

The International Study of Wheezing in Infants: Questionnaire Validation

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Key Words

Asthma • Children • Epidemiology • Infant • Questionnaire • Wheezing

Abstract

Background: There are no internationally validated questionnaires to investigate the prevalence of infant wheezing. This study was undertaken to validate a questionnaire for the International Study on the Prevalence of Wheezing in Infants (Estudio Internacional de Sibilancias en Lactantes, EISL). **Material and Methods:** Construct and criterion validity were tested for the question 'Has your baby had wheezing or whistling in the chest during his/her first 12 months of life?'. Construct validity (i.e. the ability of parents and doctors to refer to the same symptoms with the same words) was tested in a sample of 50 wheezing and 50 non-wheezy infants 12–15 months of age in each of 10 centres from 6 different Spanish- or Portuguese-speaking countries. Criterion validity (i.e. the ability of parents to correctly detect the symptom in the general population) was evaluated in 2 samples (Santiago, Chile and Cartagena, Spain) of 50 wheezing

and 50 non-wheezing infants (according to parents) of the same age, randomly selected from the general population, who were later blindly diagnosed by a paediatric pulmonologist. **Results:** Construct validity was very high (κ test: 0.98–1) in all centres. According to Youden's index, criterion validity was good both in Cartagena (75.5%) and in Santiago (67.0%). Adding questions about asthma medication did not improve diagnosis accuracy. **Conclusions:** The EISL questionnaire significantly distinguished wheezy infants from healthy ones. This questionnaire has a strong validity and can be employed in large international multicentre studies on wheezing during infancy.

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Introduction

Recurrent wheezing in infants plays an important role in the morbidity at this age, both in developing and developed regions of the world. Despite the large public health impact of wheezing in infancy, especially in developing countries, there is no comparative information on

its prevalence, particularly during the first year of life, when the individuals are probably more vulnerable to complications due to the immunologic, functional and anatomic characteristics of their airways. Contrary to what occurs in schoolchildren and adults – where well-standardized and validated questionnaires for use in international or multicentre studies have been globally tested and are easily available – there is very little information on respiratory surveys in infants [1–6].

There is a surprising lack of information with respect to the validity of questionnaires employed to assess wheezing in infants and toddlers, and there is no ‘gold standard’ for these questionnaires. We could only find 1 study, originally designed to validate a questionnaire to be responded by parents of wheezy infants in the UK [7]. However, no information has yet been published which can provide internationally validated and standardized wheezing-related questions to be used in comparative studies between different countries or populations. A standardized and validated international questionnaire for wheezing in infants would certainly help to decrease the potential biases derived from the dissimilarities in cultural and socio-economic aspects between countries, as well as from the differences related to parental interpretation, identification and reporting of symptoms, and from the variability of doctors’ labelling of wheezing [8–10].

Therefore, prior to starting large-scale multinational studies on the prevalence, severity and risk factors of wheezing in infants, even when similar languages are employed, it appears to be necessary to validate the parental ability to identify and report wheezing in their infants. This study was undertaken to validate a questionnaire to be used in the first international comparative study on wheezing during the first year of life to be undertaken in centres from Latin America and Spain.

Methods

The International Study of Wheezing in Infants (or EISL from the Spanish Estudio Internacional de Sibilancias en Lactantes) has been developed to know and compare the prevalence of recurrent wheezing (3 or more episodes in the first year of life) in infants from Latin America and Spain. Other centres in other countries, as in the Netherlands, have already joined this initiative and are on their way to validate the questionnaire in their own language. Additionally, the study also aims to examine the severity of wheezing and its relationship with other respiratory diseases such as pneumonia, together with its potential risk factors. The EISL is a multicentre, international, population-based and cross-sectional study on wheezing in infants during the first year of life,

and employs the same epidemiological instrumentation in all its centres. It is mainly based on the International Study of Asthma and Allergies in Childhood (ISAAC) methods. Most of the EISL participating centres have already formed part of the ISAAC phases 1 and/or 3. The methodology of EISL has been extensively described elsewhere (www.respirar.org/eisl).

Validation

The aim of the present study was to validate the construct and criterion validity of the question ‘Has your baby had wheezing or whistling in the chest during his/her first 12 months of life?’, considering that in Spanish or Portuguese there is no exact equivalent to the English word ‘wheezing’.

To evaluate the construct validity (i.e. the ability of parents and doctors to refer to the same symptoms with the same words) across centres, an approximate number of 50 cases and 50 controls were selected at random from 10 centres in several countries (Chile, Peru, Brazil, Bolivia, Mexico and Spain) in a similar way to a previous study on questionnaire validation for wheezing in infants [7]. Cases were defined as those children who had recurrent wheezing (diagnosed by a paediatric respiratory specialist) during their first year of life and were followed up at the paediatric respiratory outpatient clinic. Controls were healthy infants without a history of wheezing or pneumonia during the same period of time. These controls were selected when parents took their infants aged 12–15 months to primary health care centres for routine health controls.

To test the instrumental or criterion validity (i.e. the ability of parents to correctly detect the symptom in the general population) across countries with different socio-economic backgrounds but the same language, the EISL questionnaire was administered to a sufficient number of parents of infants randomly selected from a general population to obtain at least 50 infants whose parents said that their offspring had wheezed during their first year of life (cases). This part of the study was performed in Cartagena (Spain) and Santiago (Chile). The 50 cases and 50 controls (children randomly selected among those infants whose parents answered that their offspring had not suffered from wheezing during their first year of life) were blindly evaluated by a paediatric pulmonologist who – after reviewing the clinical records and discussing them with the infant’s primary care paediatrician – answered the same key question as the parents. Previous studies on asthma questionnaires have calculated reliability, internal consistency and aspects of validity using between 40 and 160 subjects [7, 11–14]. This part of the validation study was carried out in the same setting where the main study was going to take place, and was addressed to the same eligible parents (namely primary health care centres and parents of children attending to receive mumps-rubella-measles vaccination at 12 or 15 months of age, depending on the country).

Analysis

Convergent and discriminant validity (construct validity) were expressed as the percent agreement between parents and doctors, as the κ statistic and also as the percentage of negative answers among parents of ‘true wheezing’ and of positive answers among parents of ‘true non-wheezing’ infants. Criterion validity was additionally evaluated by means of the diagnostic tests, i.e. sensitivity, specificity as well as positive and negative predictive values, considering the paediatric pulmonologist’s diagnosis as

Table 1. Construct validity of the concept ‘sibilancias silbido o pitos en el pecho’ (Spanish) or ‘sibilancias ou chiado no peito’ (Portuguese) for the English ‘wheezing or whistling in the chest’ across several Spanish- and Portuguese-speaking countries

Centre	Country	Cases/ controls	Agreement %	κ	Parents+ physician– %	Parents– physician+ %
Belo Horizonte	Brazil	50/50	100	1.0	0	0
Curitiba	Brazil	35/54	100	1.0	0	0
Lima	Peru	51/50	99	0.98	0	1.0
Merida	Mexico	52/52	100	1.0	0	0
Punta Arenas	Chile	74/25	100	1.0	0	0
Porto Alegre	Brazil	52/50	100	1.0	0	0
Santa Cruz	Bolivia	40/40	100	1.0	0	0
Santiago	Chile	40/46	98.8	0.98	1.2	0
Valdivia	Chile	50/50	100	1.0	0	0
Cartagena	Spain	48/51	97.9	0.98	2.0	0

Parents’ answers in 2 different settings (wheezing infants from a respiratory unit vs. healthy selected infants from a routine health control) are compared to the paediatric pulmonologist diagnoses.

the gold standard. As the aim of the EISL study is to compare prevalences between different populations, Youden’s index (percentage of sensitivity plus percentage of specificity minus 100), which provides a good measure of the criterion validity for a determined question [15], was also employed for the analysis.

Ethics Committee Approval and Informed Consent

This study had the approval of the Scientific Ethics Committee, Chilean Ministry of Health, Southern Metropolitan Area of Santiago de Chile (Chile) and of the Ethics Committee, University of Murcia (Spain). Full informed written consent was obtained from all parents.

Results

To test the construct validity, a total of 960 (492 cases and 468 controls) questionnaires from 10 different centres were collected. The agreement between doctors and parents of the Spanish (‘sibilancias silbido o pitos en el pecho’) or Portuguese (‘sibilancias ou chiado no peito’) words for ‘wheezing or whistling in the chest’ was very good, and the κ statistic was 1.0 in most centres (table 1).

For the criterion validation, a total of 203 questionnaires was collected, 105 in Santiago (50 cases and 55 controls) and 98 in Cartagena (50 cases and 48 controls). The agreement between parents and doctors with regard to the question about ‘wheezing or whistling in the chest’ was quite good, with a κ slightly higher in Cartagena than

Table 2. Agreement between the medical diagnosis of ‘wheezing’ and the parent’s answer to the question ‘Has your baby had wheezing or whistling in the chest during his/her first 12 months of life?’ on its own or combined with asthma medication, using the doctor’s diagnosis of ‘wheezing’ as the gold standard

	Agreement %	κ	Parents+ Physician– %	Parents– Physician+ %
Questionnaire				
Santiago	83.0	0.67	4.8	12.4
Cartagena	87.7	0.75	6.1	6.1
Inhaled BD				
Santiago	72.4	0.43	18.1	9.5
Cartagena	79.6	0.59	3.1	17.3
Any asthma drug				
Santiago	73.3	0.45	18.1	8.6
Cartagena	79.6	0.59	6.1	14.3
Questionnaire or inhaled BD				
Santiago	73.3	0.45	18.1	8.6
Cartagena	86.7	0.73	9.2	4.1
Questionnaire and inhaled BD				
Santiago	81.9	0.64	4.8	13.3
Cartagena	80.6	0.61	0	19.4
Questionnaire or any asthma drug				
Santiago	73.3	0.45	18.1	8.6
Cartagena	83.7	0.68	12.2	4.1
Questionnaire and any asthma drug				
Santiago	82.7	0.66	4.7	12.3
Cartagena	83.7	0.67	0	16.3

BD = Bronchodilator.

Table 3. Diagnostic tests and Youden's index of the question 'Has your baby had wheezing or whistling in the chest during his/her first 12 months of life?' on its own or combined with asthma medication, using the doctor's diagnosis of 'wheezing' as the gold standard

	Sensitivity	Specificity	PPV	NPV	Youden's index
Questionnaire					
Santiago	77.6 (69.6–85.6)	89.4 (83.5–95.3)	90.0 (84.3–95.7)	76.4 (68.2–84.5)	67.0
Cartagena	88.0 (81.6–94.4)	87.5 (80.9–94.0)	88.0 (81.6–94.4)	87.5 (80.9–94.0)	75.5
Inhaled BD					
Santiago	82.7 (75.5–90.0)	59.6 (50.2–69.0)	71.6 (63.0–80.3)	73.7 (65.3–82.1)	42.3
Cartagena	66.0 (56.6–75.4)	93.7 (88.7–98.5)	91.7 (86.2–98.1)	72.6 (63.7–81.4)	59.7
Any asthma drug					
Santiago	84.5 (77.6–91.4)	59.6 (50.2–69.0)	72.1 (63.5–80.6)	75.7 (67.5–83.9)	44.1
Cartagena	72.0 (63.1–80.9)	87.5 (81.0–94.0)	85.7 (78.8–92.6)	75.0 (66.4–83.6)	59.5
Questionnaire or inhaled BD					
Santiago	84.5 (77.6–91.4)	59.6 (50.2–69.0)	72.1 (63.5–80.6)	75.7 (67.5–83.9)	44.1
Cartagena	92.0 (86.6–97.4)	81.2 (73.5–89.0)	83.6 (76.3–91.0)	90.7 (85.0–96.4)	73.2
Questionnaire and inhaled BD					
Santiago	75.9 (67.7–84.0)	89.4 (83.5–95.3)	89.8 (84.0–95.6)	75.0 (66.7–83.3)	65.3
Cartagena	62.0 (52.4–71.6)	100	100	71.6 (62.7–80.6)	62.0
Questionnaire or any asthma drug					
Santiago	84.5 (77.6–91.4)	59.6 (50.2–69.0)	72.1 (63.5–80.6)	75.7 (67.5–83.9)	44.1
Cartagena	92.0 (86.6–97.4)	75.0 (66.4–83.6)	79.3 (71.3–87.3)	90.0 (84.1–95.9)	67.0
Questionnaire and any asthma drug					
Santiago	77.6 (69.6–85.6)	89.4 (83.4–95.3)	90.0 (84.3–95.7)	76.4 (68.2–84.5)	67.0
Cartagena	68.0 (58.7–77.2)	100	100	75.0 (66.4–83.6)	68.0

Figures are presented as percentages with ranges in parentheses. PPV = Positive predictive value; NPV = negative predictive value; BD = bronchodilator.

in Santiago (0.75 vs. 0.67; table 2). The best diagnostic value was also obtained with just the question on 'wheezing or whistling in the chest', this being very similar in terms of positive predictive value between Cartagena and Santiago (88.0 vs. 90.0%, respectively). However, although the negative predictive value of that question was quite different between the 2 cities, it did not reach statistical significance (87.5% in Cartagena vs. 76.4% in Santiago; table 3). Other combinations of answers to questions related to asthma medication did not improve the agreement or diagnostic accuracy.

Discussion

This study shows that the EISL questionnaire for wheezing in infants correctly detects infants who have suffered from wheezing during their first year of life, independently of the settings and countries in which it was applied. Furthermore, this ability is maintained in inter-

national comparisons between centres of different socio-cultural background.

There has been some debate as to whether asthma questionnaires designed for epidemiological studies correctly detect asthma cases when compared to bronchial hyperresponsiveness (BHR) [5, 15]. Most of the current evidence suggests that, both for children and for adults, symptom questionnaires are better than BHR tests for this purpose. Jenkins et al. [16] performed a validation study in a population-based group of children 13–14 years old and observed a greater sensitivity (85 vs. 54%), a slightly lower specificity (81 vs. 89%) and a substantially higher Youden's index (66 vs. 43%) when asthma was diagnosed by the ISAAC questionnaire compared to a BHR test with hypertonic saline. A positive answer to the questionnaire plus a positive BHR test substantially increased the specificity to 94% but decreased the sensitivity to 47%, thus reducing the Youden's index to 41%. Furthermore, BHR and other lung function tests are difficult to perform and interpret in young children, particularly

in infants, and there is no information comparing wheezing questions with any specific pulmonary function test in children during their first year of life.

There are several studies validating asthma questionnaires against the clinical diagnosis of asthma, including at least clinical history and physical examination. In children 7–12 years of age, Remes et al. [17] defined asthma as a positive answer to either 1 of 3 questions – doctor diagnosis of asthma ever, attacks of ‘wheezing’ or episodes of ‘breathlessness’ in the last 12 months – and achieved a sensitivity of 88%, a specificity of 97% and a Youden’s index of 85%. Using the doctor diagnosis of asthma ever, the corresponding figures were 82, 99 and 81%. In the same age group, Steen-Johnsen et al. [18] by asking about ‘asthma ever’ obtained a sensitivity of 63%, a specificity of 99% and a Youden’s index of 62%. Wolf et al. [19] found a sensitivity of 65% and a specificity of 88% (Youden’s index 53%) to the question of a wheezing episode among parents of children in elementary schools (5- to 13-year-olds). More recently, the same group has updated their questionnaire (Brief Paediatric Asthma Screen, BPAS, to BPAS+) and has included additional questions to detect allergy as well as asthma [20]. In the same age group, parents reached 73% sensitivity and 74% specificity (Youden’s index 47%) when answering positively to any of 4 items (wheeze, persistent cough, night cough and response to change in air temperature).

In younger children (grades kindergarten through 6 years), also using the clinical diagnosis as the gold standard, Redline et al. [21] reached a sensitivity of 80% and a specificity of 75% (Youden’s index 55%) when considering the presence of cough (sometimes or more) and/or breathing problem (rarely or more). Similar results have been obtained by the same authors in children 7–13 years of age [22]. The Easy Breathing Survey, in its validation study performed in children 0–17 years old (including 40% of 0- to 4-year-olds), found a sensitivity of 73% (newly diagnosed) or 82% (previously diagnosed) and a specificity of 83% for the question about wheezing based on the International Union Against Tuberculosis and Lung Diseases (IUATLD) [23]. Other questions obtained poorer results in the diagnostic tests and the combination of any of 4 questions improved sensitivity but decreased specificity. The best Youden’s index was obtained with the question about wheezing (65% among those previously diagnosed and 56% among those newly diagnosed).

As already mentioned and to the best of our knowledge, only 1 study has been performed to validate a questionnaire on infant wheezing [7]. However, in that study

the main objective was to compare the score achieved in children referred to the paediatric pulmonology clinic with that obtained in children with no or minimal symptoms. From this report, no idea of validity of the questionnaire as a diagnostic test can be inferred; furthermore, the choice of the groups for the criterion validity is somewhat debatable [24].

The results of the present study show that when administering the EISL questionnaire to a general population (where EISL is being performed), parents of infants 12–15 months of age, from different countries and socio-cultural levels, are able to reliably identify episodes of wheezing which occurred during the first year of their child’s life. Moreover, in a very different setting such as the emergency room, this questionnaire can reliably identify wheezing in infants by their parents at the moment the symptom is occurring, with a high specificity and sensitivity. This has recently been demonstrated by Chong Neto et al. [25] when validating the questions ‘Has your baby had wheezing in the last 12 months?’ and ‘Is your baby wheezing now?’.

Although asking for ‘asthma diagnosis’ has been the question with greater criterion validity in children 10–17 years of age in phase III of the ISAAC study in Spain [26], this question is probably less useful during the first years of life because there is still an important controversy as to which infants should be diagnosed as asthmatics. Moreover, non-uniform criteria (either on asthma diagnosis or treatment) are applied in different parts of the world. This variation in labelling and treatment uses could introduce important variability in parents’ responses to questions specifically asking for ‘asthma’. Consequently, the present questionnaire did not refer to ‘asthma’ but to ‘wheezing’. It has been very reassuring that the Spanish/Portuguese words for ‘wheezing’ (‘silbidos’/‘sibilància’) and for ‘whistling’ (‘pitos’/‘pieira’) were understood in the same way by parents and doctors, allowing the conclusion that the main question of the EISL questionnaire has a good construct validity.

With respect to the criterion validity, and since there is no gold standard test which can be used to categorize infants into wheezers and non-wheezers to compare the questionnaire to, the opinion of the paediatric pulmonologist was chosen as the standard. They are more aware of the different wheezing phenotypes at this age, and despite certain variability among them, it appears much more reliable as the gold standard than any laboratory test available at present.

The Youden’s indexes found for the question ‘Has your baby had wheezing or whistling in the chest during his/her

first 12 months of life?’ compared to the paediatric pulmonologist’s diagnoses are quite comparable to the best obtained in validation studies in older children (75% in Cartagena and 67% in Santiago). The greater agreement found in Cartagena compared to Santiago could be explained by the differences in socio-economic and socio-cultural levels between the 2 populations, with them being much lower in the district of Santiago where the study was performed than in Cartagena. This different agreement seems to be due to an over-reporting of parents in Santiago compared to Cartagena, which is consistent with a higher negative predictive value in Cartagena than in Santiago. Considering the balance between misreported cases and supposing the large epidemiological study would repeat exactly the same findings, the prevalence would reflect reality very accurately in the case of Cartagena and would over-estimate the true prevalence in Santiago, by about 7%. This means that if the questionnaire estimates a prevalence of 35% of at least 1 episode of wheezing during the first year of life (which is the prevalence found in the pilot study and should be taken with caution; data not shown), the true prevalence would be about 32.5%. This deviation is not important in this type of study, and would be less so with decreasing prevalences. However, it is important to underline that the difference in the negative predictive value between the two cities is not statistically significant and thus could be closer, should this study be repeated.

Furthermore, it is noteworthy that specificity was quite high and similar in both cities, approaching 90%. As specificity is the most important validity measure in

studies where the relative risk is the way of measuring an effect, it is likely that the results obtained with the present questionnaire will approach the true value. On the other hand, the Youden’s index is comparable to or even better than that obtained by Jenkins et al. [16] in the ISAAC validation study (66%) and probably allows that if a difference in prevalence between cities is found, this corresponds to a true difference, especially if the sample population is large and if the participation rate is high. If parents are reliable at detecting wheezing episodes with the EISL questionnaire at the population level, as shown here, it is quite probable that they can properly inform about the exact number of episodes that occurred during their child’s first year of life.

In summary, this study shows that the EISL questionnaire is a valid instrument to detect infants 12–15 months of age who have suffered from wheezing during their first year of life, independently of the setting in which it is applied. Based on the present questionnaire, the EISL will allow for the first time to know and compare the prevalence of wheezing during the first year of life among the participating centres from Latin America and Spain.

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