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Differential Diagnosis in a Primary Care Population with Presumed Airway Obstruction: A Real-Life Study

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Key Words
Chronic obstructive pulmonary disease · Asthma · Differential diagnosis · Spirometry · Family practice · Diagnostic accuracy

Abstract
Background: Asthma and chronic obstructive pulmonary disease (COPD) have major symptoms in common. However, the mode of the underlying chronic airway inflammation is different. There is still no single diagnostic test that can be considered a gold standard to distinguish asthma from COPD. ***Objectives:*** To determine the diagnostic accuracy for asthma and COPD of a series of diagnostic steps in a population older than 40 years with probable obstructive airway disease (OAD) in primary care. ***Methods:*** In this prospective cohort study, patients without a certain diagnosis underwent a work-up, including office spirometry by their general practitioner (GP). They were then referred to a pulmonologist, and they had control visits with their GP. The diagnostic gain of subsequent steps was calculated for 2 endpoints, namely the specialist's opinion and the GP's final opinion. ***Results:*** Up to 60% of the patients failed to consult with the pulmonologist. For this subgroup, the office spirometry induced significantly more diagnostic congruency than any other diagnostic step. The specialists rejected 44.5% of the diagnoses made by the GPs, including spirometry. High values of diagnostic gain were found after the office spirometry and after the specialist's advice. Up to 25% of the population taking bronchodilators were judged not to suffer from OAD. ***Conclusions:*** Office spirometry added significantly more to the diagnostic certainty of the GPs than questionnaires, history and clinical examination. A pulmonologist's advice contributed more to diagnostic certainty than any other diagnostic step. Nevertheless, 26% of the diagnoses made by the chest physicians were reconsidered by the GPs.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) have major symptoms in common [1, 2]. However, the mode of the underlying chronic airway inflammation is very different [3–6]. The natural history of the 2 diseases, their prognosis and guidelines for their management are also quite different [1, 2]. An important diagnostic difference is shown by lung function tests [7]. The airflow obstruction is often completely reversible in patients with asthma, whereas by definition it is not fully

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reversible in those with COPD [1, 2, 8]. Nevertheless, there is some overlap between asthma and COPD. Some smokers with asthma may develop a mixture of 'asthma-like' inflammation and 'COPD-like' inflammation [9]. Long-standing asthma on its own can lead to airway remodelling and partly irreversible airflow limitation [10, 11]. Furthermore, patients with COPD show varying degrees of reversibility of airflow obstruction [12]. There is still no single diagnostic test or combination of tests that can be considered a gold standard to distinguish asthma from COPD. It thus remains difficult to make a distinction between the 2 diseases in some individuals, especially in older age groups [13–16].

Most patients with obstructive airway disease (OAD) receive care in a primary care setting [13, 17]. However, misclassification of asthma and COPD is common [14, 15, 18–20]. The lack of diagnostic certainty in patients with known or presumed OAD in primary care was confirmed in the first step of the second Differential Diagnosis between Asthma and COPD study [21]. In a population older than 40 years and using bronchodilators, at least 46.4% of the patients needed a diagnostic work-up. The introduction of office spirometry in primary care has raised the hope for more accurate diagnosis in the domain of respiratory medicine. However, the evidence for this point of view is only just emerging [17, 22, 23]. This paper describes the evolution of the diagnostic opinion and diagnostic certainty of general practitioners (GPs) during different steps of a work-up in patients older than 40 years with presumed OAD.

Methods

General Design of the Study

This was a prospective cohort study carried out in 20 Belgian family medicine teaching practices in the first half of 2006. The participating practices were recruited on a voluntary basis. GP practices in both the French-speaking (8 centres) and the Dutch-speaking (12 centres) parts of the country participated, including rural and urban practices. In a first step, the GPs were asked to review their electronic medical files and to select the last 50 contacts with different patients over 40 years of age who were taking bronchodilators and/or inhaled corticosteroids or who had been given a diagnosis of OAD. In 1,172 patients, the following data on file were recorded: demographic data, smoking habits, respiratory diagnoses, technical examinations in the respiratory field during the past 2 years, co-morbidity, respiratory medication and other medication. After reviewing these data, the GPs were asked to give their actual diagnostic opinion. Six options were pre-defined: (1) asthma; (2) COPD; (3) asthma and COPD; (4) other OAD; (5) no OAD, or (6) 'I don't know'. The GPs also indicated their degree of certainty of this diagnosis on a Likert-type scale ranging from 1 (totally uncertain) to 5 (absolutely certain). Airway obstruction was defined as a ratio of the forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) of less than 0.7. An absolutely certain diagnosis of asthma was defined as a clinical history consistent with a diagnosis of asthma and evidence of reversible airway obstruction, with an increase in the FEV_1 of at least 12% or at least 200 ml and if the FEV_1 reached at least 80% of the predicted value after medication. For the reversibility test, salbutamol (400 μg) was used (with a new assessment after 15 min) for patients younger than 60 and ipratropium bromide (800 μg; new assessment after 45 min) for older patients.

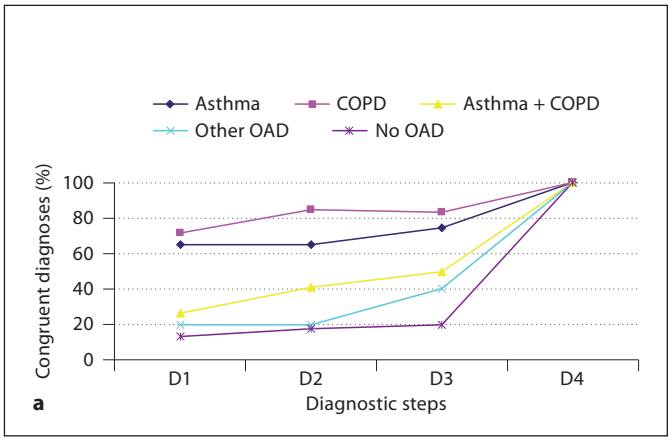
An absolutely certain diagnosis of COPD was defined as a clinical history consistent with COPD and evidence of airway obstruction that was not completely reversible; i.e. the increase in the FEV_1 did not exceed 12% and did not reach 80% of the predicted value after medication, including high doses of corticosteroids, either by inhalation or by mouth. For patients classified as having asthma or COPD, the GPs also gave their opinion about the staging of the disease according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and Global Initiative for Asthma criteria.

Consequently, in each practice, 15 patients without a certain diagnosis were selected at random to undergo a diagnostic work-up. In the same period, the GPs undertook an internet-based course on office spirometry. This included an update on the diagnosis and management of asthma and COPD. It was followed by 2 practical workshops of 150 min each on the performance and interpretation of office spirometry. A first diagnostic visit (visit A) for those patients without a certain diagnosis included 3 different steps: firstly, the International Primary Care Airways Group (IPAG) differential diagnosis questionnaire [24]; secondly, specific history taking and clinical examination based on a standardized form, including the Medical Research Council and modified Borg scales for dyspnoea, and thirdly, office spirometry with a bronchodilator reversibility test using 400 μg of salbutamol, if appropriate. After each diagnostic step, the GPs stated their diagnostic opinion and their degree of certainty of this diagnosis in the same way as they did after the review of their data on file.

The GPs were instructed to offer a corticosteroid reversibility test to all patients with OAD but without complete reversibility after administration of 400 μg of salbutamol per inhalation. The corticosteroid challenge was to be performed either by mouth (32 mg of methylprednisolone per day over 2 weeks) or by inhalation (1 mg of fluticasone per day or 1.2 mg of budesonide per day over 3 months). After this period, a new spirometry test was to be performed.

At this stage, the GPs were asked to refer all included patients to the local pulmonologist for diagnostic advice. The pulmonologists were provided with all relevant information, including the results of the office spirometry. The performance of other diagnostic tests was left to the discretion of the pulmonologists. Their diagnostic opinion was recorded in the same standardized way using the same predefined diagnostic categories and degrees of certainty.

Control visits with the GP were planned 3 months (visit B) and 6 months (visit C) after the initial diagnostic work-up. On these occasions, the GPs repeated the history taking, clinical examination and office spirometry. They once more stated their diagnostic opinion and their degree of certainty on this diagnosis. This



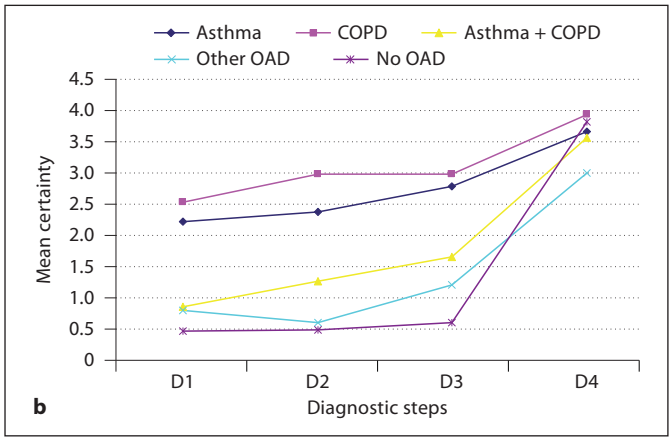


Fig. 1. Percentage of congruent diagnoses (**a**) and mean degree of diagnostic certainty (**b**) at subsequent steps for different diagnostic labels, with the diagnosis by the GP after the first spirometry as reference (n = 298). The diagnostic steps were defined as follows: D1, after review of the files; D2, after the spirometry course and the IPAG questionnaire; D3, after history taking and clinical examination, and D4, after the spirometry. The mean degree of certainty was measured on a scale ranging from 0 (other diagnosis) and 1 ('correct' diagnosis, very uncertain) to 5 ('correct' diagnosis, absolutely certain).

procedure led to 8 subsequent diagnostic opinions: D1, after having reviewed the data on file; D2, after the spirometry course and the IPAG questionnaire; D3, after the history taking and the clinical examination; D4, after the first spirometry; D4A, after the corticosteroid test; Dpn, the pulmonologist's opinion; D5, after control visit B and the pulmonologist's advice, and D6, after control visit C. These diagnostic opinions were compared with 3 references: the diagnosis after the first visit including spirometry (D4), the pulmonologist's opinion and the 'GP's final diagnostic opinion', i.e. D6, or D5 if D6 was not available. The study protocol was approved by the Ethical Board of the Université Catholique de Louvain (26/10/2006/198).

Statistical Methods

The data were analysed using diagnostic test statistics with MedCalc® version 4.1 (Mariakerke, Belgium).

Results

Inclusion and Drop-Out

We received 312 work-up reports (visit A) from the 20 practices. There was a significant drop-out rate during the follow-up. Only 13 practices (9 Dutch-speaking and 4 French-speaking practices) managed to perform any control visits (visit B after 3 months and visit C after 6 months). From the 180 patients who underwent control visits, 126 (70.0%) had received a pulmonologist's advice. We performed separate analysis for the group that completed visit A and for the group that had follow-up visits as well as a specialist's advice.

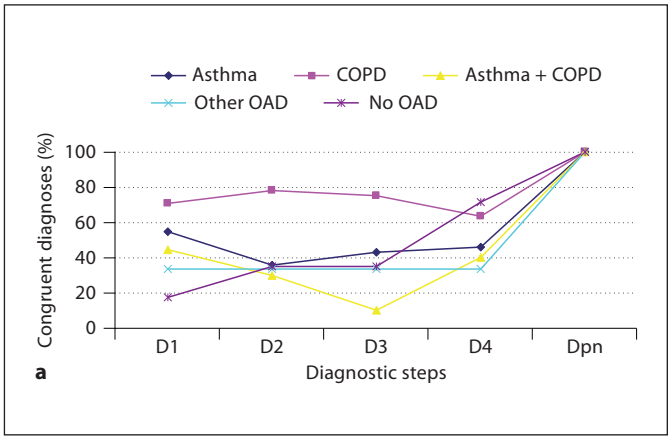
The Initial Work-Up Visit

We were able to compare the diagnostic opinion at D1 (after having reviewed the data on file), D2 (after the spirometry course and the IPAG questionnaire), D3 (after history taking and a clinical examination) and D4 (after the first spirometry with reversibility testing) for 298 cases. The number of labels of 'COPD' decreased from 121 (41%) at D1 to 84 (28%) at D4. The number of patients judged to have no OAD increased from 14 (5%) at D1 to 75 (25%) at D4. The number of labels of 'asthma' decreased from 91 (31%) to 71 (24%) at D2.

Figure 1 shows the percentages of congruent diagnostic labels at various points compared with D4. At D1, we noted 71.4% 'correct' diagnoses for COPD and 65.5% for asthma. For the label 'no OAD', only 13.3% of the cases were 'correct' at D1. These ratios increased gradually, with a steep slope after the spirometry for all diagnoses. Figure 1 also shows the mean degree of certainty per diagnostic label at various points in time. For all diagnoses, the steepest slope of change, indicating the largest gain in diagnostic certainty, was found from D3 to D4. The highest degree of certainty was reached for the diagnosis of COPD. The lowest degree of certainty was observed for the label 'no OAD' until D3, but spirometry led to a dramatic increase in certainty for this group.

The Corticosteroid Challenge Test

According to the study protocol, patients with a probable but not certain diagnosis of COPD (n = 70) or a prob-



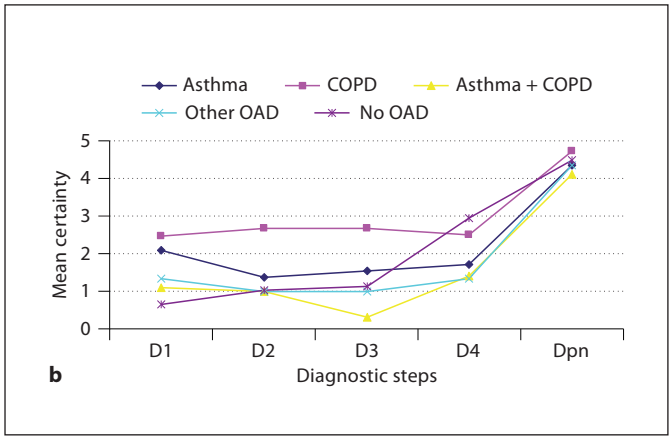


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Fig. 2. Percentage of congruent diagnoses (**a**) and mean degree of diagnostic certainty (**b**) at subsequent steps for different diagnostic labels, with the diagnosis by the pulmonologist as endpoint (n = 122). The diagnostic steps were defined as follows: D1, after review of the files; D2, after the spirometry course and the IPAG questionnaire; D3, after history taking and clinical examination; D4, after the first spirometry, and Dpn, diagnostic opinion of the pulmonologist. The degree of certainty was measured on a scale ranging from 0 (other diagnosis) and 1 ('correct' diagnosis, very uncertain) to 5 ('correct' diagnosis, absolutely certain).

able but uncertain diagnosis of asthma plus COPD (n = 34) should have undergone a corticosteroid challenge test. We received only 13 reports (12.5% of the expected number). Only 1 case of former 'COPD' turned into 'asthma'. In 7 cases, the diagnosis of COPD was confirmed. In 3 cases of presumed asthma plus COPD, the diagnosis of asthma was reconsidered.

Pulmonologists' Opinions

We were able to analyse 122 cases with the initial work-up visit by their GP, a pulmonologist's advice and at least 1 follow-up visit. Table 1 shows the extra diagnostic tests that were performed. Spirometry was repeated by the specialist in 94% of the cases, and the diffusion capacity was measured in 50%. Only in 4% was a bronchial provocation test performed, and only in 1.6% was exhaled nitric oxide measured.

The pulmonologists rejected 44.5% of the former diagnoses made by the GPs. Mainly the labels 'asthma and COPD' (n = 13; 76%) and 'no OAD' (n = 15; 51%) were changed (table 2). All of the former labels 'I don't know' (n = 6) disappeared. There was an important increase in the number of diagnoses of 'asthma' (50.0%) and 'COPD' (36%), even though more than 25% of the former labels for these diagnoses were changed.

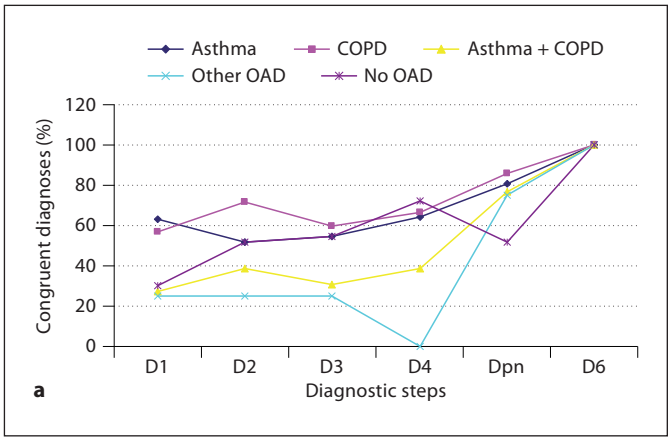
Figure 2 shows the evolution of the rate of congruent diagnostic labels in relation to the pulmonologist's opinion. After some diagnostic steps, this rate decreased, i.e. at D2 for asthma, at D2 and D3 for 'asthma and COPD' and after the spirometry for COPD. A parallel evolution was shown for the mean degree of diagnostic certainty. For all diagnoses, the largest gain in certainty was seen after the examination by the pulmonologists, except for the label 'no OAD', where the initial spirometry by the GP added the most certainty.

Table 1. Diagnostic tests performed by the pulmonologists (122 patients)

Test	n	%
Spirometry	114	93.4
Bronchodilator reversibility test	32	26.2
Diffusion capacity	61	50.0
Bronchial provocation test	5	4.1
Exhaled nitric oxide	2	1.6
X-ray of the chest	39	32.0
CT scan of the chest	9	7.4
Allergy tests	19	15.6
Ventilation/perfusion scan	3	2.5
Oxygen saturation	15	12.3
Body plethysmography	8	6.6
Six-minute walking test	1	0.8
Other	5	4.1

Follow-Up Visits by the GPs

Once more, 26.2% of the former diagnostic labels were reconsidered (table 2). Almost half of the rejected



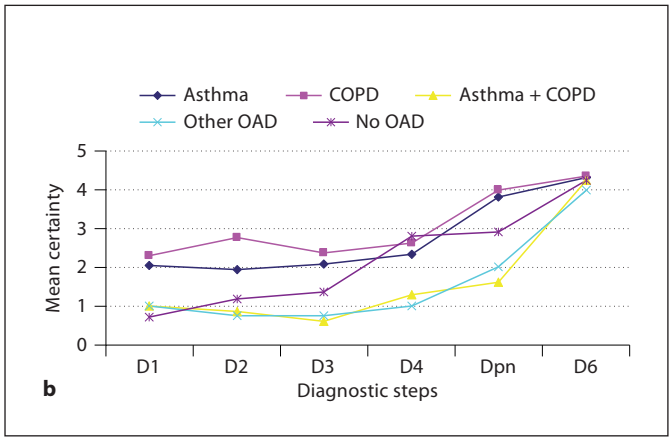


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Fig. 3. Percentage of congruent diagnoses (**a**) and mean degree of diagnostic certainty (**b**) at subsequent steps for different diagnostic labels, with the final diagnosis by the GPs as endpoint (n = 122). The diagnostic steps were defined as follows: D1, after review of the files; D2, after the spirometry course and the IPAG questionnaire; D3, after history taking and clinical examination; D4, after the first spirometry; Dpn, diagnostic opinion of the pulmonologist, and D6, final diagnosis after control visits by the GP. The degree of certainty was measured on a scale ranging from 0 (other diagnosis) and 1 ('correct' diagnosis, very uncertain) to 5 ('correct' diagnosis, absolutely certain).

Table 2. Diagnostic labels rejected after subsequent diagnostic steps in 122 patients

	D2	D3	D4	Dpn	D6	Total
Asthma	13 (38.2%)	1 (3.8%)	10 (32.3%)	8 (28.6%)	15 (35.7%)	52 (32.3%)
COPD	9 (19.1%)	9 (16.5%)	17 (35.4%)	10 (27.8%)	6 (14.3%)	45 (19.7%)
Asthma + COPD	11 (55.0%)	7 (35.0%)	13 (65.0%)	13 (76.5%)	5 (50.0%)	38 (43.7%)
Other OAD	5 (83.3%)	1 (50.0%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	7 (41.2%)
No AOD	2 (28.6%)	0	3 (21.4%)	15 (51.2%)	3 (13.0%)	37 (43.0%)
'I don't know'	3 (75.0%)	2 (50.0%)	3 (60.0%)	6 (100%)	2 (100%)	20 (90.9%)
Total rejected	43 (36.4%)	20 (16.5%)	47 (38.8%)	53 (44.5%)	32 (26.2%)	199 (33%)

Values represent numbers of cases, with the percentage of total diagnoses in parentheses. Diagnostic steps: D2, after the spirometry course and the IPAG questionnaire; D3, after history taking and clinical examination; D4, after the spirometry; Dpn, diagnosis by the pulmonologists, and D6, final diagnosis after 1 or 2 control visits.

diagnoses were 'asthma' (n = 15; 36% of all diagnoses). Major numbers of new diagnoses at the control visits were observed for 'asthma and COPD' (n = 8; 61%) and for 'no OAD' (n = 11; 48%). Table 3 gives an overview of the number of diagnostic labels at each step, as well as the number of new diagnostic labels compared with the previous step.

Figure 3 shows the rate of congruent diagnoses with the GP's final diagnosis as reference. D2 showed increased scores for 'COPD' and 'asthma and COPD' but a decreased score for 'asthma'. The pulmonologist's advice increased all scores, except for 'no OAD'. The overall degrees of diagnostic certainty increased most after the pulmonologist's advice, but still rose significantly after the control visits.

The Predictive Value of Each Diagnostic Step

Table 4 shows the predictive value of the diagnostic opinion after different diagnostic steps for each diagnostic label and relative to the final opinion of the GP. Table 5 shows the same parameters related to the pulmonologist's opinion. In determining the predictive values, we computed the exact label-specific prevalence immediately before each diagnostic step. By doing this, we obtained real

Table 3. Number of diagnostic labels after subsequent diagnostic steps in 122 patients who had a complete set of diagnostic visits including spirometry by their GP, a pulmonologist's advice and control visits

	D1	D2	D3	D4	Dpn	D6
Asthma	34 (29%)	26 (22%; 3)	31 (26%; 6)	28 (28%; 7)	42 (34%; 21)	31 (25%; 4)
COPD	47 (40%)	55 (45%; 17)	48 (40%; 2)	36 (30%; 5)	42 (34%; 15)	42 (34%; 6)
Asthma + COPD	20 (17%)	20 (16%; 10)	20 (16%; 8)	17 (14%; 9)	10 (8%; 6)	13 (11%; 8)
Other OAD	6 (5%)	2 (2%; 1)	3 (2%; 2)	3 (2%; 1)	3 (2%; 2)	4 (3%; 2)
No OAD	7 (6%)	13 (11%; 6)	14 (12%; 1)	26 (24%; 20)	23 (19%; 7)	23 (19%; 11)
Don't know	4 (3%)	5 (4%; 4)	5 (4%; 2)	6 (5%; 5)	2 (2%; 2)	1 (1%; 1)

Values in parentheses represent the percentage of the total number with this diagnosis and the number of new cases with this label, respectively. Diagnostic steps: D1, after review of the files; D2, after the spirometry course and the IPAG questionnaire; D3, after history taking and clinical examination; D4, after the spirometry; Dpn, diagnosis by the pulmonologists, and D6, final diagnosis after 1 or 2 control visits.

Table 4. Predictive value of the diagnostic steps for different diagnoses compared with the final diagnostic opinion of the GP

	D2/D6	D3/D6	D4/D6	Dpn/D6
Asthma				
Positive LHR	4.65 (2.36–9.14)	4.02 (2.24–7.22)	7.10 (3.49–14.44)	5.28 (3.26–8.56)
Negative LHR	0.54 (0.38–0.79)	0.49 (0.32–0.75)	0.39 (0.24–0.63)	0.15 (0.06–0.39)
Diagnostic gain	36.6	30.9	45.8	37.8
COPD				
Positive LHR	3.84 (2.44–6.06)	3.43 (2.17–5.42)	6.66 (3.34–13.26)	11.43 (5.24–24.92)
Negative LHR	0.22 (0.11–0.41)	0.33 (0.20–0.56)	0.35 (0.22–0.56)	0.15 (0.07–0.32)
Diagnostic gain	31.5	29.5	42.4	51.9
Asthma + COPD				
Positive LHR	1.47 (0.50–4.34)	1.47 (0.50–4.34)	3.72 (1.58–8.74)	8.38 (2.80–25.14)
Negative LHR	0.91 (0.67–1.24)	0.91 (0.67–1.24)	0.66 (0.41–1.06)	0.64 (0.42–0.99)
Diagnostic gain	5.8	5.0	23.5	41.0
Other OAD				
Positive LHR	29.25 (2.2–388.53)	14.62 (1.65–129.88)	14.37 (1.62–127.4)	59.0 (6.64–523.97)
Negative LHR	0.76 (0.43–1.33)	0.76 (0.43–1.33)	0.76 (0.43–1.33)	0.50 (0.19–1.34)
Diagnostic gain	51.7	9.6	17.8	48.0
No OAD				
Positive LHR	34.84 (4.7–257.1)	17.42 (4.13–73.54)	6.47 (3.43–12.21)	19.57 (6.24–61.38)
Negative LHR	0.62 (0.47–0.82)	0.63 (0.47–0.83)	0.33 (0.19–0.60)	0.37 (0.23–0.59)
Diagnostic gain	65.4	4.9	34.9	62.7

Values in parentheses represent 95% confidence intervals. Diagnostic gain was calculated as the positive predictive value minus the pre-test prevalence. Diagnostic steps: D2, after the spirometry course and the IPAG questionnaire; D3, after history taking and clinical examination; D4, after the office spirometry; Dpn, the pulmonologist's diagnosis, and D6, the final diagnosis as comparator. LHR = Likelihood ratio.

incremental predictive values. This permitted us to compute the diagnostic gain inherent in each step, defined as the positive predictive value minus the prior chance, i.e. the pre-test prevalence. In general, the predictive values were higher for COPD than for asthma. High negative predictive values were found for several diagnostic opinions, while the positive predictive values were in general low. One negative diagnostic 'gain' was recorded, namely after history taking and clinical examination for the label 'asthma and COPD'.

Table 5. Predictive value of the diagnostic steps for different diagnoses compared with the diagnostic opinion of the pulmonologists

	D2/Dpn	D3/Dpn	D4/Dpn
Asthma			
Positive LHR	2.56 (1.30–5.07)	2.60 (1.42–4.78)	4.58 (2.21–9.50)
Negative LHR	0.75 (0.59–0.95)	0.68 (0.52–0.90)	0.58 (0.43–0.79)
Diagnostic gain	22.4	18.7	37.1
COPD			
Positive LHR	2.66 (1.74–4.06)	3.43 (2.17–5.42)	4.77 (2.55–8.90)
Negative LHR	0.42 (0.25–0.71)	0.33 (0.20–0.56)	0.44 (0.29–0.65)
Diagnostic gain	23.0	34.5	36.4
Asthma + COPD			
Positive LHR	2.20 (0.49–90.9)	0.58 (0.09–3.92)	3.35 (1.34–8.37)
Negative LHR	0.79 (0.49–1.26)	1.09 (0.87–1.36)	0.68 (0.41–1.14)
Diagnostic gain	12.8	–5.7	22.3
Other OAD			
Positive LHR	39.33 (3.15–490.8)	19.67 (2.39–162.1)	19.33 (2.35–159.3)
Negative LHR	0.67 (0.30–1.50)	0.68 (0.30–1.51)	0.68 (0.30–1.51)
Diagnostic gain	58.4	32.2	22.7
No OAD			
Positive LHR	6.82 (2.46–18.92)	5.68 (2.18–14.78)	11.56 (5.02–26.59)
Negative LHR	0.69 (0.51–0.93)	0.69 (0.51–0.94)	0.35 (0.19–0.65)
Diagnostic gain	25.0	31.2	46.5

Values in parentheses represent 95% confidence intervals. Diagnostic gain was calculated as the positive predictive value minus the pre-test prevalence. Diagnostic steps: D2, after the spirometry course and the IPAG questionnaire; D3, after history taking and clinical examination; D4, after the office spirometry, and Dpn, the pulmonologist's diagnosis as comparator. LHR = Likelihood ratio.

Discussion

The present study confirms that a considerable number of the Belgian population with a probable diagnosis of OAD do not consult with a pulmonologist [25]. For this subgroup, office spirometry added more to the diagnostic congruency and certainty of the GPs than any other step in the work-up. A specialist's advice was an important step towards the certainty of the final diagnosis, but the chest physicians and the GPs disagreed on the final diagnostic label in 26% of the cases. After using spirometry, there was a major increase in the number of patients judged not to suffer from OAD. The corticosteroid test was not feasible in this primary care setting. The positive predictive value of any diagnostic test on its own was rather low. With regard to the GP's final opinion, the highest diagnostic gain for asthma was obtained after office spirometry, whereas for patients with COPD and mixed disease, the diagnostic gain was higher after the pulmonologist's advice. When looking at the pulmonologist's opinion as an endpoint, the largest diagnostic gain was obtained after the office spirometry for all diagnoses. The large confidence intervals for 'other OAD' and 'no OAD' preclude valid conclusions on the predictive values for these labels. This is obviously because of the small sample sizes for these diagnoses.

Implications of the Lack of a Gold Standard

At present, there is no single test or combination of tests to discriminate with certainty between asthma and COPD. In this study, several factors were taken into consideration by the physicians to establish a diagnosis in these patients with suspicion of and treatment for OAD, i.e. the data on file, the IPAG differential diagnosis questionnaire, the patient's specific history and clinical characteristics, spirometry measures, the pulmonologist's advice and the evolution of the disease under treatment. The core criterion of the present study was the 'diagnostic opinion' of the chest physician and the GP. This can be considered a weakness, because it is not an objective measurement; however, it is also a strength, because it reflects real-life conditions and deals with the complexity of the

question. We were astonished by the large number of diagnostic shifts during the procedures. It is clear that differentiating between asthma and COPD in the studied population was not easy for the clinicians. This is in line with previous findings [13–17]. We do not know to what extent the pre-existing treatment played a role in this difficulty. Nearly half of the patients in this study were taking a combination of long-acting β-mimetics and inhaled corticosteroids over a prolonged time [21]. These patients are likely to react differently during spirometry and a bronchodilator reversibility test compared with 'naive' patients with OAD who have never been treated [26–28]. Therefore, our findings will not automatically apply to patients with newly found OAD.

Previous studies have examined the ability of bronchodilator testing to distinguish between patients with asthma or COPD and found no clear distinction based on spirometric criteria alone [12, 29, 30]. However, omission of the reversibility test is likely to increase the number of misclassifications [31]. The criteria used in this study for an 'absolutely certain diagnosis of COPD' state that the FEV_1 should not reach 80% of the predicted value after maximal bronchodilation. This excludes patients with COPD GOLD stage I from 'absolute certainty'. The purpose of this criterion was to obtain a better differentiation between asthma and COPD with partial reversibility. This measure must artificially lower the diagnostic certainty for patients with mild COPD.

Another weakness in the study design was at step D2. This diagnostic opinion was recorded after completion of the IPAG differential diagnosis questionnaire [24]. However, between D1 (after having reviewed the medical files) and D2, the GPs took an intensive course on spirometry, including an update of their knowledge and skills in the diagnosis and management of chronic respiratory diseases. This implies that we cannot exactly measure the influence of the IPAG questionnaire or that of the spirometry course. Because of the lack of a validated reference standard for the correct diagnosis, we decided to compare several endpoints. This is one of the methods to deal with the absence of a gold standard [32]. Given the large number of patients who failed to consult with the pulmonologist, the first important endpoint was the diagnostic opinion of the GP after the initial work-up. The opinion of the chest physician after the performance of extra diagnostic tests is obviously an important reference. The final diagnostic opinion of the GP after several months and with the pulmonologist's opinion in mind is a third endpoint.

The Impact of the Pulmonologist

Our results confirm that a diagnostic referral to the pulmonologist had a major impact on the final diagnostic opinion of the GP. The rate of congruent diagnostic labels as well as the mean diagnostic certainty increased to a larger extent after the visit with the chest physician than after the office spirometry by the GPs for all diagnoses, except for the label 'no OAD'. A significant number of patients failed to consult with the chest physician, including 30.0% of the group who had control visits with the GP and even 59.6% of the group who had a complete work-up visit with their GP. This finding is in line with other studies [25]. We have no systematic record of why the referrals were declined. We noted a large variation between doctors. Some comments were often heard, as follows: many patients did not understand the usefulness of specialized advice; financial aspects precluded a referral; the participating GP was not motivated to refer patients with an almost certain diagnosis, and some patients with significant co-morbidity were unable to leave their homes. This finding indicates that GPs will have to continue working with their own diagnostic hypothesis for an important number of patients with OAD, whereas for this subgroup of difficult-to-evaluate patients, a specialist's opinion clearly has an added value.

Our data confirm that GPs and specialists disagree on the diagnostic label in a significant number of patients with OAD. A study by Raghunath et al. [33] indicated that there are significant differences in the interpretation of spirometry data between GPs and specialists. Marklund et al. [34] examined adults with a diagnosis of asthma from 2 general practices, where in only 60% of patients was this diagnosis confirmed by specialist examination. In patients with newly found OAD, Lusuardi et al. [35] estimated the agreement in diagnosis between specialists and GPs to be 69.2% without spirometry in general practice and to be 78.6% after the introduction of spirometry. To the best of our knowledge, the present study is the first to examine the degree of integration of a specialist's advice into the subsequent follow-up in primary care. No fewer than 26% of the diagnostic labels given by the pulmonologists were reconsidered by the GPs at the control visits. GPs and specialists seem to disagree mainly on the diagnosis of 'asthma' in a significant number of patients. Our data did not permit us to explain this difference in opinion, and more research in this domain would be informative.

The widespread use of bronchial provocation tests in these patients would probably have led to a larger number of subjects with a certain diagnosis of asthma. Our 'real-

life' study indicates that this test was seldom used (table 1) but does not explain the reason why. The same applies for measurements of exhaled nitric oxide; this test was hardly used at the time of this survey in 2006.

Other Diagnostic Steps

At D1, the diagnostic certainty compared with all endpoints was slightly higher for patients with COPD than for those with asthma, and it was significantly higher for both of these diagnoses than for other labels. D2 added slightly to the certainty for most diagnoses but not for asthma. We will report separately about the validity of the IPAG differential diagnosis questionnaire for this population; obviously, the diagnostic opinion after this test showed no added value for a final diagnosis of asthma. The specific anamnestic and clinical information (D3) did not induce much certainty for most diagnoses, especially for the label 'asthma and COPD', where the parameters declined compared with the endpoints. The results of the office spirometry had a major influence on the certainty of all diagnostic labels given by the GPs, as well for the immediate endpoint at D4 and for the endpoint after several months. However, the diagnostic opinion of the GPs after the spirometry did not add many diagnoses congruent with the pulmonologist's opinion, except for the labels 'asthma and COPD' and 'no OAD'. These findings confirm that office spirometry is an invaluable tool for the management of those patients with possible chronic airway disease who do not go to a chest physician.

There is still some doubt as to whether a corticosteroid challenge test has an added value in the differential diagnosis between asthma and COPD. Earlier studies indicated that the potential risks of a steroid course outweighed any likely benefit from the small gain in information [31]. Our study shows that this test is simply not feasible in our primary care setting in Belgium. If this group of highly motivated GPs in teaching practices was unable to implement the corticosteroid challenge test under study protocol circumstances, we cannot expect this to be done by physicians in broad primary care. The number of completed challenge tests was too small to draw any other valid conclusion.

The Importance of the Diagnostic Work-Up

One can wonder if the differential diagnosis between asthma and COPD in this population had other than an academic significance. Is it not more pragmatic to start with a maximal inhalation therapy and to tailor the therapeutic regimen up or down in line with the results regardless of the diagnosis? We believe that there is a series of reasons to make the distinction as clear as possible. The implications of a diagnosis are not only relevant for pharmacotherapy. The prognosis, the therapeutic goals, the action plans and the instructions to be given to the patients are quite different for the 2 diseases. Inhaled corticosteroids are the cornerstone of asthma therapy, whereas they are only indicated in patients with severe COPD. Long-acting anticholinergic drugs have proven their benefit for patients with COPD but not for those with asthma [36, 37]. The diagnostic label 'COPD' is still largely unknown in the broad population and merits more attention [38, 39]. Therapeutic nihilism may have influenced the relative lack of interest in COPD [40]. Overall, patients with an initial diagnosis of asthma or mixed disease were more likely to have their diagnosis changed than those with an initial label of COPD. This is in line with previous findings [41].

A striking observation is the fact that in this primary care population, 19% of all patients taking bronchodilators were judged not to suffer from OAD in the final diagnostic opinion. At the least, a trial to stop this form of medication is justified. However, careful observation of these patients is indicated; after the initial diagnostic work-up, 25% of this population was thought to have no OAD. It is likely there was an underestimation of the real morbidity at that time based on the good results of the current pharmacotherapy. After the control visits, 34% of these patients received another diagnostic label, spread equally between asthma, COPD and mixed disease. Other patients joined the category 'no OAD' at the end of the diagnostic track. Withdrawal of long-standing inhalation therapy thus merits careful observation [26–28]. A limitation of our study is that only a few patients were assessed by a bronchial provocation test, which could be considered the gold standard for asthma. However, this reflects how diagnostic labels are attributed in 'real-life' conditions. Visser et al. [42] recently showed that in a group of patients with suspected obstructive lung disease, a protocol-driven, pulmonary function test-based selection is more cost-effective than test selection at the discretion of lung physicians.

Conclusion

In this group of patients already under treatment in primary care, the differential diagnosis between asthma and COPD remains difficult, even after the introduction of office spirometry and after a specialist's advice. Between 30 and 60% of the patients with an uncertain diag-

nosis of OAD failed to consult with the pulmonologist. For this subgroup, office spirometry added significantly more to the diagnostic certainty of the GPs than did questionnaires, careful history taking and clinical examination. A pulmonologist's advice contributed more to diagnostic certainty than any other diagnostic step. Nevertheless, 26% of the diagnoses given by the chest physicians were reconsidered by the GPs. Between 19 and 25% of the population taking bronchodilators were judged not to suffer from an OAD after different points in the diagnostic work-up. After computing the predictive values of the different steps, we found high diagnostic gain after a specialist's advice and after applying office spirometry.

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