Prim Care Respir J 2011; **20**(4): 396-402

Primary Care RESPIRATORY JOURNAL
www.thepcrj.org

RESEARCH PAPER

Factors associated with misdiagnosis of COPD in primary care

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Received 16th November 2010; revised 8th February 2011; accepted 22nd February 2011; online 17th June 2011

Abstract

Aim: To assess the misclassification of chronic obstructive pulmonary disease (COPD) in Australian primary care.

Methods: A cross-sectional study was performed in 31 (19%) practices in one Australian state. 341 patients with COPD (database diagnosis or current use of tiotropium plus GP confirmation) completed spirometry and questionnaires. Predictors of misclassification were investigated with multi-level mixed-effects logistic regression allowing for clustering by practice.

Results: Spirometric confirmation of COPD (forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio <0.7) was not present in 107 (31%) patients; 60 (56%) had normal lung function, seven (7%) had scalloped flow-volume curves and FEV_1 <80% predicted, 40 (37%) had restriction (FVC <80% predicted). Among 107 misclassified patients the bronchodilators used were tiotropium in 26% and long-acting β_2-agonists in 22%. The likelihood of misclassification increased with overweight/obesity (odds ratio (OR) 2.66; 95% CI 1.50 to 4.70) and self-reported allergic rhinitis/hay fever (OR 1.72; 95% CI 1.13 to 2.64) after adjustment for age, gender, and smoking.

Conclusions: Symptom-based diagnosis of COPD in primary care is unreliable, especially if patients are overweight, so diagnostic spirometry is essential to avoid inappropriate management.

JA Walters *et al*. *Prim Care Respir J* 2011; **20**(4): 396-402
http://dx.doi.org/10.4104/pcrj.2011.00039

Keywords COPD, primary care, diagnosis, spirometry, misclassification

Introduction

Chronic obstructive pulmonary disease (COPD) is recognised as a preventable chronic respiratory disease primarily linked to smoking or indoor air pollution.[1] It has both airway (bronchitis) and lung parenchymal (emphysema) pathophysiological components.[2] The impact of COPD is increasing worldwide in terms of years lost to disability[3] and mortality.[4] This reflects both the high smoking rates in many countries and ageing in developing countries.[1] Healthcare expenditure on COPD is a major burden.[1,5] In 2008 Australian expenditure on COPD was estimated at over AU$850 million, the major contributors being hospital (55%) and pharmaceutical costs (30%). Since the introduction of newer drugs for COPD, especially tiotropium and combination inhaled corticosteroid/long-acting β_2-agonists, pharmaceutical costs have increased by over 70% to around AU$215 per person with COPD per annum.[5]

COPD is still underdiagnosed in most countries, especially in its early stages,[6-8] with a major contributory factor being underutilisation of spirometry in primary care.[9-13] Spirometry in the general practice or office setting is feasible with the development of accurate, stable, portable devices,[14,15] and the majority of practices in the UK and Australia now report ownership of a spirometer.[16,17] However, from evidence in studies based on self-reported data,[18] medical claims data,[19] or medical records,[9] it is evident that spirometry is not routinely used to diagnose COPD in primary care – this despite diagnostic criteria for COPD and classification of severity being based on measurements of post-bronchodilator airflow 'fixed' obstruction.[20-22]

The number of spirometry tests performed in primary care in

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Australia on adults aged >55 years and reimbursed under the national government rebate scheme only increased by 1.6% between 2004 and 2008 to 154,379 tests.[23] In the absence of spirometric confirmation, misdiagnosis and an associated underdiagnosis of COPD are likely.

The aims of this study were to assess the extent of misclassification and the impact of this on management of patients. We also examined factors influencing the accuracy of diagnosis of COPD in Australian general practice.

Methods

Recruitment

In 2008 we recruited eligible practices with computerised clinical records from the three Tasmanian geographical mainland regions. Patients identified as having COPD within the practice were invited to participate in a study of self-management support from health mentors.[24] We searched practice databases by diagnosis of COPD (using all equivalent terms in the relevant practice software) and/or current prescription of tiotropium. General practitioners (GPs) reviewed search results to confirm patients had a COPD diagnosis. Patients thus identified in the absence of predefined exclusion criteria (resident in nursing home, terminal condition, previously participated in pilot self-management study, never smoked or pack-year smoking history <10 years) were invited for spirometry screening to determine their eligibility. GPs and participating patients gave written informed consent.

Definitions and measurements

Spirometry was performed pre- and post-bronchodilator (15-30 min after 400µg salbutamol administered via spacer device) using the EasyOne™ spirometer to achieve three acceptable expiratory manoeuvres according to ATS/ERS criteria,[25] of which at least two forced expiratory volume in 1s (FEV_1) and forced vital capacity (FVC) measurements were reproducible within 200ml. Participants who had used bronchodilators within manufacturer-specified periods of effectiveness performed post-bronchodilator tests only. The criterion for confirmation of a diagnosis of COPD was a post-bronchodilator FEV_1/FVC ratio of <0.7.[1] The severity of airway obstruction was graded according to Global Obstructive Lung Disease (GOLD) criteria using the third National Health and Nutrition Examination Survey (NHANES III) reference values for predicted FEV_1[26] (mild: FEV_1 ≥80%, moderate: FEV_1 50-79%, severe: FEV_1 30-49%, very severe FEV_1 <30%).[1] Participants' demographic data, self-reported co-morbidity, height and weight measurements were collected and the following questionnaires were administered: the Baseline Dyspnoea Index (BDI);[27] modified Medical Research Council (MRC) scale for functional dyspnoea;[28] breathlessness, cough and sputum scale (BCSS 12 point scale);[29] St George's Respiratory Questionnaire (SGRQ) quality of life measure;[30] and Hospital Anxiety and Depression (HADS) screening (presence of clinical anxiety or clinical depression defined as scores ≥11).[31]

Data analysis

Where data were missing, no imputations were performed. Data were analysed using statistical software STATA v10. Descriptive statistics are presented as mean with standard deviation (SD) and were compared using t-tests or ANOVA with Bonferroni correction for multiple groups if normally distributed, or presented as median and interquartile range (IQR) and compared using Mann-Whitney or Kruskal-Wallis tests if non-normally distributed. Mean difference (MD) and standard error (SE) are presented for between-group differences for continuous variables. Multi-level mixed-effects logistic regression with practice as the random variable was performed to investigate variable associations with COPD misclassification. Associations are presented as odds ratio (OR) with 95% confidence intervals (95% CI).

Ethics

The study was registered with the Australian and New Zealand Clinical Trials Research network (ACTR 12608000112368) and approved by the Human Research Ethics Committee of the University of Tasmania (H0009777).

Results

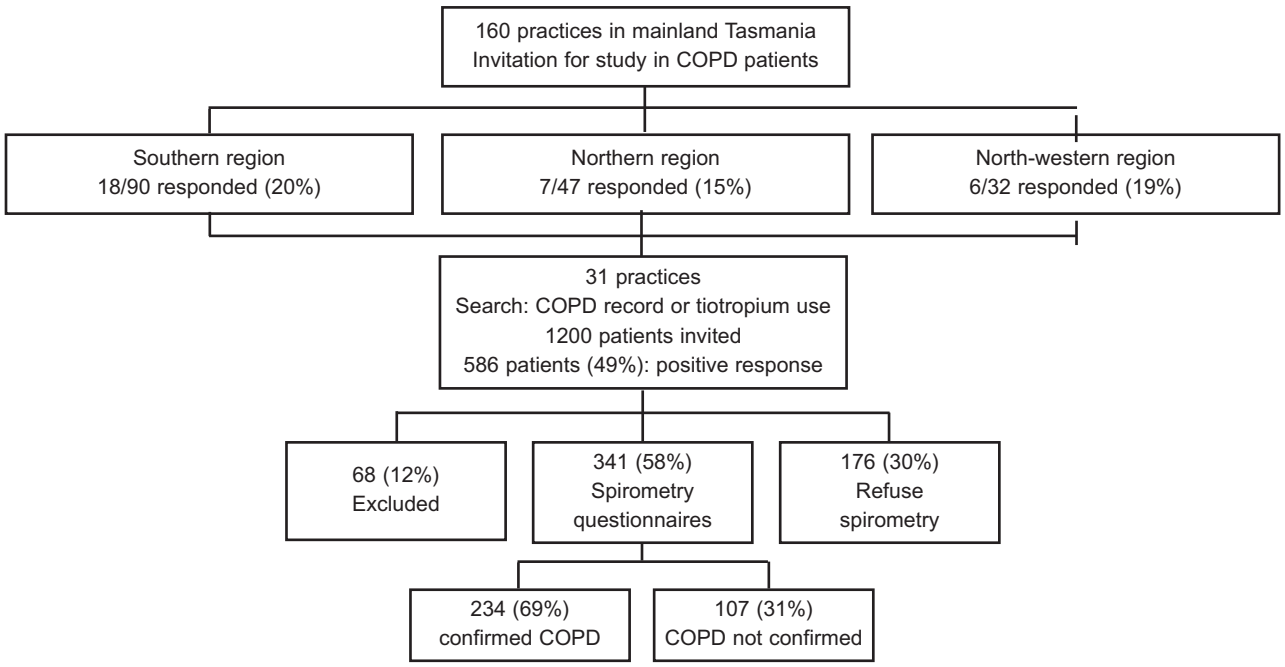
Patient recruitment

Of 160 eligible general practices, 31 (19%) agreed to participate (Figure 1), comprising five solo practices (16%), 18 group partnerships (58%), six corporate group practices (19%), and two government-administered practices (7%). The median number of GPs per practice was 4 (range 1-11). The geographical distribution by Rural, Regional and Metropolitan Area classification was 36% metropolitan, 10% large rural centre (catchment population 25,000-99,000), 3% medium rural centre (catchment population 10,000-24,999), and 51% small rural centre (catchment population <10,000). Of the patients who responded to the invitation to participate (Figure 1), 68 (12%) were excluded (64 had a cigarette smoking history <10 pack-years and four had previously participated in a self-management support study). Compared with the 341 participants, 176 (30%) patients who refused to participate were significantly older (mean age 69.0 vs 62.4 years, p<0.001), had a lower smoking exposure (median pack-year history 35 vs 42, p=0.004), and fewer were current smokers (28% vs 41%, p=0.01).

Confirmation of COPD diagnosis

A diagnosis of COPD was confirmed in 234 (69%) study participants. In these confirmed COPD subjects, severity grading was mild in 23 (10%), moderate in 114 (49%), severe in 69 (30%), and very severe in 28 (11%). Those with confirmed COPD were significantly older (MD 5.3, SE 1.0 years, p<0.001) and less likely to be currently employed (p<0.01). There was no

Figure 1. Spirometric confirmation of COPD diagnosis in patients recruited from 31 general practices in Tasmania



difference between confirmed or refuted COPD subjects in the proportions of current smokers or with any self-reported co-morbidities (asthma; ischaemic heart disease; hypertension; hypercholesterolaemia; diabetes; depression; anxiety; neurological, gastrointestinal and musculoskeletal conditions) except allergic rhinitis/hay fever (Table 1).

Misclassification of COPD

Lung function

Among the participants in whom COPD was refuted, normal lung function (FEV_1 >80% predicted, FVC >80% predicted) was present in 60 (56%) participants, and 7/107 (7%) participants had scalloping in the flow-volume curve and a borderline ratio FEV_1/FVC just greater than 0.7 with FEV_1 <80% predicted (mean 77%, 95% CI 76% to 80%). Apparently restrictive lung function (FVC <80% predicted) was present in 40 (37%) participants with median FEV_1 74% predicted (IQR 69–78%).

Treatment

The proportions of participants with confirmed COPD currently using tiotropium and long-acting β_2-agonists with or without corticosteroid were 51% and 50%, respectively (Table 1), significantly more than the proportions of those in whom COPD was refuted overall (26% and 22%, respectively, p<0.0001). The proportions using both tiotropium and long-acting β_2-agonists with or without corticosteroids did not differ significantly between those with normal, restrictive or borderline lung function (data not shown). Use of tiotropium or long-acting β_2-agonists with or without corticosteroid was more frequent in overweight or obese individuals than in those with normal weight in the misclassified participants (tiotropium 29% vs 15%, long-acting β_2-agonists with or without corticosteroids 26% vs 5%), but these differences were not statistically significant.

Vaccination status, exacerbations and hospital admissions

Annual influenza vaccination occurred at similar rates in the COPD group and the misclassified group (Table 1). A higher proportion of the COPD group had received scheduled pneumococcal vaccination although at least 50% of the misclassified groups had also received it. At least one acute respiratory 'exacerbation' had occurred in the previous 12 months in both the COPD and the misclassified groups, treated with antibiotics in similar proportions (51%, 49%) and treated with oral corticosteroids in the same proportions (24%). Although a respiratory-related emergency department attendance or hospital admission had occurred within the previous 12 months at similar rates in the groups with and without COPD (Table 1), in the misclassified group most episodes (71%) occurred in participants with restriction.

Respiratory symptoms and quality of life

Breathlessness and functional impairment were greatest in the group with confirmed COPD, but both the restrictive and borderline lung function groups had similar levels of impairment (Table 2). Impairment in quality of life domains of symptoms, activity limitation and impacts was as great in the restrictive lung function group as in the COPD group. Paradoxically, some impairment in symptom and activity limitation domains also existed in the normal lung function

Table 1. Baseline characteristics by spirometry-confirmed COPD in 341 participants recruited from 31 practices by database searches (COPD diagnosis and/or current tiotropium use) with GP confirmation of COPD diagnosis

	COPD (n=234)	Not COPD (n=107)	p value
Mean (SD) age (years)	64.0 (8.1)	58.7 (8.5)	<0.0001
Median (IQR) smoking history (pack-years)	45 (31)	39 (34)	0.07
Current smoker (%)	90 (39)	48 (45)	0.26
Male (%)	125 (53)	56 (52)	0.85
Living with partner (%)	95 (41)	46 (43)	0.67
Highest education level (%)			0.09
Primary	22 (9)	11 (10)	
Year 7–10	149 (64)	55 (52)	
Year 11 or 12	21 (9)	8 (8)	
Certificate/diploma	27 (12)	24 (23)	
University	15 (6)	7 (7)	
Employed currently (%)	44 (19)	35 (32)	0.005
Self-report asthma (%)	88 (38)	38 (37)	0.87
Self-report allergic rhinitis/hay fever (%)	61 (27)	39 (38)	0.03
Self-report IHD (%)	43 (18)	20 (19)	0.94
Self-report hypertension (%)	81 (35)	31 (29)	0.3
Self-report diabetes (%)	19 (8)	14 (13)	0.15
Long acting β-agonist ± corticosteroid	118 (50)	23 (22)	<0.0001
Tiotropium	119 (51)	28 (26)	<0.0001
Influenza vaccination within 12 months	193 (83)	78 (75)	0.11
Pneumococcal vaccination within 5 years	155 (66)	53 (51)	0.04
Antibiotics for exacerbation in 12 months	119 (51)	52 (49)	0.70
Oral corticosteroids for exacerbation in 12 months	56 (24)	26 (24)	0.94
Respiratory-related ED attendance or hospital admission in 12 months	21 (9)	7 (7)	0.45

IHD=ischaemic heart disease; ED=emergency department.

Table 2. Symptoms and quality of life by lung function group based on post-bronchodilator spirometry

	Normal LF (n=60)		Restrictive LF (n=40)		Borderline LF (n=7)		COPD (n=234)		p value†
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)	
BMI (kg/m^2)	60	29.4 (4.8)	40	30.3 (5.7)	7	30.0 (5.8)	233	26.4 (5.0)	<0.0001
Functional capacity (MRC 1–5)	52	2.0 (0.9)	33	2.7 (1.2)	6	2.7 (1.0)	231	2.7 (1.1)	<0.001
Breathlessness (BDI 0–12)	49	3.3 (2.4)	32	4.9 (2.7)	6	4.8 (3.1)	231	5.1 (2.5)	<0.001
Quality of life (SGRQ)									
Overall	23	39.3 (17.7	22	40.8 (18.7)		N/A	202	40.9 (18.7)	0.25
Symptoms	25	36.5 (22.5)	21	48.2 (26.7)		N/A	202	54.0 (21.6)	<0.001
Activity limitation	23	36.7 (24.2)	21	56.8 (23.4)		N/A	201	58.1 (20.8)	<0.0001
Impacts	24	19.2 (15.7)	21	24.7 (17.6)		N/A	200	31.0 (18.5)	0.006
Anxiety (HADS 0–21)	48	7.6 (4.4)	36	7.5 (3.6)	5	9.4 (8.6)	229	7.2 (4.1	0.61
Depression (HADS 0–21)	48	5.8 (3.4)	36	5.2 (2.8)	5	6.6 (7.3)	230	5.1 (3.3)	0.71
Co-morbidities*	107	1 (0–2)	40	1.5 (1–2.5)	7	1 (0–4)	234	1 (1–3)	0.47

LF=lung function, BMI=body mass index, MRC=MRC breathlessness score, BDI=Baseline dyspnoea index, SGRQ=St George's Respiratory Questionnaire, HADS=Hospital Anxiety and Depression Scale. *Median and interquartile range. †p value from ANOVA with Bonferroni correction or Kruskal-Wallis test.

group, which may relate to the symptoms for which they presented to their GP.

BMI and other co-morbidities

BMI was higher in those misclassified in the normal, restrictive and borderline lung function groups than in the COPD group (mean differences in BMI units between normal and restrictive lung function groups from the COPD group 2.9 and 3.8 units respectively, Table 2). There were no significant differences between any groups for anxiety or depression scores or the number of co-morbidities reported by participants.

Predictors of COPD misclassification

In univariate analyses the likelihood of misclassification decreased with increasing age (OR 0.93, 95% CI 0.90 to 0.95). Current smoking status, male gender, self-reported asthma, clinical anxiety or depression were not independent predictors of misclassification. After adjustment for age,

Table 3. Predictors of misclassification with COPD in 341 subjects in primary care in a multivariate logistic regression model taking into account clustering within practices

	Odds ratio	95% CI	p value
Age years	0.90	0.86 to 0.95	<0.0001
Gender: female [1]	0.85	0.47 to 1.58	0.66
Current smoker [2]	1.95	0.69 to 3.96	0.06
Clinical anxiety [3]	0.47	0.25 to 0.92	0.03
Clinical depression [4]	1.10	0.29 to 4.33	0.88
At least moderate obstruction (FEV_1 ≤80% predicted), [5]	0.04	0.02 to 0.10	<0.0001
Overweight or obese [6]	1.13	1.02 to 1.25	0.001
Allergic rhinitis/hay fever [7]	2.30	1.43 to 3.68	<0.0001

Odds ratio indicating the increase of the odds for a 1-point increase on the scale or compared with the reference group.
Reference categories: 1=male, 2=ex-smoker, 3=anxiety state not present (HADS anxiety <11), 4=depression not present (HADS depression <11), 5=mild airflow obstruction (FEV_1 >80% predicted), 6=BMI <25, 7=no self-report of allergic rhinitis/hay fever.

gender and smoking status, the likelihood of misclassification decreased with increasing breathlessness (BDI) (OR 0.83, 95% CI 0.73 to 0.95) and with greater functional limitation (MRC) (OR 0.72, 95% CI 0.53 to 0.99), while the likelihood of misclassification increased in those who were overweight or obese (OR 2.66, 95% CI 1.50 to 4.70) and with self-reported allergic rhinitis/hay fever (OR 1.72, 95% CI 1.13 to 2.64).

In a multivariate regression model, factors significantly associated with increased likelihood of misclassification of COPD were being overweight or obese and a self-reported diagnosis of allergic rhinitis/hay fever, while a decreased likelihood of misclassification was associated with increasing age and the presence of a clinical anxiety state (Table 3).

Discussion

Our study showed that, of 341 patients in general practice with either a recorded diagnosis of COPD and/or a record of current treatment with the specific COPD therapy tiotropium, only 69% had spirometrically confirmed COPD (i.e. non-reversible airflow obstruction) with a post-bronchodilator FEV_1/FVC ratio <0.7. Among the 107 (31%) patients who did not meet the criteria for COPD, three patterns were found on spirometry testing: 56% had normal lung function; 7% had mild airflow limitation (FEV_1 <80% predicted) but an FEV_1/FVC ratio just above 0.7; and 37% had restrictive lung function. Misclassification of COPD in practices was more likely in overweight or obese patients and in those with allergic rhinitis or hay fever, and less likely in patients with more symptoms of breathlessness and more functional impairment.

Varying levels of misclassification have been found in previous studies that used the criterion FEV_1/FVC <0.7. In 319 clinically diagnosed COPD patients in eight general practices in Greece where spirometry is rarely used, 50% were misclassified by GOLD criteria.[32] Other studies also required FEV_1 <80% predicted for COPD diagnosis, and the misclassification rate in our study with this criterion was 38% (data not shown). By this criterion, in Canada where spirometry is widely used, COPD was misdiagnosed in 12% of 382 patients aged >40 years who underwent spirometry testing in three practices, despite the majority having spirometry documented in their practice records.[33] In 580 patients coded as having COPD who underwent spirometry in 13 UK practices, 80% had COPD confirmed but 16% had normal lung function and 4% had restrictive lung function.[34] In a Spanish study of 330 randomly selected patients of 32 family physicians and 44 respiratory specialists who underwent spirometry, 28% did not fulfil the criteria for COPD.[35] We do not have data from practice records for patients in our study on whether spirometry had been performed; however, the majority of diagnoses of COPD made in primary care in Australia are made solely on clinical grounds[36] and are not based on spirometry.[9] The variation in the rate of misclassification seen in other studies may be related to differences in the use of spirometry for diagnosis,[18,19] and the finding that an incorrect COPD diagnosis was less likely when airflow obstruction was moderately severe is reassuring.

Data on associations between patient factors and misclassification of COPD from previous studies are limited. Our study found associations between an incorrect diagnosis of COPD and obesity and allergic rhinitis or hay fever. Nasal obstruction, defined by symptoms and low anterior rhinomanometry flow, was detected in 45% of patients misclassified with COPD in Greece[32] compared with 28% of the general population.[37] The presence of allergic rhinitis or hay fever in our study was based on patient response to a single question and we were not able to discriminate between recurrent or permanent symptoms, or episodic symptoms provoked by extrinsic factors. The significance of such symptoms requires further investigation using validated tools.[38]

In a population survey conducted in Sweden among participants with a self-reported but unconfirmed diagnosis

of chronic bronchitis or emphysema, 40% had recurrent or permanent nasal symptoms and 30% had nasal symptoms due to an extrinsic allergic factor, higher than in the general population.[39] A significant association between self-reported COPD and symptoms of nasal blockage was found (OR 1.9, 95%CI 1.2 to 2.8) at follow-up 8 years later,[40] suggesting that the presence of nasal symptoms may contribute to overdiagnosis. An increased prevalence of nasal inflammation has been described in biopsy and lavage studies of patients with COPD[40,41] compared with never-smokers and ex-smokers, but the cause of this relationship – whether it is independent, co-existent, or in some way a confounder on the making of the diagnosis – remains unclear.[41]

Similar to the finding in our study, an association was found in Canadian family practices between an increase in the number of respiratory symptoms (cough, breathlessness, wheeze, phlegm, and colds) and decreasing misclassification of COPD (OR 0.29, p=0.045), but no associations were found for age (p=0.99), gender (p=0.25), current smoking status (p=0.56), or increasing number of respiratory-related visits to a primary care physician (p=0.37).[33]

The relationship between misclassification and obesity we found – which was also seen in an open access spirometry service in the UK[42] – is plausible since obesity causes breathlessness on exercise,[43] affecting exercise performance due to the higher metabolic demand at any given power output as a result of an increased oxygen cost.[44,45] The work and oxygen cost of breathing is also increased at rest.[44] Patients with obesity may also have expiratory flow limitation at rest which, when compounded by high ventilatory requirements, leads to significant air trapping and dynamic increase in end-expiratory lung volume during exercise.[45] By contrast with COPD, overdiagnosis of asthma was not more likely to occur among obese individuals than among non-obese individuals (OR 1.21, 95% CI 0.82 to1.78).[46] However, the results of the US NHANES III study indicated that obesity was a risk factor for self-reported asthma in the absence of objective airflow obstruction on spirometry.[47]

From a clinical perspective, an accurate diagnosis of COPD is important because of its specific therapeutic and prognostic implications for patients. Conversely, inappropriate use of tiotropium and long-acting β_2-agonists with or without corticosteroids in participants misclassified with COPD has cost implications for the health system. There is also the burden of anxiety due to misdiagnosis for patients and their families and the opportunity cost of foregone treatment of the true underlying pathology.

Our study achieved high participation within the state, with almost half those identified with COPD in database searches in 31 practices responding to an invitation to participate and around 30% of responders undergoing spirometry. Practices participating represented 19% of eligible practices, and although these practices had a similar distribution to all practices by Rural, Regional and Metropolitan Area classification, the misclassification rate may be even greater in practices not participating in a research project. Our findings are limited to those with a recorded COPD diagnosis or being prescribed tiotropium in general practices, but they are likely to be representative of patients labelled with COPD in this community and the similarity of prevalence and management findings in COPD in different states means the results of this study are also likely to apply across Australia.[10,48,49]

Conclusions

This study identified a high rate of misclassification of COPD in primary care, including patients with normal lung function, and therefore considerable inappropriate use of respiratory medications and foregone therapeutic benefits. These findings highlight the need for adequately performed and interpreted spirometry to be used at diagnosis rather than relying on symptoms and a clinical diagnosis. This will avoid exposing patients to potentially adverse medication effects and reduce unnecessary healthcare expenditure. In addition, the true nature of respiratory symptoms in those misclassified (mainly obese subjects and those with nasal pathology) needs recognition and appropriate management.

Handling editor
Chris Griffiths

Statistical review
Gopal Netuveli

Conflicts of interest
The authors declare that they have no conflicts of interest in relation to this article.

Contributorship
Walters J coordinated data collection and analysis, wrote first draft of paper, prepared manuscript for publication; Walters E and Wood-Baker R supervised data collection, contributed to revisions of paper and writing discussion; Nelson M and Robinson A contributed to revisions of paper and writing discussion, Scott J and Turner P read and contributed to revisions of paper.

Funding
The study was supported by an Australian Lung Foundation/Boehringer Ingelheim COPD Research Fellowship (JW) and an NHMRC Australia project grant.

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