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Prediction of childhood atopy by questionnaire

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To The Editor,

In clinical and epidemiological studies of childhood asthma and allergy, questionnaire responses are often used as a surrogate for measurement of atopy by skin prick testing (SPT) or allergen-specific IgE level and may be applied to classify participants based on atopic status. In the literature, questionnaire-reported symptoms of hayfever and other allergic conditions have had 28-77% reported sensitivity and 21-94% reported specificity compared to the gold standard of atopy determination by SPT [1-5]. We evaluated the sensitivity, specificity and Youden Index of questionnaire definitions of atopy among Canadian children.

A nested case-control sample of 208 11- to 12-year old children, half of whom had a history of asthma or wheezing, was randomly selected from the 5619 Toronto school children who participated in the Toronto Child Health Evaluation Questionnaire (TCHEQ) study [6] and invited to take part in the “Lung Health Study” from December 2008 to October 2010. Parents completed International Survey of Asthma and Allergy in Children (ISAAC)-based questionnaires reporting their child’s physician diagnoses of asthma, hayfever, eczema and food allergy. A study worker blinded to the history performed SPT to 14 common aeroallergens, including house dust mites (*Dermatophagoides farinae* [DF] and *Dermatophagoides pteronyssinus* [DP]), cat, dog, cockroach, feathers, mouse, horse, tree mix, grass mix, ragweed mix and molds (*Alternaria*, *Hormodendrum* and *Aspergillus*). The TCHEQ-Lung Health Study received ethical approval from the Research Ethics Board at the Hospital for Sick Children (REB number 1000012801).

SPT was considered valid if the largest histamine control wheal diameter was at least 3 mm greater than the largest saline control wheal diameter. Skin prick tests were considered positive if the largest wheal diameter was at least 3 mm greater than the largest saline control wheal diameter. Atopy by SPT was defined as a positive SPT to any aeroallergen. Three questionnaire definitions of atopy included having any 1, any 2 or all 3 parent-reported physician diagnoses of hayfever/rhinitis, eczema or food allergy. Compared with the gold standard atopy definition of any positive SPT to an aeroallergen, we calculated the sensitivity, specificity and Youden Index of the 3 questionnaire definitions of atopy, the reported physician diagnoses of individual atopic conditions, and the individual hayfever/rhinitis, asthma and eczema questionnaire items. Different definitions of a positive SPT were evaluated in sensitivity analyses.

One hundred and sixty-nine children had valid SPT data. The sensitivity, specificity and Youden index of atopy by questionnaire compared with the SPT gold standard were 58.4%, 72.7% and 31.1% for 1 reported atopic condition and 17.6%, 100% and 17.6% for 2 reported atopic conditions (Table 1).

Defining atopy as at least 2 or at least 3 positive SPT instead of at least 1 positive SPT and defining a positive SPT as a wheal length of 2 mm or 4 mm greater than the saline control instead of 3 mm greater or by rectangular or elliptical area rather than by length did not change the sensitivity or specificity of the questionnaire definitions of atopy, demonstrating a robust SPT definition. The Youden Index was optimized by the original positive SPT definition of a wheal length at least 3-mm greater than the saline control.

Physician diagnosis of individual atopic conditions (Table 1) had lower sensitivity for prediction of atopy than considering hayfever/rhinitis, eczema and food allergy diagnoses together.

However, physician diagnosis of eczema had a reasonably high Youden Index (24.2). Among individual rhinitis questionnaire items, sensitivity for predicting atopy by positive SPT and Youden Index were highest for any history of rhinitis (63.7% and 32.4%, respectively) and rhinitis symptoms in the past 12 months (60.8% and 32.4%, respectively); specificity was highest for rhinitis with conjunctivitis (89.6%) and rhinitis symptoms interfering with activity in the past 12 months (89.6%) (Table 1). Individual asthma and eczema questionnaire items showed lower Youden Indices, although the absence of a rash in a typical distribution for eczema was highly specific (91.8) and the absence in the past 12 months of wheezing or a relapsing-remitting rash were reasonably specific (Table 1).

Overall, reporting of 1 atopic condition by questionnaire had higher sensitivity and Youden Index and lower specificity for atopy prediction than reporting of 2 atopic conditions, which had a lower Youden Index, excellent specificity and poor sensitivity. Defining atopy by any one of physician-diagnosed hayfever/rhinitis, eczema or food allergy had similar sensitivity and specificity to parent reporting of individual rhinitis symptoms, and the Youden Indices for any history of rhinitis and rhinitis symptoms in the past 12 months were comparable to that of physician-diagnosed atopic conditions.

In this study, the sensitivity, specificity and Youden Indices for physician diagnoses of at least 1 atopic condition and rhinitis ever or in the past 12 months were comparable to other studies that have evaluated the ability of clinical questionnaire definitions to predict atopy.

Studies in adults have shown good prediction of atopy by questionnaires. Among 788 adults in Italy [1], questionnaire definitions of atopy including atopic eczema, rhinitis, respiratory distress with bronchial wheezing, and conjunctivitis symptoms compared with SPT to 9 aeroallergens had comparable sensitivity (75%) and specificity (60.6%) to our study. The Score for Allergic Rhinitis [2] had a higher sensitivity (74%; 95% CI: 69%, 79%), specificity (83%; 95% CI: 79%, 87%) and Youden Index (57%) compared with SPT, likely because it included items such as a previous positive allergy test, triggers, a diagnosis of allergy and a family history of allergy, as well as symptoms. Among 16- to 79-year old participants, atopy prediction by experienced allergists using non-standardized patient interviews [3] showed a sensitivity and specificity of 77%.

Among 307 children attending a public elementary school in a medically underserved area of East Dallas [4], hayfever reported on the ISAAC rhinitis questionnaire compared with SPT to 14 aeroallergens had similar sensitivity (43%), specificity (80%), and Youden Index (23%) to the present study. A limitation of activity due to nose problems in the past 12 months had higher sensitivity (76%) and lower specificity (29%) and Youden Index (5%). Among 2954 Swiss children, hayfever reported in ISAAC core rhinitis questions predicted a positive SPT to one of 6 common aeroallergens with a sensitivity of 28.4% and specificity of 93.8%, similar to atopy defined by 2 atopic conditions in the current study [5].

Although a history of eczema and factors associated with atopy, such as eosinophil counts, parental history of allergic conditions and symptoms associated with aeroallergens have been

used to predict the persistence of wheezing or asthma symptoms in children [7-9], to our knowledge, symptoms of asthma and eczema have not been routinely used as predictors of atopy.

While atopy definitions of any 1 and any 2 atopic conditions by questionnaire are legitimate and show reasonable overall optimization of sensitivity and specificity in the Youden Index, the usefulness of a more sensitive or specific questionnaire definition would depend on the purpose of the future study. Population-based cohort studies evaluating associations with development of atopy and atopic conditions could be conducted with a less-specific questionnaire definition of atopy, because development of asthma, rhinitis and food allergy symptoms in children without sensitization to aeroallergens may be relevant to these research questions. In studies where IgE-mediated allergic mechanisms are important in the casual pathway, for example genetic association studies or evaluating treatment effects of medications among atopic individuals, a specific definition of atopy would be more useful to ensure exclusion of non-atopic participants.

This study was conducted using detailed questionnaire items based on a validated measure and had a gold-standard definition of atopy by SPT. Potential limitations included the parent-reporting of physician-diagnosed hayfever/rhinitis, food allergy and eczema, the small number of children and the absence of additional measures of sensitization, such as allergen-specific IgE levels.

We conclude that questionnaire definitions of atopy based on parent-reported physician-diagnosed atopic conditions have moderate sensitivity and specificity among Canadian children,

and that the usefulness of a more sensitive or specific questionnaire definition would depend on the purpose of the study.

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Conflict of Interest

The authors declare no conflict of interest.

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Table 1 : Sensitivity and specificity of questionnaire-based definitions and individual allergy questionnaire items compared to the gold standard of atopy (any skin prick testing wheal at least 3mm larger than saline control)*

Reported variables	Sensitivity % (95% CI)	Specificity % (95% CI)	Youden Index %
Any 1 atopic condition	58.4 (48.8, 68.0)	72.7 (62.0, 83.5)	31.1
Any 2 atopic conditions	17.6 (10.2, 25.0)	100	17.6
Any 3 atopic conditions	1.96 (0, 4.65)	100	1.96
Physician-diagnosed			
Asthma	53.9 (44.2, 63.6)	64.2 (52.7, 75.7)	18.1
Hayfever	8.91 (3.35, 14.5)	100	8.91
Eczema	50.0 (40.3, 59.7)	74.2 (63.7, 84.8)	24.2
Food allergy	18.6 (11.1, 26.2)	98.5 (95.6, 100)	17.1
Rhinitis** (lifetime)	63.7 (54.4, 73.1)	68.7 (57.5, 79.8)	32.4
Rhinitis** (in the past 12 months)			
Without conjunctivitis***	60.8 (51.3, 70.3)	71.6 (60.8, 82.4)	32.4
With conjunctivitis	35.3 (26.0, 44.6)	89.6 (82.2, 96.9)	24.8
Interfering with activity	34.3 (25.1, 43.5)	89.6 (82.2, 96.9)	23.9
Perennial	32.4 (23.3, 41.4)	82.1 (72.9, 91.3)	14.4
Seasonal	53.9 (44.2, 63.6)	76.1 (65.9, 86.3)	30.0
Wheeze (lifetime)	77.2 (69.0, 85.4)	49.3 (37.3, 61.2)	26.5
Wheeze (in the past 12 months)	43.6 (33.9, 53.2)	82.1 (72.9, 91.3)	25.7
Chronic cough	31.4 (22.4, 40.4)	80.6 (71.1, 90.1)	12.0
Relapsing-remitting rash (past 12 months)	14.7 (7.61, 21.9)	86.9 (78.4, 95.4)	1.62
Rash in typical location for eczema	10.5 (4.35, 16.7)	91.8 (84.9, 98.7)	2.33

*For those with valid prick skin tests (histamine control wheal ≥ 3 mm larger than saline control),

N = 169

**Rhinitis = sneezy, runny or blocked nose when he or she did not have a cold or the flu

***Conjunctivitis = itchy, watery eyes