

# International Study of Asthma and Allergies in Childhood (ISAAC)

## Validation of the Written Questionnaire (Eczema Component) and Prevalence of Atopic Eczema among Brazilian Children

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**Summary.** Although Hanifin and Rajka's criteria have been used for the diagnosis of atopic eczema (AE), there is no instrument destined for epidemiological studies on AE that actually uses them. Written questionnaires (WQ) have generally been used, but when translated into another language they must be validated. The International Study of Asthma and Allergies in Childhood (ISAAC) WQ was previously validated in a comprehensive study, but its validation in Brazil had not been done. Our objective was to validate the eczema component of the self-applicable ISAAC's WQ following its translation into Portuguese. The group of 10 pediatricians and 10 pediatric allergologists graded the questions from 0 to 2 and established the maximum score for each question. The WQ was answered by parents or guardians of children with atopic dermatitis (AE), aged 6–7 years ( $n = 23$ ) and of non-AE control children of the same age ( $n = 46$ ) as well as by AE ( $n = 24$ ) and non-AE ( $n = 48$ ) adolescents, aged 13–14 years. In order to evaluate the reproducibility of the ISAAC WQ, half of these individuals answered the same questionnaire after 2 to 4 weeks. The maximum possible global scores were 13 for the children aged 6–7 years and 11 for the adolescents, and the cutoff level for both groups was 3. In both age periods the WQ was reproducible (Kappa and McNemar tests) in a significant way (6–7 years,  $Kw = 0.79$ ; 13–14 years,  $Kw = 0.73$ ). The prevalence of AE, using the validated WQ, was then studied. The WQ was applied to the parents of 3005 children aged 6–7 years and to 3008 children aged 13–14 years. Response rates were 72% and 94% for the 6–7-year-old children and the 13–14-year-old children, respectively. There was a slight predominance of male children in the studied population. In the group of the 6–7-year-old children, the cumulative prevalence of AE was 13.2% for boys and for girls; in the group of the 13–14-year-old children, it was 12.5% and 15.4%, respectively. AE severity was similar for both age groups. Using the criteria of global cutoff score, in the group of the 6–7-year-old children, the prevalence of AE was 12.6% for boys and 13.8 for girls; in the group of the 13–14-year-old children, it was 11.7% and 12.4%, respectively. There were no significant differences between them. In conclusion, the AE component of the ISAAC WQ proved to be reproducible, adequate, and able to discriminate between AE and control children. A significant concordance was observed between the criteria utilized in this study (ISAAC  $\times$  global cutoff score).

**Keywords:** atopic eczema, atopic dermatitis, written questionnaire, ISAAC, eczema epidemiology

## Introduction

Atopic eczema (AE) is a characteristic inflammatory disease of the skin that usually occurs in individuals with positive personal and/or familiar history of atopy. AE predominates in infants, and its prevalence and severity decrease with age. In infants and young children AE frequently occurs on the scalp, face, and other surfaces. In older children and adults, with long-standing disease, there are flexural involvement, dry and thickened skin (lichenification), and fibrotic papules [1].

Different from others skin diseases, there is no lab test or primary and/or specific lesion of EA capable of identifying it correctly. In general, the diagnosis of AE is based on a group of clinical aspects [2]. However, such criteria are complex, and their use in epidemiologic studies is difficult. Recently, one study pointed out a list of reliable items able to diagnose EA, allowing their use in epidemiologic studies [3, 4].

There are few studies of AE prevalence, mainly from Europe, and several factors interfere with the obtained data. The mild disease may go unknown or be forgotten,

1. Has your child (you) ever had an itchy rash that came and went for at least 6 months? Yes ( ) No ( )  
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 7
- 
2. Has your child (you) had this itchy rash at any time in the last 12 months? Yes ( ) No ( )  
IF YOU ANSWERED "NO" PLEASE SKIP TO QUESTION 7
- 
3. 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? Yes ( ) No ( )
- 
- 4\*. At what time did this itchy rash start:  
before 2 years of age ( ) 2 to 4 years of age ( ) After 5 years of age ( )
- 
5. Has this rash cleared up completely at any time during the last 12 months? Yes ( ) No ( )
- 
6. In the last 12 months, how often, on average, has your child (you) been kept awake at night by this itchy rash?  
Never ( ) Less than one night per week ( ) One or more nights per week ( )
- 
7. Has your child (you) ever had eczema? Yes ( ) No ( )
- \* only in the questionnaire for 6–7-year-old children

Figure 1. ISAAC core questionnaire eczema module for 6–7-year-old (13–14-year-old) children

and in older children, it can be confused with other skin diseases [5]. In addition, the several types of AE existing may add to the confusion and hinder its identification.

Recent epidemiological studies evaluating the frequency of EA in several countries showed differences in its prevalence. Like asthma, the prevalence of AE has been on the increase [6–11]. However, the different definitions, the different manner of patient identification, and the different methods used in those studies make comparisons of the results unreliable.

The acquisition of a standardized questionnaire, used by the International Study of Asthma and Allergies in Childhood (ISAAC) [12] allowed us to get a valid pattern of comparison. However, its validation is essential for preparing its application in different regions. In the present study we validated the ISAAC written questionnaire (WQ, eczema module) after its translation into Portuguese (Brazilian culture) and evaluated the prevalence of eczema in schoolchildren living in the city of São Paulo, Brazil.

## Materials and Methods

The study was performed in two complementary stages: validation of WQ (eczema module) followed by its application to school children to determine the prevalence of eczema in that population.

### Validation of the Written Questionnaire

#### Patients

Two groups of children, one consisting of 6–7-year-old and the other of 13–14-year-old children, participated in

the present study. Children with AE were selected among those who had attended the Pediatric Allergy Clinic at UNIFESP-EPM and had been followed-up for at least one year. Non-AE control (C) children were selected among children who attended the General Pediatrics Clinic of the same institution. To validate the WQ, parents or guardians of 23 EA and 46 C children between 6–7 years, and 24 EA and 48 C in the group of 13–14-year-olds were interviewed. Half of these individuals responded to the same questionnaire after 2 to 4 weeks. The second response allowed the evaluation of the reproducibility of the ISAAC WQ.

#### Translation and Scoring of the Questionnaire

The standardized ISAAC WQ, originally written in English (Figure 1), was translated into Portuguese (Brazilian culture), and the adequacy of the translated questionnaire was confirmed by a pilot study with a group of school children or their guardians. Back-translation to English resulted in few modifications of the original questionnaire. In the present study, we addressed only the eczema component of the WQ, comprising questions 1–7 of Part III. For the validation of the WQ, 10 general pediatricians and 10 pediatric allergologists were asked to grade each question from 0 to 2 according to their own view regarding importance for AE diagnosis. The maximum value for each question was considered the one chosen by 70% or more of the physicians. Using this approach, questions 1, 2, 3 were graded a score of 2 for an affirmative answer and zero for a negative answer. Question 4 was graded 2 for the answer "under the age of 2 years," 1 for "aged 2 to 4 years," and zero for "aged over 5 years." Question 5 was scored 2 for a negative answer and zero for an affirmative answer. Question 6 was scored 2 for the answer "one or more nights per week," 1 for "less than one night

**Table 1.** School children with atopic eczema (AE) and nonatopic controls (C) according to the affirmative answers (N, %) to the ISAAC WQ-eczema module

Question	6–7 years old		13–14 years old	
	E (n = 23)	C (n = 46)	E (n = 24)	C (n = 48)
1. Has your child (you) ever had an itchy rash that came and went for at least six months?	23 (100)	3 (6.5)	22 (91.7)	4 (8.3)
2. Has your child (you) had this itchy rash at any time in the past 12 months?	20 (86.9)	1 (2.1)	20 (83.3)	2 (4.1)
3. Affecting the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?	19 (82.6)	0 (0.0)	19 (79.2)	1 (2.1)
4. At what age did this itchy rash first occur?				
Under 2 years	19 (82.6)	0 (0.0)	–	–
Age 2–4 years	0 (0.0)	0 (0.0)	–	–
Age 5 or more	2 (8.7)	1 (2.1)	–	–
5. Has this rash cleared up completely at any time during the last 12 months?	7 (30.4)	2 (4.3)	7 (29.2)	1 (2.1)
6. How often, on average, has your child (you) been kept awake at night by this itchy rash?				
Never in the last 12 months	7 (30.4)	1 (2.1)	9 (37.5)	0 (0.0)
Less than one night per week	5 (21.7)	0 (0.0)	5 (20.8)	1 (2.1)
One or more nights per week	9 (39.1)	0 (0.0)	10 (41.7)	0 (0.0)
7. Has your child (you) ever had eczema?	18 (78.3)	2 (4.3)	18 (75.0)	2 (4.1)

**Table 2.** Statistical analysis summary of the ISSAC WQ (Eczema module) validation: score cut-off, likelihood ratio and concordance between answers obtained in first and second fulfill

Children (years)	Score cutoff	Likelihood ratio		McNemar test concordance (%)	Kappa test	
		Atopic eczema	Control		Kw	Z calculated
6–7	3	22.0	0.05	90.0	0.79	3.54*
13–14	3	22.5	0.14	86.7	0.73	2.84*

\*  $p < 0.05$

per week” and zero for “never.” Question 7 was scored 1 for an affirmative answer and zero for a negative answer. The maximum score to the WQ for the school children aged 6–7 years was 13 and for the adolescents it was 11.

## Study Design

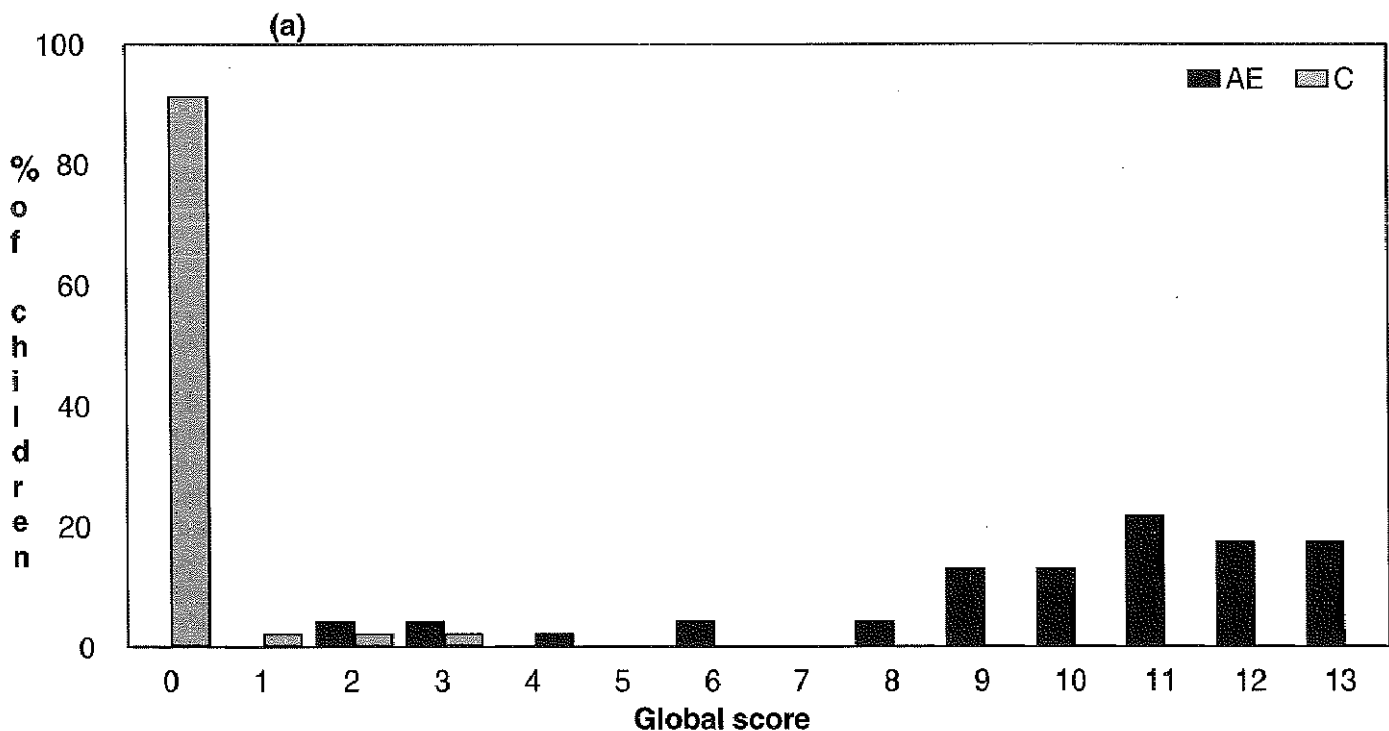
The ISAAC WQ was applied to both AE and C children aged 13–14 years, and to the parents or guardians of children aged 6–7 years (Table 1). After the questionnaire had been completed, the interviewers gave scores to the answers to each question as outlined above, and a global score was calculated for each child. The sensitivity and specificity of the scores were calculated, and the cutoff values (receiving operator curve, ROC curve) [13] were established (Figure 2). The likelihood ratio was calculated to evaluate the probability of the result of a diagnostic test being expected in patients with and without the studied disease [13] (Table 2). In order to evaluate the ISAAC WQ reproducibility, half of the individuals filled out the questionnaire a second time, 2 to 4 weeks apart. These

responses were compared based on the global cutoff score value (Table 2).

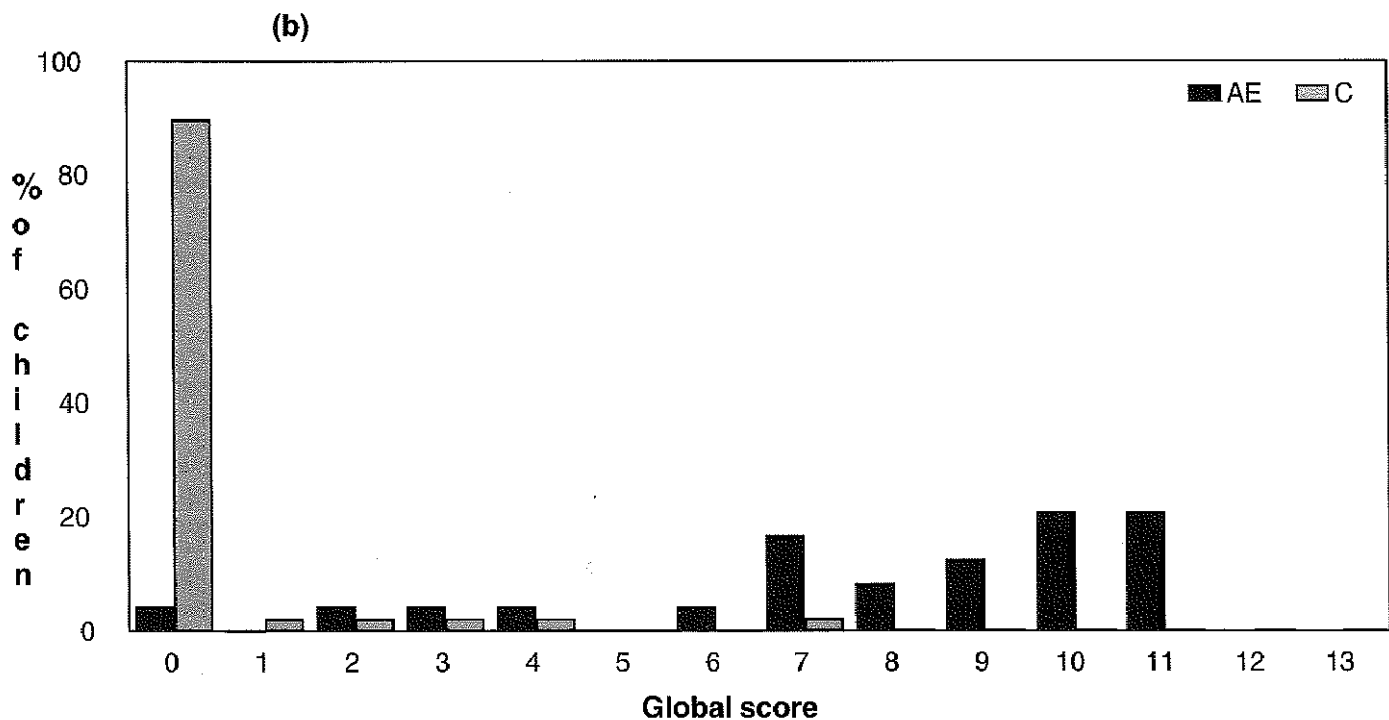
## Prevalence of Eczema

### Subjects

Subjects were selected among children who attended public and private schools in the southern area of São Paulo, where the population consists mostly of middle and lower socioeconomic classes. Information regarding the number of schools and students in the area was obtained from the official records of the city of São Paulo Bureau of Education. The schools that had students in the age groups of 6–7 years and 13–14 years were selected. Twenty-seven schools comprising 4127 students 6–7 years old were taken at random from the 167 schools in the area. Twenty-eight schools comprising 3200 students 13–14 years old were randomly selected from the 124 schools in the area (Table 3).



<b>Sensitivity -</b>	1	1	1	0.96	0.91	0.91	0.91	0.87	0.87	0.83	0.70	0.57	0.35	0.17
<b>Specificity -</b>	0.91	0.91	0.93	0.96	0.98	1	1	1	1	1	1	1	1	1



<b>Sensitivity -</b>	0.96	0.96	0.96	0.92	0.87	0.83	0.83	0.79	0.62	0.54	0.42	0.21
<b>Specificity -</b>	0.89	0.89	0.91	0.96	0.98	0.98	0.98	1	1	1	1	1

Figure 2. Global score obtained regarding questions of the eczema component of ISAAC questionnaire and its sensitivity and specificity among (a) 6–7-year-old and (b) 13–14-year-old children with atopic eczema (AE) and controls (C)

Table 3. Characteristics of selected schools<sup>#</sup>

	6–7 yrs old	13–14 yrs old
Schools	27	28
Public schools, n (%)	11 (40.7)	13 (46.4)
Number of students	4174	3200
Responders, n (%)	3005 (72%)	3008 (94%)

<sup>#</sup>Schools were selected taken at random from the public and private schools in the southern region of the city of São Paulo. Data were collected from June to October 1995.

### Study Design

WQ were completed by parents of the 6–7-year-old children and by the 13–14-year-old children themselves, during the period of June to October 1996, as recommended by the ISAAC, under the supervision of the investigators ATV or EY. The Epi-Info database, provided by the ISAAC coordinators, was used to analyze the data. The frequency of responses to each question was evaluated, according to sex and age range (Table 4). The answer to

the question number 7 (“Has your child ever had eczema?”; 6–7 years old) or question number 6 (“Have you ever had eczema?”; 13–14 years old) was cross-checked with answers to other questions in order to verify eventual discordances. According to the global cutoff score (equal or higher than 3), children were classified as AE patients and these results were compared to the medical diagnosis of eczema (Table 5).

### Statistical Analysis

The following statistical tests were used in the present study: sensitivity (true positives) and specificity (true negatives), measured by comparison between the global score in each questionnaire and the clinical diagnosis; ROC curve to obtain the global cutoff scores, likelihood ratio, McNemar test, to compare the answers to the questions, considering the diagnosis of AE; and Kappa test, to compare the frequency of AE children identified by the global cutoff score in both WQ [13]. The level for rejection

Table 4. Prevalence of atopic eczema and related-symptoms among 6–7-year-old and 13–14-year-old children, using the ISAAC WQ<sup>#</sup>

Question	6–7 years old			13–14 years old		
	M (n = 1456)	F (n = 1546)	All (n = 3005)	M (n = 1465)	F (n = 1543)	All (n = 3008)
1. Has your child (you) ever had an itchy rash that came and went for at least six months?	13.0	14.2	13.8	11.7	13.4	12.6
2. Has your child (you) had this itchy rash at any time in the past 12 months?	9.9 <sup>b</sup>	11.3 <sup>b</sup>	10.5 <sup>c</sup>	7.5	8.6	8.1
3. Affecting the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?	7.1 <sup>b</sup>	8.0 <sup>b</sup>	7.5 <sup>c</sup>	4.6	5.1	4.8
4. At what age did this itchy rash first occur?						
Under 2 years	3.3	3.3	3.3			
Age 2–4 years	3.8	4.7	4.3			
Age 5 or more	4.6	5.0	4.8			
5. Has this rash cleared up completely at any time during the last 12 months?	8.2	9.1	8.6	11.7 <sup>a,b</sup>	8.0	9.8
6. How often, on average, has your child (you) been kept awake at night by this itchy rash?						
Never in last 12 months	97.5	97.4	97.4	97.2	96.7	96.5
< 1 night per week	2.0	2.0	2.0	2.0	2.5	2.3
≥ 1 nights per week	0.5	0.6	0.6	0.8	0.8	0.8
7. Has your child (you) ever had eczema?	13.2 <sup>b</sup>	13.2	13.2	12.5	15.4 <sup>a,b</sup>	14.0
Global score	12.6	13.8	13.2	11.7	12.4	12.1

<sup>#</sup> Data represent the percentage of the total in each column; M = male, F = female

<sup>a</sup> Significantly higher values comparing sex in the same age group ( $p < 0.05$ ;  $\chi^2$ )

<sup>b</sup> Significantly higher values comparing ages in the same sex ( $p < 0.05$ ;  $\chi^2$ )

<sup>c</sup> Significantly higher values comparing ages ( $p < 0.05$ ;  $\chi^2$ )

tion of the null hypothesis was fixed at 5% ( $\alpha < 0.05$ ), and significant values are indicated by an asterisk.

## Results

### Validation

Figure 2 shows the frequency of global scores in both the 6–7-year-old and 13–14-year-old EA and C children, along with the sensitivity and specificity for each of the scores. There is a clear separation between AE and C children defined by the global score. For children of both age groups a global score of 3 revealed to be the cutoff for discriminating AE from C (i. e., a child with a global score of 3 or more had atopic eczema, and one less than 3 was judged to be normal). Considering these global cutoff scores, the likelihood ratio was 22.0 for a positive test and 0.05 for a negative test among 6–7-year-old children ( $p < 0.05$ ) (Table 2). Among the adolescents, the likelihood ratio was 22.5 for a positive test and 0.14 for a negative test ( $p < 0.05$ ) (Table 2). According to the global cutoff score, children were defined as AE and C, in the questionnaires filled out after 2 to 4 weeks. The WQ reproducibility was evaluated using those criteria. In both age periods the WQ was reproducible (Kappa and McNemar tests) in a significant way (6–7 years,  $Kw = 0.79$ ; 13–14 years,  $Kw = 0.73$ ) (Table 2).

### Prevalence

Response rates of 72% and 94% were obtained among 6–7-year-old and 13–14-year-old children, respectively

(Table 3). Approximately 51% of the responders were female in both groups.

According to results from the WQ, the prevalence of itchy rash symptoms varied from 11.7% to 14.2% without differences between age and gender (Table 4). The prevalence of itchy rash symptoms in the last year showed significantly higher values in the 6–7-year-old school children when compared to the adolescents, for both boys (9.9%  $\times$  7.5%) and girls (11.3%  $\times$  8.6%). Evaluating the group as a whole, we observed a significantly higher prevalence among the children aged 6–7 years (10.5%  $\times$  8.1%, respectively) (Table 4). Similar results were obtained regarding prevalence of lesions at AE characteristic sites (Table 4).

The age at onset of lesions was similar in both groups (Table 4). Among the 6–7-year-old school children, the time of disappearance of the lesion was similar for boys and girls. However, among the adolescents lesions disappeared most frequently among boys (Table 4). There was a remaining impairment because of disease activity in a small number of children (Table 4).

The prevalence of medical diagnosis of AE (eczema ever) was similar among the two age groups of school children (13.3%  $\times$  14.0%). However, among the boys this prevalence was significantly higher in the 6–7-year-olds (13.2%  $\times$  12.5%), whereas in the girls it was exactly the opposite (13.2%  $\times$  15.4%). Among the adolescents, the prevalence of medical diagnosis of eczema was always significantly higher for girls than for boys (12.5%  $\times$  15.4%) (Table 4).

Considering the global cutoff score, we verified a similar distribution of AE in both groups of children (13.2%  $\times$  12.1%), without differences according to gender (Table 4).

**Table 5.** Concordance (%) between affirmative answers to questions 1 to 6 and to having a global score equal to or higher than the global cutoff score (3) and to the question 7 (ever had eczema?)

Question	6–7 years old		13–14 years old	
	M	F	M	F
1. Has your child (you) ever had an itchy rash that came and went for at least 6 months?	91.2	91.2	92.2	92.0 <sup>a</sup>
2. Has your child (you) had this itchy rash at any time in the past 12 months?	90.9 <sup>a</sup>	91.2 <sup>a</sup>	90.8 <sup>a</sup>	89.3 <sup>a</sup>
3. Affecting the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes?	89.7 <sup>a</sup>	91.3 <sup>a</sup>	89.3 <sup>a</sup>	87.2 <sup>a</sup>
4. At what age did this itchy rash first occur? Under 2 years $\geq$ 2 years	87.8 <sup>a</sup>	87.3 <sup>a</sup>	–	–
5. Has this rash cleared up completely at any time during the last 12 months?	89.0 <sup>a</sup>	90.0 <sup>a</sup>	19.8 <sup>c</sup>	18.0 <sup>c</sup>
6. Has your child (you) been kept awake at night by this itchy rash?	88.2 <sup>a</sup>	87.5 <sup>a</sup>	89.0 <sup>a</sup>	87.0 <sup>a</sup>
Global score $\geq$ 3 (all)	92.2 <sup>b</sup>		92.9 <sup>b</sup>	

Teste de McNemar

<sup>a</sup> significant discordances being more to diagnose to have eczema than they have symptoms of eczema

<sup>b</sup> significant discordances being more to diagnose to have atopic eczema by ISAAC protocol than global cut-off score

<sup>c</sup> significant discordances being more the disappearance among those didn't have eczema

The comparison between response to "eczema ever" and the others showed significant levels of concordance for all combinations. There were also significant discordances (Table 5). The comparisons between to "have had eczema ever" and the global score higher than the cutoff, using the Kappa coefficient, were significant for the 6–7-year-old children ( $Kw = 0.658^*$ ) as well as for the adolescents ( $Kw = 0.69^*$ ) (Table 5).

## Discussion

In order to be useful, a WQ should be validated and reproducible. The validity is the ability of a WQ to measure what it was intended to measure, and this is expressed as sensitivity and specificity. Reproducibility measures the consistency of answers obtained during reapplication, and it is a measure of reliability. Validated in an English pilot study, the eczema component of the ISAAC's self-applicable WQ was designed as a minimum set for inclusion in self-completed or interview-administered questionnaires used in population surveys of allergic or skin diseases in children [12, 14].

Question number 1 was evaluated in a pilot study of factors that discriminated "typical" mild-to-moderate atopic dermatitis from nonatopic eczema and other inflammatory dermatoses presenting for the first time in hospital outpatient clinics. A positive response to this question was obtained for all patients with AE presenting at ages of 5–19 years and 91% of patients of all ages. Taken alone, however, it had a specificity of only 44% at ages 5–19 and 48% at all ages [14]. The specificity of the WQ (i. e., the power to exclude nonatopic forms of eczema and other inflammatory dermatoses) was improved substantially by considering flexural involvement and age at onset (questions 3 and 4). In the 5–19-year-old age group the sensitivity was 92% and specificity 96%, if case definition was based on both flexural involvement and onset before 5 years of age [14]. The question of age at onset was excluded from the self-reported version because recollection of rashes in infancy by children in their teens is likely to be incomplete [14].

Questions 5 and 6 were included as measures of the severity of the dermatitis, one assessing chronicity, the other morbidity. A question on the extent of skin involvement was considered and rejected as unfeasible for questionnaire-based studies [14]. Question 7 discloses medical diagnosis of eczema and may be changed as well as the different denominations of AE in that place [14].

In our study, the validation of the questionnaire translated into Portuguese (Brazilian culture) was accomplished by evaluating its sensitivity and specificity. Comparisons between a global score attributed to the answers to the questionnaire and the respective diagnosis were used to assess the ability of the questionnaire to discriminate true AE from true non-AE, according to previously

described guidelines [12–14]. For children 6–7 years old, the global score of 3 had 96% sensitivity and 96% specificity, allowing a clear separation of AE children from normals (Table 2). For the adolescents, the global score of 3 had 92% sensitivity and 93% specificity. The likelihood ratio demonstrated for both age groups that the chance of having a global score equal or superior to 3 was approximately 22 times higher among the children with AE than among controls.

In order to evaluate the reproducibility of self-applicable WQ, the interval of time between the two responses should be long enough so that the individuals have forgotten their answers, but not so long that the symptoms have changed. For the two age groups the concordance indexes were approximately 90%. The reproducibility of the ISAAC questionnaire, assessed by test-retest and evaluation of the Kappa coefficient [11] shows that it is reproducible in a significant way (Table 3).

The frequency of affirmative answers to questions that evaluate the presence of skin rash in the last year, involving characteristic sites and start before the age of two was 82.6% for 6–7-year-old children. This observation corroborates the previously observed in the initial validation of the ISAAC WQ.

The prevalence of AE among our children were similar to the observed by other authors [15–18]. They were between the range observed by the AE-ISAAC's report [15]: from 2 to 16% for the 6–7-year-old children, and from 1 to 17% for the adolescents. Atopic eczema is a common health problem for children and adolescents in São Paulo, Brazil.

In conclusion, the eczema component of the ISAAC WQ, translated into Portuguese (Brazilian culture), provides an adequate and a reproducible way to differentiate between AE and non-AE among Brazilian children.

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