

International Study of Wheezing in Infants (EISL): Validation of Written Questionnaire for Children Aged Below 3 Years

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■ Abstract

Background: The multicenter International Study of Wheezing in Infants (EISL) was developed to study the prevalence of recurrent wheezing and related risk factors in infants during the first year of life using a written questionnaire (EISL-WQ).

Objectives: To constructively validate a modified, shortened version of the EISL-WQ in children up to 36 months of age in São Paulo, Brazil, and to verify its usefulness in diagnosing probable asthma in these children.

Methods: The parents of 170 infants aged 12 to 36 months answered the shortened EISL-WQ in an emergency room and were asked if their child was currently wheezing before a diagnosis was made by a physician. The consistency between parent perception and the physician's diagnosis was then evaluated. A second group (n = 55) participated in the validation of the short-term repeatability of the shortened questionnaire by completing it twice (mean interval, 23 days).

Results: There was good agreement between parent perception of wheezing and the physician's diagnosis following auscultation (Kappa statistic = 0.7; odds ratio = 38.33; 95% confidence interval, 15.8 to 92.8; $P < .001$); sensitivity (82.8%), specificity (85.0%), positive predictive value (81.5%), and negative predictive value (86.0%) were all high. The short-term repeatability of the shortened version of the EISL-WQ was also high ($\kappa > 0.75$). Questions added to the shortened EISL-WQ improved the internal consistency of the original questionnaire (Cronbach $\alpha = 0.823$, $P < .001$) and a high Youden index was found for patients defined as probable asthmatics.

Conclusions: The shortened version of the EISL-WQ translated into Portuguese has high internal consistency, and is a valid, reliable, and reproducible instrument for obtaining data on wheezing in children below 36 months of age and for identifying those with probable asthma.

Key words: Asthma. Infants. Written questionnaire. Reproducibility. Validation.

■ Resumen

Antecedentes: El Estudio Internacional de Sibilancias en lactantes (EISL) fue desarrollado para valorar la prevalencia de las sibilancias recurrentes y factores de riesgo relacionados en niños durante el primer año de vida usando un cuestionario escrito (EISL-CE).

Objetivos: Validar constructivamente una versión reducida y modificada de EISL-CE en niños con edades inferiores a 36 meses en São Paulo, Brasil, y comprobar su utilidad diagnosticando el probable asma en estos niños.

Métodos: Los padres de 170 niños con edades comprendidas entre 12 y 36 meses respondieron a una versión reducida de EISL-CE en una sala de urgencias y se les preguntó si el niño presentaba sibilancias en ese momento antes de ser diagnosticado por un médico. Se evaluó la consistencia entre la percepción de los padres y el diagnóstico del médico. Un segundo grupo (n = 55) participó en la validación de la reproducibilidad a corto plazo del cuestionario reducido rellenándolo en dos ocasiones (intervalo medio de tiempo, 23 días).

Resultados: Existía una buena concordancia entre la percepción de los padres sobre las sibilancias y el diagnóstico del médico tras la auscultación (el índice Kappa = 0,7; la odds ratio = 38,33; el intervalo de confianza al 95%, de 15,8 a 92,8; $P < ,001$); la sensibilidad (82,8%), la especificidad (85,0%), el valor predictivo positivo (81,5%), y el valor predictivo negativo (86,0%) fueron altos. La reproducibilidad a corto plazo de la versión reducida del EISL-CE fue también alta ($\kappa > 0,75$). Las preguntas añadidas al EISL-CE reducido mejoraron la

consistencia interna del cuestionario original (Cronbach $\alpha = 0,823$, $P < ,001$) y se encontró un elevado índice Youden para los pacientes definidos como probablemente asmáticos.

Conclusiones: La versión reducida del EISL-CE traducida al portugués tiene una alta consistencia interna, y es un instrumento válido, fiable y reproducible para obtener datos sobre las sibilancias en niños con menos de 36 meses de edad y para identificar aquellos con probable asma.

Palabras clave: Asma. Niños. Cuestionario escrito. Reproducibilidad. Validación.

Introduction

During the first years of life, pulmonary and nonpulmonary diseases can clinically manifest as recurrent wheezing [1]. It is difficult to establish the period prevalence of the wheezy baby syndrome, defined as recurrent episodes of wheezing. Studies evaluating the prevalence of recurrent wheezing in children younger than 1 year old have found rates varying from 10% to 42% [2-4]. The lack of a standardized and properly validated method capable of identifying wheezy babies may account for the scarcity and wide variability of data available.

It is unknown if the prevalence of recurrent wheezing in infants during the first year of life is increasing at a similar rate to that observed for asthma prevalence [5,6]. In Brazil, the prevalence of recurrent wheezing during the first year of life is unknown. The International Study of Wheezing in Infants (Estudio Internacional de Sibilancias en Lactantes, EISL) was designed to determine wheezing prevalence, characteristics (frequency, severity), and risk factors in infants under the age of 1 in different parts of Latin America, Spain, and Holland [7]. The main tool used in this study is a standardized written questionnaire (EISL-WQ) composed of 45 questions about demographic characteristics, wheezing and respiratory symptoms, medication use, physician diagnosis, and possible risk factors. The EISL-WQ was designed to be answered by the infant's parents or guardians [7].

The Spanish and Portuguese versions of the EISL-WQ, validated in different settings [8,9], have shown good agreement between objective physical examination and wheezing reported by parents/guardians of 12- to 15-month-old infants. The questionnaire has also proven to be a reliable means of obtaining data on wheezing in the first year of life, with high sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) [8,9].

As the EISL-WQ was specifically designed to evaluate the prevalence of wheezing in children during their first year of life, we decided to check if the original questionnaire, translated into Portuguese (Brazilian culture) and used in combination with a series of additional questions would be suitable for use in children between 12 and 36 months old. Furthermore, it was necessary to evaluate the repeatability and internal consistency of the EISL-WQ, as this had not been done in either of the validation studies [8,9].

Methods

Children

Children aged 12 to 36 months and their parents/guardians were involved in the study. They were divided into 2 groups

according to where they had been recruited. Each group was used to evaluate a different study objective.

Group 1 was constituted by children ($n = 176$ [91 boys]; mean age [SD], 20.9 [7.2] months) whose parents/guardians had sought medical care for respiratory and other problems in the emergency room of Hospital São Paulo, Brazil (UNIFESP-EPM) (Table 1). They participated in the construct validation of the shortened version of the EISL-WQ (February to December 2005). Group 2 was constituted by children ($n = 55$ [24 boys]; mean age [SD], 17.1 [5.3] months) who had visited the pediatric outpatient clinic at the UNIFESP-EPM for regular, routine follow-up. They were involved in the evaluation of the test-retest reliability of the shortened EISL-WQ (February to August 2006), which they completed on 2 occasions, 2 to 4 weeks apart (mean, 23 days).

Parents/guardians of the children in group 1 answered the questionnaire and were then asked if their children had current wheezing or whistling in the chest area. This was done before the children were examined and a diagnosis made. The answer was then compared to the pediatrician's findings. Wheezing was characterized by the presence of inspiratory or expiratory whistling, diffuse or local, of any intensity, and accompanied or not by respiratory distress.

Shortened Version of the EISL Written Questionnaire

The original EISL-WQ, which is in Spanish, contains 45 questions on demographic characteristics, wheezing and respiratory symptoms, medication use, medical diagnosis and possible risk factors [7]. It was translated into Portuguese and backtranslated into Spanish with no modifications [8]. Although already validated in Spanish [8] and Portuguese [9], specific questions about wheezing and asthma (1 to 13 and 17 in the EISL-WQ) are related to the diagnosis of wheezing and must be well understood by parents.

The shortened EISL-WQ was composed of questions 1 to 13 and 17 of the original questionnaire in addition to 4 other questions: 1A, Has your baby had wheezing or whistling in the chest or bronchitis in the last 12 months? ("Seu bebê teve sibilâncias ou chiado no peito ou bronquite nos últimos 12 meses?"); 6A, Has your baby been treated with oral corticosteroids? ("Seu bebê recebeu tratamento com corticóides orais?"); 15, Has a doctor diagnosed your baby as having atopic dermatitis? ("Seu bebê tem diagnóstico médico de dermatite atópica?"); and 16, Has a doctor diagnosed your baby as having food allergy? ("Seu bebê tem diagnóstico médico de alergia alimentar?").

Infants were considered probable asthmatics if they had had at least 3 wheezing episodes in the last year and any of the

following: atopic dermatitis, a medical diagnosis of asthma, or a parental history of asthma [10].

All the parents/guardians signed an informed consent form before enrollment in the study. The study was approved by the ethics committee at the UNIFESP-EPM.

Statistical Analysis

Sample size (wheezing children = 60) was calculated on the basis of a difference ratio of 2:1 for parents/guardians correctly versus not correctly identifying wheezing in their children, with a power of 80% and an α error of 5%. The data obtained were transferred to a Microsoft Excel 2000 database and analyzed using SPSS for Windows (versions 11.0 and 13.0).

Parametric (*t* test) and nonparametric tests (χ^2 test, Fisher exact test, Mann-Whitney test, κ statistic, and Cronbach α) were employed. The Cronbach α was calculated to check the internal consistency of the questionnaire and a value higher than 0.8 was considered acceptable. PPV, NPV, accuracy, sensitivity, and specificity were calculated on the basis of agreement between the answer given by the parents/guardians and the presence of wheezing during the physical examination. Sensitivity, specificity, PPV, NPV, and the Youden index were calculated for the following variables: history of wheezing, history of frequent wheezing (3 or more episodes), and diagnosis of probable asthma [11].

Results

Six children from group 1 were withdrawn because their questionnaires had not been correctly completed. Valid group 1 questionnaires ($n=170$) had been filled in mainly by the children's mothers (87.1%); 10.6% of those who had filled in the forms were fathers and 2.3%, grandmothers. The main characteristics of the children in this group are shown in Table 1. There was a modest predominance of boys and there was no difference between boys and girls in terms of age at the time of the study, age at which they had experienced the first wheezing episode, or weight at birth (Table 1). No significant differences were found for reported wheezing between children with and without current wheezing (data not shown).

A previous episode of wheezing was reported for 123 (72.4%) of the 170 children from group 1 and 61 (49.6%) of these had had 3 or more episodes in the first year of life (recurrent wheezers, Table 2). On comparing children with and without a history of wheezing, we found a significantly higher frequency of affirmative responses to the majority of the questions for the former. The exceptions were questions 5 (use of inhaled corticosteroids), 6 (use of antileukotrienes), 11 (asthma diagnosed by a physician), 12 (pneumonia diagnosed by a physician), 13 (hospital admission due to pneumonia), 14 (positive family history of asthma), 15 (positive history of atopic eczema), and 16 (medical diagnosis of food allergy) (Table 2). Children who had had 3 or more episodes of wheezing were significantly younger than those who had fewer than 3 episodes (4.7 [2.5] months vs 9.8 [7.4] months; $P < .001$). They also had a higher prevalence of wheezing episodes in the first year of life, a higher use of oral corticosteroids, a higher

frequency of hospitalization due to wheezing episodes, and more frequent wheezing at admission (Table 2).

There was significant agreement between answers to question 1 "Has your baby had wheezing or whistling in the chest area or bronchitis in the first 12 months of life?" and question 1A "Has your baby had wheezing or whistling in the chest area or bronchitis in the last 12 months?" and all the other questions in the shortened EISL-WQ. A κ value of higher than 0.5, however, was only observed for a few of these, most of which were related to treatment (Table 3).

Internal consistency, measured by the Cronbach α , was statistically significant for the original EISL-WQ ($\alpha=0.804$, $P < .001$) and even higher for our shortened version ($\alpha=0.823$; $P < .001$). Test-retest reliability for the shortened questionnaire showed a high level of agreement ($\kappa > 0.75$) for questions 1, 1A, 5, 6A, 8, 10, 12, 13, and 14, and moderate agreement (κ range, 0.45-0.75) for questions 2, 4, 9, 11, and 15 (Figure 1).

Agreement between reported wheezing and auscultation at the physical examination was highly significant ($\kappa=0.716$, $P < .001$) (sensitivity, 83.3%; specificity, 88.5%; PPV, 82.0%; and NPV, 89.3%). This was also the case when children with a previous history of wheezing were analyzed separately ($\kappa=0.66$, $P < .001$).

A significantly higher frequency of affirmative answers was observed for the majority of questions in the shortened version of the questionnaire in infants identified as asthmatics, except for questions on the previous use of leukotriene receptor antagonists, wheezing episodes associated with shortness of breath, pneumonia, hospitalization due to pneumonia, and food allergies (Table 4). In an individual analysis of all the questions, higher Youden indexes were found for infants that had had 3 or more wheezing episodes, been treated with inhaled corticosteroids, or diagnosed as having asthma or atopic dermatitis by a physician (Table 4).

Table 1. Main Characteristics of Infants Seen in the Emergency Room for Respiratory and Other Conditions (Group 1)

Variable	Gender		Total
	Boys	Girls	
Children, No. (%) ^a	88 (52)	82 (48)	170
Mean (SD) age mo ^b	21 (6.9)	21 (8.1)	20.9 (7.2)
Children weighing < 2500 g at birth, ^a No. (%)	16 (18.2)	11 (13.4)	27 (15.9)
Mean (SD) age at first wheezing episode, mo ^b	5.0 (4.8)	6.0 (6.8)	7.6 (6.3)

^a Studied using χ^2 test (no significant differences found between sexes).

^b Studied using *t* test (no significant differences found between sexes).

Table 2. Frequency (%) of Affirmative Answers in the Shortened Version of the Written EISL Questionnaire for Children With Previous Wheezing and Those With 3 or More Episodes in the Last 12 Months^a

Questions	Previous Wheezing		Three or More Wheezing Episodes	
	Yes (n=123) %	No (n=47) %	Yes (n=62) %	No (n=61) %
1. Did your baby have wheezing/bronchitis in the first 12 months of life?	82.1 ^b	0.0	98.4 ^b	65.6
1A. Has your baby had wheezing/bronchitis in the last 12 months?	89.4 ^b	0.0	92.0	86.7
2. Did your baby have 3 or more wheezing episodes in the first year of life?	49.6 ^b	0.0	–	–
4. Has your baby been treated with inhaled short-acting β 2-agonists by metered dose inhaler or nebulizer?	94.3 ^b	23.4	98.4	90.2
5. Has your baby been treated with inhaled corticosteroids?	0.6	0.0	11.3	1.6
6. Has your baby been treated with antileukotrienes?	0.2	0.0	3.2	1.6
6A. Has your baby been treated with oral corticosteroids?	72.3 ^b	6.4	87.1 ^b	57.4
7. Has your baby been aroused at night due to cough, wheezing or suffocation more than once in the last 12 months?	52.8 ^b	21.2	66.1	50.1
8. Has your baby had wheezing episodes severe enough to require emergency care in the last 12 months?	52.8 ^b	2.1	38.7	47.5
9. Has your baby had a wheezing episode associated with shortness of breath in the last 12 months?	48.0 ^b	8.5	53.2	42.6
10. Has your baby been hospitalized due to a wheezing episode?	24.4 ^b	0.0	33.9 ^c	14.8
11. Has a doctor diagnosed your baby as having asthma?	5.7	0.0	6.5	4.9
12. Has your baby had pneumonia?	43.0 ^b	17.0	43.5	42.7
13. Has your baby been hospitalized due to pneumonia?	19.5 ^c	6.4	22.6	16.4
14. Does your baby have any relatives with asthma?	29.3	25.6	35.5	23.0
15. Has a doctor diagnosed your baby as having atopic eczema?	16.3	12.8	22.6	9.8
16. Does your baby have food allergy?	6.5	4.2	8.1	4.9
17. Is your child wheezing at this moment?	49.6 ^b	12.8	58.1	41.0
18. Did your child wheeze during the physical examination?	48.8 ^b	12.8	61.3 ^b	36.1

^aThe items shown have been translated into English by the authors of the study for comprehension purposes only.

^b $P < .001$ (Fisher exact test)

^c $P < .05$ (Fisher exact test)

Table 3. Agreement^a Between Answers to Questions of the Shortened Version of the Written EISL Questionnaire With the Questions "Did your baby have wheezing in the first 12 months of life" and "Has your baby had wheezing in the last 12 months"^b

	Infants With Wheezing in the	
	First 12 Months of Life	Last 12 Months
1A. Has your baby had wheezing/bronchitis in the last 12 months?	0.56	–
2. Has your baby had 3 or more wheezing episodes?	0.54	0.36
4. Has your baby been treated with inhaled short-acting β 2-agonists by metered dose inhaler or nebulizer?	0.54	0.64
6A. Has your baby been treated with oral corticosteroids?	0.56	0.47
8. Has your baby had wheezing episodes severe enough to require emergency care in the last 12 months?		
9. Has your baby had a wheezing episode associated with shortness of breath in the last 12 months?	0.30	0.38
10. Has your baby been hospitalized due to a wheezing episode?	0.21	0.17
11. Has a doctor diagnosed your baby as having asthma?	0.06	0.05
12. Has your baby had pneumonia?	0.19	0.14
13. Has your baby been hospitalized due to pneumonia?	0.08	0.08

Abbreviation: EISL indicates Estudio Internacional de Sibilancias en Lactantes (International Study of Wheezing in Infants).

^aLevel of agreement measured using the κ statistic. Only questions with a statistically significant level of agreement ($P < .05$) are shown.

^bThe items shown have been translated into English by the authors of the study for comprehension purposes only.

Table 4. Frequency (%) of Affirmative Answers in the Shortened Version of the Written EISL Questionnaire in Infants With and Without a Diagnosis of Asthma. Determination of Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV), and the Youden index (Y)^a.

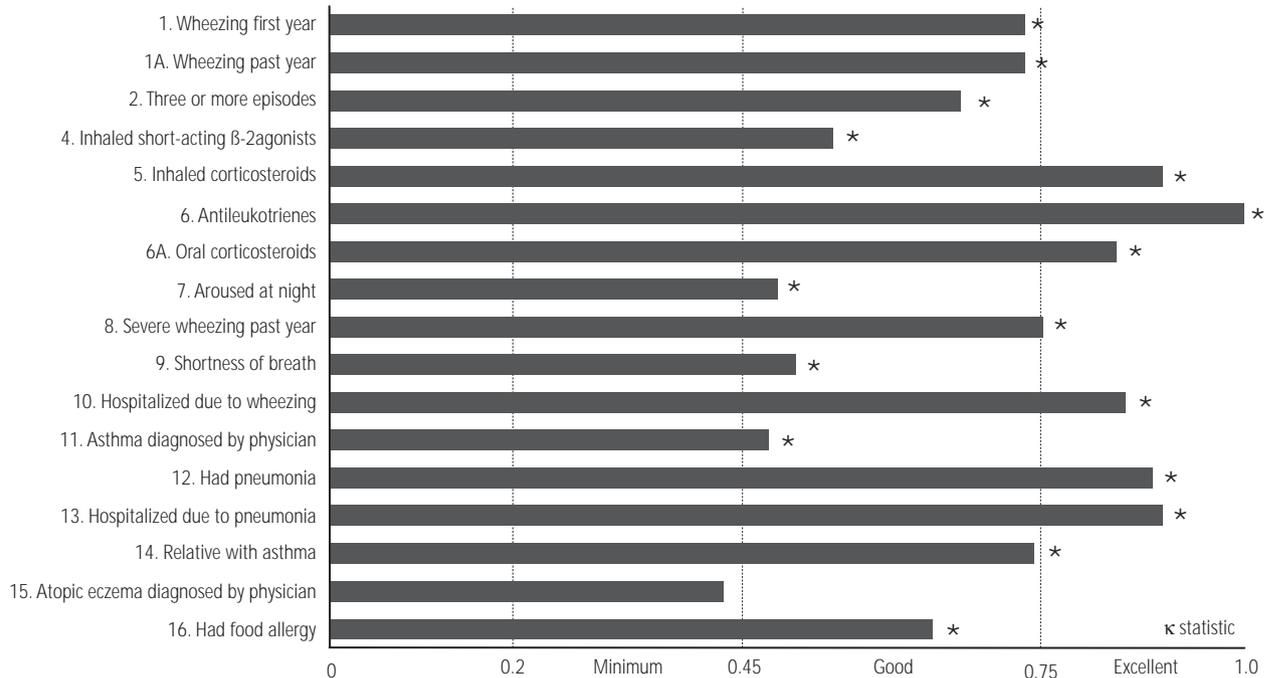
	Children With Probable Asthma						
	Yes (n=27) %	No (n=143) %	Se	Sp	PPV	NPV	Y
1. Did your baby have wheezing/bronchitis in the first 12 months of life?	100.0 ^b	51.7	27	100	100	49	.27
2. Has your baby had wheezing/bronchitis in the last 12 months?	96.3 ^b	58.8	24	98	96	41	.22
4. Has your baby been treated with inhaled short-acting β 2-agonists by metered dose inhaler or nebulizer?	100.0 ^b	24.5	43	100	100	76	.43
5. Has your baby been treated with inhaled corticosteroids?	100.0 ^b	69.9	21	100	100	30	.21
6. Has your baby been treated with antileukotrienes?	18.5 ^b	2.1	63	86	19	98	.44
6A. Has your baby been treated with oral corticosteroids?	0	2.1	0	83	0	98	.17
7. Has your baby been aroused at night due to cough, wheezing or suffocation more than once in the last 12 months?	92.6 ^b	46.9	27	98	93	53	.25
8. Has your baby had wheezing episodes severe enough to require emergency care in the last 12 months?	74.1 ^b	43.4	25	92	74	57	.17
9. Has your baby had a wheezing episode associated with shortness of breath in the last 12 months?	66.7 ^b	36.4	26	91	67	64	.17
10. Has your baby been hospitalized due to a wheezing episode?	51.9	34.3	22	88	52	66	.10
11. Has a doctor diagnosed your baby as having asthma?	33.3 ^c	14.7	30	87	33	85	.17
12. Has your baby had pneumonia?	14.8 ^b	3.2	57	86	15	98	.43
13. Has your baby been hospitalized due to pneumonia?	51.9	32.9	23	88	52	67	.11
14. Does your baby have any relatives with asthma?	22.2	14.7	22	85	22	85	.07
15. Has a doctor diagnosed your baby as having atopic eczema?	63.0 ^b	21.7	35	92	63	78	.27
16. Does your baby have food allergy?	51.9 ^b	8.4	54	91	52	92	.45
17. Is your child wheezing at this moment?	14.8	4.2	40	86	15	96	.26
18. Did your child wheeze during the physical examination?	63.0 ^b	35.0	26	90	63	65	.16

Abbreviation: EISL indicates Estudio Internacional de Sibilancias en Lactantes (International Study of Wheezing in Infants).

^aThe items shown have been translated into English by the authors of the study for comprehension purposes only.

^b $P < .001$ (Fisher exact test)

^c $P < .05$ (Fisher exact test)



* $P < .001$

Figure. Shortened EISL-WQ test-retest repeatability: Kappa coefficient (κ) calculation between answers obtained from the same subjects in 2 different interviews (first vs second) 23 days apart.

Discussion

We found no significant differences between boys and girls in group 1 in terms of the frequency of positive answers. More than 72% of these children had a previous history of wheezing and at least half of them were identified as recurrent wheezers. As expected, among the wheezy infants there was a significantly high frequency of reported daily and nocturnal symptoms, severe symptoms, use of rescue medication, hospitalization due to wheezing, and wheezing at the moment of clinical evaluation (Table 2).

In the subgroup of recurrent wheezers, we observed a high and significant frequency of wheezing in the last 12 months, use of oral corticosteroids, hospitalization for wheezing, and wheezing during physical examination. Because oral corticosteroids are widely used in patients of this type—much more so than inhaled corticosteroids—we do not believe that use of oral corticosteroids was a good marker for the risk of recurrent wheezing in our series (Table 2).

The association between pneumonia and recurrent wheezing in infants is well known [12,13]. While the parents of wheezy infants have indicated a high frequency of pneumonia and hospitalizations due to pneumonia in their children, we were unable to confirm this association in our study. Possibly the size and composition of the sample did not provide sufficient statistical power.

Despite the high prevalence of recurrent wheezing in our study, only a few of the children had been diagnosed as asthmatic. In many cases, a diagnosis had probably been missed

at the primary care level because of a low frequency of wheezing episodes, failure to refer the child to a specialized center, and a lack of specific treatment for infants with recurrent wheezing. When we applied the criteria proposed by Castro-Rodriguez et al [10] for identifying probable asthmatic infants, we found a significantly higher prevalence of affirmative answers to virtually all the questions in children with recurrent wheezing. However, the best relationship between sensitivity and specificity (Youden index) was found for use of inhaled short-acting β_2 -agonists, use of antileukotrienes, previous pneumonia, and a diagnosis of food allergy by a physician (Table 4).

There is no consensus about the time interval between interviews for the evaluation of the short-term repeatability of written questionnaires [14-17]. In this study, the shortened version of the EISL-WQ proved to be reliable after a mean interval of 23 days (Figure 1). Questions dealing with previous wheezing episodes, use of medication, severe symptoms, diagnosis of pneumonia, hospitalization due to pneumonia, and family history of asthma, proved to be very reliable ($\kappa > 0.75$). The short period of time between the first wheezing episode and the completion of the questionnaire might explain these results as questions regarding more severe pictures and objective data are easily remembered for more time. Questions dealing with other aspects such as the age of onset of symptoms, the use of inhaled bronchodilators, diagnosis of asthma, number of emergency room visits, and association with atopic dermatitis were also seen to be significantly reliable (κ range, 0.45-0.75). Strippoli et al [18] also observed good repeatability for questions on wheezing in a written questionnaire sent by mail

for use in a community-based study of respiratory symptoms in children aged between 1 and 2 years.

We confirmed that the original EISL-WQ has strong repeatability and high internal consistency (Cronbach $\alpha=0.804$). The internal consistency of the shortened version was slightly higher than that of the original questionnaire (Cronbach $\alpha=0.823$). Powell et al [19] presented similar results for a respiratory symptom questionnaire designed for use in epidemiological and follow-up studies in infants and preschool children. The validity of this instrument was assessed using a diagnosis of asthma by a respiratory expert and was considered to be very strong and to have excellent internal consistency; its questions showed good to moderate short-term reliability.

Although several authors have questioned parents' ability to inform on their children's respiratory symptoms [20-23], others have demonstrated that they are able to do so correctly [24-27]. In our study, we observed a good level of agreement between reported wheezing and objectively confirmed wheezing, even though the analysis was limited to infants without a previous history of this symptom. The short period of time between these events could explain this finding. We can therefore state that parents of infants aged between 12 and 36 months with recurrent wheezing, rare episodes of wheezing, or no wheezing (current) are able to correctly identify if their children are wheezing or not over a statistically significant period of time.

In conclusion, the shortened Portuguese version of the EISL-WQ proved to be a valid and reproducible means of obtaining reliable data on wheezing in infants aged 12 to 36 months. Like the original EISL-WQ, the shortened version had high sensitivity, specificity, PPV, NPV, reliability, agreement, and internal consistency. Finally, it also proved capable of identifying infants with probable asthma.

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