rhinitis, asthma and atopic eczema in the International Study of Asthma and Allergies in Childhood (ISAAC). Clinical & Experimental Allergy. 2003;33(12):1675-80.

17. Anderson HR, Poloniecki JD, Strachan DP, Beasley R, Bjorksten B, Asher MI, et al. Immunization and symptoms of atopic disease in children: results from the International Study of Asthma and Allergies in Childhood. American Journal of Public Health. 2001;91(7):1126-9.

18. Mitchell EA, Stewart AW, Asthma IPOSGISo, Allergy in C. The ecological relationship of tobacco smoking to the prevalence of symptoms of asthma and other atopic diseases in children: the International Study of Asthma and Allergies in Childhood (ISAAC). European Journal of Epidemiology. 2001;17(7):667-73.

19. Weiland SK, Husing A, Strachan DP, Rzehak P, Pearce N, Group IPOS. Climate and the prevalence of symptoms of asthma, allergic rhinitis, and atopic eczema in children. Occupational & Environmental Medicine. 2004 Jul;61(7):609-15.

20. Foliaki S, Nielsen SK, Bjorksten B, Von Mutius E, Cheng S, Pearce N. Antibiotic sales and the prevalence of symptoms of asthma, rhinitis, and eczema: The International Study of Asthma and Allergies in Childhood (ISAAC). International Journal of Epidemiology. 2004;33(3):558-63.

21. Shirtcliffe P, Weatherall M, Beasley R, International Study of A, Allergies in C. An inverse correlation between estimated tuberculosis notification rates and asthma symptoms. Respirology. 2002;7(2):153-5.

22. von Mutius E, Pearce N, Beasley R, Cheng S, von Ehrenstein O, Bjorksten B, et al. International patterns of tuberculosis and the prevalence of symptoms of asthma, rhinitis, and eczema [see comments]. Thorax. 2000;55(6):449-53.

23. Ellwood P, Asher MI, Björkstén B, Burr M, Pearce N, Robertson CF, et al. Diet and asthma, allergic Rhinitis and atopic eczema symptom prevalence: an ecological analysis of the International Study of Asthma and Allergies in Childhood (ISAAC) data. European Respiratory Journal. 2001;17(3):436-43.

24. Stewart AW, Mitchell EA, Pearce N, Strachan DP, Weiland SK, on behalf of the Isaac Steering Committee. The relationship of per capita gross national product to the prevalence of symptoms of asthma and other atopic diseases in children (ISAAC). [see comments.]. International Journal of Epidemiology. 2001;30(1):173-9.

25. Intake of trans fatty acids and prevalence of childhood asthma and allergies in Europe, Pub. L. No. 9169(1999) [cited 2015/05/20]. Available from: http://dx.doi.org/10.1016/S0140-6736(99)01609-8

26. Weiland SK, Björkstén B, Brunekreef B, Cookson WO, von Mutius E, Strachan DP, et al. Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC II): rationale and methods. European Respiratory Journal. 2004;24(3):406-12.

27. 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.

28. ISAAC Steering Committee. International Study of Asthma and Allergies in Childhood. ISAAC Phase One Manual (2nd Edition). Auckland/Münster. Auckland/Münster: 1993.

29. Crane J, Mallol J, Beasley R, Stewart A, Asher MI, and the International Study of Asthma and Allergies in Childhood. Agreement between written and video questions for comparing asthma symptoms in ISAAC. European Respiratory Journal. 2003;21(3):455-61.

30. Weiland SK, Kugler J, von Mutius E, Schmitz N, Fritzsch C, Wahn U, et al. The language of pediatric asthma patients. A study of symptom description. Monatsschrift Kinderheilkunde. 1993 Nov;Organ der Deutschen Gesellschaft fur Kinderheilkunde. 141(11):878-82.