

Validation of the Finnish ISAAC questionnaire on asthma against anti-asthmatic medication reimbursement database in 5-year-old children

Bright Ibeabughichi Nwaru¹, Mirka Lumia², Minna Kaila³, Päivi Luukkainen⁴, Heli Tapanainen², Maijaliisa Erkkola⁵, Suvi Ahonen^{1,6}, Juha Pekkanen^{7,8}, Timo Klaukka^{*,9}, Riitta Veijola¹⁰, Olli Simell¹¹, Mikael Knip^{3,4,6} and Suvi Mirjami Virtanen^{1,2,3,6}

¹ Tampere School of Public Health, University of Tampere, Tampere, Finland

² Nutrition Unit, Department of Lifestyle and Participation, National Institute for Health and Welfare, Helsinki, Finland

³ Department of Pediatrics, Tampere University Hospital, Tampere, Finland

⁴ Hospital for Children and Adolescents, Helsinki University Hospital, Helsinki, Finland

⁵ Division of Nutrition, Department of Applied Chemistry and Microbiology, University of Helsinki, Helsinki, Finland

⁶ Tampere University Hospital Research Unit, Tampere, Finland

⁷ National Institute for Health and Welfare, Kuopio, Finland

⁸ School of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland

⁹ Social Insurance Institution, Helsinki, Finland

¹⁰ Department of Pediatrics, University of Oulu, Oulu, Finland

¹¹ Department of Pediatrics, University of Turku, Turku, Finland

Abstract

Background: Valid identification of childhood asthma at the population level for epidemiological purposes remains a challenge. We aimed at validating the Finnish version of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire based on parental-reported childhood asthma.

Materials and Methods: The ISAAC questionnaire has been validated against anti-asthmatic medication reimbursement data of the Finnish Social Insurance Institution, being the gold standard, among 2236 5-year-old consecutively born children (1996–2004) carrying human leukocyte antigen (HLA)-conferred susceptibility to type 1 diabetes. Two combined questionnaire questions (any wheezing symptom or use of asthma medication during the preceding 12 months *plus* ever asthma; any wheezing symptom or use of asthma medication during the preceding 12 months *plus* ever doctor-diagnosed asthma) were validated against valid reimbursement with purchase of at least one anti-asthmatic medication during a 12-month period. The validity of the questionnaire was estimated as the sensitivity, specificity, positive predictive value, negative predictive value, and Youden's index.

Results: The sensitivity 0.98 [95% confidence interval (CI) = 0.92–0.99]; specificity 0.98 (95% CI = 0.97–0.98); negative predictive value 1.00 (95% CI = 1.00–1.00); and Youden's index 0.96 (95% CI = 0.96–0.96) were the same for each of the two sets of combined questions. The positive predictive value for the first combined question was 0.63 (95% CI = 0.55–0.71), while it was 0.64 (95% CI = 0.57–0.72) for the second combined question.

Conclusion: The Finnish ISAAC questionnaire was highly valid and is an acceptable instrument for the survey of the prevalence of parental-reported childhood asthma for epidemiological purposes.

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Key words

asthma – child – International Study of Asthma and Allergies in Childhood – medication reimbursement data – questionnaire – validation

Correspondence

Bright I. Nwaru, MPhil, MSc, Tampere School of Public Health, FIN-33014, University of Tampere, Tampere, Finland.

Tel: +358449127647

Fax: +358335516057

email: bright.nwaru@uta.fi

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*Deceased.

Abbreviations:

CI confidence interval

ISAAC International Study of Asthma and Allergies in Childhood

SII Social Insurance Institution

Introduction

Valid identification of childhood asthma at the population level for epidemiological purposes remains a challenge (1–3). This challenge is partly protracted by the fact that most epidemiological studies have self-employed or parental-reported symptom questionnaires in the assessment of asthma in children (1–4). In this respect, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire has been the most widely used (5), and accordingly it has been translated and modified into several languages and contexts (5–7).

Because of the potential challenges in questionnaire assessment of asthma symptoms, such as recall and subjective symptom recognition (1, 8), and in particular the different contextual modifications to the ISAAC core questions, it becomes necessary to validate them against more objective measures (1, 5). Studies validating the ISAAC questionnaire have reported variable degrees of validity (9–12). These findings are believed to reflect the cultural disparities in interpretation of asthma symptoms in children (13, 14). They may also result from the questions chosen for validation and the gold standards employed (1, 6).

Although using clinical diagnosis is a preferred gold standard in validating questionnaire data (1, 5), it has also been subject to under-diagnosis (15) and some variations in clinical practice (16, 17). In Finland, like in several other countries, a special reimbursement database is kept for anti-asthmatic medications, as well as for other specified diseases, by the Social Insurance Institution (SII) (18). To be eligible for the reimbursement, a patient must provide a doctor's certificate confirming that asthma has been diagnosed (18, 19). Such a database has been shown as a valid source of prevalence data in different countries as it is able to accurately identify asthma cases in the general population, and it is useful in health services and epidemiological research (15, 18, 20).

In the present study, we aimed at validating the Finnish version of the ISAAC questionnaire based on parental-reported symptoms of asthma against the SII anti-asthmatic medication reimbursement data (as the gold standard) among 5-year-old children. This validation would facilitate the use of the questionnaire for epidemiological research purposes.

Materials and methods

Study population

We analyzed the data for subjects participating in the Type 1 Diabetes Prediction and Prevention (DIPP)

Nutrition Study in Finland, which falls within the framework of the larger DIPP study. The DIPP study, an ongoing population-based prospective birth cohort study, started in 1994 (21). It is aimed at exploring possible means to prevent the development of type 1 diabetes. All newborn infants with human leukocyte antigen (HLA)-conferred susceptibility to type 1 diabetes from the university hospital areas of Turku, Oulu and Tampere were invited to participate in the study. The nutrition study was started within the DIPP project in Oulu and Tampere in September 1996 and October 1997, respectively (22). That study examined the relation of maternal diet during pregnancy and lactation in line with the child's diet during infancy and childhood to the development of type 1 diabetes, allergic diseases and asthma in children. At age 5 years, the children were invited to take part in the allergy component of the DIPP Nutrition Study. A questionnaire modified from the ISAAC questionnaire was administered to the participating families, gathering information concerning the child's history and symptoms of asthma, allergic rhinitis and atopic eczema. The study was approved by the Ethical Committees of the Universities of Oulu and Tampere, Finland, and informed consent was obtained from the parents.

Of the 4065 children invited to the allergy study (born between 2 September 1996 and 5 September 2004), 3130 (77%) completed the ISAAC questionnaire on the child's allergic history. Two children who had no information on their social security number and date of completing the questionnaire were excluded. Because the SII reimbursement data were available only up to the end of December 2007, we included only the children who completed the ISAAC questionnaire by the end of June 2007. This enabled us to get the reimbursement data of the children 12 months prior to the filling of the ISAAC questionnaire, and 6 months after the filling of the questionnaire for those who had not started receiving the reimbursement at the time of completing the questionnaire. The final sample size for this study was a total of 2236 children.

The SII anti-asthmatic medication reimbursement database

In Finland, the SII houses the Special Reimbursement Register, where certain prescribed medications, including anti-asthmatic medications, are recorded (19). Anti-asthmatic medications receive a 75% reimbursement package. Eligibility for the reimbursement requires that each child provides a doctor's certificate stating that the diagnostic criteria for asthma are

fulfilled (18). The anti-asthmatic medications are classified according to the Anatomical Therapeutic Chemical Classification System. Record is also kept for date of purchase of each medication and personal identification code of each child, which allows for a valid linkage between the SII and questionnaire data (19).

In this study, we defined an asthma case within the SII reimbursement database for any child who had a valid reimbursement (within 12 months before or 6 months after completing the ISAAC questionnaire) and at least one purchase of any of the following anti-asthmatic medications: inhaled corticosteroids (R03BA01, R03BA02, R03BA05); inhaled corticosteroids in fixed combination with long-acting beta agonists (R03AK06, R03AK07); or leukotriene receptor antagonists (R03DC03). We included cases recorded 6 months after completing the ISAAC questionnaire because reimbursement for children is usually not started until the child has used anti-asthmatic medications for at least 6 months after confirmation of the diagnosis by a doctor so as to exclude symptoms resulting from other illnesses.

The Finnish ISAAC questionnaire

The Finnish ISAAC questionnaire was administered to the children at the age of 5 years. It was sent to parents at home; the parents completed and returned the questionnaire to the study clinics, where it was checked by a study nurse. In addition to the original ISAAC core questions on wheezing symptoms and asthma (ever wheezing, ever asthma, wheezing sounds in the chest or wheezing attacks and number of episodes during the last 12 months), the following questions were added to our modified ISAAC questionnaire: *whether asthma has ever been diagnosed by a doctor; age of the child when asthma was diagnosed; and whether the child has used asthma medication during the preceding 12 months*. In the present study, we are interested in validating two sets of combined definitions of asthma from the questionnaire against the SII data, rather than each of the specific questions. This decision was based on the aim of excluding asthma cases that may be a result of viral infections. The two combined questions are: (i) any wheezing symptom or use of asthma medication during the preceding 12 months *plus* asthma ever; and (ii) any wheezing symptom or use of asthma medication during the preceding 12 months *plus* ever doctor-diagnosed asthma. A third combined question [at least 'yes' answer to two of: (i) any wheezing symptoms during the last 12 months; (ii) any asthma medication during the last 12 months; (iii) ever

doctor-diagnosed asthma] was also included in the validation, although this was not given emphasis.

Statistical analysis

The validity of the questionnaire questions vs the SII reimbursement data was estimated by the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). In addition, Youden's index (sensitivity + specificity – 1) (23) was calculated to estimate the overall validity of each set of asthma definition. Youden's index is particularly useful when comparing validity estimates across populations. The 95% confidence intervals (CI) of the estimates were computed using Wilson's method (24, 25). SPSS for Windows version 15 was used for the analysis.

Results

During the time frame of the study (i.e. within 12 months before or 6 months after completing the ISAAC questionnaire), 4.5% ($N = 2236$) of the children had valid special reimbursement for anti-asthmatic medications. Altogether, the prevalence of asthma in the SII reimbursement data during this period (defined by valid reimbursement and at least one purchase of any of the anti-asthmatic medications) was 4%. According to the questionnaire, the prevalence of ever asthma was 6.9%; ever doctor-diagnosed asthma was 6.8%; and 6.4% had used asthma medication during the preceding 12 months. Of the children, 11.3% were positive for any wheezing symptom during the preceding 12 months. Using the two primary combined questionnaire questions, we found that 6.2% of the children were positive for asthma according to the first combined question and 6% were positive according to the second combined question.

Within the SII reimbursement data, higher prevalence of asthma was seen among boys and among children with parental history of asthma and allergic rhinitis (Table 1). In the questionnaire, higher prevalence of asthma was seen among boys and among children with parental history of asthma and allergic rhinitis (Table 1).

The validity estimates of the questionnaire asthma specific questions and the two combined questions are given in Table 2. Table 3 shows the number of subjects used for the calculations. The validity estimates of each of the specific questions (except for wheezing symptoms in the previous 12 months) and the combined questions were very close to each other. These esti-

Table 1. Prevalence of asthma in the SII reimbursement database and ISAAC questionnaire by background variables

Background variables	All (N = 2236)		Asthma according to SII (n = 90)		<i>P</i> value [‡]	Asthma according to questionnaire definition 1* (n = 138)		<i>P</i> value [‡]	Asthma according to questionnaire definition 2 [†] (n = 135)		<i>P</i> value [‡]
	<i>n</i>	%	<i>n</i>	%		<i>n</i>	%		<i>n</i>	%	
Sex					<i>P</i> = 0.02			<i>P</i> < 0.01			<i>P</i> < 0.01
Boys	1176	53	58	5		91	8		89	8	
Girls	1060	47	32	3		47	4		46	4	
Parental asthma					<i>P</i> < 0.01			<i>P</i> < 0.001			<i>P</i> < 0.001
No	1833	82	64	4		90	5		88	5	
Yes	353	16	25	7		45	13		44	13	
No information [§]	30	1	0	0		1	3		1	3	
Missing	20	1									
Parental allergic rhinitis					<i>P</i> = 0.001			<i>P</i> < 0.001			<i>P</i> < 0.001
No	752	34	12	2		22	3		22	3	
Yes	1373	61	74	5		108	8		105	8	
No information [§]	97	4	4	4		7	7		7	7	
Missing	14	1									

*Any wheezing symptom or use of asthma medication during the last 12 months *plus* ever asthma.

[†]Any wheezing symptom or use of asthma medication during the last 12 months *plus* ever doctor-diagnosed asthma.

[‡]*P* values for two-sided Pearson's χ^2 test.

[§]Refers to the case where a parent does not know whether the spouse has an allergy.

mates remained unchanged among the subgroups of children with parental history of asthma or allergic rhinitis and among children with parental history of asthma and allergic rhinitis.

Discussion

In this study, the validity estimates of each of the specific questions and the combined questionnaire questions were very high, except for the question on wheezing symptoms during the preceding 12 months. Based on the sensitivity and specificity, about 98% of the children with asthma were correctly classified as such by each of the combined questions, while 98% without asthma were correctly excluded as non-asthmatics. While the PPV of the combined questions was above average, the NPV was perfect. The overall validity of the questionnaire, indicated by Youden's index, was very high. Overall, our results indicated that the misclassification of asthma by the questionnaire was very minimal. Consequently, the Finnish ISAAC questionnaire represents a valid instrument for the assessment of parental-reported childhood asthma for epidemiological research purposes.

The subjects in our study were originally selected based on HLA-conferred susceptibility to type 1 diabetes. This may limit the postulation of our results to the general population. The HLA DR-DQ haplotypes

associated with type 1 diabetes have not been shown to be associated with asthma (26). Our subjects were unselected because of family history with allergic diseases. The prevalence of asthma in our study population is comparable to that of the general Finnish population (27). Therefore, it is unlikely that the HLA-based selection would bias our results. Our validity estimates remained unchanged among children with parental history of asthma and allergic rhinitis, indicating lack of differential errors by the questionnaire in detecting asthma in the population. Although family history of atopy is an important consideration when diagnosing asthma in children, our results showed that regardless of a child's family history of allergy, the questionnaire was able to differentiate between asthmatics and non-asthmatics.

There is no true gold standard for the diagnosis of asthma (2, 28). Doctor's diagnosis and bronchial hyperactivity have been the most widely used to validate questionnaire data. Although these methods are seen as more objective measures to identify asthmatics, the lack of a common definition of asthma and variation among physicians in diagnosis may hamper their validity and reliability (1, 6, 16, 17, 20). We chose the Finnish SII reimbursement data on anti-asthmatic medications as the gold standard for the current study. This database has been systematically developed, and represents a valid source of information both for

Table 2. Estimates and 95% confidence interval (CI) of sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and Youden's index

Validated questionnaire questions	Sensitivity			Specificity			PPV			NPV			Youden index*		
	Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI		Estimate	95% CI	
Any wheezing symptoms during the last 12 months	0.88	0.79–0.93		0.75	0.73–0.77		0.13	0.11–0.16		0.99	1.00–1.00		0.63	0.63–0.63	
Used any asthma medication during the last 12 months	0.98	0.92–0.99		0.97	0.97–0.98		0.60	0.52–0.68		1.00	1.00–1.00		0.95	0.95–0.95	
Asthma ever	0.98	0.92–0.99		0.97	0.97–0.98		0.57	0.49–0.65		1.00	1.00–1.00		0.95	0.95–0.95	
Ever doctor-diagnosed asthma	0.98	0.92–0.99		0.97	0.97–0.98		0.58	0.50–0.66		1.00	1.00–1.00		0.96	0.95–0.95	
At least 'yes' answer to two of: (i) any wheezing symptoms during the last 12 months; (ii) any asthma medication during the last 12 months; (iii) ever doctor-diagnosed asthma.	0.99	0.93–1.00		0.97	0.96–0.98		0.60	0.52–0.68		1.00	1.00–1.00		0.96	0.96–0.96	
Any wheezing symptoms during the last 12 months or use of any asthma medication during the last 12 months plus asthma ever.	0.98	0.92–0.99		0.98	0.97–0.98		0.63	0.55–0.71		1.00	1.00–1.00		0.96	0.96–0.96	
Any wheezing symptoms during the last 12 months or use of any asthma medication during the last 12 months plus ever doctor-diagnosed asthma.	0.98	0.92–0.99		0.98	0.97–0.98		0.64	0.57–0.72		1.00	1.00–1.00		0.96	0.96–0.96	

*Sensitivity + specificity – 1.

health services utilization, research on health care and epidemiology (18). A child is required to present a doctor's certificate confirming the diagnosis of asthma as a prerequisite for receiving reimbursement (18). However, the reimbursement package is not given until after 6 months of use of the prescribed medications. This enables the reimbursement of actual asthmatics, excluding symptoms that may result from other illnesses, which usually disappear with time (30). With these strict criteria, the SII reimbursement data represent an acceptable gold standard for the validation of parental-reported asthma in children. Similar data from other countries have shown that the use of such a database in evaluating asthma is warranted (8, 20, 29–32). To our knowledge, no previous report has validated questionnaire data on parental classification of asthma in children using anti-asthmatic medication reimbursement data.

One of the potential limitations to the SII data, particularly, to our definition of asthma in the database based on the medications we selected, is that our asthma subjects may be restricted predominantly to those with moderate to severe disease. Accordingly, the asthmatics in our study may be more appropriately referred to as moderate to severe asthma rather than just asthma. This may therefore underestimate the overall prevalence of asthma, because of children with symptomatic or mild asthma may be excluded (20). Apart from the medications selected for the present study, the SII also gives reimbursement for purchases of other anti-asthmatic medications, such as sympato-mimetic drugs. These medications are also used by many children. However, the medications used in our study included those that are used almost daily as maintenance medications for long-term asthma. The excluded medications are primarily used to treat symptomatic or mild asthma. The excluded medications are also used for treating many illnesses other than asthma. By excluding them we are confident that the selected medications may represent the best case scenario for identifying children with actual asthma within the SII data. It is unlikely that during the study time frame, an asthmatic child may not have purchased any of the medications we have studied; otherwise, that child may have had an incorrect diagnosis despite the doctor's certificate of confirmation. Doctor's diagnosis of asthma (17) as well as prescription for anti-asthmatic medications (33) has been reported to vary across contexts. Furthermore, among countries with similar reimbursement packages, implementation may also differ (8, 18). These variations should be taken into account when comparing studies using reimbursement data.

Table 3. Two by two table showing the number of parental-reported asthma in children according to the two primary combined questionnaire questions by the SII reimbursement data*

Sets of combined questions from the ISAAC questionnaire		Asthma according to SII reimbursement data		Total
		Positive	Negative	
Any wheezing symptoms during the last 12 months or use of any asthma medication during the last 12 months plus ever asthma.	Positive	87	51	138
	Negative	2	2083	2085
	Total	89	2134	2223
Any wheezing symptoms during the last 12 months or use of any asthma medication during the last 12 months plus ever doctor-diagnosed asthma.	Positive	87	48	135
	Negative	2	2086	2088
	Total	89	2134	2223

*These are numbers used for calculating the validity estimates in Table 2.

The Finnish ISAAC questionnaire included two additional questions to the asthma core questions: use of asthma medications during the preceding 12 months and ever doctor-diagnosed asthma. Although we validated each of the specific questionnaire questions and a third combined question, our primary aim was to validate the two sets of combined questions: (i) any wheezing symptom or use of asthma medication during the preceding 12 months *plus* asthma ever; and (ii) any wheezing symptom or use of asthma medication during the preceding 12 months *plus* ever doctor-diagnosed asthma. The estimates from each of the specific and third combined questions were high and comparable to those for each of the combined questions, except for lower, but reasonable, estimates obtained from the question on any wheezing symptom during the preceding 12 months. Some previous reports have shown that symptom questions had the best ability in discriminating asthmatics from non-asthmatics (2, 31), although this was contrary to another survey (34). The appropriateness of the gold standards used in these studies may be of concern, especially since the use of BHR in defining asthma in epidemiological studies has been questioned (2, 28) because it agrees unsatisfactorily with clinical diagnosis. In questionnaire surveys, symptom history has been used most often to estimate the prevalence of asthma (4). Although there is no common definition of asthma (6), using symptom questions alone may present some drawbacks. Only a minority of children positive for wheezing symptoms subsequently presented with actual asthma since childhood wheezing is often associated with viral infections with no long-term manifestation of asthma (30). The difficulty in finding equivalent words to describe these symptoms in some contexts can make the comparison of estimates across populations challenging (4, 28). Parents, particu-

larly those without asthmatics in their homes, may fail to recognize such symptoms or can define symptoms of other illnesses as asthma (4, 6). This may overestimate the prevalence of asthma. In our study, the prevalence of any wheezing symptom during the preceding 12 months (11.3%) was about two times higher than the other questionnaire asthma questions (6.5%).

Despite high validity estimates seen with the question on use of asthma medication during the preceding 12 months, it may also have some potential shortcomings. Importantly, the use of asthma medication may not signify that the child has asthma because such medications may be used by patients for other ailments (14). In our questionnaire, the questions on the use of asthma medication and doctor-diagnosed asthma were asked only from those who had a 'yes' answer to the question on ever asthma. While the mismatch between doctor-diagnosed asthma and ever asthma was only 2%, the proportion of children whose parents indicated that they had used asthma medication during the preceding 12 months but who had a negative answer to the question on ever asthma was 10%. In a study from the United States, 45% of children for whom asthma medications were purchased were reported by their parents not to have asthma (14). A recent Dutch study found that only 49% of children receiving asthma medication were diagnosed as asthmatic (30). Because of these shortcomings, the use of the symptom and use of medication questions alone may be constrained. The questions on ever asthma (4) and ever doctor-diagnosed asthma (30) may represent more objective questions to estimate asthma. Because these two questions estimate lifetime prevalence of asthma, it was justifiable in our study to combine them with the symptom and use of medication questions in order to estimate the prevalence of current asthma in children

(i.e. asthma during the preceding 12 months). A 12-month time window seems more reliable when estimating asthma prevalence by means of a questionnaire, thereby minimizing memory errors (4).

A few studies have validated the parental-reported asthma component of the ISAAC questionnaire for the 6- to 7-year-old group, while more studies have validated the version for 13- to 14-year-old children. The latter questionnaire has been completed by the adolescents. Parental understanding and response to asthma questions may differ from that of their children (4). Our ISAAC questionnaire was completed by parents of 5-year-old children and so would be rightly compared with the ISAAC questionnaire for children aged 6–7 years. However, cultural and linguistic considerations that have resulted in modifications of the ISAAC questionnaire may limit the extent of comparison between countries. In addition, our choice of gold standard and pattern of combination of the questionnaire questions would also need to be considered when comparing our results with other studies. Regardless of these concerns, the estimates obtained in our study are comparable to the results of the studies from Brazil (4), Spain (7) and Sweden (12), which validated this particular ISAAC questionnaire on asthma. These concordant findings are indication that the ISAAC questionnaire, despite contextual modifications, represents a standardized instrument for assessing the prevalence of childhood asthma for epidemiological research across countries and cultures (28).

The clinical implications of our results, indicated by the positive and negative predictive values, imply that for both sets of combined questionnaire questions, a patient with a positive test has slightly over 60% chance of being diagnosed as asthmatic, whereas a child with a negative test has a perfect chance of being diagnosed as non-asthmatic. These are reasonable posterior probabilities to guide clinical decisions in our study population.

In conclusion, the validity estimates of the Finnish ISAAC questionnaire were high. The questionnaire represents a valid instrument for the survey of asthma in children for epidemiological purposes. We propose that the combination of questions on wheezing symptoms or use of asthma medication plus more objective asthma questions in the ISAAC questionnaire as the best case scenario to validly identify asthmatic children in the population.

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