Validation of the Spanish version of the Phase III ISAAC questionnaire on asthma

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Summary. The prevalence of allergic diseases in childhood has increased significantly over the last decades. This increase seems to be closely associated with the way of life of western societies. The high prevalence differences on different regions may be due to linguistic and cultural reasons and not to real variations in prevalence. This is the reason why several authors felt the need to perform an objective validation of their versions. Our working group has published the results of the Phase I validation and now is publishing the Phase III validation in order to guarantee the reliability of this phase results.

The study sample is formed by 366 children aged 3 to 17 years.

The following steps were followed in this study:

1. Assessment of the "Criterion validity" of the Spanish ISAAC-Bronchial Asthma questionnaire, evaluating the sensitivity, specificity, relative value, and positive and negative predictive values.
2. Determine the questionnaire reliability, analysing its "Inner consistency".
3. Statistical comparison between our ISAAC-Bronchial Asthma results and the ones obtained by other groups (external concordance and consistency), in order to prove the previously evaluated reliability.
4. Comparison between the ISAAC-Bronchial asthma questionnaire diagnostic ability and the standard diagnostic criteria universally used in clinical praxis.

We could confirm that there is a high and very significant concordance between the questions aimed to detect children with asthma. In this sense, it is especially useful the question about "ever had wheezing" because of its high sensitivity (93.3%) and specificity (89.9%), that make it able to be used as initial screening test in a general population, and that has shown a high concordance percentage with the questions "ever had asthma" (98%), "wheezing with exercise" (75%), and "cough at night"(80%).

The questions that give more information about the evolution and control of the asthmatic disease are "wheezing in the last 12 months", "number of attacks in the last 12 months", "wakening at night", "wheezing with exercise" and "dry cough at night in the last 12 months". The questions more related to asthma severity were "number of attacks in the last 12 months", "wakening at night", "stop speaking in order to breath", and "wheezing with exercise".

We conclude that ISAAC-Asthma questionnaire Phase III is a useful tool for the assessment of childhood asthma due to its criterion validity, inner consistency and external concordance.

Key words: Prevalence of asthma; ISAAC questionnaire; children.

Introduction

The prevalence of allergic diseases in childhood has increased importantly over the last decades. This increase seems to be closely associated with the way of life in western societies. This increasing trend of allergic diseases over the world has generated a great interest in knowing its prevalence in the different geographical areas, as well as the risk factors associated with them. Among the different studies designed for this objective, the ISAAC project has had universal acceptance. ISAAC, (International Study of Asthma and Allergies in Childhood), was created in 1991 to facilitate research into asthma, allergic rhinitis and eczema by promoting a standardised methodology.

ISAAC developed from a merger of two multinational collaborative projects, each of them examining variations in childhood asthma. These were an initiative from Auckland, New Zealand to conduct an international comparative study of asthma severity, and an initiative from Bochum, Germany for an international study to monitor time trends and determinants of the prevalence of asthma and allergies in children. The ISAAC project is made up of three phases: Phase I, Phase II and Phase III.

Firstly, most researchers limited themselves to achieve the aim of Phase I [1], measuring directly the prevalence of the different diseases in the different countries and areas in the world. The results, already published, showed some remarkable variations in prevalence [2]. The important differences observed among the prevalences in the different regions gave rise to the idea that some of these variations could be due to linguistic or cultural reasons and not to true variations in prevalence. This is why several authors felt the need to perform an objective validation of their versions, which had been translated and adapted by themselves. Our group has published the results of the Phase I validation [3] and is currently working on the Phase III validation which will guarantee the reliability of the results obtained in this phase. In this work we expose the validation study of the Spanish version of the Phase III-ISAAC Bronchial Asthma questionnaire (Appendix 1).

Material and methods

Patients

The study sample was made up of 366 children aged 3 to 17 years and the study time frame was from January 1999 to May 2001. Out of the 366 children, 78 (21.3%) came from the Department of Allergology of the University Clinic of Navarra, and 288 (78.7%) from Pediatric Primary Care clinics of the Navarra province. The split by age group was: 173 children (47.3%) were 10 to 17 years old, 98 of whom (56.6%) were males and

75 (43.4%) females. The other 193 children (52.7%) were 3 to 9 years old, 100 (51.8%) males, and 93 (48.2%) females.

Questionnaires

Before handing out the questionnaire to the children aged 10-17, the doctor informed their parents about the purpose of the study, explaining their right to take their children out of the study. Concerning the children aged 3-9 years, the parents' consent was required before answering the questionnaire. After handing out the questionnaires, the nurse or doctor in charge gave the necessary instructions for its fullfilment and was available to explain any doubts concerning the questions.

The documentation to be filled in was a personal data card and the three parts of the Phase III ISAAC questionnaire (ISAAC Bronchial Asthma questionnaire, ISAAC Allergic Rhinitis questionnaire and ISAAC Atopic Dermatitis questionnaire).

Regarding the ISAAC-Asthma questionnaire the children were classified as cases or controls for this disease, depending on whether they had been diagnosed bronchial asthma or not. The diagnostic clinical criteria used for asthma were the ones from the Asthma Committee of the Spanish Society of Allergology and Clinical Immunology [4], highly concordant with the GINA's criteria [5]. The diagnostic criteria were uniform and evaluated by at least two doctors, and the doubtful cases were discarded.

Study design

The following steps were followed:
1. Assessment of the "criterion validity" of the ISAAC-Bronchial Asthma questionnaire referred to clinical diagnosis (sensitivity, specificity, relative value, and positive and negative predictive values).
2. Determination of the questionnaire reliability (inner consistency).
3. Comparison between the ISAAC-Bronchial Asthma diagnostic ability and the standard diagnostic criteria universally used in clinical praxis.

Results

Criterion validity

Of the total 366 children, 112 (30.6%) were diagnosed bronchial asthma. Table 1 shows the results of the diagnostic ability parameters obtained by comparison of our ISAAC questionnaire and the reference gold standard (diagnostic clinical criteria).

Appendix 1.

ESTUDIO INTERNACIONAL DE SALUD INFANTIL.
CUESTIONARIO PARA PADRES DE NIÑOS/AS DE 6 A 7 AÑOS.

En esta página hay preguntas sobre su hijo por favor escriba una letra o número en cada casilla con letra de imprenta. En las preguntas marque con una X la casilla adecuada

1. ¿Alguna vez ha tenido su hijo silbidos o pitidos en el pecho en el pasado?

    SI ☐   NO ☐

    Si ha contestado "NO" por favor salte a la pregunta 6

2. ¿En los últimos 12 meses, ha tenido su hijo silbidos o pitidos en el pecho?

    SI ☐   NO ☐

    Si ha contestado "NO" por favor salte a la pregunta 6

3. En los últimos 12 meses, ¿cuantos ataques de silbidos o pitos en el pecho ha tenido su hijo?

    Ninguno ☐   1 a 3 ☐   4 a 12 ☐   Más de 12 ☐

4.   En los últimos 12 meses ¿cuántas veces se ha despertado su hijo de noche por los silbidos o pitos?

    Nunca ☐   Menos de una noche por semana ☐   Una o más noches por semana   ☐

5. En los últimos 12 meses ¿han sido tan importantes los silbidos o pitos en el pecho como para que su hijo no pudiera decir dos palabras seguidas sin tener que pararse a respirar?

    SI ☐   NO ☐

6. ¿Ha tenido su hijo, alguna vez, asma?

    SI ☐   NO ☐

7. En los últimos 12 meses ¿ha notado en el pecho de su hijo pitos al respirar durante o después de hacer ejercicio?

    SI ☐   NO ☐

8. En los últimos 12 meses ¿ha tenido su hijo tos seca por la noche que no haya sido la tos de resfriado o infección de pecho?

    SI ☐   NO ☐

ESTUDIO INTERNACIONAL DE SALUD EN LOS ADOLESCENTES.
CUESTIONARIO PARA CHICOS/AS DE 13 A 14 AÑOS.

Por favor escriba una letra o número en cada casilla con letra de imprenta. En las
preguntas marque con   una "X" la casilla adecuada.

1. ¿Alguna vez has tenido o silbidos o pitidos en el pecho en el pasado?

    SI ☐   NO ☐

    Si has contestado "NO por favor salta a la pregunta 6

2. ¿En los últimos 12 meses, has tenido silbidos o pitidos en el pecho?

    SI ☐   NO ☐

    Si has contestado "NO" por favor salta a la pregunta 6

3. En los últimos 12 meses, ¿cuantos ataques de silbidos o pitos en el pecho has tenido ?

    Ninguno ☐   1 a 3 ☐   4 a 12 ☐   Más de 12 ☐

4. En los últimos 12 meses ¿cuántas veces te has despertado de noche por los silbidos o pitos?

    Nunca ☐   Menos de una noche por semana ☐   Una o más noches por semana   ☐

5. En los últimos 12 meses ¿han sido tan imporantes los silbidos o pitos en el pecho como para que no
    pudieras decir dos palabras seguidas sin tener que pararte a respirar?

    SI ☐   NO ☐

6. ¿Has tenido, alguna vez, asma?

    SI ☐   NO ☐

7. En los últimos 12 meses ¿has notado en tu pecho pitos al respirar durante o después de hacer ejercicio?

    SI ☐   NO ☐

8. En los últimos 12 meses ¿has tenido tos seca por la noche que no haya sido la tos de resfriado
    o infección de pecho?

    SI ☐   NO ☐

The 112 patients with asthma provided 723 answers to the 8 questions of the corresponding questionnaire, which means a 80.7% global response rate.

The maximum completion was obtained in questions 1, 6, 7 and 8 (92.9%), and the minimum in questions 3, 4 and 5 (62.5%).

The greater diagnostic sensitivity (96.2%) was obtained with question 6 ("ever had asthma"), which represents the cumulative prevalence of asthma. The questions with the lowest diagnostic sensitivity were the ones regarding "wheezing with exercise" (47.1%), "wheezing that makes speaking difficult" (5.8%) or "wheezing that wakes you up in the night" (40.8%). Questions 5 and 7, however, were those that obtained the higher specificity. The global diagnostic sensitivity of the questionnaire was relatively low (64.7%), but it has a high specificity (91.6%) and satisfactory positive and negative predictive value.

Reliability-reproducibility

Inner consistency

The analysis of the inner consistency or concordance degree between the sentences with similar meaning in the ISAAC-Asthma questionnaire is shown in table 2 with the most representative results of the statistical tests.

The great concordance of "night cough not associated with a cold in the previous 12 months" with the rest of the questions is remarkable. This question is, on its own, a prove of highly positive inner reliability, given its high specificity (84.8%) and its important concordance with the rest of the questions (with very significant concordance values). Besides, it is important to notice the associations between questions 1 and 6 (98% concordance; OR=19; K=0.331; $p_k<0.0001$; $p_{\chi 2}<0.02$); 1 and 7 (75% concordance; K=0.121; $p_k<0.01$; $p_{\chi 2}<0.02$); 2 and 7 (80% concordance; OR=17; K=0.527; $p_{\chi 2}<0.0001$); and 4 and 7 (62% concordance; $p_{\chi 2}<0.02$).

Discussion

In our country, phase II and phase III of the ISAAC project are now being developed. Phase III is a repetition of phase I with small modifications, whose objective is to know the prevalence trends of atopic diseases in childhood. In the last few years, previous phases of ISAAC have been validated [3,7-12], but phase III has not been validated yet. Besides, our study gathers a greater number of cases than most of the ISAAC validation studies published until now.

Regarding the **Validity criterion,** we analyse below the results obtained for each question of the questionnaire, and comment their clinical and practical

significance, comparing our results with the ones obtained in similar studies.

The first question of the ISAAC-Asthma questionnaire is whether the child had **ever had wheezing**. Thirty-three point six percent of the children answered affirmatively, which means a cumulative prevalence of the asthma-related symptoms in our sample. The sensitivity of the question for the diagnosis of bronchial asthma was 93.3%. Due to this high sensitivity, the question is valid for the screening of patients. Nevertheless, wheezing is not exclusive of bronchial asthma, since we found 10.2% of children without a diagnosis of bronchial asthma who had " had wheezing" (specificity 89.9%).

The second question in the ISAAC-Asthma questionnaire was about the current prevalence: **wheezing in the previous 12 months**. Of all the children who had ever had wheezing, a little more than half had wheezing in the previous year, corresponding to the highest percentage of children diagnosed bronchial asthma, and within this group, the ones who had the worst evolution. According to this, this question could partially indicate the evolution of the disease. The question's sensitivity to detect children diagnosed asthma is not too high (SE=65.3%), since a child could have asthma and not have had wheezing in the previous 12 months. It is interesting to note that among the children who had wheezing in the **previous year**, a great percentage had attacks, and frequently one to three asthma attacks. Therefore, wheezing in the previous year predisposes to suffer from asthma attacks. This is why this question could indicate the severity of the asthmatic disease, which agrees with the previous statement that one of the severity criteria for bronchial asthma is suffering more than three wheezing attacks in the previous year.

According to this reference, also **night wakening due to wheezing** is a severity criterion since it gives information about the severity and the good or bad control of the disease. These questions assess the severity of asthma following the scheme of the GINA scores [13,14].

A third question that gives us information about the severity of the disease is **wheezing that forces the child to stop speaking**. In our sample, the total percentage of children who suffered from this problem is very low (6%), and coincides with the data given by Esteve [15] who obtained 7.8% positive answers among 6720 school children from a general population. Nevertheless, in the validation of the Portuguese version of the Phase I ISAAC-Asthma, Solé [7] obtained a higher percentage: 15%. However, in our sample 100% of children who reported having to stop speaking had been diagnosed bronchial asthma, and therefore the question is valid to confirm this diagnosis (Sp=100%).

The sixth question in the questionnaire, answered by all the children, is also referred to diagnosis: **Have you ever had asthma?** This is a key question due to its high sensitivity (Se=96.2%) and specificity (Sp=96%)

Table 1. Criterion Validity of the ISAAC-Bronchial Asthma questionnaire

QUESTIONS:	Total number of answers		Se	Sp	Younden index	PPV	NPV
	Controls	Cases					
1. Ever had wheezing?	240	105	93.3	89.9	0.83	79.7	96.9
2. Wheezing in the previous 12 months?	69	98	65.3	91.3	0.57	91.4	64.9
3. How many wheezing crisis in the previous 12 months? (Never, 1-3 attacks, 4-12 attacks, >12 attacks)	27	69	89.9	77.8	0.68	91.2	75.0
4. How many nights did you wake up due to wheezing in the previous 12 months? (Never, <1/week, >1/week)	23	71	40.8	87.0	0.28	90.6	32.3
5. Did wheezing ever prevent you from speaking in the previous 12 months?	24	69	5.8	100	0.06	100	27.0
6. Ever had asthma?	247	104	96.2	96.0	0.92	90.9	98.3
7. Wheezing with exercise in the previous 12 months?	244	104	47.1	97.1	0.44	87.5	81.2
8. Night dry cough, not having a cold, in the previous 12 months?	243	103	60.2	84.8	0.45	62.6	83.4
Medium Values			64.7	91.6	0.56	83.3	80.0

Se: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value
Note: Questions 3 and 4 are not specifically used to diagnose asthma but to inform about asthma severity

Table 2. Inner consistency of the Asthma questionnaire: Concordance between the questions of the same or similar meaning. In the upper right boxes, the values corresponding to the degree of association between both questions are assigned, for which the box is the crossing point in the following order: concordance percentage ([1]); Kappa concordance coefficient ([2]); significance ([3]) of the kappa coefficient. Odds Ratio values ([4]), and the test significance values χ^2 are included in the lower box ([5]).

QUESTIONS	1	2	3	4	5	6	7	8
1. Ever had wheezing?						98[1] 0.331[2] 0001[3]	75[1] 0.121[2] 01[3]	80[1] 0.151[2] 01[3]
2. Wheezing in the previous 12 months?			64[1]	62[1]			80[1] 0.527[2] 0001[3]	70[1] 0.317[2] 0001[3]
3. How many wheezing attacks in the previous 12 months?		0001[5]					62[1]	57[1]
4. How many nights did you wake up due to wheezing?		05[5]					62[1]	72[1]
5. Did wheezing ever prevent you from speaking in the previous 12 months?								
6. Ever had asthma?	19[4] 02[5]							81[1] 0.119[2] 01[3]
7. Wheezing with exercise in the previous 12 months?	7[4] 02[5]	17[4] 0001[5]	001[5]	0.2[4] 02[5]				69[1] 0.327[2] 001[3]
8. Night dry cough, not having a cold/previous 12 months?	10[4] 02[5]	11[4] 003[5]	8[4] 006[5]	0.1[4] 0001[5]		9[4] 02[5]	4[4] 0001[5]	

[1]% Concordance; [2]Kappa Coefficient ([3]signif:$p<0.00$); [4]Odds Ratio; [5]χ^2(signif: $p<0.00$).

which supports it as a useful screening tool in asthma population-based studies, since the children diagnosed asthma admit having it even though they feel asymptomatic. This means that it detects children with bronchial asthma who could have answered negatively to the questions related to asthmatic symptoms.

Wheezing with exercise is a symptom of bronchial hyperreactivity, which is sometimes an early sign of asthma, although it is not identified as such [15,16]. In other occasions, wheezing can be the expression of the last phase of an attack resolution. In our sample 15.3% of the children have sometimes had **wheezing during or after the exercise**. There are very significant differences in the prevalence of symptoms with exercise between children diagnosed asthma and not diagnosed (p<0.001); almost half the children diagnosed asthma had wheezing with exercise and only 3% of children with no diagnosis had it. The specificity of this question was, nonetheless, very high (SP=97.1%). This high specificity is useful to confirm the diagnosis and agrees with the results obtained by Solé [7] who found that among the 13-14 year old children diagnosed asthma, up to 30% reported "wheezing with exercise", whereas none of the children who were not diagnosed asthma reported them. In our validation of the Phase I ISAAC-Asthma, our group [3] also observed that cough during the exercise had a statistically significant relation with the diagnosis of bronchial asthma.

This question, together with the one regarding **"wheezing in the previous 12 months"** (nº 2), are the basic questions in the ISAAC questionnaire for the diagnosis of bronchial asthma, as they showed the highest specificity according to our results, which are in agreement with the other studies as indicated previously [3,7].

An asthma attack usually starts with respiratory symptoms of the high airways, which in some hours or days progresses to cough and wheezing together with dyspnea of varying severity. In small children and school children, dry cough during the night could be the only symptom.

In our study group, 27% of the children had dry cough at night, and the differences between children with or without asthma were very significant (p<0.001): whereas 60% of the children with asthma had cough at night, only one sixth of the children without asthma had it and therefore this symptom behaved as really asthma specific (SP=84.8%).

Our data confirmed that cough is an asthmatic equivalent among the youngest children (GINA 1998) because in our group of children aged 3-9 years, 73.6% have dry cough at night, whereas only 46% of the asthmatics aged 10-17 have cough, a significant difference (p<0.05).

The total validation of a Quality of Life Questionnaire or an Epidemiological Questionnaire demands a guarantee of reliability of the data, meaning that the questionnaires would reach the same results if applied at different times by different observers. The most immediate and most frequent way of checking this reproducibility is the test called Test-Retest, which administers the same questionnaire to the same patient at two successive moments separated by a not-too-long lapse of time. The problem with the Test-Retest is that if it is repeated in a too short period of time, the results could be tampered by the previous memorisation of the question; on the contrary if it is repeated in a too long period of time, the own evolution of the disease or the effect of the therapeutic prescription (due to forceful ethical reasons) could induce an unavoidable bias [17,18]. The largeness and complexity of our study group made it difficult to perform the Test-Retest in the optimum time and therefore we decided to assess the reliability of our results by the determination of the concordance percentage, the *Odds Ratio* association and the Kappa concordance coefficient and its statistical significance [19]; this is by assessment of the so called Concordance or "Inner consistency" [20], which seems to have nowadays a more frequent application.

After analysis of all the questions from the ISAAC-Asthma questionnaire, we considered the sensitivity, specificity and clinical significance that we observed for each question jointly, and the concordance between the questions of the same meaning. We could confirm that there is an optimum and very significant concordance between the questions aimed at **detecting** children with asthma. In this sense, the question about **"ever had wheezing"** is especially useful due to its high sensitivity and specificity, as it is able to be used as initial screening test in a general population, and that has shown a high concordance percentage with other questions equally useful for asthma confirmation because of its high specificity. These questions were, in order of importance: **"ever have asthma"**, the need to **"stop breathing in order to continue speaking"**, **"wheezing with exercise"** (especially in the oldest group) and **"cough at night"** (mainly in the youngest group). All of them showed a high and statistically significant concordance percentage. We could also show that the questions that contribute with more information about the **evolution** and control of the asthmatic disease were significant and highly concordant. These questions were the following: **"having had wheezing in the previous 12 months"**, the frequency of **"attacks in the previous 12 months"**, the number of times **"wakening at night"** per week, having or not **"wheezing with exercise"**, and having or not **"dry cough at night in the previous 12 months"**.

Finally, the questions informing about asthma **severity** were also very concordant with significant Kappa, OR and χ^2 coefficients. These questions were: the frequency of **"attacks in the previous 12 months**, the number of times **"wakening at night"** per week, the need to **"stop breathing in order to continue speaking"**, and the **"wheezing with exercise".**

In the light of our results, we could state that the Inner Consistency of the ISAAC-Asthma questionnaire

is important and supported by statistical tests that have contributed significant results. It is also necessary to stress that the reliability confirmed by this important Inner Consistency is further guaranteed by the significant external concordance between our results and the other groups'.

In order to prove the external concordance of the Spanish version of the ISAAC Asthma questionnaire, we analysed the degree of similarity or coincidence between our results and the average results communicated in the literature of the different versions of the ISAAC questionnaire (about sensitivity, specificity, relative value and positive and negative predictive value).

The scarce data we have been able to gather show a discrete variability among them, even though they come from very distant groups and geographical areas. This confers them a universally representative character that guarantees that no bias is produced in the comparative study due to the influence of local factors.

In Table 3 the individual results obtained with the ISAAC-Asthma questionnaire are exposed, as well as the comparison between our questionnaires and the global values of the questionnaires of other groups.

A good concordance between all our diagnostic parameter values and other groups' is observed, except our Positive Predictive Value that is lower than the other groups' for most of the questions. This means that the number of affirmative answers given by our controls was higher than in other groups, that is, that in our case a systematic bias is produced due to underdiagnosis of asthma, this bias being equal to 10%. The noticed bias of our Positive Predictive Value estimation is due in a not statistically significant small proportion (2%) to the lower sensitivity of our questionnaire. Most of this difference must be attributed to the application of more strict or restrictive diagnostic criteria in our consultation than the reference theoretical criteria.

The questions whose responses differed most from the ones obtained by other groups were number 5 ("wheezing that prevents from speaking in the previous 12 months"), less times affirmative than in the other groups, and number 6 ("ever had asthma") and number 7 ("wheezing with exercise in the previous 12 months"), where we obtained more affirmative answers than the other groups.

Therefore, we conclude that the phase III of the ISAAC-Asthma questionnaire is a useful tool for the study of childhood asthma because it has Criterion validity (with high values of sensitivity, specificity and positive and negative predictive values), inner consistency in its questions and external concordance of its results with the ones obtained by other groups.

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