

Misdiagnosis of Asthma in Schoolchildren

C.L. Yang,^{1,2} E. Simons,^{3,4} R.G. Foty,³ P. Subbarao,^{1,2,4} T. To,^{3,4} and S.D. Dell^{1,2,3,4*}

Summary. Background: A correct diagnosis of asthma is the cornerstone of asthma management. Few pediatric studies have examined the accuracy of physician-diagnosed asthma. Objectives: We determined the accuracy of parent reported physician-diagnosed asthma in children sampled from a community cohort. Methods: Nested case-control study that recruited 203 children, aged 9–12, from a community-based sample. Three groups were recruited: asthma cases had a parental report of physician-diagnosed asthma, symptomatic controls had respiratory symptoms without a diagnosis of asthma, and asymptomatic controls had no respiratory symptoms. All participants were assessed and assigned a clinical diagnosis by one of three study physicians, and then completed spirometry, methacholine challenge, and allergy skin testing. The reference standard of asthma required a study physician's clinical diagnosis of asthma and either reversible bronchoconstriction or a positive methacholine challenge. Diagnostic accuracy, sensitivity and specificity were calculated for parent-reported asthma diagnosis compared to the reference standard. Results: One hundred two asthma cases, 52 controls with respiratory symptoms but no asthma diagnosis, and 49 asymptomatic controls were assessed. Physician agreement for the diagnosis of asthma was moderate (kappa 0.46–0.81). Compared to the reference standard, 45% of asthma cases were overdiagnosed and 10% of symptomatic controls were underdiagnosed. Parental report of physician-diagnosed asthma had 75% sensitivity and 92% specificity for correctly identifying asthma. Conclusions: There is significant misclassification of childhood asthma when the diagnosis relies solely on a clinical history. This study highlights the importance of objective testing to confirm the diagnosis of asthma. **Pediatr Pulmonol.** 2016; 9999:XX–XX. © 2016 Wiley Periodicals, Inc.

Key words: asthma; pediatrics; child; diagnosis; accuracy; asthma overdiagnosis.

Funding source: Ontario Lung Association Grant-in-Aid Program; Restrcomp Fellowship.

INTRODUCTION

Asthma is one of the most common chronic conditions of childhood and affects 10–15% of children.^{1,2} Guidelines state that establishing a diagnosis of asthma in adults and children over the age of 5 years requires evidence of reversible airway obstruction or bronchial hyperreactivity in addition to compatible clinical symptomatology.^{3,4} A recent study highlighted the importance of obtaining objective measures to diagnose asthma, revealing that 30% of adults in a community-based sample did not have asthma when assessed with pulmonary function testing.⁵

Previous studies in children have found that asthma was underdiagnosed and subsequently undertreated.⁶ This led to an increased awareness of asthma and some speculate that the pendulum has swung the other way such that asthma is now overdiagnosed in children.⁷ Our objective was to determine the accuracy of parental reported physician-diagnosed asthma in a community-based sample of children compared to a guideline based reference diagnosis (the current gold standard).

¹Division of Respiratory Medicine, The Hospital for Sick Children, Toronto, Ontario, Canada.

²Department of Pediatrics, University of Toronto, Toronto, Ontario, Canada.

³Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Ontario, Canada.

⁴Institute of Health, Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada.

Conflict of interest: None.

Dr. Yang is currently on faculty in the Division of Respiratory Medicine, British Columbia Children's Hospital, University of British Columbia, Vancouver, Canada.

*Correspondence to: S.D. Dell, MD, FRCPC, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada, M5G 1x8. E-mail: sharon.dell@sickkids.ca

Received 22 April 2016; Revised 22 June 2016; Accepted 2 July 2016.

DOI 10.1002/ppul.23541

Published online in Wiley Online Library (wileyonlinelibrary.com).

MATERIALS AND METHODS

This was a prospective nested case-control study. Study visits and testing were completed at The Hospital for Sick Children, which is a tertiary care hospital in Toronto, Canada.

Subjects

Subjects were recruited randomly between December 2008 and October 2010, from a community-based sample of 5,619 grades 1 and 2 children from 231 public schools who had originally participated in the Toronto Child Health Evaluation Questionnaire (T-CHEQ) study in 2006. The T-CHEQ participants had characteristics (income adequacy, education, household size, asthma, and smoking rates) similar to the Toronto area childhood population when compared to national census and health survey data.⁸ A letter describing the study was sent to parents of potential subjects who had agreed to future research (95% of the original TCHEQ sample). Research staff then contacted the parents via telephone. Eligible children (9–12 years of age, able to perform study investigations, free of upper respiratory tract infections in the 3 weeks prior to participation, term birth, absence of chronic disease other than asthma) who agreed to participate were booked for a study visit.

Asthma Diagnosis

Parent Reported Asthma Diagnosis (Parent-Reported Diagnosis)

Subjects were identified as asthma cases if, on the T-CHEQ questionnaire, the parent responded yes to their child having physician-diagnosed asthma. Subjects without reported asthma were divided into two groups: (i) symptomatic controls (parents reported their child had respiratory symptoms: wheeze or nocturnal cough not associated with a cold, and/or use of asthma medication) and (ii) asymptomatic controls (parents reported no symptoms or asthma medication use).

Study Physician Clinical Diagnosis (Clinical Diagnosis)

All subjects were assessed by an asthma expert physician (pediatric respirologist (CY, SD) or pediatric allergist (ES)) who was blind to the parent-reported diagnosis and assessed the subjects prior to any objective testing. The subjects were given a clinical diagnosis of asthma or not asthma based on a standardized history and physical exam. A history consistent with asthma required recurrent episodes of wheezing or increased work of breathing that responded to standard asthma management. To assess inter-rater agreement between physicians, the physician's data collection form from 56 randomly selected subjects was independently re-assessed by a second physician.

Reference Standard Diagnosis (Reference Diagnosis)

After being assessed by the study physician, all subjects performed the following tests, administered by experienced pulmonary function technologists: spirometry, methacholine challenge test and allergy skin prick testing. Those with parent-reported asthma diagnosis also completed the Children's Asthma Control Test, with a score less than 19 indicating poor asthma control.⁹ A reference standard diagnosis of asthma (reference diagnosis) was given if the subject had both an affirmative clinical diagnosis and objective evidence of reversible airway obstruction (either a positive methacholine challenge or a significant bronchodilator response as described below).

Spirometry was done according to ATS criteria¹⁰ using a mass flow sensor (VMAXTM, Carefusion, United States). The forced expiratory volume in 1 sec (FEV1), forced vital capacity (FVC), and the forced expiratory flow between 25% and 75% of the FVC (FEF25-75) were recorded for tests that were acceptable and reproducible. The data was interpreted using reference values from Stanojevic et al.¹¹

The methacholine challenge was done using the 2 min tidal breathing technique¹² with an English Wright nebulizer. The first inhalation was done with normal saline and the concentrations then doubled incrementally from 0.03 to 16 mg/ml. A "shortened protocol"^{12,13} was used for subjects that met all of the following criteria: (i) no previous history of asthma symptoms, (ii) FEV1/FVC over 80% predicted, (iii) FEV1 over 70% predicted and over 2L, (iv) less than 10% fall in FEV1 after saline inhalation, and (v) on no medication or only on occasional bronchodilators (Supplementary Methods). For subjects with an FEV1 less than 65% of predicted, the methacholine challenge was not performed and 400 µg of salbutamol (via meter-dose inhaler and holding chamber) was given to assess for reversibility of airways obstruction. A 12% increase in FEV1 from baseline was considered a significant bronchodilator response.

Allergy skin testing was performed using a multi-test device placed on the volar surface of the forearms (Multi-Test[®] II, Lincoln Diagnostics Inc, Illinois) (Supplementary Methods). A test was considered positive if the resulting wheal was ≥ 3 mm larger than the saline control. Subjects were defined as atopic if they had ≥ 1 positive skin test. The skin tests of subjects with negative histamine controls were categorized as missing atopic status.

Subjects were asked to hold all asthma medication for 48 hr and all antihistamines for 5 days prior to participation in the study.

Outcomes

The primary outcome was the accuracy of parent-reported asthma compared to the reference diagnosis of asthma.

Statistical Analysis

The sample size was calculated using assumptions of the binomial proportion distribution¹⁴ and an estimated parent-reported diagnostic sensitivity of 0.85 and specificity of 0.81 as described in previous literature.¹⁵ Using a sample size of 200, we estimated a precision of 4.9% for sensitivity and 5.5% for specificity.

Data was analyzed using SAS version 9.3. A chi-square test with Yates correction was used to compare differences in baseline proportions between groups and a Student's *t*-test was used to compare differences in means. For comparison of multiple proportions, if the overall chi-square test was significant a multiple comparisons test for proportions was conducted to determine which pairs were significantly different.¹⁶ Sensitivity, specificity and predictive values of the parent-reported diagnosis compared to the reference diagnosis were calculated.¹⁷ Sensitivity and specificity were adjusted for the sampling scheme (subjects with parent-reported diagnosis and symptomatic controls were more likely to be sampled) in order to correct for potential verification bias according to the method described by Begg et al.¹⁸ and assuming an asthma prevalence of 15.5% from the original T-CHEQ sample.⁸ This prevalence was also used to calculate positive and negative predictive values. Kappa values were calculated to measure inter-rater physician agreement of clinical diagnosis.¹⁹ Ninety-five percent confidence intervals were calculated for all proportions using Gaussian approximation.

Sensitivity analyses were conducted to test the robustness of our findings. These included: excluding subjects that did not report asthma symptoms or medication use in the previous year (potential of outgrown asthma); excluding subjects taking inhaled corticosteroids at the time of study (potential false

negative methacholine challenges due to drug effects); changing the cut-off value for a positive methacholine challenge from ≤ 16 to ≤ 8 mg/ml.

This study was approved by the Research Ethics Board of the Hospital for Sick Children. Written informed parental consent and child assent was obtained for each participant.

RESULTS

Study disposition is illustrated in Figure 1. Four hundred thirty-four subjects were contacted: 34 were ineligible, 75 consented but recruitment was completed prior to their study visit, 114 did not consent and eight did not arrive for their study visit. A total of 203 subjects consented and participated in the study. Six subjects were excluded from the final analysis: four were unable to do the methacholine challenge and two took long-acting beta agonists on the day of testing. Compared to the original T-CHEQ sample, participants were more likely to be male (58% vs. 49%), be in the highest income bracket (64% vs. 40%), and less likely to be exposed to tobacco smoke (3% vs. 12%) (Table S1).

Of the 203 participants, 102 had a parent-reported diagnosis of asthma, 52 were symptomatic controls, and 49 were asymptomatic controls. Of the 102 children with parent-reported asthma, 72% had wheezing or used medication in the last year. In the past year, rates of respiratory related hospital admission were 0%, emergency room visits were 5% and systemic steroid use was 4% (Table 1). Eight percent of those with parent-reported asthma had poor asthma control as assessed by the Childhood-Asthma Control Test. Only 18% had previous pulmonary function testing although 52% had previous chest x-rays and 56% had previous skin testing for aeroallergens (Table 1). The subjects with parent-reported

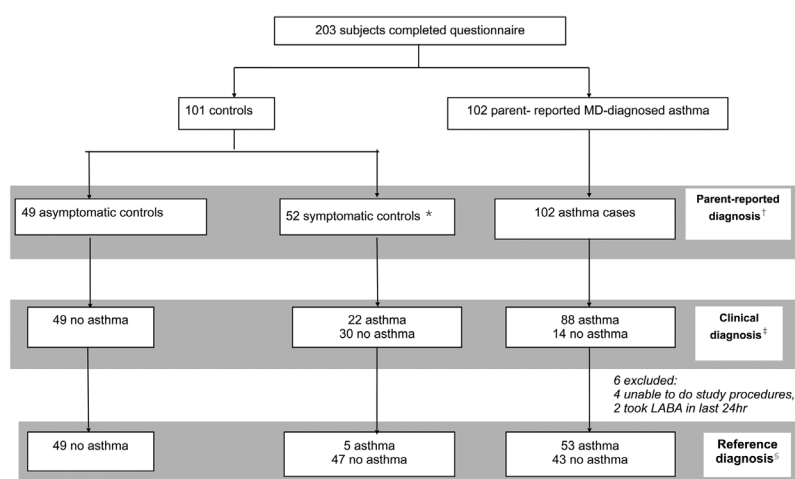


Fig. 1. Flowchart of diagnostic accuracy of parent-reported asthma diagnosis[†].

TABLE 1—Characteristics of Study Subjects According to Parent-Reported Asthma Diagnosis¹

	n	Parent-reported asthma (n = 102)	Symptomatic controls (n = 52)	Asymptomatic controls (n = 49)
Median Age yrs (range)	203	10 (9–12)	10 (9–12)	10 (9–12)
Male Sex	203	66 (65%)	27 (52%)	25 (51%)
Race ²	194			
White		76 (79%)	43 (88%)	43 (88%)
Asian		13 (14%)	2 (4%)	3 (6%)
Black		4 (4%)	1 (2%)	1 (2%)
Arab		1 (1%)	1 (2%)	0
Mixed		2 (2%)	2 (4%)	2 (4%)
Weight ³	203			
Under weight or normal weight		70 (69%)	38 (73%)	35 (71%)
Over weight or obese		32 (31%)	14 (27%)	14 (29%)
Income adequacy ⁴	196			
Lowest		4 (4%)	2 (4%)	0
Lower middle		13 (13%)	7 (14%)	6 (13%)
Upper middle		22 (22%)	7 (14%)	6 (13%)
Highest		60 (61%)	33 (67%)	36 (75%)
Exposure to environmental tobacco smoke (%)	203	2 (2%)	2 (4%)	2 (4%)
Atopy ⁵	198	72 (73%)	36 (69%)	20 (42%)
Parental history of asthma	203	46 (45%)	15 (29%)	13 (27%)
Previous investigations	203			
Pulmonary function test		18 (18%)	2 (4%)	1 (2%)
Methacholine challenge		1 (1%)	0	0
Chest x-ray		53 (52%)	18 (35%)	12 (25%)
Skin testing		57 (56%)	10 (19%)	5 (10%)
Self reported symptoms				
Wheeze				
Lifetime ⁶	202	95 (94%)	43 (83%)	0
In last 12 months ⁷	202	58 (57%)	10 (19%)	0
Chronic cough ⁸	203	41 (42%)	18 (35%)	0
Physician obtained history				
Wheeze	202			
Lifetime		91 (90%)	32 (62%)	2 (4%)
In last 12 months		56 (55%)	6 (12%)	0
Chronic cough		86 (85%)	26 (50%)	1 (2%)
Difficulty breathing		74 (73%)	16 (31%)	2 (4%)
Asthma medication in last 12 months	202			
Inhaled corticosteroid (ICS)		47 (46%)	5 (10%)	0
ICS regular ⁹		9 (9%)	1 (2%)	0
ICS + Long acting beta agonist		9 (9%)	0	0
Leukotriene receptor antagonist		5 (5%)	0	0
Short acting beta agonist		57 (57%)	4 (8%)	0
Systemic steroids in lifetime	203			
0		58 (57%)	45 (87%)	48 (98%)
1–4		27 (26%)	7 (13%)	1 (2%)
5–10		4 (4%)	0	0
>10		4 (4%)	0	0
Systemic steroids in last 12 months				
0		98 (96%)	52 (100%)	49 (100%)
1–2		3 (3%)	0	0
3		1 (1%)	0	0
Hospitalizations for respiratory reasons				
Lifetime	200			
0		76 (76%)	45 (88%)	2 (4%)
1–5		24 (24%)	6 (12%)	0
Last 12 months		0	0	0
ER visits for respiratory reasons				
Lifetime	200			

TABLE 1—(Continued)

	n	Parent-reported asthma (n = 102)	Symptomatic controls (n = 52)	Asymptomatic controls (n = 49)
0		39 (39%)	37 (73%)	44 (90%)
1–5		50 (50%)	14 (27%)	5 (10%)
>5		11 (11%)	0 (0%)	0
Last 12 months		6 (5%)	1 (2%)	0
Childhood asthma control test $\leq 19^{10}$	89	8 (8%)	0	0

Percents are column percents.

¹Parents responded yes to questions “Has your child ever had asthma?” and “Was this diagnosed by a physician?”

²Self identified race.

³According to BMI percentiles: >95%ile obese, 85–95%ile overweight, 5–85%ile healthy, <5%ile underweight.

⁴Derived variable defined by Statistics Canada as total household income adjusted for the number of persons in the household. Lowest income: <\$15,000, 1–2 or <\$20,000, 3–4 or <\$30,000 ≥ 5 ; Lower middle income: \$15,000–29,999, 1–2 or \$20,000–39,999, 3–4 or \$30,000–59,999 ≥ 5 ; Upper middle income: \$30,000–59,999, 1–2 or \$40,000–79,999, 3–4; Highest income: $\geq$ \$60,000, 1 or 2, $\geq$ \$80,000 ≥ 3 .

⁵Atopy defined as ≥ 1 positive skin test (≥ 3 mm above saline control).

⁶Positive answer to “Has your child ever had wheezing or whistling in the chest at any time in the past?”

⁷Positive answer to “Has your child had wheezing or whistling in the chest in the past 12 months?”

⁸Positive answer to “In the past 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?”

⁹Regular use defined as 3 or more consecutive months of use.

¹⁰Children’s asthma control test score: scores less than 19 indicate poor control, data only available for those that self-reported asthma on the questionnaire.

asthma were more likely to be atopic and to report respiratory symptoms, and medication use compared to asymptomatic controls (Table 1).

Accuracy of Clinical and Parent-Reported Asthma Diagnosis

Eighty-six percent (88 of 102) of subjects with parent-reported asthma had a clinical diagnosis of asthma assigned by the study physician; however, only 60% (53 of 88) of those had objective evidence of reversible airway obstruction and therefore had a reference diagnosis of asthma (Fig. 1). Of the 52 symptomatic controls, 42% (22) had a clinical diagnosis of asthma but only 23% (5 of 22) had a reference diagnosis of asthma. Overall 47% (52 of 110) of those with a clinical diagnosis of asthma were overdiagnosed compared to the reference diagnosis. The agreement between the three study physicians was 73–91% for the clinical diagnosis of asthma (kappa 0.46–0.81).

Of the 197 subjects with complete data, there was a 45% (95% CI 35–55%) rate of overdiagnosis in those with parent-reported asthma and a 10% (95% CI 2–18%) rate of underdiagnosis in the symptomatic control group. All subjects in the asymptomatic control group were correctly classified (Fig. 1). Almost all children with a reference diagnosis of asthma had past wheeze (98%) and they had lower pulmonary function compared to children with no asthma (Table 2).

The parental report of physician-diagnosed asthma had a sensitivity of 75% (95% CI 64–86%), a specificity of 92% (95% CI 88–97%) when corrected for verification bias, and a positive and negative predictive value of 55% (95% CI 45–65%), and 96% (95% CI 93–100%), respectively (Table 3).

Sensitivity Analyses

Using a cutoff of 8 mg/ml to define methacholine challenge test positivity increased the overdiagnosis rate to 53% (95% CI 45–65%) and decreased the underdiagnosis rate to 8% (95% CI 0.4–15%). Excluding subjects who did not report asthma symptoms or medication use in the last year (n = 28) did not affect the rate of over or underdiagnosis (40% and 8%, respectively) or sensitivity and specificity (Table 3). Of the eight subjects taking inhaled corticosteroids at the time of study, seven had objective evidence of asthma therefore excluding these subjects did not affect results.

DISCUSSION

We found a high rate of diagnostic misclassification for asthma: 45% of children with parent-reported asthma were overdiagnosed and 10% of children with respiratory symptoms but no asthma diagnosis were underdiagnosed. A previous study of adults with asthma showed a similar overdiagnosis rate of 30% but was unable to calculate an underdiagnosis rate due to the case-only design.⁵ Other pediatric studies have reported asthma overdiagnosis in subjects presenting with exercise induced symptoms²⁰ and chronic cough²¹; however, these studies are subject to referral bias given that subjects were sampled from tertiary care respiratory clinics. This is the first study in a community-based sample of children to demand a guideline-based reference standard for the diagnosis of asthma that includes objective measures of reversible airway obstruction.

Establishing an accurate diagnosis of asthma is important for patients to guide therapy and to ensure

TABLE 2— Characteristics of Subjects According to Reference Diagnosis of Asthma¹

	n	Asthma (n = 58)	No asthma (n = 139)
Median age yrs (range)	197	11 (9–12)	10 (9–12)
Male sex	197	35 (60%)	79 (57%)
Self-identified race ²	188		
White		37 (69%)	119 (89%)
Asian		9 (17%)	9 (7%)
Black		3 (6%)	3 (2%)
Arab		1 (2%)	1 (1%)
Mixed		4 (7%)	2 (1%)
Weight ³	197		
Underweight or normal weight		44 (76%)	96 (69%)
Overweight or Obese		14 (24%)	43 (31%)
Income adequacy ⁴	190		
Lowest		2 (4%)	3 (2%)
Lower middle		5 (9%)	20 (15%)
Upper middle		12 (21%)	21 (16%)
Highest		38 (67%)	89 (67%)
Exposure to environmental tobacco smoke	197	1 (2%)	5 (4%)
Atopy ⁵	192	47 (84%)	77 (57%)
Parental history of asthma	197	21 (36%)	49 (35%)
Physician obtained history			
Wheeze	197		
Lifetime		57 (98%)	63 (45%)
In last 12 months		42 (72%)	18 (13%)
Chronic cough	197		
Lifetime		51 (88%)	58 (42%)
Last 12 months		42 (72%)	37 (27%)
Difficulty breathing	197		
Lifetime		48 (83%)	40 (29%)
Asthma medication in last 12 months	197		
Inhaled corticosteroid (ICS)		35 (60%)	21 (15%)
ICS + long acting beta agonist		2 (1%)	5 (9%)
Leukotriene receptor antagonist		2 (3%)	2 (1%)
Short acting beta agonist		35 (66%)	23 (17%)
Systemic steroids in lifetime	197		
0		35 (60%)	119 (86%)
1–4		18 (31%)	17 (12%)
5–10		2 (3%)	2 (1%)
>10		3 (5%)	1 (1%)
Systemic steroids in last 12 months			
0		55 (95%)	138 (99%)
1–2		2 (3%)	1 (1%)
3		1 (2%)	0
Childhood asthma control test ≤ 19 ⁶	90	8 (15%)	1 (0.8%)
Hospitalizations for respiratory reasons			
Lifetime			
0	197		
1–5		44 (76%)	120 (87%)
Last 12 months		14 (24%)	18 (13%)
0		0	0
ER visits for respiratory reasons			
Lifetime	196		
0		25 (43%)	95 (69%)
1–5		29 (50%)	37 (27%)
>5		4 (7%)	6 (4%)
Last 12 months		3 (5%)	4 (3%)
Positive bronchodilator response ($\geq 12\%$)	2	2	0
Methacholine PC20 ⁷	195		
>16 mg/ml		0 (0%)	110 (79%)
8– ≤ 16 mg/ml		9 (16%)	10 (7%)
4– ≤ 8 mg/ml		12 (21%)	6 (4%)
≤ 4 mg/ml		35 (63%)	13 (9%)
Mean FEV1/FVC %pred (SD)	197	90 (10.4)	95 (5.2)

TABLE 2—(Continued)

	n	Asthma (n = 58)	No asthma (n = 139)
Mean FEV1 %pred (SD)		91 (12.7)	100 (10.5)
Mean FVC %pred (SD)		100 (13.1)	103 (10.7)
Mean FEF25-75 %pred (SD)		71 (22.5)	92 (18.0)

Percents are column percents.

¹Study physician clinical diagnosis of asthma and positive methacholine challenge or positive bronchodilator response.

²Self identified race.

³According to BMI percentiles: >95%ile obese, 85–95%ile overweight, 5–85%ile healthy, <5%ile underweight.

⁴Derived variable defined by Statistics Canada as total household income adjusted for the number of persons in the household. Lowest income: <\$15,000, 1–2 persons per household or <\$20,000, 3–4, or <\$30,000 ≥ 5; Lower middle income: \$15,000–29,999, 1–2 or \$20,000–39,999, 3–4 or \$30,000–59,999 ≥ 5, Upper middle income: \$30,000–59,999, 1–2 or \$40,000–79,999, 3–4; Highest income: ≥ \$60,000, 1 or 2, ≥ \$80,000 ≥ 3.

⁵Atopy defined as ≥1 positive skin test (≥3 mm above saline control).

⁶Children's asthma control test score: scores less than 19 indicate poor control, data only available for those that self-reported asthma on the questionnaire.

⁷Results of methacholine challenge expressed as the concentration of methacholine that caused a 20% decrease in the FEV1 from baseline.

that another diagnosis is not missed. Our study sample identified mainly children with mild asthma and low rates of exacerbation, as would be expected with a community based sample. Although we did not find that chronic inhaled corticosteroid use was a problem in children misdiagnosed with asthma, a large proportion reported using asthma medications in the past 12 months (Table 2). Hence other potential harms of asthma misdiagnosis include the expense of purchasing ineffective medications, families restricting activity in children to limit respiratory symptoms, and overuse of medications such as oseltamavir for influenza because of a perceived increased risk.

One factor that contributes to the misdiagnosis of asthma in children is that objective testing is not often pursued, which is evident in that only 18% of children with reported asthma in our study had previous pulmonary function testing. This is congruent with existing studies that report underutilization of spirometry in asthma management,²² particularly in children.^{23,24} This issue may be more significant in the pediatric age

group because children present with symptoms and are diagnosed with asthma before they are able to do pulmonary function testing. Once the clinical diagnosis has been made it may seem unnecessary to perform objective testing when the children are older. The diagnosis of asthma is therefore often made on the basis of response of symptoms to asthma medication such as bronchodilators and inhaled corticosteroids. However, a recent study highlights the danger of this approach as subjects reported the same improvement in asthma symptoms whether they received a bronchodilator, a placebo inhaler, or sham acupuncture.²⁵ Most international guidelines require that objective measures of reversible obstruction be present in order to diagnose asthma^{3,4,26,27}; however, other guidelines²⁸ advocate that objective testing is only required if there is uncertainty after a history and physical exam. Our study utilized study physicians that were experienced in diagnosing asthma and found that 47% of those that were given a clinical diagnosis of asthma by the study physician had no evidence of airway obstruction by spirometry or

TABLE 3—Diagnostic Properties of Parent-Reported Diagnosis of Asthma on Questionnaire

	Gold standard	n	Sensitivity	Specificity	PPV ³	NPV ³
Parent-reported diagnosis ¹	Reference diagnosis ² with a PC20 ≤ 16 mg/ml	197	75% 53–89	92% 90–94	55% 45–65	96% 93–100
Parent-reported diagnosis ¹	Sensitivity analysis Reference diagnosis ² with a PC20 ≤ 8 mg/ml	197	76% 51–91	90% 88–92	46% 37–57	97% 74–100
Parent-reported diagnosis ¹ excluding subjects with no symptoms in last 12 months	Reference diagnosis ²	163	81% 56–93	92% 90–94	58% 47–69	97% 94–100

¹Parent-reported diagnosis: Parent answered yes to the following questions “Has your child ever had asthma?” and “Was this diagnosed by a physician?”

²Reference standard diagnosis: Study physician clinical diagnosis of asthma and evidence of either bronchial hyperreactivity or reversible bronchoconstriction.

³Predicted values calculated based on prevalence rate of 15.5% from the original T-CHEQ study.

methacholine challenge testing. Similarly, a community based study from the UK found that only 50% of children with a diagnosis of asthma in an electronic patient record had evidence of bronchial hyperreactivity.²⁹ Some authors have suggested that measures of bronchial hyperreactivity are insensitive for the clinical diagnosis of asthma, and this highlights one of the fierce debates in the asthma literature: should a clinical diagnosis of asthma be considered the gold standard or should there also be a requirement for objective tests confirming bronchial hyperreactivity or airway obstruction? A pitfall with the clinical diagnosis of asthma is that symptoms are non-specific, particularly in children who frequently have recurrent respiratory symptoms due to viral illnesses. Although a clinical diagnosis may be more accurate in a primary-care setting where patients acutely present with symptoms, a community based study found that clinical symptoms did not accurately predict which patients had abnormal pulmonary function tests with 53% of patients having an FEV1 less than 80% in the absence of wheezing.³⁰ A previous study found that one barrier to spirometry is that primary care physicians do not believe that this test is necessary for the accurate diagnosis of asthma.²² Spirometry is normal in 40–90% of children with stable asthma depending on which parameter is assessed.^{31–33} When children are acutely symptomatic, it is likely more sensitive³⁰ with one study finding up to 67% with abnormal spirometry in patients presenting with symptoms. Exhaled nitric oxide (FeNO) testing is a marker of airway inflammation and has been studied as a diagnostic test for asthma³⁴; however, concerns that it only captures eosinophilic inflammation and falsely identifies non-asthmatic atopic patients has led to the recommendation that it be used to assess steroid responsiveness, and not used to confirm a diagnosis of asthma.³⁵

This study also has implications for epidemiologic asthma research which measures asthma prevalence and risk factors for the development, and maintenance of the disease. For example, the National Longitudinal Survey of Children and Youth (NLSCY) in Canada and the National Health Interview Survey (NHIS) in the United States use a question regarding physician-diagnosed asthma to estimate asthma prevalence in Canada and the United States, respectively.^{1,2} Our results suggest that this method of diagnostic ascertainment has a sensitivity of 75% and a specificity of 92% for correctly classifying asthma diagnosis. Previous international studies have shown similar estimates (sensitivity of 82–85% and specificity of 81–99%) for the questionnaire diagnosis of asthma.^{15,36} Assuming that our data is generalizable across the Canadian population, the asthma prevalence of 16.7% reported by the NLSCY yields a corrected prevalence rate of 12.5% once the effects of diagnostic misclassification are accounted for.

Limitations

This study has several limitations which may affect its generalizability to rates of asthma misdiagnosis in all children. Several limitations would be expected to improve diagnostic accuracy in our participants compared to the general population: we included children between the ages of 9 and 12 and children under the age of 5,³⁷ and adolescents^{38,39} have been shown to be at increased risk for underdiagnosis of asthma; our study was conducted in an urban setting where there is increased access to physicians and diagnostic testing facilities; the participants of this study were from a higher socioeconomic strata compared to non-participants and previous studies from the United States have shown that children from lower socioeconomic classes are more likely to be underdiagnosed with asthma.⁴⁰ Conversely, one of the reasons that our study may show a high diagnostic misclassification rate is that our community based sampling strategy identified predominantly children with mild asthma and results should not be generalized to the moderate to severe asthma population.

Another limitation is that our study is cross-sectional. Previous longitudinal follow-up of subjects with a clinical diagnosis of asthma but a negative methacholine challenge show that up to 30% of these subjects may later develop reversible bronchoconstriction³⁶ or use asthma medication.⁵ Conversely, up to 50% of asymptomatic subjects with positive methacholine challenges would be expected to develop asthma symptoms in the future.⁴¹ Finally, parent-reported asthma diagnosis is susceptible to recall bias; however, a previous study in this population showed that parent-reported asthma is highly specific (95.9%) for physician coded asthma in administrative billing records.⁴²

In summary, this study shows that there is significant misclassification of physician-diagnosed asthma in children. National asthma guidelines stress the need for objective testing to confirm a diagnosis of asthma in children who are able to perform pulmonary function testing; however, this is only occurring in a minority of children given a diagnosis of asthma. Further studies are needed to determine the barriers for pulmonary function testing in the community and to find better diagnostic tests for asthma in children.

ACKNOWLEDGMENTS

The authors thank Kathleen Nelligan and Laura Marshall, undergraduate summer research students, for their participation in subject recruitment and data collection. We also thank Laura Seed, David Wilson, Emma Abad, and Amanda Walker (Hospital for Sick Children, Toronto, ON) for their technical expertise in acquiring pulmonary function test and allergy skin prick test laboratory data for our study subjects.

REFERENCES

- Garner R, Kohen D. Changes in the prevalence of asthma among Canadian children. *Health Rep* 2008;19:45–50.
- Moorman JE AL, Bailey CM, Zahran HS, King ME, Johnson CA, Liu X. National Surveillance of Asthma: United States, 2001–2010. In: Statistics. NCFH, editor. Volume 3, Vital Health Stat 2012.
- Lougheed MD, Leniere C, Ducharme FM, Licskai C, Dell SD, Rowe BH, FitzGerald M, Leigh R, Watson W, Boulet LP. Canadian thoracic society guideline update: diagnosis and management of asthma in preschoolers, children, and adults: executive summary. *Can Respir J* 2012;19:e81–e88.
- Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. Volume 3: National Heart, Lung, and Blood Institute.
- Aaron SD, Vandemheen KL, Boulet LP, McIvor RA, Fitzgerald JM, Hernandez P, Lemiere C, Sharma S, Field SK, Alvarez GG, Dales RE, Doucette S, Fergusson D. Overdiagnosis of asthma in obese and nonobese adults. *CMAJ* 2008;179:1121–1131.
- Speight AN, Lee DA, Hey EN. Underdiagnosis and undertreatment of asthma in childhood. *Br Med J (Clin Res Ed)* 1983;286:1253–1256.
- Bush A, Fleming L. Is asthma overdiagnosed? *Arch Dis Child* 2016;101:688–689.
- Dell SD, Foty RG, Gilbert NL, Jerret M, To T, Walter SD, Stieb DM. Asthma and allergic disease prevalence in a diverse sample of Toronto school children: results from the Toronto Child Health Evaluation Questionnaire (T-CHEQ) Study. *Can Respir J* 2010;17:e1–e6.
- Schatz M, Sorkness CA, Li JT, Marcus P, Murray JJ, Nathan RA, Kosinski M, Pendergraft TB, Jhingran P. Asthma Control Test: reliability, validity, and responsiveness in patients not previously followed by asthma specialists. *J Allergy Clin Immunol* 2006;117:549–556.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
- Stanojevic S, Wade A, Stocks J, Hankinson J, Coates AL, Pan H, Rosenthal M, Corey M, Lebecque P, Cole TJ. Reference ranges for spirometry across all ages: a new approach. *Am J Respir Crit Care Med* 2008;177:253–260.
- Guidelines for methacholine and exercise challenge testing—1999. *Am J Respir Crit Care Med* 2000;161:309–329.
- Cockcroft DW, Marciniuk DD, Hurst TS, Cotton DJ, Laframboise KF, McNab BD, Skomro RP. Methacholine challenge: test-shortening procedures. *Chest* 2001;120:1857–1860.
- Fosgate GT. Modified exact sample size for a binomial proportion with special emphasis on diagnostic test parameter estimation. *Stat Med* 2005;24:2857–2866.
- Jenkins MA, Clarke JR, Carlin JB, Robertson CF, Hopper JL, Dalton MF, Holst DP, Choi K, Giles GG. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol* 1996;25:609–616.
- Zar J. Biostatistical analysis. Prentice Hall 1999. p 563.
- Fletcher R, Fletcher S. Clinical epidemiology: the essentials. Philadelphia: Lippincott Williams and Wilkins; 2005. pp 252.
- Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. *Biometrics* 1983;39:207–215.
- McGinn T, Wyer PC, Newman TB, Keitz S, Leipzig R, For GG. Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic). *CMAJ* 2004;171:1369–1373.
- Seear M, Wensley D, West N. How accurate is the diagnosis of exercise induced asthma among Vancouver schoolchildren? *Arch Dis Child* 2005;90:898–902.
- Thomson F, Masters IB, Chang AB. Persistent cough in children and the overuse of medications. *J Paediatr Child Health* 2002;38:578–581.
- O'Dowd LC, Fife D, Tenhave T, Panettieri RA, Jr. Attitudes of physicians toward objective measures of airway function in asthma. *Am J Med* 2003;114:391–396.
- Gershon AS, Victor JC, Guan J, Aaron SD, To T. Pulmonary function testing in the diagnosis of asthma: a population study. *Chest* 2012;141:1190–1196.
- Looijmans-van den Akker I, van Luijk K, Verheij T. Overdiagnosis of asthma in children in primary care: a retrospective analysis. *Br J Gen Pract* 2016;66:e152–e157.
- Wechsler ME, Kelley JM, Boyd IOE, Dutile S, Marigowda G, Kirsch I, Israel E, Kaptchuk TJ. Active albuterol or placebo, sham acupuncture, or No intervention in asthma. *N Engl J Med* 2011;365:119–126.
- Global Initiative for Asthma. Global Strategy for Asthma Diagnosis and Prevention. Global Initiative for Asthma (updated 2009). Available from <http://www.ginasthma.org> 2009.
- Loo J DS. Asthma diagnosis criteria in adult and pediatric asthma guidelines: a systematic review. *Can Respir J* 2010;17:14–15.
- British Guidelines on the Management of Asthma: British Thoracic Society and Scottish Intercollegiate Guidelines Network; January 2012.
- Cornish RP, Henderson J, Boyd AW, Granell R, Van Staa T, Macleod J. Validating childhood asthma in an epidemiological study using linked electronic patient records. *BMJ Open* 2014;4:e005345.
- Holt EW, Tan J, Hosgood HD. The impact of spirometry on pediatric asthma diagnosis and treatment. *J Asthma* 2006;43:489–493.
- Fuhlbrigge AL. Asthma severity and asthma control: symptoms, pulmonary function, and inflammatory markers. *Curr Opin Pulm Med* 2004;10:1–6.
- Paull K, Covar R, Jain N, Gelfand EW, Spahn JD. Do NHLBI lung function criteria apply to children? A cross-sectional evaluation of childhood asthma at National Jewish Medical and Research Center, 1999–2002. *Pediatr Pulmonol* 2005;39:311–317.
- Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Jr, Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med* 2004;170:426–432.
- Smith AD, Cowan JO, Filsell S, McLachlan C, Monti-Sheehan G, Jackson P, Taylor DR. Diagnosing asthma: comparisons between exhaled nitric oxide measurements and conventional tests. *Am J Respir Crit Care Med* 2004;169:473–478.
- Dweik RA, Boggs PB, Erzurum SC, Irvin CG, Leigh MW, Lundberg JO, Olin AC, Plummer AL, Taylor DR. An Official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602–615.
- Remes ST, Pekkanen J, Remes K, Salonen RO, Korppi M. In search of childhood asthma: questionnaire, tests of bronchial hyperresponsiveness, and clinical evaluation. *Thorax* 2002;57:120–126.
- Bisgaard H, Szefer S. Prevalence of asthma-like symptoms in young children. *Pediatr Pulmonol* 2007;42:723–728.
- Magzamen S, Tager IB. Factors related to undiagnosed asthma in urban adolescents: a multilevel approach. *J Adolesc Health* 2010;46:583–591.
- Siersted HC, Boldsen J, Hansen HS, Mostgaard G, Hyldebrandt N, Rees PJ, Evans SJW. Population based study of risk factors for underdiagnosis of asthma in adolescence: odense schoolchild study. *BMJ* 1998;316:651–657.

40. Yeatts K, Johnston Davis K, Peden D, Shy C. Health consequences associated with frequent wheezing in adolescents without asthma diagnosis. *Eur Respir J* 2003;22:781–786.
41. Rasmussen F, Taylor DR, Flannery EM, Cowan JO, Greene JM, Herbison GP, Sears MR. Outcome in adulthood of asymptomatic airway hyperresponsiveness in childhood: a longitudinal population study. *Pediatr Pulmonol* 2002; 34:164–171.
42. Yang CL, To T, Foty RG, Stieb DM, Dell SD. Verifying a questionnaire diagnosis of asthma in children using health claims data. *BMC Pulm Med* 2011;11:52.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.