JAMA | Original Investigation

Reevaluation of Diagnosis in Adults With Physician-Diagnosed Asthma

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IMPORTANCE Although asthma is a chronic disease, the expected rate of spontaneous remissions of adult asthma and the stability of diagnosis are unknown.

OBJECTIVE To determine whether a diagnosis of current asthma could be ruled out and asthma medications safely stopped in randomly selected adults with physician-diagnosed asthma.

DESIGN, SETTING, AND PARTICIPANTS A prospective, multicenter cohort study was conducted in 10 Canadian cities from January 2012 to February 2016. Random digit dialing was used to recruit adult participants who reported a history of physician-diagnosed asthma established within the past 5 years. Participants using long-term oral steroids and participants unable to be tested using spirometry were excluded. Information from the diagnosing physician was obtained to determine how the diagnosis of asthma was originally made in the community. Of 1026 potential participants who fulfilled eligibility criteria during telephone screening, 701 (68.3%) agreed to enter into the study. All participants were assessed with home peak flow and symptom monitoring, spirometry, and serial bronchial challenge tests, and those participants using daily asthma medications had their medications gradually tapered off over 4 study visits. Participants in whom a diagnosis of current asthma was ultimately ruled out were followed up clinically with repeated bronchial challenge tests over 1 year.

EXPOSURE Physician-diagnosed asthma established within the past 5 years.

MAIN OUTCOMES AND MEASURES The primary outcome was the proportion of participants in whom a diagnosis of current asthma was ruled out, defined as participants who exhibited no evidence of acute worsening of asthma symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness after having all asthma medications tapered off and after a study pulmonologist established an alternative diagnosis. Secondary outcomes included the proportion with asthma ruled out after 12 months and the proportion who underwent an appropriate initial diagnostic workup for asthma in the community.

RESULTS Of 701 participants (mean [SD] age, 51 [16] years; 467 women [67%]), 613 completed the study and could be conclusively evaluated for a diagnosis of current asthma. Current asthma was ruled out in 203 of 613 study participants (33.1%; 95% CI, 29.4%-36.8%). Twelve participants (2.0%) were found to have serious cardiorespiratory conditions that had been previously misdiagnosed as asthma in the community. After an additional 12 months of follow-up, 181 participants (29.5%; 95% CI, 25.9%-33.1%) continued to exhibit no clinical or laboratory evidence of asthma. Participants in whom current asthma was ruled out, compared with those in whom it was confirmed, were less likely to have undergone testing for airflow limitation in the community at the time of initial diagnosis (43.8% vs 55.6%, respectively; absolute difference, 11.8%; 95% CI, 2.1%-21.5%).

CONCLUSIONS AND RELEVANCE Among adults with physician-diagnosed asthma, a current diagnosis of asthma could not be established in 33.1% who were not using daily asthma medications or had medications weaned. In patients such as these, reassessing the asthma diagnosis may be warranted.

JAMA. 2017;317(3):269-279. doi:10.1001/jama.2016.19627

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Asthma is defined as a disease characterized by chronic airway inflammation that results in respiratory symptoms of wheeze, dyspnea, chest tightness, or cough that vary over time and in intensity, together with variable expiratory airflow limitation.[1] A necessary condition of all guideline definitions of asthma is that tests of expiratory airflow are needed to confirm the diagnosis.[2-4]

Diagnosis of asthma in the community can be difficult. Various phenotypes of asthma have been identified, including atopic, nonallergic, and late-onset asthma, all of which potentially have different triggers and clinical presentations.[5] Furthermore, asthma can be episodic or can follow a relapsing and remitting course, which further complicates attempts to arrive at a diagnosis based on a single patient-physician encounter. Studies have shown that many physicians choose to diagnose and treat patients empirically for asthma and that in the community asthma is sometimes poorly investigated, with fewer than half of patients receiving spirometry testing to confirm variable expiratory airflow limitation prior to diagnosis.[6-8]

Contemporary asthma guidelines suggest stepping down asthma treatment once good asthma control has been achieved and maintained for 3 months.[3] The goal of stepping down treatment is to find the patient's minimum effective treatment that maintains good control of symptoms and exacerbations and minimizes the costs of treatment and potential for adverse effects. However, few experimental data have been reported on the optimal timing, sequence, and magnitude of treatment reductions in asthma. Furthermore, the expected rate of spontaneous remission of adult asthma, allowing for complete cessation of asthma therapy, is unknown.

The primary objective of this study was to determine whether a diagnosis of current asthma could be ruled out in randomly selected adult patients with recent physician-diagnosed asthma and whether these patients could be safely weaned off asthma medications.

Key Points

Question Can current asthma be ruled out and can asthma medications be safely stopped in some adult patients with physician-diagnosed asthma?

Findings In this multicenter cohort study that enrolled 701 randomly selected adults with physician-diagnosed asthma, current asthma was excluded in 33% of the 613 participants who completed the study.

Meaning Among some adult patients with physician-diagnosed asthma, reassessing that diagnosis may be warranted.

Methods

Study Participants

Study participants were recruited from the general population from January 2012 to February 2015 via random digit dialing of both landlines and cellular phones. Potential participants were randomly sampled from the 10 largest cities in Canada and from surrounding areas. The target population included residents in these cities and rural or suburban residents residing in telephone exchanges known to be located within a 90-minute drive of each of the 10 metropolitan areas. For the urban, suburban, and semirural subpopulations within Canada, telephone coverage is almost universal; thus, the sampling technique was meant to approximate a true random sample of the Canadian adult population with asthma.

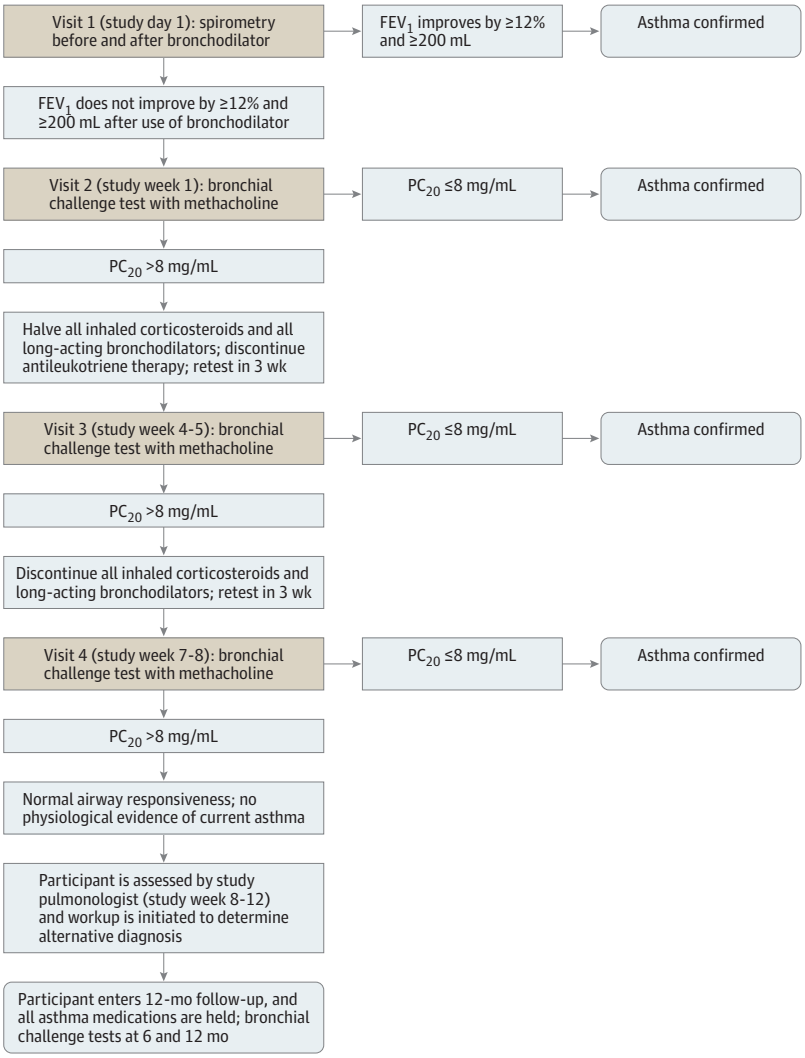
Telephone respondents were asked the following question via a recorded message from the local study coordinator: "Is there a member of your household aged 18 years of age or older who has been diagnosed with asthma within the last 5 years?" If the telephone respondent indicated yes, the study coordinator subsequently contacted the identified person with asthma in the household directly. Participants were informed that patients with asthma were being studied, but the participants were not informed of the objectives of the study to avoid biasing enrollment in favor of those participants who potentially doubted their asthma diagnosis. Participants who fit the screening eligibility criteria were then invited to the local study center for a complete eligibility assessment and entry into the study. The study was approved by the research ethics boards of the 10 participating study hospitals, and all patients who participated in the study provided written informed consent.

Eligible participants were at least 18 years old and had physician-diagnosed asthma established within the past 5 years. The rationale for choosing only individuals with recently diagnosed asthma was to evaluate contemporary diagnostic practices. Evaluation of individuals with recently diagnosed asthma also allowed collection of medical records available from the original diagnosing physicians to determine how asthma was diagnosed in the community. Patients were excluded from participating if they were using long-term oral steroids; if they were pregnant, breastfeeding, or unable to perform spirometry; if a bronchial challenge test was contraindicated (because of known aortic or cerebral aneurysms or history of myocardial infarction or stroke within 3 previous months); or if they had a smoking history greater than 10 pack-years (to exclude patients with possible chronic obstructive pulmonary disease).

Participant Study Assessments

Prior to undergoing spirometry, participants completed the European Community Respiratory Health Survey,[9] the Asthma Quality of Life Questionnaire,[10] and assessments of their asthma medical history and health care utilization. They then were evaluated using the diagnostic algorithm for confirming current asthma as shown in **Figure 1**. They performed prebronchodilator spirometry according to American Thoracic Society standards.[11] Postbronchodilator spirometry was assessed 15 minutes later after administration of 400 µg of albuterol given by a pressurized metered dose inhaler with a spacer device. Patients whose forced expiratory volume in the first second of expiration (FEV_1) improved by at least 12% and at least 200 mL after bronchodilator administration were considered to have reversible airflow obstruction characteristic of current asthma.[1]

Figure 1. Diagnostic Serial Testing Algorithm to Confirm or Rule Out Asthma



FEV_1 indicates forced expiratory volume in the first second of expiration; PC_{20}, the concentration of methacholine needed to produce a 20% decrease in FEV_1 from baseline.

Patients who did not exhibit reversible airflow obstruction returned to the pulmonary function laboratory for a bronchial challenge test. They were asked to withhold long-acting β-agonists for 48 hours and short-acting β-agonists for 8 hours prior to testing. The FEV_1 was measured at baseline and again after inhalation of normal saline, then doubling concentrations of methacholine from 0.03 to 16.0 mg/mL in normal saline solution were delivered using a Wright or Puritan-Bennett twin nebulizer and inhaled by tidal breathing for 2 minutes with the nose clipped. The FEV_1 was measured at 30 seconds and 90 seconds after each dose. Doubling concentrations of methacholine were given at 5-minute intervals until the FEV_1 decreased by 20% from baseline or until a dose of 16 mg/mL had been reached. Individuals with a decrease in FEV_1 of 20% or more with 8 mg/mL of methacholine or less were defined as having airway hyperresponsiveness characteristic of current asthma.[12]

Participants who had a negative bronchial challenge test result at visit 2 and who reported not using any asthma-controlling medications within the previous 3 weeks proceeded to assessment by a study pulmonologist (Figure 1). Those participants with a negative bronchial challenge test result at visit 2 who were using daily asthma-controlling medications were gradually tapered from their asthma maintenance medications (Figure 1). They were asked to halve their usual inhaled steroid dose and long-acting bronchodilator, to discontinue their antileukotriene medication, and to keep a daily symptom diary and record daily peak flow rates using a peak flow meter. They were permitted to use short-acting bronchodilators on an as-needed basis. At the third study visit 3 weeks later, symptom assessments and home peak flow measurements were reviewed and bronchial challenge testing was repeated. If the patients had no intercurrent acute worsening of symptoms, their peak flow measurements showed no variable declines in airflow, and their bronchial challenge test result was negative, then their inhaled steroid and their long-acting β-agonist were completely stopped, and they returned for a fourth study visit and bronchial challenge testing 3 weeks later.

Patients who had exacerbations of asthma symptoms at any point during their medication tapering period were seen by study pulmonologists and had spirometry performed. If the study physician determined that the patient was having an asthma exacerbation or worsening, a diagnosis of current asthma was confirmed.

Patients who did not experience exacerbations of symptoms and who continued to have negative results on bronchial challenge testing despite having discontinued all asthma medications were classified as having normal airway responsiveness and were then formally assessed by a study pulmonologist in consultation. The study pulmonologists assessed the patients' symptoms and physical findings and were instructed to order any additional diagnostic testing they felt was clinically indicated to attempt to reach a diagnosis. Once the diagnostic workup was completed, the study pulmonologist was asked to assign a diagnosis to each patient. Two independent pulmonologists reviewed the consultation reports to determine agreement with the treating pulmonologist's diagnosis. Patients who were assigned diagnoses other than current asthma by the study pulmonologist were asked to not use asthma medications for the remainder of the study period (12 months after visit 4).

All patients in whom current asthma had been excluded were followed up for 12 months and had repeat bronchial challenge tests at 6 and 12 months in addition to regular telephone follow-up with assessment of health care outcomes every 3 months. Participants were encouraged to present to the study pulmonologist if they experienced any worsening of respiratory symptoms during this period.

Assessment of How the Asthma Diagnosis Was Initially Established in the Community

The physician of each study participant was contacted and asked to review the patient's medical record and to answer a questionnaire that inquired whether the diagnosis of asthma was initially made based on symptoms alone, based on symptoms and physical findings, or based on symptoms, physical findings, and diagnostic tests such as spirometry, peak expiratory flows, and/or bronchial challenge testing. If objective diagnostic testing was performed, faxed copies of the test results were requested from the physician's office. Physicians were offered a standard reimbursement to provide these data.

The diagnostic tests received from the community were reviewed by 2 study pulmonologists blinded to the patients' outcomes. The study pulmonologists assessed whether the tests done in the community were of adequate quality and whether the tests were diagnostic of asthma (ie, improvement in FEV_1 by ≥12% after bronchodilator use, positive bronchial challenge test result, or average daily diurnal peak expiratory flow variability >10%). A third pulmonologist blinded to the patients' outcomes adjudicated decisions in cases for which there was disagreement.

Study Outcomes

The primary outcome was the proportion of patients in whom the diagnosis of current asthma was ruled out. Patients who did not have evidence of acute worsening of asthma symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness despite discontinuing all asthma medications during the 4-visit study algorithm and who were assessed by the study pulmonologist as having a diagnosis other than current asthma were considered to have met the primary outcome.

The proportion of patients in whom the diagnosis of current asthma was ruled out after 12 months of further follow-up was evaluated as a secondary outcome. Those who did not have evidence of acute worsening of asthma symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness after 12 months of follow-up without use of asthma medications were considered to have met this outcome. Other secondary outcomes included the proportion of enrolled participants who previously had undergone an appropriate initial workup for diagnosis of asthma in the community (with assessment of variable expiratory airflow limitation by spirometry, bronchial challenge testing, or serial peak flow measurements) and the proportion of individuals whose community diagnostic workup was positive for asthma.

Statistical Analysis

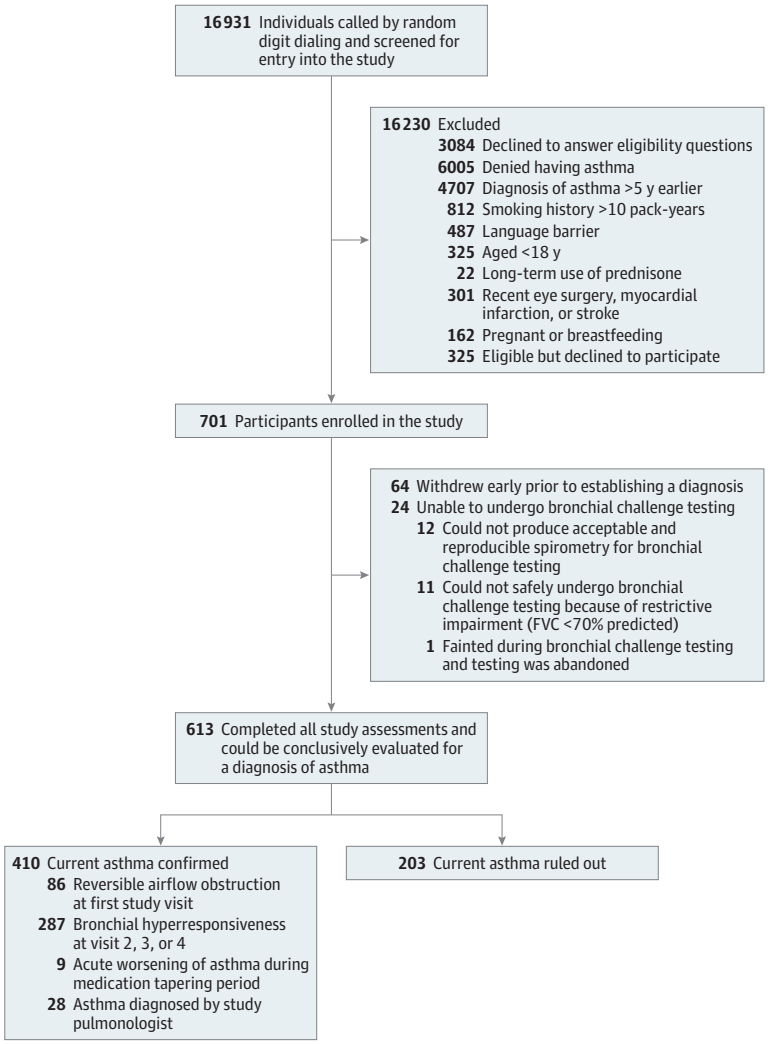
Prior to commencing the study, it was estimated that a sample size of 644 participants would allow, after premature dropouts, for conclusive assessment for current asthma in 580 participants. This sample size was calculated, based on results from a previous study, to allow for expected exclusion of current asthma in 20% of the cohort with 95% confidence intervals of ±3.5%.[13] The principal analysis was descriptive and included estimates of proportions with 95% confidence intervals. A 2-sided $P \leq .05$ was considered statistically significant. Multivariable logistic regression procedures were used to examine the determinants of confirmation of current asthma, after controlling for 3 prespecified, clinically important variables: age, sex, and body mass index (BMI; calculated as weight in kilograms divided by height in meters squared). The other variables included in the model (age at diagnosis, diagnosis by a specialist, airflow testing done in the community, use of daily asthma medications, FEV_1 percentage predicted, dyspnea within 12 months, wheeze within 12 months, and Asthma Quality of Life Questionnaire total score) were chosen post hoc based on analyses that showed statistically strong associations (P threshold < .10) between the individual variables and confirmation or exclusion of current asthma. SAS version 9.3 statistical software (SAS Institute Inc) was used for all analyses.

Results

Recruitment of Participants

A total of 16 931 potential participants were contacted by random digit dial calls over the 3-year study recruitment period. Reasons for exclusion of participants from enrollment are shown in **Figure 2**. Ultimately 1026 potential participants fulfilled eligibility criteria during telephone screening; of these,

Figure 2. Recruitment of Study Participants and Study Outcomes



FVC indicates forced vital capacity.

701 (68.3%) presented to a study site for assessment and were entered into the study. Demographic information was not collected from the 325 participants who were eligible to enter the study but chose not to participate.

Assessment of Current Asthma in the Study Cohort

Of 701 participants who entered into the study (mean [SD] age, 51 [16] years; 467 women [67%]), 64 withdrew early prior to establishment of a diagnosis and 24 could not undergo bronchial challenge testing for reasons described in Figure 2. Ultimately 613 participants completed the study assessment procedures and could be conclusively evaluated for a diagnosis of current asthma (Figure 2 and **Table 1**). Of these 613 participants, 531 (86.6%) reported recent use of asthma medications and 273 (44.5%) reported daily use of asthma-controlling medications (inhaled corticosteroids and/or antileukotriene medications).

Three hundred eighty-two individuals (62.3%) were confirmed to have current asthma during the 4-visit diagnostic assessment period. The diagnosis of asthma was confirmed in 86 of these individuals (22.5%) by demonstrating reversibility in airflow obstruction after albuterol administration at the first study visit, in 287 (75.1%) by demonstrating bronchial hyperresponsiveness via bronchial challenge testing at the second, third, or fourth study visit, and in 9 (2.4%) based on an acute worsening of asthma symptoms during the medication tapering period.

Two hundred thirty-one participants had no evidence of airflow obstruction, bronchial hyperresponsiveness, or worsening of symptoms after being tapered off all asthma medications. Of these 231 participants, 213 (92.2%) were assessed by a study pulmonologist in face-to-face consultation and 18 (7.8%) were assessed remotely by telephone. The study pulmonologist diagnosed asthma in 28 participants after completion of the face-to-face consultation and diagnostic workup, but alternative diagnoses were made for the remainder (**Table 2**). Eighteen participants did not attend their scheduled consultation appointment with the pulmonologist and were instead assessed by telephone; they each denied respiratory symptoms and were considered asymptomatic.

Table 1. Baseline Characteristics of Individuals Whose Diagnosis of Current Asthma Was Confirmed or Ruled Out

Characteristic	Current Asthma		Absolute Difference (95% CI)[a]	*P* Value
	Confirmed (n = 410)	Ruled Out (n = 203)		
Age, mean (95% CI), y	50.6 (49.0 to 52.1)	52.5 (50.1 to 54.8)	−1.9 (−4.7 to 0.9)	.18
Female, No. (%)	266 (64.9)	139 (68.4)	−3.6 (−11.5 to 4.3)	.38
White, No. (%)	368 (89.8)	186 (91.6)	−1.9 (−6.7 to 2.9)	.46
Height, mean (95% CI), cm	166.1 (165.2 to 167.0)	166.3 (165.0 to 167.5)	−0.2 (−1.7 to 1.4)	.83
Weight, mean (95% CI), kg	81.7 (79.8 to 83.5)	82.8 (79.9 to 85.7)	−1.1 (−4.5 to 2.3)	.51
BMI, mean (95% CI)	29.6 (28.9 to 30.2)	29.9 (28.9 to 30.9)	−0.4 (−1.5 to 0.8)	.52
College and/or university education, No. (%)	286 (69.8)	139 (68.5)	1.3 (−6.5 to 9.1)	.79
Current smoker, No. (%)	29 (7.1)	8 (3.9)	3.1 (−0.5 to 6.8)	.13
Asthma diagnosis				
Age at asthma diagnosis, mean (95% CI), y	44.9 (43.2 to 46.5)	47.4 (44.9 to 50.0)	−2.6 (−5.6 to 0.4)	.09
Time since asthma diagnosis, mean (95% CI), y	4.1 (3.8 to 4.4)	4.2 (3.7 to 4.7)	−0.1 (−0.7 to 0.5)	.65
Asthma diagnosed by family physician or emergency physician, No. (%)	230 (56.1)	138 (67.9)	−11.8 (−19.6 to −4.0)	.003
Asthma diagnosed by pulmonologist, allergist, internist, or pediatrician, No. (%)	178 (43.6)	62 (31.0)	12.6 (4.6 to 20.6)	.003
Patient recalled having spirometry performed at time asthma was diagnosed, No. (%)	298 (72.7)	119 (58.6)	14.1 (6.0 to 22.1)	<.001
Evidence that spirometry, bronchial challenge testing, or serial peak flow testing was done in the community, No./participants with available data, No. (%)	179/322 (55.6)	64/146 (43.8)	11.8 (2.1 to 21.5)	.02
Within previous year, No. (%)				
Urgent visit to health care facility for asthma	73 (17.8)	29 (14.3)	3.5 (−0.2 to 6.9)	.27
Hospitalization for asthma	4 (1.0)	3 (1.5)	−0.5 (−2.4 to 1.4)	.69
Use of oral or intravenous corticosteroids for asthma	49 (12.0)	11 (5.4)	6.5 (2.1 to 11.0)	.01
Asthma medication use, No. (%)				
Currently using asthma medications	370 (90.2)	161 (79.3)	10.9 (4.7 to 17.2)	<.001
Using asthma-controlling medications daily	202 (49.3)	71 (35.0)	14.3 (6.1 to 22.4)	<.001
Using ICS or ICS with LABA daily	181 (44.2)	68 (33.5)	10.7 (2.6 to 18.7)	.01
Using antileukotriene daily	30 (7.2)	12 (5.9)	1.4 (−2.7 to 5.5)	.52
Baseline lung function				
Prebronchodilator FVC, mean (95% CI), L	3.63 (3.53 to 3.74)	3.74 (3.61 to 3.88)	−0.11 (−0.28 to 6.13)	.22
FEV_1, mean (95% CI), L				
Prebronchodilator	2.64 (2.56 to 2.71)	2.92 (2.81 to 3.03)	−0.29 (−0.42 to −0.15)	<.001
Postbronchodilator	2.81 (2.73 to 2.89)	3.02 (2.90 to 3.13)	−0.21 (−0.34 to −0.07)	.003
FEV_1 % predicted, mean (95% CI)				
Prebronchodilator	88 (86 to 89)	98 (96 to 100)	−10.3 (−12.7 to −7.9)	<.001
Postbronchodilator	93 (92 to 95)	101 (99 to 103)	−7.4 (−9.9 to −4.9)	<.001
Postbronchodilator improvement in FEV_1 by ≥12% and ≥200 mL, No. (%)	86 (21.0)	0	21.0 (17.1 to 25.0)	<.001

(continued)

Table 1. Baseline Characteristics of Individuals Whose Diagnosis of Current Asthma Was Confirmed or Ruled Out (continued)

Characteristic	Current Asthma		Absolute Difference (95% CI)[a]	*P* Value
	Confirmed (n = 410)	Ruled Out (n = 203)		
Patients with symptoms as assessed using ECRHS, No. (%)				
During past 12 mo				
Dyspnea	354 (86.3)	157 (77.3)	9.0 (2.4 to 15.6)	.005
Wheeze	337 (82.2)	137 (67.5)	14.7 (7.3 to 22.1)	<.001
Current				
Chest tightness	113 (27.6)	42 (20.7)	6.9 (−0.2 to 13.9)	.07
Cough	217 (52.9)	99 (48.8)	4.2 (−4.2 to 12.6)	.33
Dyspnea	174 (42.4)	69 (34.0)	8.4 (0.4 to 16.5)	.04
Sputum production	170 (41.5)	68 (33.5)	8.0 (−0.1 to 16.0)	.06
Wheeze	149 (36.3)	39 (19.2)	17.1 (10.0 to 24.3)	<.001
AQLQ score, mean (95% CI)[b]				
Symptom	5.28 (5.17 to 5.40)	5.62 (5.48 to 5.76)	−0.34 (−0.53 to −0.15)	<.001
Activity	5.66 (5.55 to 5.77)	5.85 (5.71 to 5.99)	−0.19 (−0.37 to −0.02)	.04
Emotion	5.51 (5.39 to 5.64)	5.76 (5.59 to 5.93)	−0.25 (−0.46 to −0.04)	.02
Environmental stimuli	5.29 (5.16 to 5.42)	5.51 (5.33 to 5.70)	−0.22 (−0.46 to 0.01)	.06
Total	5.44 (5.35 to 5.55)	5.70 (5.57 to 5.85)	−0.26 (−0.43 to −0.09)	.004
Patients with comorbidities, No. (%)				
History of GERD	122 (29.8)	49 (24.1)	5.6 (−1.8 to 13.0)	.14
Diabetes	25 (6.1)	17 (8.4)	−2.3 (−6.7 to 2.2)	.29
Hypertension	95 (23.2)	63 (31.0)	−7.9 (−15.4 to −0.3)	.04
Vocal cord dysfunction	10 (2.4)	9 (4.4)	−2.0 (−5.2 to 1.2)	.18
Depression	130 (31.7)	72 (35.5)	−3.8 (−11.7 to 4.2)	.35

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECRHS, European Community Respiratory Health Survey; FEV_1, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; GERD, gastroesophageal reflux disease; ICS, inhaled corticosteroid; LABA, long-acting β-agonist bronchodilator.

[a] For variables presented as number (percentage), the absolute difference is expressed as the difference in percentages.

[b] Scores range from 1 to 7, with higher scores indicating better asthma-specific quality of life.

Current asthma was ruled out in 203 of 613 study participants (33.1%; 95% CI, 29.4%-36.8%).

Patient Characteristics Associated With Exclusion of Current Asthma

Table 1 shows the baseline characteristics of the 203 participants in whom current asthma was ruled out, compared with the 410 participants in whom asthma was confirmed. Those in whom current asthma was ruled out, compared with those with confirmed asthma, had significantly better lung function and were less likely to be using asthma medications (79.3% vs 90.2%, respectively; absolute difference, 10.9%; 95% CI, 4.7%-17.2%) or daily asthma-controlling medications (35.0% vs 49.3%, respectively; absolute difference, 14.3%; 95% CI, 6.1%-22.4%). Those in whom asthma was excluded were less likely to report that they had spirometry performed at the time of asthma diagnosis, and this was confirmed on receipt of the diagnosing community physicians' reports; only 43.8% of participants in whom asthma was ruled out had evidence of having undergone assessment of variable airflow limitation (spirometry, bronchial challenge testing, or serial measurements of peak flows) in the community, compared with 55.6% of those in whom asthma was confirmed (absolute difference, 11.8%; 95% CI, 2.1%-21.5%).

Multivariable logistic regression analysis confirmed that lower FEV_1 percentage predicted, daily use of asthma medications, objective confirmation of airflow limitation in the community through diagnostic testing, and history of wheezing were significantly associated with confirmation of current asthma after controlling for participants' age, sex, and BMI (**Figure 3**).

There was no significant difference in the proportion of participants who were enrolled into the study during the winter (24.1%), spring (25.1%), summer (22.2%), and fall (28.6%) months in those in whom asthma was ruled out compared with those in whom asthma was confirmed (23.2%, 32.0%, 21.4%, and 23.5%, respectively), excluding potential seasonal confounding effects on asthma diagnosis ($P = .30$ for χ^2 test across the 4 seasons).

Assessment of Asthma Diagnostic Testing in the Community

Of the community physicians who were contacted and had initially diagnosed asthma in each of 701 study participants, 530 (75.6%) responded by completing a questionnaire and

Table 2. Study Pulmonologist's Diagnosis in Participants Who Had No Evidence of Airflow Obstruction, Bronchial Hyperreactivity, or Worsening of Asthma Symptoms After Having All Asthma Medications Tapered Off

Pulmonologist's Diagnosis	Participants, No. (%) (n = 213)
Asymptomatic	61 (28.6)
Allergic or nonallergic rhinitis	54 (25.3)
Asthma	28 (13.1)
GERD	18 (8.5)
Anxiety or hyperventilation	8 (3.8)
Obesity or deconditioning	7 (3.3)
Eosinophilic bronchitis	6 (2.8)
Ischemic heart disease	4 (1.9)
COPD	4 (1.9)
Chronic cough due to ACE inhibitors	4 (1.9)
Postviral cough	4 (1.9)
Bronchiectasis	2 (0.9)
Subglottic stenosis	2 (0.9)
Environmental chemical sensitivity	2 (0.5)
Interstitial lung disease	1 (0.5)
Kyphoscoliosis	1 (0.5)
Pulmonary hypertension	1 (0.5)
Costochondritis	1 (0.5)
Sarcoidosis	1 (0.5)
Vocal cord dysfunction	1 (0.5)
Tracheobronchomalacia	1 (0.5)
Recurrent viral bronchitis	1 (0.5)
Chronic cough of unknown etiology	1 (0.5)

Abbreviations: ACE, angiotensin-converting enzyme; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease.

medical record review. The diagnosing physician provided evidence of spirometry and/or bronchial challenge testing and/or serial peak flow testing having been done to confirm the diagnosis of asthma in 269 of 530 patients (50.8%). For the remaining patients, asthma was diagnosed based on symptoms and/or physical findings alone.

Table 3 shows the results of the diagnostic testing that had been done in the community in the 613 participants who completed the study. Patients whose current asthma was confirmed by the study protocol were more likely than those in whom asthma was ruled out to have undergone diagnostic testing for airflow limitation in the community (55.6% vs 43.8%, respectively; absolute difference, 11.8%; 95% CI, 2.1%-21.5%), and their tests in the community were more likely to have been diagnostic of asthma (35.1% vs 16.4%, respectively; absolute difference, 18.6%; 95% CI, 10.7%-26.6%).

Results of 1 Year of Additional Follow-up

After 1 year of additional follow-up, 22 of 203 participants in whom current asthma had been ruled out had a positive bronchial challenge test result at either 6 or 12 months. Of these 22 participants, 16 were asymptomatic and did not experience any respiratory exacerbations, and these participants did not resume use of their asthma medications. Six participants presented with respiratory symptoms and resumed treatment with asthma medications; 1 of these participants was also treated with a brief course of oral corticosteroid. The remaining 181 participants (29.5%; 95% CI, 25.9%-33.1%) exhibited no clinical or laboratory evidence of asthma during the 12 months of follow-up.

Alternative Diagnoses in Participants Who Did Not Have Current Asthma

Table 2 lists the pulmonologists' diagnoses in the 213 patients who had an in-person pulmonologist consultation. The most common alternative diagnoses were for relatively benign conditions, and many patients were asymptomatic. However, 12 of these patients (2.0% of the study cohort) had serious cardiorespiratory conditions that had been misdiagnosed as asthma, including 4 individuals with ischemic heart disease (2 of whom required percutaneous coronary intervention), 2 with subglottic stenosis (both of whom required airway dilatation procedures), 2 with bronchiectasis, and 1 each with interstitial lung disease, pulmonary hypertension, sarcoidosis, and tracheobronchomalacia.

Subgroup Analysis of Participants Using Daily Asthma-Controlling Medications

Of 273 participants who were using daily asthma-controlling medications at study entry, current asthma was ruled out in 71 participants (26.0%; 95% CI, 20.8%-31.2%). After 12 months of follow-up, 68 of the 273 participants (24.9%; 95% CI, 19.8%-30.0%) remained free of current asthma.

Discussion

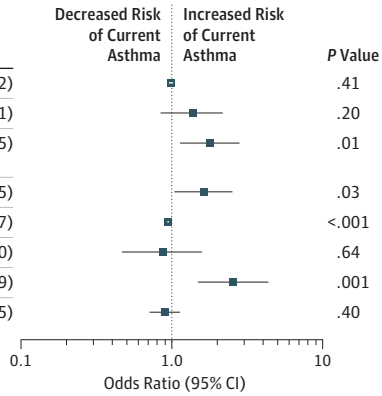
This study found that 33.1% of adult participants randomly recruited from the community who had been diagnosed with asthma in the previous 5 years had no evidence of current asthma when they were prospectively evaluated with serial assessments of symptoms, lung function, and bronchial provocation tests while not using asthma medications. More than 90% of participants in whom asthma was ruled out had asthma medications safely stopped for an additional 1-year period.

Two phenomena may account for failure to ultimately confirm current asthma in 33.1% of the study cohort: (1) spontaneous remission of previously active asthma; and (2) misdiagnosis of asthma in the community. At least 24 of 203 participants (11.8%) in whom current asthma was ruled out had undergone pulmonary function tests in the community that had been previously diagnostic of asthma. These participants presumably experienced spontaneous remission of their asthma at some time between their initial community diagnosis and entry into the study. This variability in asthma diagnosis, with opportunity for remission and relapse, is further supported by the fact that 22 participants in whom current asthma was ruled out subsequently had a positive bronchial challenge test result during 1 year of follow-up.

This study also suggests that misdiagnosis of asthma may occasionally occur in the community.[14,15] In 2.0% of study participants, a serious untreated cardiorespiratory condition was

Figure 3. Adjusted Odds Ratios and Absolute Risk Differences for Determinants of Current Asthma

	Patients With Asthma Confirmed, No./Total No. (%)	Patients With Asthma Ruled Out, No./Total No. (%)	Absolute Risk Difference (95% CI)	Odds Ratio (95% CI)	P Value
Age at diagnosis (per year)			-0.19 (-0.60 to 0.22)	0.99 (0.96 to 1.02)	.41
Diagnosis by a specialist	142/317 (44.8)	52/144 (36.1)	5.95 (-2.84 to 14.74)	1.37 (0.85 to 2.21)	.20
Airflow testing done in community at diagnosis	177/317 (55.8)	63/144 (43.8)	10.93 (2.39 to 19.48)	1.79 (1.13 to 2.85)	.01
Daily use of asthma medications	163/317 (51.4)	59/144 (41.0)	8.70 (0.45 to 16.94)	1.63 (1.04 to 2.55)	.03
FEV_1 % predicted (per increase of 1%)			-0.80 (-1.02 to -0.58)	0.95 (0.94 to 0.97)	<.001
Dyspnea within 12 mo of study entry	269/317 (84.9)	111/144 (77.1)	-2.56 (-14.93 to 9.82)	0.87 (0.47 to 1.60)	.64
Wheeze within 12 mo of study entry	261/317 (82.3)	92/144 (63.9)	19.11 (8.17 to 30.05)	2.57 (1.50 to 4.39)	.001
AQLQ mean total score (per 1-point increase)			-1.38 (-5.56 to 2.80)	0.90 (0.71 to 1.15)	.40



Adjustments were made for age, sex, and body mass index (calculated as weight in kilograms divided by height in meters squared). Sample size was 461 (317 with current asthma confirmed and 144 with current asthma ruled out) rather than 613 because data on whether testing for airflow obstruction was done in the community were not available for participants whose community physician did not answer the study questionnaire. AQLQ indicates Asthma Quality of Life Questionnaire; FEV_1, forced expiratory volume in the first second of expiration.

Table 3. Summary of the Initial Diagnostic Workup for Asthma Performed in the Community

Workup	Current Asthma, No./Total No. (%)		Absolute Difference, % (95% CI)
	Confirmed	Ruled Out	
Diagnostic report was received from community physician	322/410 (78.5)	146/203 (71.9)	6.6 (−0.7 to 14.0)
Testing of airflow limitation was done in community at time of original diagnosis	179/322 (55.6)	64/146 (43.8)	11.8 (2.1 to 21.5)
Tests done in community at time of original diagnosis were positive for asthma	113/322 (35.1)	24/146 (16.4)	18.6 (10.7 to 26.6)

identified that may have been previously misdiagnosed as asthma. In addition, the study demonstrated that failure to consistently use objective testing at the time of initial diagnosis of asthma was associated with failure to confirm current asthma. These results suggest that whenever possible, physicians should order objective tests, such as prebronchodilator and postbronchodilator spirometry, serial peak flow measurements, or bronchial challenge tests, to confirm asthma at the time of initial diagnosis.

A 2008 Canadian study failed to confirm asthma in 30% to 33% of obese and nonobese participants who had been previously diagnosed with asthma.[13] However, the 2008 study could draw only limited conclusions because participants included in that study were not recently diagnosed with asthma, the study was limited by lack of long-term follow-up to exclude possible remission and then recurrence of asthma, ascertainment for prior objective diagnosis of asthma in the community was lacking, and participants did not undergo specialist assessment to definitively rule out asthma and to determine alternative diagnoses.[13]

Studies from Italy[16] and the Netherlands[17] have suggested that asthma may be overdiagnosed in adults and children. However, these previous studies were cross-sectional studies in highly selected cohorts. The current study has the advantage of having randomly recruited participants from the community. A further strength of the current study is that participants were studied longitudinally over 12 weeks using an objective, rigorous diagnostic algorithm, which was followed by pulmonologist assessment to try to rule in or rule out current asthma.

There are consequences associated with overtreating asthma that is in remission or treating misdiagnosed asthma. Consequences include the patient's potential exposure to the adverse effects of asthma medications[18] and the costs of asthma medications.[19] Thirty-five percent of the participants in whom current asthma was ruled out were using daily asthma-controlling medications. Use of asthma medications in these patients presumably provided only risks for medication adverse effects and cost, with little opportunity for therapeutic benefit.[20] An economic analysis has previously demonstrated that ruling out active asthma in those with presumed physician-diagnosed asthma is cost-effective.[21]

Global Initiative for Asthma guidelines suggest stepping down asthma treatment once good asthma control has been achieved and maintained for 3 months.[1] Results of this study suggest that 33.1% of individuals with recently diagnosed asthma can safely have their asthma medications tapered and discontinued within 5 years of their initial diagnosis. Furthermore, the study tapering algorithm was not associated with any adverse events and represents a safe and practical approach to operationalize guideline recommendations to taper (and, if possible, to stop) asthma medications in stable patients.

Many study patients who were ultimately found to not have current asthma had already stopped use of daily asthma-controlling medications before even entering the study. Lack of use of daily asthma medications was significantly associated with exclusion of current asthma. This suggests that many patients may be able to tell when their asthma is in remission, and they may self-adjust and even stop use of their asthma medications, with or without the advice of a physician.[22]

This study has limitations. Participants in whom current asthma was ruled out were followed for up to 15 months, but it is possible that some patients in remission, such as those with intermittent asthma provoked by specific allergens, could experience subsequent recurrence of asthma beyond a 15-month follow-up period. The sensitivity of bronchial challenge tests to detect asthma is 98% but not 100%, meaning that a very small number of individuals with current asthma may have been missed by the study testing algorithm.[23] Conversely, the specificity of bronchial challenge tests is less than 80%, and the test can be falsely positive in patients with allergic rhinitis or in smokers without asthma.[23] This lack of specificity may have limited the study's ability to rule out current asthma in some participants (ie, the proportion who did not have current asthma may be even higher than detected).

Patients using long-term oral corticosteroids for asthma or for other conditions were excluded, and this could potentially skew the study sample toward those with milder asthma; however, only 22 participants initially contacted by telephone were excluded for this reason. Another limitation is that many potential participants refused to answer telephone eligibility questions, and only 68.3% of those who were judged eligible participated, which could introduce selection bias into the study. Demographic information was not collected from the 325 individuals who were eligible to enter the study but chose not to participate; therefore, a comparison of study participants with nonparticipants was not possible.

Twenty-four percent of community physicians did not respond to a request for diagnostic records, and it is thus impossible to determine whether the initial diagnostic workup and hence the initial diagnosis of asthma in these participants were appropriate. Therefore, distinguishing misdiagnosis from remission of asthma in some study participants is impossible. Even in participants who had lacked reversible airflow obstruction at diagnosis it is difficult to know with certainty whether they were misdiagnosed, because spirometry has relatively limited sensitivity to accurately confirm asthma in primary care.[24] In many cases, spirometry was performed after treatment for asthma was initiated in the community, further decreasing its sensitivity.

Conclusions

Among adults with physician-diagnosed asthma, a current diagnosis of asthma could not be established in 33.1% who were not using daily asthma medications or had medications weaned. In patients such as these, reassessing the asthma diagnosis may be warranted.

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Obtained funding: Aaron, McIvor, Hernandez.
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Supervision: Aaron, Vandemheen, FitzGerald, Gupta, Field, McIvor, Mayers, Alvarez, Pakhale.

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Ainslie reported receiving speaking honoraria from Boehringer Ingelheim Canada. Dr Lemière reported serving on advisory boards for GlaxoSmithKline, Teva, AstraZeneca, and Methapharm; and serving as a member of the Asthma Clinical Assembly of the Canadian Thoracic Society. Dr Field reported receiving grants from Boehringer Ingelheim, Novartis, AstraZeneca, GlaxoSmithKline, and Synertec; receiving speaking honoraria from Boehringer Ingelheim, Novartis, and Grifols; and serving on advisory boards for Teva and Roche. Dr Hernandez reported serving on advisory boards for Actelion, AstraZeneca, Boehringer Ingelheim, Grifols, Novartis, Bayer, and Roche; receiving fees for delivering accredited medical education for AstraZeneca, Boehringer Ingelheim, Grifols, Novartis, Bayer, and Roche; and receiving grants from Boehringer Ingelheim, CSL Behring, Grifols, and Prometic. Dr Boulet reported receiving grants from Altair, Amgen, Asmacure, AstraZeneca, Boehringer Ingelheim, Boston Scientific, Genentech, GlaxoSmithKline, Novartis, Ono Pharma, Schering, and Wyeth; serving as a consultant or on advisory boards for AstraZeneca, Novartis, and Methapharm; receiving lecture fees from AstraZeneca, GlaxoSmithKline, Merck, and Novartis; serving as a member of the Canadian Thoracic Society Respiratory Guidelines Committee; serving as chair of the Global Initiative for Asthma Guidelines Dissemination and Implementation Committee; and serving as Laval University Chair on Knowledge Transfer, Prevention and Education in Respiratory and Cardiovascular Health. No other disclosures were reported.

Funding/Support: This work was supported by grant MOP-115073 from the Canadian Institutes of Health Research. Methapharm Inc supplied provocholine; Trudell Medical International Inc supplied peak flow meters; and ASDE Survey Sampler Inc organized the random digit dialing.

Role of the Funder/Sponsor: The study sponsors had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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Meeting Presentation: This work was presented in abstract form at the American Thoracic Society 2016 International Conference; May 17, 2016; San Francisco, California.

Additional Contributions: We thank the study participants as well as the general practitioners and specialists who completed our study questionnaires. Study coordinators included Amanda Bergeron, RN, Megan Beninger, RN, and Gay Pratt, RRT, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; Francine Deschesnes, BSc, and Hélène Turcotte, MSc, Institut Universitaire de Cardiologie et de Pneumologie de Québec-Université Laval, Québec, Québec, Canada; Shelley Abercromby, BSc, Vancouver General Hospital, Vancouver, British Columbia, Canada; Cheryl Noble, RN, St Boniface Hospital, Winnipeg, Manitoba, Canada; Katherine Griffin, St Michael's Hospital, Toronto, Ontario, Canada; Simone Chaboillez, MT, Hôpital du Sacré Coeur de Montréal, Montréal, Québec, Canada; Lisette Machado, MD, and Curtis Dumonceaux, BSc, RRT, University of Calgary, Calgary, Alberta, Canada; Liz Johnson, Research Institute of St Joseph's Hamilton, Hamilton, Ontario, Canada; Kristin Osterling, MSc, BSc, and Scott Fulton, RRT, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; and Miranda Bowen, RRT, University of Alberta, Edmonton, Alberta, Canada. Data managers included Dong Vo and Jennie Cote, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada. The study coordinators and data managers received compensation for their role in the study.

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