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Do family physicians’ records fit guideline diagnosed COPD?

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Background. In family practice, chronic obstructive pulmonary disease (COPD) is usually not diagnosed until clinically apparent and of moderately advanced severity.

Objective. To analyse the diagnostic process from early development onwards and to assess the current state of underpresentation and underdiagnosis of COPD and asthma in primary care in the Netherlands.

Methods. The population-based study sample consisted of formerly undiagnosed subjects (n = 532) from family practice. Family physicians’ (FPs) chronic respiratory disease diagnoses (as recorded over 10 years in their patient records) were compared to a cross-sectional but extensive diagnostic assessment by a chest physician. Logistic regression modelling was used for a retrospective analysis on the relation between respiratory symptoms, practice visit rate and FPs’ diagnosis of COPD.

Results. After 10 years, the chest physician diagnosed 26% of subjects as COPD and 16% as (late-onset) asthma. Underpresentation of these patients in family practice was 46%, whereas under-diagnosis occurred in 37% of patients. A chest physician diagnosis of COPD was associated with the presence of chronic cough [odds ratio (OR) = 2.3, 95% confidence interval (CI) 1.1–4.6], a FP diagnosis of COPD with chronic phlegm (OR = 10.6, 95% CI 1.3–83.6). Repeated practice visits (OR = 1.8) and presence of wheeze and breathlessness (OR = 5.5) appeared to trigger the diagnostic process in family practice.

Conclusions. There is still considerable underpresentation and underdiagnosis of COPD in family practice. As FPs focus on presented symptoms and as detection increases with the frequency of practice visits, diagnostic guidelines should stress the importance of persistent cough and phlegm to support timely diagnosis of COPD in family practice.

Keywords. Asthma, COPD, early diagnosis, family medicine, guideline.

Introduction

In primary care, chronic obstructive pulmonary disease (COPD) and asthma are commonly encountered health problems. However, prevalence and morbidity data underestimate the true burden of these diseases. In particular, COPD is often not diagnosed until it has developed into a clinically advanced stage. As disease prognosis and therapeutic strategies for COPD and asthma differ, it is important to distinguish between these two chronic respiratory conditions. Distinction may be relatively easy in patients with severe disease or in older patients, but in many cases the distinction is not so clear as clinical signs and symptoms show overlap. This is particularly the case in family practice, where the diagnostic process is primarily based on symptoms and signs presented by the patient. At this point, objective parameters such as the presence and degree of airway obstruction, reversibility, diurnal peak flow variability, bronchial hyperresponsiveness (BHR) and allergies become important. Although these additional measurements

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usually help to distinguish in the overlapping part of the spectrum, they do not always allow a clear-cut differentiation between COPD and asthma. Besides the diagnostic problems, patients’ presentation of respiratory symptoms is another cause of underdiagnosis: several studies have pointed to the fact that patients may well experience symptoms, but do not always present these symptoms to their family physician (FP). There are indications that this underpresentation is at least partly explained by a lack of perceiving dyspnoea or adaptation to respiratory symptoms by patients. To further understand underdiagnosis of COPD, it is important to gain insight in the process of diagnostic labelling and differentiation by primary care physicians, from early disease development onwards. Therefore, the main objective of this study was to investigate the process of diagnosis of COPD and to assess the current state of underpresentation and underdiagnosis of patients with COPD in family practice.

Methods

Design

In this study, we compared the diagnoses of COPD and asthma from FPs’ medical records within their regular patient care, to a single cross-sectional but extensive diagnostic assessment by a chest physician. The chest physician’s diagnostic assessment was based on a standard protocol which included lung function testing (spirometry, reversibility, static lung volumes and diffusion capacity), respiratory symptoms and risk factors for chronic respiratory disease. FPs’ diagnoses were extracted by standardized medical file review for the 10 years preceding the chest physicians’ diagnostic assessment. The medical ethics review board of the Radboud University Nijmegen Medical Centre approved the study. All subjects gave written informed consent.

Study population

Data for this study came from the prospective population-based Detection, Intervention, and Monitoring of COPD and Asthma (DIMCA) programme. In summary, the DIMCA programme started in 1992 and was originally designed to investigate the feasibility and effectiveness of early detection of chronic respiratory disease in family practice. A random sample from the adult practice population (20–70 years) of 10 family practices was divided into two groups: an intervention group invited for respiratory screening and a reference group (see Fig. 1). Subjects with a medical history of COPD, asthma or other chronic respiratory conditions were excluded. Subjects in the intervention group took part in a respiratory screening programme (i.e., lung function testing and a respiratory questionnaire) to detect undiagnosed COPD or asthma. Subjects with respiratory symptoms, lung function below normal range or a relevant response on salbutamol (reversibility) were considered to be at increased risk (at risk) for developing respiratory morbidity. In a next step, all at-risk subjects were invited to participate in a 2-year monitoring programme and participation in inhaled corticosteroid trials. Reference group subjects were kept unaware of the screening and monitoring programme (through randomized consent) according to Zelen. For the current analysis, all subjects who were still in follow-up 10 years after the start of the DIMCA programme were invited for a reassessment, the results of which were assessed by a chest physician.

Measurements

All lung function measurements were performed at the pulmonary function laboratory of the University Lung Centre Dekkerswald by a certified lung function technician and included a flow–volume curve, reversibility testing, static lung volumes (total lung capacity, residual volume, functional residual capacity) and carbon monoxide diffusion capacity (DLCO, KCO). All measurements were performed according to the American Thoracic Society standards. European Community for Coal and Steel reference values were used to calculate predicted lung function values. Reversibility was defined as a 12% change of predicted forced expiratory volume in 1 second (FEV1) and a change of at least 200 ml in FEV1 after administering 800 µg salbutamol by volume spacer. BHR was assessed with a histamine challenge test (positive at a provocative histamine concentration ≤ 8 mg/ml). After lung function testing, subjects were interviewed on the presence and frequency of respiratory symptoms, allergy, hyperreactivity of the airways for inhaled trigger factors, personal or family history of respiratory diseases, occurrence and frequency of exacerbations, use of respiratory medication and smoking behaviour.

Diagnoses by chest physicians and FPs

Two chest physicians (YH and JM) performed a guideline-based diagnostic assessment of the measurements of all study subjects in order to establish the presence or absence of chronic respiratory disease. The procedure for this diagnostic assessment was based on a standardized protocol of all available diagnostic information regarding pre- and post-bronchodilator lung function, respiratory symptoms (cough, phlegm, breathlessness) and smoking behaviour. The chest physicians used a decision tree based on international guideline criteria for diagnosing COPD and asthma. By protocol, any subject who received another diagnosis than ‘no COPD or asthma’ was also presented to the other chest physician and mutually discussed. As the study aimed to reach a maximal substantiated diagnosis, the chest physicians could request additional diagnostic tests (e.g., oral steroid test,
histamine provocation test, peak expiratory flow monitoring, allergy test) when they considered this to be necessary. Together with the additional diagnostic information, the case was returned to the chest physicians who established a final diagnosis. All subjects were informed about this final diagnosis through their own FP.

FPs’ diagnoses of chronic respiratory disease were extracted from the medical files in the practices for the 10 years between the start of the DIMCA programme and the chest physicians’ diagnostic assessment. To standardize the file review, and as electronic ICPC coded information was not available for the first of these years, the investigator used a checklist that included terms and distinctive features for both established and suspected respiratory disease.

Analysis
For every study subject, the FPs’ diagnosis as documented in the subjects’ medical record (if any) was compared to the chest physicians’ standardized diagnostic assessment, in particular regarding the presence or absence of COPD and asthma. We looked at the concordance and discordance between the FP-documented diagnoses and the chest physicians’ diagnostic assessment within subjects to assess underpresentation and underdiagnosis of COPD and asthma in family practice. We used logistic regression analysis to investigate the diagnostic outcome as judged by the chest physicians in relation to respiratory symptoms at the time of reassessment and prior respiratory-related rate of FP visits. Odds ratios (ORs) for respiratory symptoms (cough, phlegm and wheeze with breathlessness) and family practice visit rate were calculated and adjusted for age, gender and smoking status during follow-up. The SAS statistical package (version V8.2 for Windows) was used for all analyses. Two-sided P values <0.05 were considered to be statistically significant.
Results

Study population
Ten years after the start of the DIMCA programme, we reinvited all 985 subjects who had previously been assessed at Year 5 (Fig. 1). In the group with previous respiratory abnormalities (n = 384), the response rate was 76% and the actual participation rate for the 10-year reassessment was 57% (n = 219). The corresponding figures for the sample without baseline respiratory abnormalities (n = 267) were 82% and 64% (n = 127) and for the subjects from the reference group in the original DIMCA study (n = 402) 73% and 46% (n = 186), respectively. Over the 10 years observation period, we found no indications for selective dropout in either of these samples compared to the initial DIMCA cohort.

Finally, a total of 532 subjects could be reassessed and their test results sent to the chest physicians for diagnostic assessment. Mean age was 43.8 (SD 10.4) years at baseline and 54.9 (SD 10.6) years at the time of the reassessment for the current study (further referred to as ‘Year 10’). Table 1 shows the characteristics of the study population, with subjects classified according to the chest physicians’ diagnoses at Year 10.

Diagnoses by chest physicians and FPs
The two chest physicians judged the respiratory status of the 532 subjects. Overall, the chest physicians assigned a respiratory diagnosis in 222 subjects (42%): 138 cases with COPD and 84 cases with asthma. Of these 222 subjects (patients), 103 had not paid a single visit for respiratory health problems (OR = 1.1) were related to a FP diagnosis of COPD.

Among the 119 patients with at least one documented respiratory FP visit, 82 (69%) had been labelled with ‘COPD’ (n = 26), ‘asthma’ (n = 22) or ‘suspect’ (i.e. a ‘tentative diagnosis’, n = 34) by their FP (see Table 2). In 31 of these patients, there was a full agreement between the chest physicians’ and the FP’s diagnoses (19 patients with COPD, 12 with asthma). In 17 cases, the FP involved had diagnosed COPD instead of asthma or vice versa, while in 27 patients the FP had only documented a tentative diagnosis of ‘suspected’ chronic respiratory disease. The FPs had not documented a diagnosis in 44 subjects who—according to the chest physicians’ assessment—had COPD or asthma, accounting for an underdiagnosis of 37%.

Of the 310 subjects who were assessed by the chest physicians to be in good respiratory health, 85 (27%) had visited their practice visit for a respiratory health problem at least once, and in 11 of them (13%) the FP had documented a tentative diagnosis of COPD or asthma.

Table 1 Characteristics of the study sample at Year 10 (figures are proportions, unless stated otherwise)

<table>
<thead>
<tr>
<th>Chest physicians’ diagnostic assessment at Year 10</th>
<th>No respiratory disease</th>
<th>Chronic respiratory disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (% of total)</td>
<td>310 (58)</td>
<td>138 (26)</td>
</tr>
<tr>
<td>Age (mean, SD)</td>
<td>54.4 (10.5)</td>
<td>57.8 (10.0)</td>
</tr>
<tr>
<td>Gender (% female)</td>
<td>56.1</td>
<td>44.2</td>
</tr>
<tr>
<td>Cougha</td>
<td>4.6</td>
<td>27.7</td>
</tr>
<tr>
<td>Phlegmb</td>
<td>2.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Breathlessnessc</td>
<td>2.9</td>
<td>20.6</td>
</tr>
<tr>
<td>Practice visit rate (mean, SD)</td>
<td>0.6 (1.6)</td>
<td>3.1 (6.4)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>18.3</td>
<td>39.0</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>65.9</td>
<td>81.0</td>
</tr>
<tr>
<td>Pack-years (mean, SD)</td>
<td>10.7 (14.1)</td>
<td>21.1 (19.5)</td>
</tr>
<tr>
<td>FEV1d (mean, SD)</td>
<td>105.2 (14.1)</td>
<td>85.6 (16.7)</td>
</tr>
<tr>
<td>FEV1/VCc (mean, SD)</td>
<td>73.8 (8.2)</td>
<td>61.4 (6.9)</td>
</tr>
<tr>
<td>VC, vital capacity; FEV1 forced expiratory volume in 1 second.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aChronic cough in winter.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bChronic phlegm (at least 3 months/year).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cWheeze with or without breathlessness (in previous 12 months).</td>
<td></td>
<td></td>
</tr>
<tr>
<td>dPost-bronchodilator FEV1, as % of the predicted value.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ePost-bronchodilator FEV1/VC (%) (mean, SD).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subject characteristics related to diagnostic outcome
Table 3 shows the associations between the chest physicians’ diagnoses of COPD and respiratory symptoms, smoking behaviour, age, gender and practice visit rate. Chronic cough (OR = 2.3), higher age (OR > 1.0), smoking (OR = 2.0) and FP visits for respiratory health problems (OR = 1.1) were related to a diagnosis of COPD.

Subjects with at least one documented respiratory family practice visit for respiratory health problems differed from the total group of COPD patients in their pattern of respiratory symptoms. In these patients, chronic phlegm (OR = 10.6–12.0) was related to a diagnosis of COPD.

From the perspective of the family practices, analysis on the diagnostic outcome showed that wheeze with breathlessness [OR = 5.5, 95% confidence interval (CI) 2.0–15.2, adjusted for age, gender and smoking behaviour] in combination with more practice visits for respiratory health problems (OR = 1.8, 95% CI 1.4–2.2) were related to a FP diagnosis of COPD or asthma. More specific, previous practice visits for respiratory health problems (OR = 1.2, 95% CI 1.1–1.4) and higher age (OR = 1.1, 95% CI 1.1–1.20) were associated with a FP diagnosis of COPD, whereas younger age (OR < 1.0, 95% CI 0.9 to <1.0),
non-smoking (OR = 0.1, 95% CI >0 to <1.0) and wheeze with breathlessness (OR = 7.0, 95% CI 2.4–21.0) were associated with a FP diagnosis of asthma. Furthermore, in case of tentative FP diagnoses of chronic respiratory disease, patients had fewer practice visits for respiratory reasons than in cases with a diagnosis of COPD or asthma documented in their medical record (mean 5.1 versus 9.1 visits; \( P = 0.005 \)).

**Table 2. Concordance and discordance between chest physicians’ diagnostic assessment and FPs’ documented diagnoses, 10 years after inclusion of undiagnosed subjects from family practice (figures in the table are numbers of subjects)**

<table>
<thead>
<tr>
<th>Chest physician diagnosis</th>
<th>Medical record in family practicea</th>
<th>No chronic respiratory disease</th>
<th>COPD</th>
<th>Asthma</th>
<th>Suspectb</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No chronic respiratory disease</td>
<td>74</td>
<td>1c</td>
<td>3c</td>
<td>1c</td>
<td>85</td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>27d</td>
<td>19</td>
<td>10</td>
<td>14</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>17d</td>
<td>7</td>
<td>12</td>
<td>13</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>118</td>
<td>27</td>
<td>25</td>
<td>34</td>
<td>204</td>
<td></td>
</tr>
</tbody>
</table>

FP, family physician; CPOD, chronic obstructive pulmonary disease. aSubjects who had not visited their FP for respiratory health problems (\( n = 103 \)), representing the ‘underpresentation’ of chronic respiratory conditions in family practice, are not included in this table. bTentative diagnosis, for instance based on regular FP-prescribed respiratory medication, requested additional diagnostic tests by FP (skin prick test, spirometry or peak flow, histamine challenge test, prednisolone test) or description of respiratory signs/complaints in medical record (e.g. ‘asthmatic reaction’, ‘bronchial hyperresponsiveness’, ‘allergic reaction/allergy’, ‘atopy’, ‘exacerbation’). cConsidered as (potential) ‘overdiagnosis’. dConsidered as ‘underdiagnosis’.

**Table 3. Associations between respiratory symptoms and practice visit rate in COPD patients according to the chest physicians’ assessment (ORs with 95% CIs from logistic regression analyses, adjusted for age, gender, pack-years at baseline and smoking behaviour during follow-up)**

<table>
<thead>
<tr>
<th>Respiratory symptoms</th>
<th>All subjects with COPD according to the chest physicians (( n = 138 ))</th>
<th>Subset with ( \geq 1 ) respiratory FP visits (( n = 70 ))</th>
<th>Subset with ( \geq 1 ) respiratory FP visits and FP diagnosis of COPD (( n = 19 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic cough(^a)</td>
<td>2.28 (1.13–4.60)</td>
<td>1.06 (0.39–2.89)</td>
<td>0.71 (0.11–4.57)</td>
</tr>
<tr>
<td>Chronic phlegmb</td>
<td>2.20 (0.81–5.94)</td>
<td>12.04 (2.12–68.41)</td>
<td>10.61 (1.35–83.60)</td>
</tr>
<tr>
<td>Breathlessnessc</td>
<td>0.92 (0.44–1.92)</td>
<td>1.09 (0.44–2.71)</td>
<td>0.47 (0.10–2.22)</td>
</tr>
<tr>
<td>Practice visit rate</td>
<td>1.10 (1.03–1.17)</td>
<td>1.10 (1.02–1.18)</td>
<td>1.09 (0.98–1.21)</td>
</tr>
<tr>
<td>Age</td>
<td>1.03 (1.01–1.05)</td>
<td>1.03 (1.01–1.07)</td>
<td>—</td>
</tr>
<tr>
<td>Gender</td>
<td>1.55 (0.98–2.45)</td>
<td>1.95 (0.89–4.25)</td>
<td>—</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack-years</td>
<td>1.03 (1.01–1.04)</td>
<td>1.04 (1.01–1.06)</td>
<td>—</td>
</tr>
<tr>
<td>Smoking</td>
<td>2.02 (1.16–3.51)</td>
<td>1.77 (0.65–4.85)</td>
<td>—</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>0.96 (0.51–1.81)</td>
<td>0.82 (0.30–2.26)</td>
<td>—</td>
</tr>
</tbody>
</table>

ORs printed bold are statistically significant. FP, family physician; CPOD, chronic obstructive pulmonary disease. aIn the winter season. bAt least 3 months/year. cIn the past 12 months.

**Discussion**

Ten years after inclusion of formerly undiagnosed subjects, chest physicians diagnosed 26% of subjects as having COPD, and 16% as having (late-onset) asthma. Two-thirds of these patients were not diagnosed according to their family practice medical record. The main reason for this lack of a documented diagnosis was underpresentation: 46% of patients had not even once visited the FP for reasons of respiratory nature. Underdiagnosis occurred in 37% of patients who had visited their FP for respiratory reasons in the 10-year timeframe. Furthermore, diagnostic outcome proved to be related to different respiratory symptoms: chest physician-diagnosed COPD patients were characterized by the presence of chronic cough, whereas FP-diagnosed COPD patients indicated to suffer from chronic phlegm. In our Dutch primary care setting, repeated practice visits and complaints of wheeze and breathlessness appeared to have triggered the diagnostic process. We can only speculate whether or not our findings would also apply to other populations or different health care systems.

In primary care, the ecology of medical care\(^19\) provides a framework for perceived, presented and diagnosed health problems, and thus offers a reference for our findings of FPs’ diagnosis of obstructive airway disease. Clearly, presentation of perceived respiratory signs and/or symptoms by an individual is a prerequisite to achieve a ‘timely’ diagnosis,\(^6\) with the FP in a central position in most health care systems. In our study, with access to 10-year FP records, data on respiratory signs and symptoms could be related to practice visits and reflect diagnostic outcome in family practice. The findings confirm the critical role of patients in presenting their (respiratory) signs and symptoms. In this...
context, the finding of underdiagnosis to be associated with low respiratory practice visit rate is not surprising as FPs will generally not consider a single presentation of respiratory symptoms to be a marker of chronic respiratory disease. Previous reports have shown that patients with shortness of breath only visited their FP once the quality of every day life became compromised or once they experienced variability in lung function.20 However, our current results show that some patients had not been diagnosed even after repeated practice visits. In this respect, the observed associations between respiratory symptoms and FPs’ diagnoses are relevant. It appears that FPs were mainly alerted by wheeze with breathlessness rather than chronic cough and phlegm. This should be taken into account when implementing diagnostic guidelines for chronic respiratory conditions, as signs and symptoms will trigger spirometry for further or final diagnostic assessment. This is particularly relevant in patients with chronic cough who visit their FP only a single time or infrequently.

Underdiagnosis of COPD still appears to be common, and a wide range of estimates has been presented. In a recent review study, which included both population-based and clinical studies, prevalence estimates for undiagnosed airway obstruction (including COPD and asthma) ranged from 3% to 12%.21 Population-based studies from Sweden,22 Korea23 and Greece24 produced estimates in the same range. In the early detection stage of the DIMCA study, the overall prevalence of undiagnosed COPD and asthma was 7.7%.10 In studies carried out among high-risk groups in family practice settings, up to 22% undiagnosed COPD was observed.25-27 In a population-based Swedish study, presenting a COPD prevalence of 12%, only a minority (23%) had a physician diagnosis of chronic bronchitis or emphysema,28 indicating a large underdiagnosis. In our study, FPs’ underdiagnosis (37%) solely refers to patients with former practice visits for respiratory health problems, not to those who had never consulted their FP with respiratory symptoms.

Although presentation of symptoms is essential for any reduction of underdiagnosis, the distinction between COPD and asthma is another aspect the FP has to deal with. In the primary care setting, where a limited set of diagnostic tools is available, the overlap of respiratory symptoms in the two disease entities often generates a classification problem. This is illustrated by our observation that about a quarter of the patients were diagnosed (and treated accordingly) with COPD instead of asthma or vice versa. The fact that in a third of the patients no final distinction in asthma or COPD had been made by the FP might be explained by the step-wise approach to diagnosis in family practice, where observations over time in patients with suspicious symptoms are often part of the diagnostic process.

Some comments should be made about the study setting and the procedure for diagnosis. All study subjects had participated in a study programme of early intervention in COPD and, inevitably, the FPs had been informed of the study progress for their patients. As a consequence, the findings in the current study of FP-diagnosed COPD might be an overestimation of the reality in family practice. However, in our analysis of the family practice medical records, we found that FP diagnoses had only been made in response to patient-initiated practice visits for respiratory symptoms. For that reason, we believe that the influence of the previous DIMCA screening and monitoring programme will have been limited and that our findings are representative of diagnoses of COPD in family practice.

FP diagnoses were tracked from the patients’ records over a period of 10 years, and occasionally a long period of time had passed between this diagnosis and the chest physicians’ assessment that served as the reference diagnosis in our study. Further progression of the disease and its signs and symptoms by the time of the chest physicians’ assessment is therefore likely to explain part of the underdiagnosis.

A second comment deals with the problem of differentiating between COPD and asthma. In our diagnostic decision tree (see Appendix Table 1), emphasis was put on obstruction, only further down distinguishing ‘signs of asthma’. As FPs will first focus on the symptoms as presented by the patient, early-stage COPD can easily be veiled by signs of asthma. Therefore, FP ‘misdiagnosis’ of COPD can partly be explained by those patients who had a chest physician diagnosis of ‘mild COPD with signs of asthma’.

In this study, which was performed within the context of a population-based 10-year follow-up study in formerly undiagnosed subjects from family practice, the early development of respiratory disease was assessed. After assessment of considerable underrepresentation and underdiagnosis of COPD in family practice, and after showing a substantial increase of detection after multiple FP practice visits, we conclude that a change in patients’ perception of respiratory health problems and in FPs’ focus on the main indicator for early-stage disease (i.e. chronic cough) may reduce underdiagnosis of COPD. To facilitate patients’ earlier presentation, health education is considered the main tool to raise public awareness on the risk of underlying COPD in case of chronic cough. On the primary care level, stressing the importance of chronic cough and phlegm in diagnostic guidelines could support timely diagnosis of COPD in family practice and may reduce the prevalence of undiagnosed COPD.

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Declaration

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Ethical approval: Medical Ethics Review Board of the Radboud University Nijmegen Medical Centre.

Conflicts of interest: None.

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