Marie Fisk, Viktoria McMillan, James Brown, Juliana Holzhauer-Barrie, Muhammad S Khan, Noel Baxter and C Michael Roberts

Inaccurate diagnosis of COPD:

the Welsh National COPD Audit

Abstract

Background
The diagnosis of chronic obstructive pulmonary disease (COPD) is confirmed with spirometry demonstrating persistent airflow obstruction.

Aim
To evaluate the clinical characteristics and management of patients in primary care on COPD registers with spirometry incompatible with COPD.

Design and setting
A primary care audit of Welsh COPD Read-Coded patient data from the Quality and Outcomes Framework (QOF) COPD register in Wales.

Method
Patients on the QOF COPD register with incompatible spirometry (post-bronchodilator forced expiratory lung volume in 1 second/forced vital capacity [FEV1/FVC] ratio ≥0.70) were compared with those with compatible spirometry (FEV1/FVC <0.70).

Results
This audit included 63% of Welsh practices contributing 48 105 patients. Only 19% (n = 8957) of patients were post-bronchodilator FEV1/FVC Read-Coded and were included in this study. Of these, 75% (n = 6702) had compatible spirometry and 25% (n = 2255) did not. Patients with incompatible spirometry were more likely female (P = 0.009), never-smokers (P<0.001), had higher body mass index (P<0.001), and better mean FEV1 (P<0.001). Medical Research Council (MRC) breathlessness scores, exacerbation frequency, and asthma co-diagnosis were similar between groups. Patients in both groups were just as likely to receive inhaled corticosteroid (ICS) and long-acting beta-agonists (LABAs), but patients with incompatible spirometry were less likely to receive long-acting muscarinic antagonists (LAMAs) (P<0.001) or LABA/ICS (P = 0.002) combinations.

Conclusion
Patients on the COPD QOF register with spirometry incompatible with COPD are symptomatic and managed using significant resources. If quality of care and effective resource use are to be improved, focus must be given to correct diagnosis in this group.

Keywords
chronic obstructive pulmonary disease; diagnosis; primary care; spirometry.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, complex condition that is a leading cause of mortality, disability, and poor health globally and within the UK.[1,2] It is estimated from general practice records that, in 2012, 1.2 million people were diagnosed with COPD and, in the same year, approximately 30 000 people died from COPD. These figures are likely higher now in 2018.[3] In the UK, COPD exacerbations are the second leading cause of unplanned hospital admissions; age-standardised mortality rates and disability-adjusted life years associated with COPD are higher than the European average.[4,5] In Wales, the observed prevalence of COPD was 2173 per 100 000 in 2012,[3] which is similar to that of the whole of the UK, though rates of hospital admissions and mortality due to COPD are higher than the UK average.[3]

The Welsh National COPD Audit programme seeks to support improvement in healthcare delivery in primary care by identifying areas of care where concerted interventions could produce maximum benefit to patients. Accurate diagnosis of respiratory symptoms that suggest COPD and confirmation with post-bronchodilator spirometry demonstrating airflow obstruction are essential if the implementation of evidence-based care is to be effective. Studies from different populations and countries show that a COPD clinical diagnosis can be inaccurate in as many as half of the cases compared with confirmation by spirometry.[6,7]

This study was undertaken to explore the characteristics and management of patients in primary care with a diagnosis of COPD but with spirometry results incompatible with that diagnosis in a large population sample, in order to identify factors that might better inform a more accurate diagnostic process.

METHOD

Study design

Data from the inaugural Welsh National COPD Primary Care Audit were used. This audit was commissioned by the Healthcare Quality Improvement Partnership and led by the Royal College of Physicians (RCP), London. The audit collected data regarding 48 105 patients registered living with COPD on the Quality and Outcomes Framework (QOF) COPD register from the 280 (61%) of the 462 GP practices in Wales that opted into the audit, from January 2014 to March 2015.

M Fisk, PhD, MRCP, clinical lecturer in Respiratory Medicine and Clinical Pharmacology Therapeutics, Experimental Medicine and Immunotherapeutics (EMIT) Department, University of Cambridge, Cambridge. **V McMillan**, programme manager, National COPD Audit Programme; **J Holzhauer-Barrie**, MA, project manager, National COPD Audit Programme; **MS Khan**, MPH, MSc, data analyst, National COPD Audit Programme; **N Baxter**, MRCGP, clinical lead, National COPD Audit Programme Primary Care Workstream, Royal College of Physicians, London. **J Brown**, MRCP, respiratory research fellow, Royal Free London NHS Foundation Trust and UCL Respiratory, Division of Medicine, University College London, London. **CM Roberts**, MD, FRCP, ILTHE, FAcaMEd, clinical lead, National COPD Audit Programme; associate director, Clinical Effectiveness and Evaluation Unit, Care Quality Improvement Department, Royal College of Physicians, London.

Address for correspondence
Marie Fisk, Department of Experimental Medicine and Immunotherapeutics (EMIT), University of Cambridge. Box 98, Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK.

Email: m.fisk@nhs.net

Submitted: 9 June 2018; **Editor's response:** 28 June 2018; **final acceptance:** 20 August 2018.

How this fits in

Studies have suggested that making an accurate diagnosis of chronic obstructive pulmonary disease (COPD) is challenging. This large, nationwide study provides real-world data from primary care and shows that 25% of patients recorded with COPD have spirometry incompatible with this diagnosis. However, these patients are symptomatic suggesting they have an underlying medical problem. This study suggests that a concerted effort to determine an accurate diagnosis in these patients is urgently needed, to reduce both potential harm to these patients and the financial cost from unnecessary treatments or interventions. Moreover, if these audit results were extrapolated to the estimated COPD prevalence in the population of Wales, this would imply around 16 000 misdiagnosed cases.

Electronic data were extracted from these practices by the NHS Wales Informatics Service using audit plus software and securely transferred and stored in an accredited safe haven provided by NHS Digital England.[8] NHS Digital England removed all possible patient identifiers and anonymised data at patient level, before providing an anonymised dataset to the RCP for analysis.

Study population

The audit cohort included all patients on the QOF COPD register. Only patients on the register with post-bronchodilator forced expiratory lung volume in 1 second/forced vital capacity (FEV1/FVC) ratio recorded, defined by the Read Code '339m', were included in this analysis, because this post-bronchodilator ratio is necessary to confirm the diagnosis of COPD, and is based on current National Institute for Health and Care Excellence (NICE) guidelines and Global Initiative for Chronic Obstructive Lung Disease recommendations.[9,10] Based on the most recent post-bronchodilator FEV1/FVC, Read-Coded ratio available, patients with a FEV1/FVC ≥0.70, were defined as having spirometry incompatible with their COPD diagnosis, and were compared with patients with spirometry compatible with their COPD diagnosis, that is, those with FEV1/FVC <0.70. Demographics, clinical characteristics, and management of these two groups of patients taken from the primary care clinical record were compared.

Exacerbations

Exacerbations were defined by the Read Codes for acute exacerbation of chronic obstructive airways disease, COPD with a lower respiratory tract infection, and/or associated prescription of a short course of corticosteroids and/or antibiotics for treating the specific exacerbation. Only exacerbations that were >2 weeks apart were counted and included in the analysis. A 2-week exacerbation-free time period from an index event was applied to ensure that a relapse of an exacerbation was not counted as a separate exacerbation.[11]

Prescription cost analysis

A speculative estimate of the cost of inhalers prescribed to audit patients with incompatible spirometry and no known diagnosis of asthma (which could be a reason for prescription) was also undertaken. Using prescription cost analysis,[12] the cost of the most commonly dispensed inhaler in each drug class was noted and based on expected duration of inhaler doses and number of patients prescribed this type of inhaler, and an estimated cost per annum (2014) was calculated assuming compliance and thus timely repeat prescriptions. Further information regarding this analysis is available from the authors on request.

Statistical analysis

Data analysis was carried out using SPSS (version 23) and a *P*-value of <0.05 was deemed significant for all statistical analysis. To evaluate patients with incompatible versus compatible spirometry, only patients in the audit with Read-Coded post-bronchodilator spirometry recorded were included in this analysis. The χ^2 squared test was used to evaluate differences in proportions, unpaired Student's *t*-test to evaluate for differences in mean values, and the Mann–Whitney *U* test was used to compare the distribution of non-parametric variables.

RESULTS

In total, of the 48 105 patients included in the Welsh COPD Primary Care Audit, the mean age was 72 years (standard deviation [SD] 12) (range 36–105 years), 46% (*n* = 3056) of patients were female, and the mean body mass index (BMI) was 27.42 (SD 6.33) kg/m^2. Only 19% (*n* = 8957) had the gold standard of post-bronchodilator FEV1/FVC recorded. Of these cases, 25% (*n* = 2255) had incompatible spirometry (FEV1/FVC≥0.70) and 75% (*n* = 6702) had compatible spirometry. Demographic characteristics of these two patient groups are summarised in Table 1. The age ranges for both groups were similar, and the

Table 1. Characteristics of patients included in the primary care COPD audit with compatible and incompatible spirometry, *N* = 8957[a]

Patient characteristics	Compatible spirometry, *N* = 6702	Incompatible spirometry, *N* = 2255	*P*-value
Age, years, mean (SD)	71 (10)	70 (11)	
Age range, years	36–105	37–99	0.070
Female sex, *n* (%)	3056 (46)	1100 (49)	0.009
Body mass index, mean, kg/m^2 (SD)	27.04 (5.94)	29.42 (6.69)	<0.001
Asthma co-diagnosis, *n* (%)	878 (13)	296 (13)	0.900
Asthma ever diagnosed, *n* (%)	2237 (33)	821 (36)	0.009
Smoking status			
Never smoker, *n* (%)	566 (8)	315 (14)	<0.001
Ex-smoker, *n* (%)	3731 (56)	1209 (54)	0.090
Current smoker, *n* (%)	2255 (34)	680 (30)	0.002
No record of smoking status, *n* (%)	150 (2)	51 (2)	0.700
Spirometry and COPD severity,			
FEV_1/FVC, mean (SD)	0.55 (0.10)	0.78 (0.07)	<0.001
FEV_1, l, mean (SD)	1.38 (0.60)	1.76 (0.60)	<0.001
FEV_1 % predicted, mean (SD)	58 (18)	72 (18)	<0.001
MRC breathlessness scale, %			
1	12	12	0.070
2	41	42	0.070
3	29	30	0.070
4	15	14	0.070
5	3	2	0.070
Exacerbations, events/year, median (range)	2.42 (0 to 25)	2.43 (0 to 25)	0.890
COPD clinical diagnostic code			
COPD, *n* (%)	3129 (46.7)	1029 (45.6)	0.400
Mild COPD, *n* (%)	1095 (16.3)	558 (24.7)	<0.001
Moderate COPD, *n* (%)	1237 (18.5)	325 (14.4)	<0.001
Severe COPD, *n* (%)	509 (7.6)	74 (3.3)	<0.001
Very severe COPD, *n* (%)	76 (1.1)	3 (0.1)	<0.001
COPD not otherwise specified, *n* (%)	424 (6.3)	128 (5.7)	0.700
Bronchitis, *n* (%)	56 (0.8)	52 (2.3)	<0.001
Emphysema, *n* (%)	176 (2.6)	86 (3.8)	0.004

[a]Unpaired Student's t*-tests and* χ^2 *square tests used to evaluate differences between groups. COPD = chronic obstructive pulmonary disease. FEV1/FVC = post-bronchodilator forced expiratory lung volume in 1 second/forced vital capacity. MRC = Medical Research Council. SD = standard deviation.*

proportion of patients aged <45 years was similar between both groups (14 out of 2255 for incompatible spirometry, versus 44 out of 6702 for compatible spirometry, *P* = 0.86). A further 6772 from 48 105 patients included in the audit had an FEV1/FVC recorded that was not known to be post-bronchodilator. Out of these cases, 28% (1909 out of 6772) had incompatible spirometry with an average FEV1/FVC of 0.78 (SD 0.07).

Between patient groups there were no significant differences in age or proportion of patients with a current co-diagnosis of asthma (13%), although a slightly higher percentage of patients with incompatible spirometry had a previous diagnosis of asthma, which had at the time of the audit been resolved as a diagnosis (36% [*n* = 2237] versus 33% [*n* = 821], *P* = 0.009). Patients with incompatible spirometry had a higher BMI (29.42 [SD 6.69] versus 27.04 [SD 5.94] kg/m^2, *P*<0.001), a greater percentage were female (49% versus 46%, *P* = 0.009), never-smokers (14% versus 8%, *P*<0.001), had significantly better spirometry (FEV1 1.76 l [SD 0.60] versus 1.38 l[SD 0.60], *P*<0.001), and a greater percentage had a diagnostic Code of mild COPD (25% versus 16%, *P*<0.001).

Despite this, both groups of patients had similar levels of breathlessness (median Medical Research Council [MRC] breathlessness scale: 2 [1–5] for both groups, *P* = 0.07) and frequency of recorded exacerbations (median events per year: 2.43 (0–25) versus 2.42 (0–25), *P* = 0.89 for incompatible and compatible spirometry patients respectively.

Management of incompatible versus compatible spirometry patients

Data are summarised in Table 2. Many of the management interventions were applied in

Table 2. Management of patients included in the COPD primary care audit with compatible and incompatible spirometry

Management	Compatible spirometry, % *N* = 6702	Incompatible spirometry, % *N* = 2255	*P*-value
3-month review	0.93	1.46	0.03
6-month review	1.06	1.60	0.04
12-month review	96.51	95.04	0.002
No review	1.5	1.9	0.2
Smoking cessation advice[a]	96.2	96.9	0.3
Smoking cessation referral[a]	3.7	3.1	0.3
No smoking cessation record[a]	0.1	0	0.3
Influenza vaccination	89	89	0.6
Inhaler technique	95	95	0.3
Pulmonary rehabilitation referral	23	20	0.001
Oxygen therapy	3	2	0.04
LABA	33	30	0.07
LAMA	81	73	<0.001
ICS	49	52	0.07
Combined LABA/ICS	78	75	0.002

current smokers. Unpaired Student's t *-test and* χ^2 *square test used to evaluate differences between groups. COPD = chronic obstructive pulmonary disease. ICS = inhaled corticosteroid. LABA = long-acting beta-agonist. LAMA = long-acting muscarinic antagonist.*

equal proportion across the two groups, such as smoking cessation, vaccinations, and inhaler technique checks, except for pulmonary rehabilitation referrals, which were lower in patients with incompatible spirometry (20% versus 23%, *P*<0.001).

A slightly lower percentage of patients with an incompatible spirometry result received a long-acting muscarinic antagonist (LAMA) (73% versus 81%, *P*<0.001) and long-acting beta-agonist/inhaled corticosteroid (LABA/ICS) combination inhalers (75% versus 78%, *P* = 0.002). Nevertheless, a sizeable proportion of patients with incompatible spirometry received inhaled pharmacological therapies. Therefore, the researchers sought to evaluate whether a coexisting diagnosis of asthma could explain these prescriptions. Only 13% (296 out of 2255) of these patients had a co-diagnosis of asthma (Table 3). Interestingly, there were no differences in the proportion with prescriptions for LAMA (73% versus 73%, *P* = 0.9) and LABA/ICS combined inhalers (77% versus 74%, *P* = 0.4) in patients with incompatible spirometry *with* or *without* a co-diagnosis of asthma respectively, although more patients with an asthma co-diagnosis received single LABA or ICS therapies. Furthermore, 46 (1.5%) of a total of 3058 patients ever diagnosed with asthma (2237 with compatible and 821 with incompatible spirometry) received bronchodilators (LABA and/or LAMA) without ICS.

Table 3. Inhaled therapies prescribed in patients with incompatible spirometry with a diagnosis of COPD, *N* = 2255

Inhaled pharmacology therapies	Asthma, *N* = 296, % = 13%	No asthma, *N* = 1959, % = 87%	*P*-value
ICS	169 (57)	996 (51)	0.050
LABA	115 (39)	571 (29)	0.001
LAMA	216 (73)	1430 (73)	0.900
Combined LABA/ICS	227 (77)	1455 (74)	0.400

COPD = chronic obstructive pulmonary disease. ICS = inhaled corticosteroid. LABA = long-acting beta-agonist. LAMA = long-acting muscarinic antagonist.

Cost analysis

An estimated total cost of inhalers prescribed for audit patients with incompatible spirometry and no known asthma was approximately £1 million/per year (2014).

DISCUSSION

Summary

This study has shown that in a national COPD primary care audit cohort both the poor documentation of spirometry and its interpretation challenges the accuracy of diagnosis in a significant proportion of patients appearing on the QOF COPD register. This finding has implications for population health strategies, health economic costs, and for the individuals misdiagnosed. The absence of a Read-Coded FEV1/FVC ratio does not imply that such a test has never been performed but does promote a view that its importance in ensuring an accurate diagnosis is not at the forefront of clinicians' management strategies. Moreover, the researchers observed that spirometry was misinterpreted in around one-quarter of cases, when recorded, which if extrapolated to the estimated COPD prevalence in the population of Wales would imply around 16 000 misdiagnosed cases.[13] The more prevalent use of a Code for mild COPD in this group, the fact they were seen sooner in follow-up (although actual numbers for 3–6-month review were very small), and the lower use of LAMA therapy may indicate greater diagnostic uncertainty in this group, though they were equally symptomatic as measured by MRC scores and exacerbations.

Strengths and limitations

The strength of the present study is the evaluation of real-world clinical data extracted electronically from 61% of GP practices in Wales. This is a real-life study reflecting clinical practice at scale (that is, audit data of real-life practice, not data from an observational or epidemiological cohort). There are several limitations of the study. Low levels of Read-Coded recording of the FEV1/FVC ratio reduced the cohort size for analysis to under one-fifth of the total COPD register available, and thus a major finding from the audit emphasising the need to improve recording of spirometry data. Audit data are only as accurate as the data entry; nevertheless, these data were extracted from live clinical records. Poor spirometry technique could have accounted for some of the apparent misdiagnoses and the researchers did not have access to any quality assurance measure. It was not possible to verify a sample of live GP records or compare data against alternative sources.

Furthermore, the researchers only had access to the FEV1/FVC ratio and used this to define persistent airflow obstruction in accordance with current guidance,[9,10] rather than the more accurate lower limit of normal distribution. Given that patients would have undergone clinical assessment to acquire a diagnosis of COPD, the authors feel it was appropriate to use a guideline-based definition of airflow obstruction. The authors are aware, however, that a fixed FEV1/FVC ratio can wrongly suggest airflow obstruction in older people, and therefore, in the present audit cohort, would likely increase even further the proportion of patients with an inaccurate diagnosis of COPD.[14,15]

The researchers also did not have patients' comorbidity diagnoses, which may have provided alternative explanations for this symptomatic patient group with incompatible spirometry. The authors do not know if these audit results are generalisable to other population groups or health service systems, but it is likely that they have application to those that operate a primary care system similar to that in Wales.

Comparison with existing literature

One of the primary differential diagnoses of COPD is asthma and this has previously been described as an important factor in misdiagnosis of COPD.[16] Patients with incompatible spirometry in this audit were more likely to have a previous diagnosis of asthma. Importantly, changing such patients' diagnostic code from asthma to COPD may have detrimental effects on asthma management (if asthma is the correct diagnosis) with possible reduction in ICS use, because ICS are currently not recommended in the management of mild COPD.[17]

There was, however, no difference in management between patients with incompatible versus compatible spirometry in the majority of evidence-based interventions designed for patients with COPD. Pharmacological therapy use was similar in the incompatible spirometry group *with* or *without* a current co-diagnosis of asthma, suggesting that asthma co-diagnosis was not determining management.

Patients with incompatible spirometry had a higher BMI than those with compatible spirometry, and this association with misdiagnosis has been previously reported.[18] This patient group was also more likely to be female and 14% were non-smokers (compared with 8% in patients with compatible spirometry). Population studies estimate COPD prevalence to be approximately 6% in never-smokers. However, this can increase to as high as 23% in older (≥80 years) patients.[19,20]

Previous studies in different healthcare systems have also highlighted correct COPD diagnosis as challenging. Joo *et al* showed that primary care physicians in an urban Chicago centre were accurate in their diagnosis only half of the time.[21] Jones *et al* found that 27% of patients registered with COPD in a primary care study of 16 GP practices in Devon were eligible for reclassification of their disease following structured clinical assessment by a trained nurse.[22] Roberts *et al* evaluated COPD cases referred from local GP practices to a specialist unit, and where the final diagnosis was made by specialists and confirmed with spirometry. The study found that referrals with a provisional diagnosis of both 'definite' COPD and 'suspected' COPD, were much more likely to be correct in males than females.[23] Furthermore, in a retrospective US veterans cohort study of patients empirically diagnosed and treated for COPD by their healthcare provider, only 62% actually had airflow obstruction.[24]

In contrast to these previous studies, the present study provides for the first time, an insight into real-world diagnosis and management of patients with COPD on a national level. Findings from the present study showing that 25% of patients with an inaccurate diagnosis is in keeping with these smaller studies, and the present study's

finding of a higher proportion of females with incompatible spirometry compared with patients with compatible spirometry supports the notion of a sex difference in the presentation and diagnostic accuracy of COPD.[25] The financial cost of inappropriate prescription of inhaled pharmacological therapies (estimated to be around £1 million a year) due to an incorrect diagnosis of COPD in patients who also do not have a diagnosis of asthma, as well as potential harm due to side effects, are further important considerations from these data.

Importantly, patients with an inaccurate COPD diagnosis were as symptomatic as patients with a correct diagnosis, and this group of patients represents a significant unmet clinical need requiring correct diagnosis and subsequent management. These data emphasise the need for quality improvement in making the correct diagnosis. Greater access for GPs to secondary care expertise either through diagnostic hubs or primary care 'cluster' models are possibilities to help achieve this.

Implications for research and practice

Further research is required to understand what support can be given to primary care teams to improve diagnostic accuracy. The authors recommend that primary care providers search existing COPD registers for evidence of spirometry data that confirm the diagnosis, and where this cannot be found to recall patients for further diagnostic assessment. Patients attending primary care with undiagnosed breathlessness should be investigated according to an agreed pathway that the present authors recommend includes reversibility spirometry testing and peak expiratory flow (PEF) charts in patients suspected to have asthma. Improvement in spirometry training and recording of tests using templates with standardised Systematized Nomenclature of Medicine Clinical Terms (SNOMED) coding in GP records are needed. The Royal College of Physicians COPD Audit, the Royal College of General Practitioners website, and the Primary Care Respiratory Society websites all contain improvement advice and practical tips on improving diagnostic accuracy of COPD.[25,26]

There is a significant cost to patients and to the NHS (Welsh primary care) if the present situation remains unresolved and the authors call for a concerted effort by both providers and commissioners to improve the diagnostic accuracy of COPD in primary care.

Funding

The Royal College of Physicians (RCP) COPD Audit Programme was funded by the Healthcare Quality Improvement Partnership.

Ethical approval

The RCP COPD Primary Care Audit has approval from the Confidentiality Advisory Group of the Health Research Authority to collect patient data under section 251 of the National Health Service Act 2006. No additional ethical approval for this study of the audit's data was therefore required.

Provenance

Freely submitted; externally peer reviewed.

Competing interests

The authors have declared no competing interests.

Discuss this article

Contribute and read comments about this article: **bjgp.org/letters**

REFERENCES

1. Lozano R, Naghavi M, Foreman K, *et al*. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380(9859):** 2095–2128.
2. Mannino DM, Braman S. The epidemiology and economics of chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2007; **4(7):** 502–506.
3. British Lung Foundation. Chronic obstructive pulmonary disease (COPD) statistics. 2018. https://statistics.blf.org.uk/copd (accessed 12 Nov 2018).
4. Murray CJ, Richards MA, Newton JN, *et al*. UK health performance: findings of the Global Burden of Disease Study 2010. *Lancet* 2013; **381(9871):** 997–1020.
5. British Lung Foundation, British Thoracic Society. *Ready for home? Improving hospital discharge care for people living with COPD: a report by the British Lung Foundation and the British Thoracic Society*. 2010. https://www.brit-thoracic.org.uk/document-library/clinical-information/copd/ready-for-home-improving-hospital-discharge-care-for-people-living-with-copd/ (accessed 12 Nov 2018).
6. Fortis S, Corazalla EO, Jacobs DR, Kim HJ. Persistent empiric COPD diagnosis and treatment after pulmonary function test showed no obstruction. *Respir Care* 2016; **61(9):** 1192–1200.
7. Casas Herrera A, Montes de Oca M, López Varela MV, *et al*. COPD underdiagnosis and misdiagnosis in a high-risk primary care population in four Latin American countries. A key to enhance disease diagnosis: the PUMA Study. *PLoS ONE* 2016; **11(4)**: e0152266.
8. NHS Digital. Safe haven directory. https://digital.nhs.uk/services/organisation-data-service/services-provided-by-the-organisation-data-service/safe-haven-directory. 2018 (accessed 7 Oct 2018).
9. National Institute for Health and Care Excellence. *Chronic obstructive pulmonary disease in adults. QS10*. 2011. https://www.nice.org.uk/guidance/qs10 (accessed 7 Oct 2018).
10. Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease: 2018 report*. 2018. https://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf (accessed 12 Nov 2018).
11. Mullerova H, Shukla A, Hawkins A, Quint J. Risk factors for acute exacerbations of COPD in a primary care population: a retrospective observational cohort study. *BMJ Open* 2014; **4(12):** e006171.
12. Gov.Wales. Statistics & Research. Statistics. Prescriptions dispensed in the community. Past releases. Tables — prescription cost analysis: individual preparations, 2000–2015. 2016. http://gov.wales/statistics-and-research/prescriptions-dispensed-community/?tab=previous&lang=en [accessed 27 Nov 2018].
13. NHS Wales. Health in Wales: chronic obstructive pulmonary disease. 2018. http://www.wales.nhs.uk/healthtopics/conditions/chronicobstructivepulmonarydisease (accessed 12 Nov 2018).
14. Swanney MP, Ruppel G, Enright PL, *et al*. Using the lower limit of normal for the FEV1/FVC ratio reduces the misclassification of airway obstruction. *Thorax* 2008; **63(12):** 1046–1051.
15. Miller MR, Levy ML. Chronic obstructive pulmonary disease: missed diagnosis versus misdiagnosis. *BMJ* 2015; **351:** h3021–h3142.
16. Tinkelman DG, Price DB, Nordyke RJ, Halbert RJ. Misdiagnosis of COPD and asthma in primary care patients 40 years of age and over. *J Asthma* 2009; **43(1):** 75–80.
17. Levy L, Andrews R, Buckingham R, *et al*. *Why asthma still kills: National Review of Asthma Deaths*. 2014. https://www.rcplondon.ac.uk/projects/outputs/why-asthma-still-kills (accessed 7 Oct 2018).
18. Walters JA, Walters EH, Nelson M, *et al*. Factors associated with misdiagnosis of COPD in primary care. *Prim Care Respir J* 2011; **20(4):** 396–402.
19. Tan WC, Sin DD, Bourbeau J, *et al*. Characteristics of COPD in never-smokers and ever-smokers in the general population: results from the CanCOLD study. *Thorax* 2015; **70(9):** 822–829.
20. Lamprecht B, McBurnie MA, Vollmer WM, *et al*. COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 2011; **39(4):** 752–763.
21. Joo MJ, Au DH, Fitzgibbon ML, *et al*. Determinants of spirometry use and accuracy of COPD diagnosis in primary care. *J Gen Intern Med* 2011; **26(11):** 1272–1277.
22. Jones PW, Brusselle G, Dal Negro RW, *et al*. Patient-centred assessment of COPD in primary care: experience from a cross-sectional study of health-related quality of life in Europe. *Prim Care Respir J* 2012; **21(3):** 329–336.
23. Roberts NJ, Patel IS, Partridge MR. The diagnosis of COPD in primary care; gender differences and the role of spirometry. *Respir Med* 2016; **111:** 60–63.
24. Collins BF, Feemster LC, Rinne ST, Au DH. Factors predictive of airflow obstruction among veterans with presumed empirical diagnosis and treatment of COPD. *Chest* 2015; **147(2):** 369–376.
25. Levy ML, Quanjer PH, Booker R, *et al*. Diagnostic spirometry in primary care: proposed standards for general practice compliant with American Thoracic Society and European Respiratory Society recommendations: a General Practice Airways Group (GPIAG). *Prim Care Respir J* 2009; **18(3):** 130–147.
26. Lucas AE, Smeenk FJ, Smeele IJ, van Schayck OP. Diagnostic accuracy of primary care asthma/COPD working hypotheses, a real life study. *Respir Med* 2012; **106(8):** 1158–1163.