

Albanian–International study of asthma and allergies in childhood (ALB-ISAAC): Rationale and methods

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Abstract

The ALB-ISAAC 2011 study forms a part of a series of population surveys carried out in Tirana, using the internationally recognized procedures of the International Study of Asthma and Allergies in Childhood (ISAAC). ISAAC initiative was designed to study the aetiology of asthma, allergic rhinoconjunctivitis, and atopic eczema in children in different populations using standardized methodology. In Albania, all of the three phases were carried out; Phase One (1995), Phase Two (1999-2000) and Phase Three (2001).

ALB-ISAAC specific aims are: 1) to describe the prevalence and severity of asthma, rhinitis and atopic dermatitis in children living in Tirana, Albania in 2011-2012; 2) to estimate the risk factors of asthma, allergic rhinitis and atopic dermatitis and the correlation between this risk factors and the allergic diseases; 3) to estimate to what extent the variation in the prevalence and severity of asthma and allergies in children can be explained by differences in known or suspected risk factors or by differences in disease management; 4) to examine time trends in the prevalence of asthma, allergic rhino-conjunctivitis and atopic eczema in Tirana compared to 16 years earlier (ISAAC Phase One, 1995) and also the risk factors in developing asthma.

The ALB-ISAAC 2011 repeated both the ISAAC Phase Two survey among 10-11-year-olds, and the ISAAC Phase One and Three surveys among 6-7-year-olds and 13-14-year-olds, during the school year 2011-2012. In combination with the earlier surveys, it offers both a current and a historical perspective on childhood asthma and allergy extending over 16 years.

Keywords: allergic disorders, ISAAC, prevalence.

Introduction

The concern that the prevalence of asthma and allergic disease is increasing over the world is present and ubiquitous. Wherever a child lives, in an affluent or no affluent country (1), living in a farm or not (2), in east or in west (3), in a country with industrial air pollution or not (4), in a large or small family (5), there is an enormous number of children suffering from allergic disease. According to this concern, two excellent initiatives from Auckland, New Zealand and the other one from Bochum, Germany, in 1990 gave life to the largest worldwide collaborative research project ever undertaken in children; The International Study of Asthma and Allergies in Childhood (ISAAC). This epidemiological study has measured the symptom prevalence of asthma, rhinitis and eczema in almost 2 million children in 105 countries (6). The collaborative project was conducted in three phases. Phase One used core questionnaires designed to assess the prevalence and severity of asthma and allergic disease in a defined age group of children in 1993 (7). Phase Two was been developed and involved studies in informative centers of aetiological factors, particularly those suggested by Phase One (8). Phase Three was a repetition of Phase One, after at least three years (9).

As worldwide, even in Tirana, Albania, all of three phases of ISAAC study have been carried out. In ISAAC Phase One (in Tirana in 1995) standardized questionnaires were used to ascertain the prevalence of symptoms of asthma, rhinoconjunctivitis and eczema among children aged 6-7 years (parental reports) and 13-14 years (self-reports) (10). ISAAC Phase Three (in Tirana, in 2001) repeated this survey methodology and showed a slightly rise in prevalence of asthma symptoms in Albanian children (11). In between ISAAC Phase One and Three, ISAAC Phase Two has been carried out in Tirana in 1999-2000. This studied a different age-group (10-11 years old) and included objective measurements of allergic sensitization (allergen skin prick tests and specific IgE), flexural dermatitis (standardized skin examination) and bronchial responsiveness (to

inhaled hypertonic saline and to an exercise challenge) (12).

ALB-ISAAC 2011 repeated both the ISAAC Phase Two survey among 10-11-year-olds, and the ISAAC Phase One & Three surveys among 6-7-year-olds and 13-14-year-olds, during the school year 2011-2012. In combination with the earlier surveys, it offers both a current and a historical perspective on childhood asthma and allergy extending over 16 years, a period during which Albania and its capital, Tirana, has experienced major social, economic and environmental changes.

Objective of ALB-ISAAC

The aims and the objectives of the ALB-ISAAC study are: 1) to describe the prevalence and severity of asthma, rhinitis and atopic dermatitis in children living in Tirana, Albania in 2011-2012; 2) to estimate the risk factors of asthma, allergic rhinitis and atopic dermatitis and the correlation between this risk factors and the allergic diseases; 3) to estimate to what extent the variation in the prevalence and severity of asthma and allergies in children can be explained by differences in known or suspected risk factors or by differences in disease management; 4) to examine time trends in the prevalence of asthma, allergic rhino-conjunctivitis and atopic eczema in Tirana compared to 16 years earlier (ISAAC Phase One, 1995) and also the risk factors in developing allergic disorders.

The endpoints of the ALB-ISAAC study are: 1) to provide a framework for further etiologic research into lifestyle, environmental, genetic and medical care factors affecting these diseases; 2) to describe the prevalence of 'objective' markers of asthma and allergies in children living in Tirana, Albania in 2011; 3) to assess the relation between the prevalence of 'objective' markers of asthma and allergies and the prevalence of symptoms of these conditions in children; 4) to explore new etiologic hypotheses regarding the development of asthma and allergies in children, 5) to examine hypotheses at an individual level which have been suggested by the findings of ISAAC Phase One, Phase Two, Phase Three.

Asthma

Asthma is one of the most important diseases of childhood (13). Through ISAAC, we now know that asthma occurs extremely different in all over the world, with a large variations in the prevalence of symptoms throughout the world, up to 15-fold between countries (11). Despite, the prevalence is high in low income and in high income countries; asthma is more severe in low and middle income countries (14). ISAAC found that asthma symptoms were increasing especially in low and middle income countries with large populations (15), more in West than in East, and more in developing countries (16).

Rhinitis

Allergic rhinitis is a global health problem that causes major illness and disability worldwide. Despite that many national or multinational studies are rapidly improving the knowledge in the prevalence of rhinitis and its possible risk factors; there is a constant absence of epidemiological data (17).

ISAAC demonstrated a large variation in the prevalence of rhinitis symptoms in children throughout the world. In particular it was found that countries with a very low prevalence of asthma (<5%), also had low prevalence of rhinitis. On the other hand, countries with a very high prevalence of asthma (>30%), had a high prevalence of rhinitis (15-20%). It is likely that environmental factors were responsible for major differences between countries (18). In countries where the prevalence of allergy and rhinitis is high, a reduction in increase, a plateau or a slight reduction have been observed. On the other hand, in countries with low prevalence, there is a considerable increase of allergy and rhinitis (19). Trends in asthma and rhinitis prevalence do not always accord (11).

Eczema

Little is known about the epidemiology of eczema (syn. atopic dermatitis, atopic eczema). As for the other allergic disorder, asthma and rhinitis, even for eczema has been described a large variation of the prevalence over the world and between the same

centers (20). Meantime ISAAC phase TWO found a week and variable association between atopy and flexural eczema (21). It seems that eczema is better diagnosed by objective measurement, rather than rhinitis or asthma. According to this, a list of major and minor criteria proposed by HANIFIN and RAJKA has been incorporated into the ISAAC study (22).

Rationale of ALBISAAC initiative

ISAAC has been developed to investigate a wide range of issues; why some atopic individual develops asthma and other rhinitis or eczema, why there are symptoms of asthma and no sensitization in individual level; why such a huge difference exists in the prevalence of asthma symptoms; are these changes due to increases in allergic sensitization, organ responsiveness, host susceptibility or environmental exposure. For this and more, a coordinated programme for many years would ensure the most precious epidemiological data on asthma, rhinitis and eczema.

16 years later from ISAAC Phase one, ALB-ISAAC study repeated the ISAAC Phase One, Two and Three survey, during the school year 2011-2012. In this moment, Albania, a post communist country, and especially its capital Tirana, has experienced major changes. The Albanians adapt new political, economical, social, cultural, and environmental conditions, conditions that may have a contribution in the prevalence of allergic conditions, also the trends of the risk factors.

Methods

Overview

The study was divided into two parts taking place simultaneously. Part One was the core study; the 6-7 years old children (by parental report) and the 13-14 years old children completed the ISAAC core questionnaires on asthma, rhinitis and eczema from November to February 2011-2012. Part Two involved besides the “core questionnaires” on

asthma, rhinitis and eczema, also more detailed questionnaires of aetiological factors (risk-factors for these diseases) on 10-11 years old children from February to April 2012. The all three age group was examined for flexural dermatitis. A random selected sample of 10-11 years old group was tested for atopy. The ALB-ISAAC 2011 research centre is a distinctive population in terms of its geography, race and/or ethnic characteristics, where the investigator has agreed to follow the ALB-ISAAC 2011 study protocol described. The sample of children taking part in ALB-ISAAC 2011 study has not previously been recruited systematically for research into asthma, allergies (although individual children may have been involved).

Selection of subjects

The population of interest was school children within a given geographical area. A random sample of three age groups of children was studied: 6-7 year olds, 10-11 years, and 13-14 year-old at the start of the fieldwork. The sampling unit was a school for each age group. Each school in the centre which would contain the age group of interest was allocated a number, and the schools were selected using a table of random numbers. Sampling of each age group was separate. Once a school had been chosen, three school years was selected, which included those with the greatest proportion of 6-7 year olds, those with the greatest proportion of 10-11 years old and those with the greatest proportion of 13-14 year olds. It was recognized that there would be some children outside the specified age ranges in each class chosen. The younger age group has been chosen to give a reflection of the early childhood years, when asthma is common, and admission rates are particularly high. The 10-11 years age group has been chosen because 10 year olds are known to participate and perform satisfactorily the proposed allergy skin prick test. The older age group has been chosen to reflect the period when mortality from asthma is more common. School children are the most accessible people of any age group. A minimum of 10 schools (or all the

schools) were needed to obtain a representative sample. If a selected school refused participation, it has been replaced by another chosen at random. No eligible children were excluded from the sample. Because of the probability that an absent child may be away from school due to his asthma or allergies, in this case was made a second effort to contact and to offer these children the opportunity to participate in the study. In case of the younger age group, if the initial questionnaire was not returned within one week, the questionnaire was sent again.

Sample size

The aim was to have sufficient statistical power to detect differences of epidemiological and health service significance. Therefore, the sample size has been calculated with reference to more severe atopic disease rather than to the prevalence of disease of any severity. A sample size of 3,000 has been chosen, which gives the following power for wheezing, rhinitis or eczema: if the true one year prevalence of wheezing is 30% in one centre and 25% in another centre, with the chosen sample size, the study power to detect this difference will be 95% at the 1% level of significance; if the true one year prevalence of severe symptoms is 5% in one centre and 3% in another centre, with the chosen sample size, the study power to detect this difference will be 90% at the 1% level of significance.

The questionnaires

For the 6-7 years old and 13-14 years old age group; three one page questionnaires have been developed by the ISAAC references (7). These were agreed for international use. The aim of compiling "core" questionnaire is to ensure the comparable information on the basic epidemiology of atopic illness. The 6-7 years old had taken the questionnaire home for parental/guardian completion. The 13-14 year olds had self completed the questionnaire on wheezing, rhinitis and eczema.

For the 10-11 years old group; the written core questionnaires were developed on demographics, asthma, rhinitis and eczema. The risk factor

questionnaire investigates the living condition in the first year of life of the child, also tends to collect information about such factors as birth weight, gestational age, breast feeding, family size, family history of atopic diseases, infections, vaccinations, pets, environmental tobacco smoke, cooking fuels, damp housing, type of windows, type of bedding, area of residence, physical activity and nutritional factors. All questionnaires were for completion by parents/guardian (8).

Because the responses to rhinitis questions (but not asthma or eczema questions) are affected by season (unpublished data from southern England and New Zealand), the population was investigated before the main pollen season of the study area.

The previous translation of questionnaires from English in Albanian and back was used according to guidelines (9). The core questionnaires are presented, along with an information sheet about the study and were asked to sign by parents/guardians for permission to participate in the procedures of ALB-ISAAC study. A contact telephone number was available to the parents to contact in every moment in case of any queries they might have about the study.

Prior to the start of the study was obtained the necessary National Ethics Committee approval and also the necessary Ministry of Education and Science and Directory of Education of Tirana approval.

ALB-ISAAC research staff and field workers did not use the terms "asthma", "allergy", "rhinitis", or "eczema" when advertising the study, presenting written material about the study, speaking about the study to school staff, parents, children or speaking to 13-14 years old children in the classroom. The phrases used were "a survey about breathing problems". Coding did not appear on the questionnaire delivered to the children or their parents (7). For 6-7 years old and 10-11 years old; once eligible children were identified, ALB-ISAAC staff sent the questionnaires to the parent/guardian through the school. The parent/guardian returned the questionnaires with no financial cost to them.

For the 13-14 year olds; the questionnaires was

administered to a group of children one session at time. Each session comprised verbal instruction by the staff on the three sections before the questionnaires were completed (7).

Examination for flexural dermatitis

All three age group participating children were examined for visible flexural dermatitis according to a photographic protocol (23) and detailed instructions on its use in the field. The examination involved inspection of the skin by only two specialized physician in allergy field: 1) around the eyes; 2) around the sides and front of the neck; 3) in front of the elbows; 4) behind the knees; and 5) in front of the ankles. The presence or absence of signs of visible flexural dermatitis was recorded for each of the five areas (8).

Skin-prick testing for atopy

The sensitivity to aeroallergens was assessed by skin-testing with standardized allergen extracts and was performed on 1000 children of 10-11 years old by only two specialized physician in allergy field. Extracts of six common aeroallergens (*Dermatophagoides pteronyssinus*, *D. farinae*, cat hair, *Alternaria tenuis*, mixed tree pollen and mixed grass pollen) and control solutions produced by ALK (Hørsholm, Denmark) were used. Three other allergens of local relevance were added (*Olea europea*, *Blatella germanica*, *Parietaria officinalis*). Briefly, a drop of each allergen extract and the positive (10 mg/mL- histamine) and negative (diluent) control was placed on to the skin of the volar side of the left forearm and pierced vertically using 1-mm ALK lancets. After 15 min, the outer contour of the wheal reaction was outlined using a fine felt-tip pen, and the result expressed as the mean of the lengths of the longest diameter and the perpendicular line through its centre. Using a strip of transparent tape, the prints were transferred to the data sheet. A skin test was considered positive if a mean wheal diameter of at least 3 mm to at least one allergen was present (8). The skin prick test tested was the same used in ISAAC Phase Two (2000).

Data management and statistical analysis

Field workers have checked the questionnaires at the time of conducting the survey. No alteration to the symptom and personal data was allowed, and the information was entered on to the computer exactly as it is presented on the questionnaire, with anonymity of subjects preserved. A double entry method of limiting data entry errors was applied. The data was stored on a computer with the necessary statistical analysis capabilities, and a copy of the data was kept off site in a protected environment (24). Demographic data was checked

for omissions, plausibility and inconsistencies. Symptom was checked for consistency with the coding schedule.

Conclusion

ISAAC was developed to investigate childhood asthma, allergic rhinoconjunctivitis and atopic eczema at the population level and this study has attracted worldwide interest and large-scale participation, facilitating international collaboration. In this contest, ALB-ISSAC 2011 study reflects the Albanian prevalence of allergic disorder.

Conflicts of interest: None declared.

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