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Confirmation of Asthma in an Era of Overdiagnosis

Vanessa P. Luks, M.D

Katherine L. Vandemheen, BScN

Shawn D. Aaron, M.D

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University of Ottawa (VPL)

The Ottawa Health Research Institute, University of Ottawa (KLV, SDA)

Correspondence and request for reprints:

Dr. Shawn Aaron

The Ottawa Hospital, General Campus

501 Smyth Road

Ottawa, Ontario, Canada

K1H 8L6

Telephone: (613) 739-6636

Fax: (613) 739-6266

Email: **saaron@ohri.ca**

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ABSTRACT

Background:

We recently showed that 30% of adults with a physician diagnosis of asthma did not have asthma when objectively assessed using a 4-step algorithm involving serial spirometry, bronchial challenge testing, and subsequent tapering of asthma medications. The objective of this study was to determine how many steps in the algorithm were required to confirm asthma, and whether any patient-related variables were associated with earlier asthma confirmation.

Methods:

540 subjects with a previous physician diagnosis of asthma were randomly recruited from the community. The number of subjects confirmed with asthma at each study visit was calculated. Regression analysis was used to determine variables associated with earlier asthma confirmation.

Results:

346 of 499 subjects (69%) who completed the diagnostic algorithm had asthma confirmed and 150 (30%) had asthma excluded. More than 90% of subjects in whom asthma was confirmed including those using regular asthma controlling medications, were confirmed with only one or two study visits, either by pre- and post-bronchodilator spirometry or by a single bronchial challenge test. Only 46/499 subjects (9%) required tapering of asthma medications and repeated bronchial challenge tests to exclude or confirm asthma. Lower FEV_1, and younger age were associated with earlier asthma confirmation.

Conclusions:

For the majority with a previous physician diagnosis of asthma only pre- and post-bronchodilator spirometry and a single methacholine challenge test are required to confirm asthma.

Keywords: asthma, bronchial hyperreactivity, diagnosis, spirometry

INTRODUCTION

Over the past three decades there has been a dramatic increase in the incidence and prevalence of asthma in North America [1, 2]. However, it unclear if the increased incidence of new asthma diagnoses in developed countries is appropriate, or if asthma is being overdiagnosed in developed countries due to an increased awareness of asthma amongst health care providers and patients [3]. We recently conducted a study to investigate the proportion of Canadian adults who have an incorrect diagnosis of asthma [4]. Five hundred and forty randomly recruited subjects from the community underwent a stepwise algorithm that included up to four visits to the pulmonary function laboratory to try to rule in, or rule out, physiologic evidence of asthma. We concluded that 30% of patients with a previous physician diagnosis of asthma did not have asthma when objectively assessed [4].

Currently patients diagnosed with asthma keep their diagnosis for a life time. No validated protocols exist to confirm or exclude asthma in patients with a previous physician diagnosis of asthma (who may or may not have been correctly diagnosed initially). Confirmation of asthma may be more difficult in patients who are taking regular asthma-controlling medications. Patients on inhaled corticosteroids, even for less than three months, can experience not only improvement in symptoms, but also a decrease in demonstrable airway responsiveness, even returning to the normal range on bronchial challenge testing [5]. Once started on an inhaled corticosteroid, negative bronchial challenge testing or absence of change in FEV_1 post-bronchodilator, may indicate either a well controlled asthmatic, or a non-asthmatic. Even amongst subjects

not started on inhaled corticosteroids, confirming a physician diagnosis of asthma can be difficult if there are minimal symptoms, and hence likely minimal airway inflammation, at the time of testing.

Given the associated costs of pharmacologic therapy for asthma, and the previously demonstrated overdiagnosis of asthma, developing a strategy to confirm or exclude asthma in patients with a previous physician diagnosis of asthma is important. The ideal algorithm would be both sensitive and specific, and would minimize the number of visits or tests, thereby minimizing cost and inconvenience to the patient. As no previously validated algorithm to accomplish this exists, we conducted this secondary analysis to determine how many steps in our asthma diagnostic algorithm were actually required in order to definitively confirm or exclude asthma in subjects with a previous physician diagnosis of asthma. A second objective was to determine if there were any patient-related factors associated with earlier confirmation of asthma.

METHODS

Study population

The study population consisted of 540 subjects recruited from across Canada by random digit dialing from December 2005 to December 2007, and is the same cohort of subjects described by Aaron et al in a previous publication [4]. Inclusion criteria included: age greater than 15 years, current asthma diagnosed by a physician (method of diagnosis by the physician not specified, and proof of physician-diagnosis provided only by the subject's account). Exclusion criteria included: subjects taking long-term oral corticosteroids, inability to undergo bronchial challenge testing due to other medical conditions, smoking history greater than ten cigarette pack-years, inability to undergo spirometry, or to provide consent [4].

Asthma Assessment Algorithm

The protocol to confirm or exclude asthma involved between 1 to 4 patient visits to the pulmonary function laboratory [4] as outlined in Figure 1. The first visit consisted of pre- and post-bronchodilator spirometry. If the patient had an improvement in FEV_1 of ≥ 200 mL and $\geq 15\%$ after bronchodilator was given, then asthma was confirmed and no further testing was required. If spirometry was negative then the patient returned for a bronchial challenge test with methacholine at visit 2. If the methacholine challenge test (MCT) at visit 2 was positive (i.e. revealed a $PC_{20} \leq 8$mg/mL), then asthma was confirmed. If the MCT at visit 2 was negative, asthma was excluded in subjects not taking any asthma controlling medications such as leukotriene antagonists or inhaled corticosteroids on a regular basis. Those subjects who were taking such medications on a regular basis and

had negative testing at visits 1 and 2, were required to taper their asthma medications and undergo repeat bronchial challeng testing. After visit 2, leukotriene antagonists were discontinued, and the dose of inhaled corticosteroids was halved. The subjects then returned two to three weeks later for visit 3 which consisted of another MCT. If the MCT at visit 3 was positive, asthma was confirmed, if not, long-acting beta agonists and inhaled corticosteroids were discontinued completely and the subjects returned in 2 to 3 weeks for visit 4, a final MCT. Patients with a positive MCT at visit 4 had asthma confirmed. Asthma was also confirmed in those who suffered from an asthma exacerbation during the medication taper and evaluation period. Asthma was ruled out in patients who showed no evidence of acute worsening of asthma symptoms, reversible airflow obstruction, or bronchial hyperresponsiveness at any visit, despite being completely weaned off of asthma medications. Of note, short-acting beta agonists were permitted at any time during the study algorithm but were withheld 8 h prior to a MCT. Prior to discontinuation at visit 3, long-acting beta agonists were permitted at any time, but withheld 48 h prior to a MCT.

Safety Assessment

Subjects in whom asthma was excluded were asked to remain off of asthma medications. These subjects were followed every 2 months for a period of six months to determine if they had restarted any asthma medications, had urgent visits to a health care provider or an emergency department, required a hospital admission for respiratory symptoms, or required systemic corticosteroids.

Statistical analysis

We calculated the number of subjects who were confirmed or excluded at each visit and then performed univariable analysis to examine if there were any patient-related variables associated with earlier or later confirmation of asthma. These patient-specific variables were pre-selected based on previously described associations between these variables and bronchial responsiveness, and included: age, gender, smoking status, baseline FEV_1% predicted, use of regular controlling medications, and baseline asthma symptoms based on responses to the European Community Respiratory Health Study Questionnaire (ECRHSQ). An unadjusted χ^2 test was used to compare timing of confirmation of asthma based on the presence of these variables. A multivariable analysis was also performed using logistic regression to examine patient-related factors associated with earlier confirmation of asthma which included all of the variables listed above.

RESULTS

Of the 540 participants in the study, 499 completed all of the study assessments and could be evaluated for a diagnosis of asthma. Table 1 shows the baseline characteristics of these patients. Three participants had evidence of lung restriction with a baseline FEV_1 that was less than 60%. Since these 3 participants were unable to safely undergo a bronchial challenge test they were categorized as 'unable to classify'. Of the remaining 496 subjects who completed the algorithm, 346 (70%) had asthma confirmed and 150 (30%) had asthma excluded. Figure 2 shows a breakdown of when each subject was confirmed or excluded according to the study algorithm.

Subjects in whom asthma was confirmed

Of the 346 subjects with confirmed asthma, 329 (95%) had their diagnosis of asthma confirmed within 2 visits (Figure 2 and Table 2). One hundred and sixty four of the 346 subjects (47%) in whom asthma was confirmed were using regular asthma controlling medications. In those subjects taking daily anti-inflammatory asthma medications, 90% were confirmed within 2 visits (147/164 =90%). All 182 (100%) subjects not taking regular controlling medications were confirmed within 2 visits; this was expected, since as per the study protocol, only two visits (one visit for pre- and post-bronchodilator spirometry, and one visit for a bronchial challenge test) were needed to confirm or exclude asthma in those not using regular inhaled steroid or anti-leukotriene medications.

Univariable analysis showed no difference in the timing of confirmation of asthma between males and females, younger versus older subjects, subjects with more versus

fewer respiratory symptoms based on the ECRHSQ, or subjects who were obese versus those with normal body mass index. Smokers were more likely to be confirmed earlier with asthma and many more smokers exhibited significant improvements in bronchodilator responsiveness at visit 1 compared to non-smokers (Table 3.) Similarly, subjects with a baseline percent predicted $FEV_1 \leq 80\%$ had asthma confirmed earlier compared to those with a baseline percent predicted $FEV_1 > 80\%$ (Table 3).

Subjects taking regular controlling medications required more visits to the pulmonary function lab to confirm, or exclude a diagnosis of asthma ($p<0.001$). This difference was partly due to the algorithm design which ensured subjects not taking regular controlling medications were discharged from the study with a confirmation or exclusion of asthma by visit 2, whereas those subjects who were using regular asthma controlling medication who did not have significant bronchodilator reversibility or a positive bronchial challenge test while on medications, had to undergo medication tapering with subsequent re-visits for more bronchial challenge tests.

Multivariable analysis (Table 4) revealed that better lung function (higher FEV_1 % predicted) and older age, both treated as continuous variables, were significantly associated with a greater likelihood of patients requiring more than two visits to the pulmonary function lab to confirm a diagnosis of asthma. Although non-smokers tended to require more visits to confirm asthma this was not statistically significant in the multivariable analysis. Use of regular controlling asthma medications was not included as a variable in the multivariable analysis since only those patients using regular

controlling medications required third or fourth visits to confirm asthma (as per the algorithm).

Subjects in whom asthma was excluded

Asthma was excluded in 150 out of 499 subjects (30%). The timing of exclusion of asthma was driven by the algorithm. For example, all subjects who were not on regular controlling medications and who had asthma excluded, were excluded at visit 2 as per the algorithm. Similarly, subjects taking regular controlling medications could only be excluded after tapering off of all medications, a process which required all four visits.

Safety and Follow-up

Out of the 499 patients who completed the study algorithm, there were a total of only 8 asthma exacerbations, 2 prior to tapering asthma medications, 4 after the subjects' dose of inhaled steroids was halved, and 2 after inhaled steroids and other asthma medications were discontinued completely.

Eight of the 150 patients in whom asthma was excluded were lost to follow-up. Of the 142 patients who completed follow-up, 93 (66%) did not need to take asthma medications and did not require care for respiratory symptoms over the follow-up period. The remaining 49 (34%) did resume taking an asthma medication at some point during the follow-up period; however, 17 only used bronchodilators, and 12 used asthma medications for less than two weeks. Eleven of the 142 subjects (7.7%) had unplanned

visits to a physician because of respiratory symptoms; two of these 11 patients received oral corticosteroid therapy.

DISCUSSION

We found that more than 90% of patients previously diagnosed with asthma, even those taking asthma-controlling medications on a regular basis, can have a diagnosis of asthma confirmed (if they truly have asthma) using pre- and post-bronchodilator spirometry and a single methacholine challenge test. This was unexpected given studies showing the prolonged effect of inhaled corticosteroids on dampening bronchial responsiveness [6]. Patients taking regular inhaled corticosteroids had a mean FEV_1 of 86.2% predicted at the start of the study. It is thus possible that patients in this study still had relatively poor asthma control despite using regular inhaled corticosteroids, and that this may explain why we were able to show bronchodilator responsiveness and bronchial hyperresponsiveness relatively easily

Despite the fact that the majority of subjects on regular controlling medications were confirmed without tapering off their medications, approximately 10% of participants could not be confirmed while continuing regular anti-inflammatory asthma medications. Of this group, 1/3 was found to have asthma once their medications were tapered off and bronchial challenge testing was repeated . Although applicable to only a small minority of those taking regular controlling asthma medications, this underscores the need to taper asthma medications and repeat bronchial challenge testing if test results for asthma are initially negative in this group.

The small number of exacerbations, and paucity of adverse respiratory outcomes over six months of follow-up (2 courses of oral steroids) suggest that this protocol is safe. Two

thirds of the exacerbations that occurred during inhaled steroid tapering occurred after the doses of inhaled corticosteroids were halved indicating that tapering, as opposed to abrupt discontinuation of controlling medications, is likely safer.

In our study, lower FEV_1 at baseline (≤ 80% of predicted) was associated with earlier confirmation of asthma. This is consistent with previous studies showing increased bronchial hyperresponsiveness in subjects with a lower FEV_1 [7]. The smaller the FEV_1 at baseline, the less absolute decrease in FEV_1 is required to meet a 20% percent decline following administration of methacholine [8]. Also, lower lung function, may be associated with more inflammation of the airways and hence greater bronchial hyperresponsiveness. It is not clear if central as opposed to peripheral deposition of inhaled methacholine contributes to bronchial hyperresponsiveness in those with lower baseline FEV_1. Central particle deposition occurs in all subjects during bronchoprovocation testing and is not an important determinant of responsiveness in those with normal baseline spirometry [9].

Younger age was also associated with earlier confirmation of asthma in this study. Changes in bronchial responsiveness with age are inconsistent and different studies have demonstrated increased, decreased, or no change in bronchial responsiveness with aging [10]. The effects of longer duration of disease, and longer exposure to air pollutants and/or smoking easily confound associations made between bronchial responsiveness and age. Known geometric changes to the lung that occur with aging, such as enlargement of air spaces resulting in decreased airway traction and hence reduced airway caliber are

logical explanations for an increase in bronchial responsiveness with age [10]. It is important to note that many studies examining the relationship between bronchial hyperresponsiveness and age are cross-sectional studies examining a general population, and it is possible that asthmatics have a different chronological time course in their bronchial responsiveness compared to the general population. Cuttitta et al looked at younger versus older asthmatics with similar duration of disease and baseline lung function, and found no difference in bronchial hyperresponsiveness [11]. In our study, older participants were more likely to be taking daily inhaled corticosteroids and this may be one reason why older age was associated with later confirmation of asthma. Additionally, it has been shown that elderly subjects have a reduced responsiveness to β adrenergic agonists [12], perhaps reducing the sensitivity of the pre- and post-bronchodilator test at visit 1.

Smoking is also well known to increase bronchial responsiveness [7]. Our univariable analysis showed earlier confirmation of asthma in smokers, although the association became insignificant in the multivariable analysis. Smokers in this study happened to be slightly younger, and had more respiratory symptoms, so the effect of smoking may have become insignificant when those other factors were taken into account in the multivariable analysis.

Past observations that females have greater bronchial responsiveness than males may be related to females having smaller lung size or airway caliber [7], or to an interaction between airway responsiveness and smoking in females that is not seen in males [13].

Our study results are consistent with either hypothesis as we did not find any evidence of a gender-dependent difference in the timing of asthma confirmation when accounting for both smoking status and baseline FEV_1% predicted.

The major limitation of our study is the fact that there is no absolute gold standard to apply to know if the final classification of each patient, asthma confirmed or asthma excluded, was correct. The patients in whom asthma was excluded were followed for six months; however, it is possible for asthmatics to be symptom-free and have minimal airway inflammation and hyperresponsiveness for an unknown duration of time, especially if their asthma becomes manifest with only particular exposures. In a study of patients with undiagnosed respiratory symptoms possibly consistent with asthma who were followed for six months after a methacholine challenge test, the sensitivity of the methacholine challenge test, although far superior to either peak expiratory flow variability, or change in FEV_1 post-bronchodilator, was still only 86% allowing for the possibility of false negative results [14]. It is also possible that asthma was falsely confirmed in some patients. It is well known that bronchial hyperresponsiveness can occur in non-asthmatic patients who might have been included in this study such as those with allergic rhinitis, those who have recently had a viral respiratory infection, or smokers with normal lung function [15]. However, using a PC_{20} of $\leq$ 8mg/mL, which is the value we used in our study, Goldstein et al demonstrated a specificity of 100% for the methacholine challenge test [14].

In summary, our study has shown that more than 90% of subjects who report physician-diagnosed asthma, even those who are taking regular asthma controlling medications, can have their diagnosis of asthma confirmed with only 2 testing visits to the pulmonary function laboratory. For the majority of such patients, asthma medication washout is not necessary prior to bronchial challenge testing to confirm a diagnosis of asthma.

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Table 1: Baseline characteristics of study participants who completed the study diagnostic algorithm

Characteristic	Subjects on regular asthma-controlling medications (n = 198)	Subjects not on regular asthma-controlling medications (n = 301)
Age, years (SD)	48.2 (16.3)	42.2 (15.6)
Females, no. (%)	137 (69.2)	199 (66.1)
Smokers, no. (%)	11 (5.6)	27 (9.0)
Baseline FEV1, % pred (SD)	86.2 (18.8)	92.5(15.9)
Duration of disease, years (SD)	19.9 (15.5)	17.0 (12.9)
BMI (SD)	30.2 (8.5)	29.3 (7.44)
Baseline symptoms, no. (%)		
Wheeze	61 (30.8)	82 (27.2)
Cough	95 (48.0)	131 (43.5)
Shortness of breath	76 (38.4)	107 (35.5)
Chest tightness	61 (30.8)	72 (23.9)
Sputum production	87 (43.9)	96 (31.9)
Regular medications, no. (%)		
Leukotriene antagonists	25 (12.6)	0 (0.0)
ICS	90 (45.5)	0 (0.0)
ICS/LABA	106 (53.5)	0 (0.0)

FEV_1 = Forced expiratory volume in 1 second

SD = standard deviation

BMI = body mass index

ICS = inhaled corticosteroids

ICS/LABA = combination inhaled corticosteroid and long-acting beta agonist medication

Table 2: Confirmed asthma cases by visit

	Visit 1	Visit 2	Visit 3	Visit 4	p-value
All subjects in whom asthma was confirmed (n = 346)	54 (15.6%)	275 (79.5%)	10 (2.9%)	7 (2.0%)	
Taking regular controlling medications (n = 164)	23 (14.0%)	124 (75.6%)	10 (6.1%)	7 (4.3%)	<0.001
Not taking regular controlling medications (n = 182)	31 (17.0%)	151 (83.3%)	0 (0%)	0 (0%)	

Table 3: Effects of smoking and lung function on timing of confirmation of asthma

	Visit 1	Visit 2	Visit 3	Visit 4	p-value
Smoker (n = 113)	25 (22.1%)	85 (75.2%)	3 (2.7%)	0 (0%)	0.006
Non-smoker (n = 233)	29 (12.4%)	190 (81.5%)	7 (3.0%)	7 (3.0%)	
FEV_1 > 80% predicted (n = 234)	16 (6.8%)	205 (87.6%)	8 (3.4%)	5 (2.1%)	<0.0001
$FEV_1 \leq$ 80% predicted (n = 112)	38 (33.9%)	70 (62.5%)	2 (1.7%)	2 (1.7%)	

FEV_1 = forced expiratory volume in one second

Table 4: Multivariable analysis: Patient characteristics predicting requirement for multiple visits to confirm asthma

Patient-related factor:	Multivariate Odds ratio (95% CI)	p-value
Age	1.04 (1, 1.07)	0.03
Smoking	0.38 (0.1, 1.38)	0.14
Female gender	0.60 (0.21, 1.74)	0.35
FEV_1 % predicted	1.04 (1.01, 1.07)	0.02
Obesity	0.57 (0.2, 1.62)	0.29
ECRHSQ score (maximum score 5)	1.44 (0.5, 4.13)	0.50

FEV_1 = forced expiratory volume in one second, ECRHSQ = European Community Respiratory Health Study Questionnaire, Obesity = Body Mass Index ≥ 30

Figure 1. Serial asthma testing algorithm

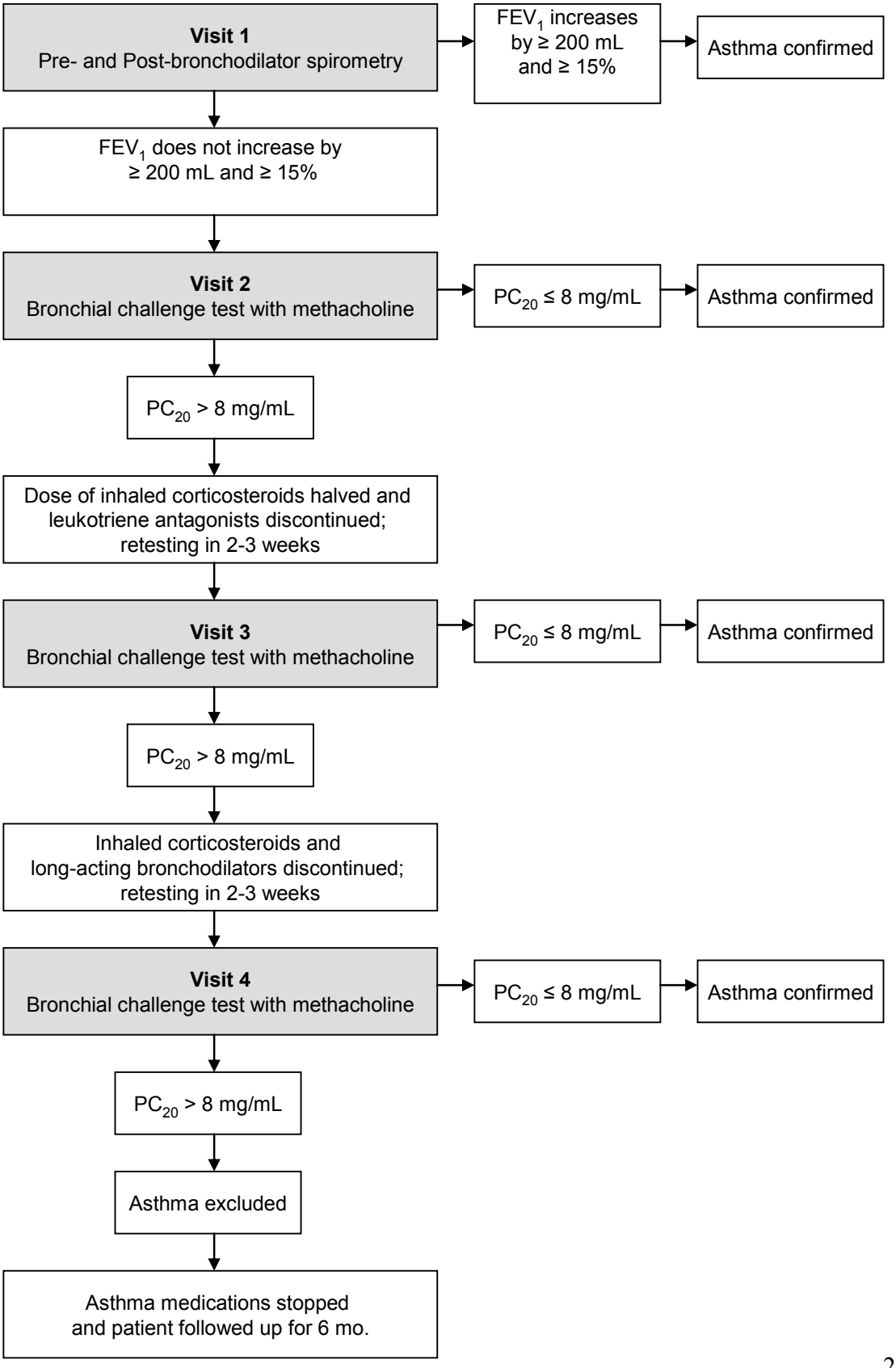

Figure 2: Timing of confirmation or exclusion of asthma in study subjects

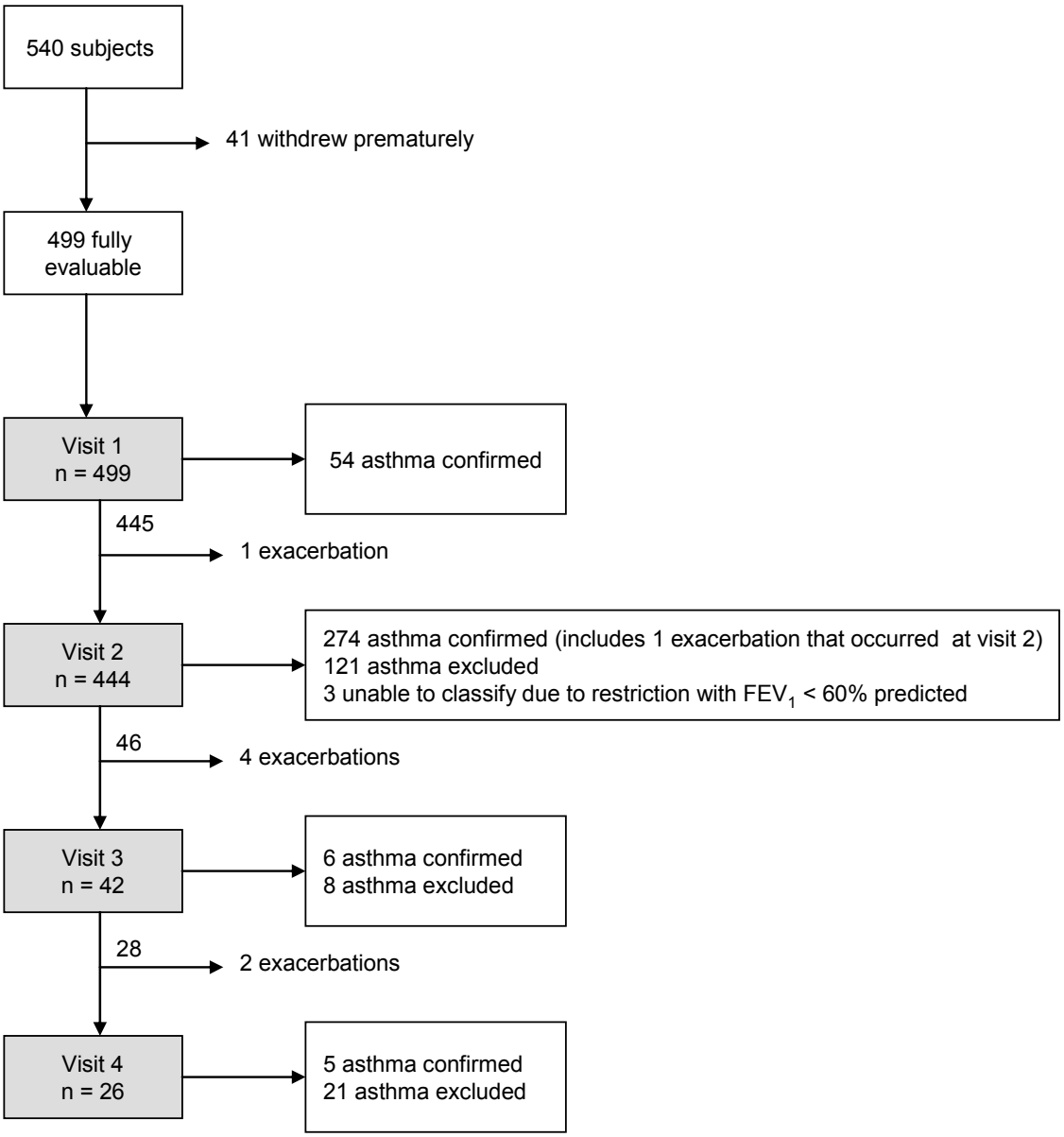

Figure Legends:

Figure 1: Serial asthma testing algorithm

FEV_1 = forced expiratory volume in one second, PC_{20} = the provocative concentration of methacholine causing a 20% decrease in the forced expiratory volume in one second

Figure 2: Timing of confirmation or exclusion of asthma in study subjects

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