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Validation of a questionnaire against clinical assessment in the diagnosis of asthma in schoolchildren

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Running head

'Validating a questionnaire for children's asthma'

Key words

Atopy, cross-sectional, epidemiology, instrument validation, reliability,

Abstract

Aim: A questionnaire has been used repeatedly in cross sectional studies to determine the prevalence of asthma, allergic rhinoconjunctivitis (AR) and eczema among schoolchildren in Nordland County, Norway. The current study was designed to validate the questionnaire against clinical assessment as the diagnostic gold standard and to investigate the extent of possible misclassification.

Methods: A subsample of 801 schoolchildren of 4150, whose parents had answered a questionnaire covering asthma and atopic diseases, underwent a detailed clinical evaluation including a standardized interview, a clinical examination, skin prick tests (SPT), blood samples, spirometry an exercise treadmill test (EIB test) and measurement of exhaled nitrogen oxide (FeNO).

Results: The questionnaire had a sensitivity of 0.96 and a specificity of 0.87 for the diagnosis of asthma ever compared to clinical assessment. The overall agreement (kappa) was 0.80. After clinical assessment the prevalence of asthma ever was adjusted from 17.6 % to 16.9 % (95% CI: 15.8-18.0). The most sensitive and specific questions in identifying asthmatic children by the questionnaire were questions asking about diagnosis ('Has the child ever had asthma?') rather than those covering asthma symptoms such as wheeze, shortness of breath and/or cough. A positive exercise test increased the posttest probability for the asthma diagnosis only to a minimal degree.

Conclusion: Based on the good agreement between the questionnaire responses and the clinical assessments, it is concluded that the questionnaire had good validity and served as a useful epidemiological tool. Detailed clinical testing added little additional information.

Introduction

In recent decades the prevalence of asthma and allergic diseases has increased substantially. This “asthma epidemic” has led it to become the most frequent chronic disease among children in developed countries (1). However, wide global variation in asthma prevalence has been reported (2), which entails a need for further studies. The best evidence of changes in disease prevalence comes from repeated studies at sufficient intervals of time using the same instrument in the same population (3). While no screening test is perfect, valid prevalence estimates require a screening test with a high sensitivity and specificity (4). Validity is the degree to which a measurement measures what it intends to measure. The most common method to validate survey instruments is to compare their results to a “gold standard” test. Several measurements can be used in such validation. Specifically, sensitivity is the proportion of subjects with "true" asthma (according to the "gold standard") and specificity is the proportion of subjects without asthma classified correctly by the survey instrument. In the absence of a standardized definition of asthma and a diagnostic ‘gold standard,’ clinical assessment is the closest we can get to a true diagnosis (5, 6). Retrospective symptom questionnaires are the most commonly used to assess the prevalence of asthma in epidemiological studies (3, 7). However, questions about asthma symptoms are non-specific and are influenced by recall, recognition and awareness (8). Another limitation is the lack of an exact translation of the term “wheeze” in most languages (5, 9), including the Scandinavian vocabularies. In some instances questions relating to diagnosis may be more useful than symptom-based questions, even though diagnosis itself does not constitute an “objective” record. Some researchers have sought to increase the diagnostic accuracy of childhood asthma by adding objective markers such as clinical testing of bronchial hyperresponsiveness (BHR). Such tests seem to add little information to what is achieved by a

questionnaire alone. Even if these tests do provide objective measures, which do not change over time, the diagnosis of asthma may (5, 10, 11).

During 1985-2008, three cross-sectional surveys have been conducted in Nordland, Norway to estimate the prevalence of parent reported asthma, allergic rhinoconjunctivitis (AR) and eczema. An identical questionnaire was used in all three surveys. The 2008 - survey included schoolchildren (7-14 years) from randomly selected schools in Nordland County and, to assess time trends, were compared to those obtained in the 1985 and 1995 surveys (12, 13) to assess time trends (14). 'Asthma ever' was recorded if the parent answered 'yes' to one or both of the key questions: *Has the child ever had asthma (Question 1)* and *Does the pupil experience wheeze, periods of coughing or acute shortness of breath (asthma) due to external factors (Question 2)?* 'Current asthma' was recorded if the affirmation applied to the last 12 months. Of the 4150 responders (63.8% oft those invited) in the 2008 survey, 729 met the definition criteria of asthma ever. This corresponds to a prevalence of "asthma ever" of 17.6% and represents a significant increase in the lifetime prevalence of asthma over a 23 year period; a substantial increase (4.8% to 9.9%) in current asthma was also demonstrated (14). Using information from the 2008 survey, a case-control study was designed to validate the questionnaire and to explore associative factors for asthmatic and allergic diseases. Assessments of its reliability and practical usefulness were additional objectives.

Patients and methods

The study area

Nordland County, Norway with a subarctic area of 38000 km^2 and has a population of 240.000. Its unique geography features a long coastline (25 % of Norway's total), with half of it located north of the Arctic Circle. Thus most of Nordlands' inhabitants live in sparsely populated areas and experience a coastal climate

Study design

Based on a questionnaire-based survey in 2008 parental-reported asthma symptoms and diagnosis in schoolchildren (7-14 years) for 729 children met the definition criteria of asthma ever. We invited a subsample of the 4150 children enrolled in the original cohort to participate in a case-control study. This follow-up study took place at four outpatient locations in Nordland (specifically, Bodø, Fauske, Mo and Sortland). The study locations were selected on the basis of capturing as many participants as possible. Children who met the questionnaire definition criteria of asthma ever and lived within 2 hours car the study locations (572/729), together with non-asthmatic controls were invited to participate (a total of 1144 children). Cases and controls were matched on individual basis for age and gender. A total of 801 children with their parents participated (70 % attendance), more controls (428) than cases (373). Although not pursued in the current study, the case-control method was chosen in order to permit a study association between the occurrence of asthma and exposure of potential risk factors. The current questionnaire validity study did not need to be in the case-control format. The participants underwent a standardized interview, a clinical examination and substantial clinical testing including skin pricks tests (SPT), spirometry, an exercise treadmill test (EIB test) and measurement of exhaled nitrogen oxide (FeNO); blood

samples were also collected. All interviews and procedures were conducted by one of the two authors (TEH and BE), and the same medical instruments were used to secure standardized measurement conditions. Parents/guardians signed a written consent for their children's participation. The study took place between March 2009 and July 2010, during the school semester.

Clinical assessment

The interview covered birth data, socio-economic conditions, health status, infections and asthma symptoms during the child's first three years of life, diet, medication, secondhand smoke exposure and household animals. A clinical examination including height, and weight measurements and assessment of skin, upper airway, lung and heart was performed. The diagnosis was based on clinical assessment (interview including disease history and clinical examination) alone, not taking clinical testing or laboratory test-results into account. This simulated a clinical setting in a doctor's office. The asthmatic children were categorized as current asthmatics or not, and asthma severity was classified according to the GINA guidelines (15). For assessment of the reliability of the original questionnaire, the parents answered a new questionnaire with the same key questions regarding asthma, AR and eczema, as done during the survey in 2008. The time interval between the original and current administration of the questionnaire was 1.5 -2 years.

Definitions

The definitions used in the case-control study were those of Lødrup Carlsen (16). Asthma ever: at least two of the following three criteria being fulfilled; re-current dyspnoea, chest tightness and/or wheezing; doctor's diagnosis of asthma; and use of asthma medication (ß-2 agonist, sodium cromoglycate, corticosteroids, leukotriene antagonists and/or aminophylline).

Current asthma: asthma as defined above plus symptoms and/or asthma medication within the last year. Allergic sensitization (atopy) was defined by a positive SPT and/or a positive sIgE (≥0.10 kU/L) to ≥1/10 of the listed allergens.

Clinical testing

The SPT was performed for the following allergens: birch, timothy, *Cladiosporium herbarium, Alternaria tenius*, *Artemisia vulgaris* (mugwort), *Dermatophagoides pteronyssinus*, cat, dog, rabbit, German cockroach, milk, egg white, peanut and cod. Total IgE and serum allergen-specific IgE (sIgE) to the above listed allergens were analyzed using the IMMULITE 2000 immunoassay (Siemens Healthcare Diagnostic Inc., Deerfield, IL, USA). Spirometry, EIB tests and measurements of FeNO were conducted in accordance with published guidelines as previously described (17). Forced expiratory volume at 1 minute (FEV_1) was measured at baseline and at 3, 6, 10, 15 and 20 min after the exercise, and a positive EIB test was defined as a decrease in FEV_1 ≥10%.

Statistical analyses

Validity of the questionnaire was determined by agreement between questionnaire responses and clinical assessments. Agreement was measured as sensitivity and specificity. Corrected estimates for the prevalence of asthma ever and current asthma was calculated as the sum of the positive predictive values for both positive and negative questionnaire replies to asthma, weighted by their relative frequencies. Agreement between EIB and clinical assessment was assessed using post-test odds and the probability for a positive EIB tests. The test-retest reliability of the questionnaire was assessed using Cohen´s kappa. Corrected inter-group comparisons were analyzed with Pearson's chi-square test for categorical data and

independent t- test for continuous data. The distribution of FeNO values was right skewed, and thus analyses were executed with natural log (ln) transformed data. The results were presented as back-transformed values and expressed as geometric means. All tests were two-sided using a significance level of 0.05. All analyses were made using the Statistical Package for Social Science (SPSS) software version 19.0 (SPSS Inc. IBM, Chicago, IL, USA).

Ethical approval

The Regional Committee for Medical and Health Research Ethics, Northern Norway and The Norwegian Data Inspectorate approved this study.

Results

Asthmatic children had higher mean body mass index (BMI) and suffered more frequently from eczema, AR and food allergy than non-asthmatic children (Table 1). Compared to the original study cohort from 2008 mean age was higher in asthmatics (12.4 versus (vs) 11.2 years) and non-asthmatics (12.6 vs 10.9 years); and there were more boys among the non-asthmatic children (46.8 % vs 59.8 %). More children were suffering from eczema in asthmatics (48.6% vs 31.4%) than in non-asthmatics (32.0 vs. 16.7) and more non-asthmatic were suffering from AR (26.6% vs. 19.5%). Other than these differences the two cohorts were similar in terms of demographic data and clinical characteristics.

Validity and reliability of the questionnaire

Of the 801 children participating, 373 had parental reported “asthma ever”. After the clinical assessment 64 of the designated 373 asthmatic children did not meet the asthma definition criteria (i.e., false positives). Of the 428 apparent non-asthmatic children, 14 met the asthma

definition criteria after the clinical assessment (i.e., false negatives) (Fig. 1). Thus the survey questionnaire had a sensitivity of 0.96 and a specificity of 0.87. Assuming that the clinical assessment represents a true diagnosis of asthma ("gold standard"), the estimated prevalence of asthma ever in the 2008 survey was adjusted from 17.6% to 16.9% [309/373 × 729/4150 + 14/428 × 3421/4150 = 0.169, standard error (SE) 0.006, 95%CI: 0.158-18.0]. In the group of asthmatic children, 153 (47.4%) children fulfilled the definition criteria of current asthma. Similarly the prevalence of current asthma was changed from 9.9% to 10.8% (SE 0.005, 95%CI: 9.8-11.8). Following the GINA guidelines (15), 69 children had intermittent and 84 children had mild persistent asthma. No children were classified as moderate or severe persistent asthmatics.

The test-retest reliability (kappa) of the asthma definition used in the 2008 survey was 0.80 (SE 0.02); for question 1 ("Has the child ever had asthma?") alone the agreement was 0.87 (SE 0.02). Analyzing individual answers from the questionnaire compared to clinical assessment revealed differences in sensitivity and/or specificity between questions covering asthma symptoms and diagnosis (Table 2).

The misclassified children

Misclassified children that were transferred from the asthmatic group to non-asthmatics (false positive) after the clinical assessment, 21/64 (32.8%) had answered affirmatively to Question 1 in the original questionnaire and 52/64 (83.9%) answered affirmatively to Question 2. The interview revealed that 25/64 (39.1%) of the children had experienced respiratory symptoms (wheezing, dyspnoea, cough), but not asthma during the first three years of life. In 22/25 (88.0%) of these children the episodes of symptoms were associated with fever, colds and other airway infections. In the false positive group 40/64 (62.5%) had atopic disease, 36/64

(56.3%) suffered from AR ever, and 28/64 (43.8%) from eczema ever. In the group of misclassified children that changed groups from non-asthmatic to asthmatic (n=14) after the clinical assessment (false negative), eight children represented new asthma cases and six represented under-diagnosis of self-reported "asthma ever" in the 2008 survey.

Examination

Asthmatic children were more often sensitized to allergens, had higher FeNO values and had more often a positive EIB test than non-asthmatics. However, spirometric values were not significantly different between the groups (Table 3). A positive exercise test yielded a sensitivity of 0.12 and a specificity of 0.92 relative to the clinical assessment. The posttest odds (= pretest probability/ (1-pretest probability) x LR+) and posttest probability (= posttest odds/(1+posttest odds)) were 0.33 and 0.25, respectively.

Discussion

The main finding in this study was the good agreement between the questionnaire-based diagnosis of asthma and the clinical assessment by a doctor. This finding is in line with a validation of a 1995 questionnaire among schoolchildren in Southern Norway (18). For a questionnaire to be a useful research tool, the responses must be repeatable (minimum measurement error). The test-retest reliability of asthma definition by questionnaire may be judged substantial (19), especially considering the time interval between the survey and the case-control study. This, together with the good agreement supports the conclusion that the questionnaire is a potential useful epidemiological tool.

Most of the misclassifications and over-diagnoses in this study were due to parent's response to Question 2 in the 2008 survey. This question covered several symptoms including the cardinal symptom of asthma, wheeze. Reported wheeze has extensive differential diagnosis and parental interpretation. Conceptual understanding of wheeze may differ from that of physicians and from epidemiology definitions (20, 21). Interpreting symptoms of reported wheeze as being asthma may result in over-estimating the prevalence of childhood asthma. In addition the higher prevalence rates of wheeze in English speaking countries have questioned the validity of translating wheeze into other languages (22, 23). The clinical assessment revealed that parents misinterpreted their child's symptoms associated with respiratory infections in early life as asthma. This finding is in line with results from a USA and European study among preschool children (9). In this study, 32 % of the children reported recurrent asthma symptoms, while only 20 % reported a doctor's diagnosis of asthma. If one uses questions covering only symptoms, one risks more false positive and "over-diagnosing". In our opinion the false positive children in the study may represent 'transient infantile wheeze' (24). Thus, in this present population, questions covering diagnosis rather than symptoms in the 2008 survey provided a better prediction of the asthma prevalence. Some of the misclassification may have been due to the large number of children suffering from AR in the over-diagnosed group. Symptoms of AR and asthma resemble each other, and this can make it difficult for parents to distinguish between the two diseases.

The diagnosis of asthma is problematic as episodic symptoms and exacerbations are essential components of the disease. This makes the use of clinical testing as an epidemiological tool challenging. In agreement with other studies (4, 11, 25), the intensive examinations performed yielded little additional information. Spirometric values were not significantly different in the subgroups and posttest probability increased only to a minor degree for the

EIB test. Baseline FeNO was significantly higher in asthmatic than in non-asthmatic children, in line with findings from other studies (26, 27). This is probably caused by a higher proportion of asthmatic children suffering from AR (17). Hence clinical testing, while essential both in the diagnosis of asthma and in clinical management of current asthma, is less important as an epidemiological tool.

Studies validating epidemiological tools are important. The present study combines the best qualities of questionnaires and testing, namely, by first performing a questionnaire survey and subsequently conducting more intensive examinations on a large subsample of children. Since both symptomatic and non-symptomatic study subjects were examined, it was possible to estimate the extent of misclassification in the questionnaire survey. To ensure reproducibility the sample was large and two doctors performed all assessments and examinations.

Our study has a number of limitations. First, a problem inherent to asthma questionnaires is that questions covering diagnosis and clinical assessment may not be truly independent of each other. As a diagnosis is not merely an objective record, it could include an intervention that may affect parental perception. Hence, it might be difficult to evaluate as to whether parents are just recalling previous outcomes when answering questions concerning diagnoses. In addition, studies have shown substantial inconsistency concerning information on children's chronic health conditions (asthma) based on medical record data and parents-reports (28, 29). The inconsistency may be due to a misunderstanding of the conditions and the reliability of parental reporting. This illustrates the need for caution in making definitive statements. Secondly, the reviewers were not blinded to the previous parental reported asthma status. Ideally, the reviewers should have been blinded, but this was not possible within the organization of the study. However, the reviewers had no knowledge about the specific

answers to the individual questions in the 2008 survey. We believe that this has only influenced the results in a minor way. A third limitation may be that participation in asthma studies may be associated with more awareness of symptoms and interest which could have introduced a selection bias. Selection bias is best avoided by achieving a high response rate. The response rate in the 2008 survey was lower than desirable, as discussed in an earlier publication (14). Even though a high participation rate is preferable, most empiric work suggests that lower participation rates are not likely to have a substantial influence on the measures of interest (30).

Conclusion

The questionnaire used appears to be a valid proxy for clinical assessment in terms of identifying cases of asthma in schoolchildren. Detailed clinical testing adds little additional information in such diagnoses. Within the limitations of our case-control study design, questions covering disease predicted asthmatic children better (with higher sensitivity) than those covering symptoms. Thus the questionnaire might bee a good research tool for future cross-sectional surveys.

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TABLE 1. Demographic data of the cases and controls in the study "Asthma and allergy among schoolchildren in Nordland" after clinical assessment.

	Asthmatic n = 323	**Non-asthmatic** n = 478	**P - value**
Boys*	204 (63.2)	286 (59.8)	0.343
Girls*	119 (36.8)	192 (40.2)	0.343
Age (years)**	12.4 (1.9)	12.6 (1.9)	0.185
Body mass index (BMI)**	20.3 (4.2)	19.6 (3.7)	0.014
Birth weight in (grams)**	3467 (646.3)	3537 (651.1)	0.150
Gestation age (weeks)**	39.3 (2.5)	39.5 (2.0)	0.222
Number of siblings**	1.9 (1.0)	2.0 (1.0)	0.309
Fathers years in school (years)**	13.2 (2.7)	13.5 (2.7)	0.103
Mean mothers years in school (years)**	14.0 (2.6)	14.1 (2.6)	0.529
Secondhand smoke exposure**	116 (35.9)	143 (29.9)	0.075
Comorbidity			
Eczema*	157 (48.6)	153 (32.0)	0.000
Allergic rhinoconjunctivitis*	156 (48.3)	127 (26.6)	0.000
Food allergy*	49 (15.2)	32 (6.7)	0.001
Urticaria*	56 (17.3)	93 (19.5)	0.441

*Results are given in exact numbers (percentages).
**Results are given as means (standard deviation).

TABLE 2. The agreement between parents answers to questions about asthma and asthma symptoms in the cross-sectional survey compared to clinical assessment in the case-control study (from the study: "Asthma and allergy among schoolchildren in Nordland" (14)).

	Asthmatic n = 323	**Non-asthmatic** n = 478	**Sensitivity**	**Specificity**
1. Has the pupil ever had asthma? (Question 1)	290/323	21/476	0.90	0.96
2. Has the pupil had asthma in the past 12 months?	144/289	4//92	0.96	0.50
3. Does the pupil experience wheeze, periods of coughing or acute shortness of breathes due to external factors? (Question 2)	182/316	53/460	0.58	0.88
4. Does the pupil experience wheeze, periods of coughing or acute shortness of breath (asthma) due to external factors in the past 12 months?	142/241	39/156	0.75	0.59
5. Has the pupil ever experienced episodes of dyspnoea?	164/303	47/441	0.54	0.89
6. Has your child chest ever sounded wheezy during or after exercise?	139/316	21/446	0.44	0.95
7. Has your child had ever a dry cough at night, apart from a cough associated with a cold or chest infection?	205/315	94/449	0.65	0.79
8. Has your child ever used asthma medication?	304/322	42/456	0.94	0.91
9. Did a doctor diagnose your child with asthma?	270/318	15/456	0.85	0.97

The number (n) varies due to missing data.

TABLE 3. The test results from the case-control study in "Asthma and allergy among schoolchildren in Nordland" (14).

	Asthmatic n = 323	**Non-asthmatic** n = 478	**P - value**
Allergic sensitization (% of total)	218 (67.5)	259 (54.2)	0.000
Mean baseline FeNO (95%CI)	14.74 (13.38-16.24)	10.75 (10.12-11.41)	0.000
Positive exercise test (% of total)	57/315 (18.1)	26/466 (5.6)	0.000
Mean baseline lung function			
FEV1 (95% CI)	2.59 (2.51-2.67)	2.63 (2.56-2.69)	0.492
FVC (95% CI)	3.00 (2.90-3.09)	3.06 (2.98-3.14)	0.273
FEV1% (95% CI)	86.1 (85.4-86.8)	85.8 (85.3-86.4)	0.547
FEF50 (95%CI)	3.13 (3.01-3.24)	3.15 (3.06-3.24)	0.695

The numbers (n) are presented as exact numbers and percentages or means

Figure legend

Figure 1.

Participant flowchart for the study "Asthma and allergy among schoolchildren in Nordland" (14).