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Title: Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

Running head: Comparison of different spirometric cut-offs

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ABSTRACT

Objectives: Consistent estimation of the burden of chronic obstructive pulmonary disease (COPD) has been hindered by differences in methods, including different spirometric cut-offs for impaired lung function. The impact of different definitions on the prevalence of potential airflow obstruction, and its associations with key risk factors, is evaluated using cross-sectional data from two general population surveys.

Design: Pooled cross-sectional analysis of Wave 2 of the UK Household Longitudinal Survey and the Health Survey for England 2010, including 7879 participants, aged 40-95 years, who lived in England and Wales, without diagnosed asthma, and with good-quality spirometry data. Potential airflow obstruction was defined using self-reported physician-diagnosed COPD; a fixed threshold (FT) forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70; and an age-, sex-, height- and ethnic-specific lower limit of normal (LLN). Standardised questions elicited self-reported information on demography, smoking history, ethnicity, occupation, respiratory symptoms, and cardiovascular disease.

Results: Consistent across definitions, participants classed with obstructed airflow were more likely to be older, currently smoke, have higher pack-years of smoking, and be engaged in routine occupations. The prevalence of airflow obstruction was 2.8% (95% CI 2.3-3.2), 22.2% (21.2-23.2), and 13.1% (12.2-13.9) according to diagnosed COPD, FT and LLN, respectively. The gap in prevalence between FT and LLN increased in older age-groups. Sex differences in the risk of obstruction, after adjustment for key risk factors, was sensitive to the choice of spirometric cut-off, being significantly higher in men when using FT, compared with no significant difference using LLN.

Conclusions: Applying FT or LLN spirometric cut-offs gives a different picture of the size and distribution of the disease burden. Longitudinal studies examining differences in

unscheduled hospital admissions and risk of death between FT and LLN may inform the choice as to the best way to include spirometry in assessments of airflow obstruction.

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Keywords: airflow obstruction; chronic obstructive pulmonary disease; fixed thresholds; Health Survey for England; lower limit of normal; respiratory; sensitivity; specificity; spirometry; United Kingdom Household Longitudinal Survey

Strengths and limitations of this study

- Estimates of the burden of chronic obstructive pulmonary disease (COPD) using spirometry data collected in epidemiological studies are inconsistent through differences in methods, including different spirometric cut-offs.
- Our study combined two nationally representative samples of adults living in England and Wales, with standardised protocols and objective measurements of lung function, and a wide-range of clinically-relevant conditions including self-reported respiratory symptoms and breathlessness.
- Consistent definitions and up-to-date reference equations were used, providing baseline data for monitoring purposes in the UK, and facilitating comparison with international studies.
- Prevalence estimates were based on pre-bronchodilator lung function measurements, and so are likely to overestimate true prevalence.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by a progressive decline in lung function.[1;2] 2.9 million deaths were attributed to COPD in 2010, making it the third leading global cause of death.[3] The National Outcomes Strategy for COPD estimated that 835,000 people living in the UK are currently diagnosed with COPD, with a further 2.2 million being undiagnosed.[4] COPD is the second most common cause of emergency hospital admission and is one of the most costly diseases in terms of acute hospital care in England.[4]

Budgeting of healthcare is often contingent upon the estimated burden of disease. Spirometry, the mainstay of lung function assessment, has been used in nationally-representative surveys to estimate the COPD burden in terms of prevalence, associated comorbidities, and mortality. Estimation of the disease burden has been hindered, however, by differences in methods, including different spirometric cut-offs.[5-8] Fixed thresholds (FTs) use cut-offs for lung function measurements (e.g., forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70) regardless of age, sex, height, and ethnicity.[9] An additional threshold for percent-of-predicted FEV_1 (expected for persons of a given age, sex, height and ethnicity) is also commonly used for severity classification. In contrast, a lower limit of normal (LLN) cut-off uses a statistical definition of abnormal/normal (e.g., below/above the lower 5th percentile of the distribution of age-, sex-, height-, and ethnic-specific FEV_1/FVC values from a healthy, lifelong non-smoking population).[10]

At present, applying FTs such as FEV_1/FVC <0.70 is the standard approach. However, the European Respiratory Society Task Force on epidemiology recently advocated using the LLN in epidemiological studies as FTs both overestimate airflow obstruction in older populations, due to the physiological reduction of FEV_1/FVC with age, and underestimate in young adults, compared with LLN.[11-16] The controversy over FT-versus-LLN thresholds is well-known and

has been fiercely debated with no signs of a consensus among expert groups being agreed.[17-21]

Partly as a result of this controversy, the COPD epidemiological database, within and across countries, shows heterogeneity in both definitions and consequential estimates of the disease burden.[5;22] Therefore, the primary objective of the present study was to compare the prevalence of 'potential' airflow obstruction according to FT- and LLN-thresholds in a representative sample of persons aged 40-95 years living in England and Wales: potential in the sense that the administration of bronchodilators to measure the extent of reversibility in airflow obstruction was not used. As a secondary aim, we compared the sensitivity of associations with risk factors including age, sex, smoking history, and socioeconomic position. Using the same variables, we also examined the characteristics associated with spirometry in connection with self-reported physician-diagnosed COPD.

METHODOLOGY

Study design and setting

Two nationally-representative samples, Wave 2 (2010-2012) of the UK Household Longitudinal Survey (UKHLS, 'Understanding Society') and the Health Survey for England (HSE) 2010, were pooled to increase sample size. Both surveys selected participants using stratified multi-stage probability sampling designs [23], with similar measurement protocols and specialist equipment for collecting spirometry.

Self-reported health information, risk factors and demographics was collected through face-to-face interviews, followed by a visit from a trained nurse during which lung function was measured. Response rates for the Wave 2 interview (among individuals issued) and nurse-visit (among eligible participants in the Wave 2 interview) were 61% and 59% respectively in UKHLS. In HSE 2010, interview (among the estimated total number of adults in sampled

households) and nurse-visit (adults in co-operating households) response rates were 59% and 57%. Sampling methods are described in detail elsewhere.[24-26] Ethical approval for the UKHLS was obtained from the Oxfordshire A Research Ethics Committee (10/H0604/2); approval for HSE 2010 was obtained from the Oxfordshire B Research Ethics Committee (09/H0605/73). Eligible participants gave written consent to participate in spirometry.

Questionnaire and procedures

Participants were excluded from spirometry for the following safety reasons: pregnancy; had in the last 3 months abdominal or chest surgery, a heart attack, detached retina or eye or ear surgery; admitted to hospital with a heart complaint in the preceding month; a resting pulse rate >120 beats/minute; or currently taking medications for the treatment of tuberculosis. Spirometry, without bronchodilator use, was conducted using NDD EasyOne PCC spirometers (NDD Medical Technologies, Zurich, Switzerland), a hand-held, battery-operated device that uses an ultrasonic sensor to measure airflow. Calibration of spirometers was checked with a 3l syringe prior to use the following day. Participants performed the manoeuvre in a sitting position wearing a nose-clip to prevent air leaks during testing. Systematic quality control procedures were used, summarised in a session grade based on the number of technically acceptable blows and their reproducibility. Sessions graded A (3 acceptable manoeuvres, 2 highest FVC and FEV_1 within 100 ml), B (3 acceptable manoeuvres, 2 highest FVC and FEV_1 within 150 ml), and C (2 or 3 acceptable manoeuvres within 200 ml) were considered good-quality. In HSE, 1-in-4 spirometry sessions were over-read by an experienced respiratory physiology consultant. Full details on measurement procedures are available elsewhere.[25;27]

The highest values for FEV_1 and for FVC, from at least 3 and up to 8 blows, were used. Age-, sex-, height-, and ethnic-specific predicted values and Z-scores (FEV_1, FVC and FEV_1/FVC)

were computed using the European Respiratory Society Global Lungs Initiative (GLI 2012, www.lungfunction.org) reference equations. These have been prepared by an international collaboration based on data spanning 26 countries from over 70,000 healthy individuals across four ethnic groups (Caucasian, African-American, and North- and South-East Asian), valid for persons aged 3-95 years [28;29] and have been shown to fit contemporary Australasian spirometric data.[30]

FT and LLN spirometric cut-offs

Using FTs, we applied the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [31], which was designed for use with post-bronchodilator spirometry: potential airflow obstruction was defined as $FEV_1/FVC < 0.70$ (FT). Disease stage was defined by the reduction in FEV_1 relative to percent-of-predicted values as follows: stage I ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ predicted); stage II ($FEV_1/FVC < 0.70$ and FEV_1 50-79% predicted); and stage III+ ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted).[32] Participants with $FEV_1/FVC \geq 0.70$ were defined as non-obstructed.

Using the lambda-mu-sigma method [33], participants with $FEV_1/FVC <$ LLN (below the lower 5th percentile of the distribution of Z-scores) were defined as obstructed (LLN). Disease stage was defined by FEV_1 relative to LLN as follows: stage I ($FEV_1/FVC <$ LLN and $FEV_1 \geq$ LLN), and stage II ($FEV_1/FVC <$ LLN and $FEV_1 <$ LLN). Participants with $FEV_1/FVC \geq$ LLN were defined as non-obstructed. The 5th percentile was chosen due to its established associations with respiratory symptoms and all-cause mortality.[34]

Physician-diagnosed COPD

In UKHLS, disease status was ascertained through questions asking "*has a doctor or other health professional ever told you that you have [disease]?"* Diagnosed COPD was defined as a positive response to either chronic bronchitis or emphysema. In HSE, diagnosed COPD was

defined as a positive response to the question "*did a doctor ever tell you that you had chronic bronchitis, emphysema or COPD?*"

Risk factors, measurements of lung function, and comorbidities

Key subgroups were defined by age (40-54, 55-64, 65-74, 75-95); sex; smoking status (current, former, never); pack-years of cigarette smoking (a cumulative total reflecting the amount and duration of consumption, with 1 pack-year equating to an average of 20 cigarettes smoked/day for 1 year); and socioeconomic position, defined by the National Statistics Socio-Economic Classification (NS-SEC), grouped into professional, intermediate, and routine occupations.

Three lung function measurements (FEV_1, FVC, and FEV_1/FVC) on a continuous scale were expressed as percent-of-predicted values. Additional variables included current use of respiratory medicine; area of residence, defined as urban or rural, used as a possible proxy for traffic-related air pollution; body mass index (BMI: weight in kilograms divided by the square of height in metres), grouped into normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2); diagnosed diabetes; poor self-rated health; and reported cardiovascular disease (stroke, angina, myocardial infarction). In HSE, participants were asked to name any long-standing illnesses: respiratory diseases were identified using *International Classification of Diseases, Tenth Revision* codes J00 to J99. Standard questions in the HSE covered a range of respiratory symptoms including wheeze, dyspnoea, chronic cough, and phlegm. Presence of respiratory symptoms was defined as usually coughing first thing in the morning, for at least 3 months a year, and bringing up phlegm from the chest most days for 3 consecutive months in a year. In the HSE, participants with some limitation of activity due to breathlessness during daily life were identified by a score of 3+ on the Medical Research Council (MRC) dyspnoea scale, a validated method of categorising

patients with COPD in terms of their disability.[35] Exposure to passive smoking in the HSE was measured by reported number of weekly hours currently exposed to cigarette smoke (0, 1-9, and ≥10 hours).

Statistical analyses

A lower age limit of 40 years was used due to the low prevalence of non-asthma airflow obstruction in the youngest age-groups.[36] As bronchodilators were not used, we excluded participants who reported diagnosed asthma.[34;37-39] Five sets of analyses were conducted across the categories of diagnosed COPD, FT, and LLN. First, participants' characteristics (demographics, health information, risk factors, comorbidities and percent-of-predicted FEV_1, FVC, and FEV_1/FVC) were summarised as means, accompanied by standard deviations, or as counts accompanied by percentages. Participants were counted under each relevant definition. Participants with/without obstruction were compared using the χ^2 test and analysis of variance for categorical and continuous variables respectively.

Secondly, prevalence estimates were computed for a subset of socio-demographic variables defined by age, sex, smoking status, pack-years of cigarette smoking, and NS-SEC. Thirdly, in the absence of a gold standard, we calculated the sensitivity and specificity of each spirometric criterion, using the alternative cut-off as the reference standard.[40]

Fourth, regression analyses were performed using age, sex, pack-years of smoking, and NS-SEC as independent variables with airflow obstruction as outcome. Current smoking status could not be entered in the same model as pack-years due to significant collinearity. The dependent variable based on FTs had 4 categories: non-obstructed, stage I, stage II, and stage III+. The LLN-derived outcome had 3 categories: non-obstructed, stage I, and stage II. In each case, multinomial logistic regressions were used to estimate relative risk ratios (RRRs), with non-obstructed as the reference category. Diagnosed COPD was analysed as a binary

dependent variable (not reported/reported): logistic regression was therefore used to estimate odds ratios (ORs). The overall association with categorical independent variables was computed using the adjusted Wald test. The likelihood-ratio test was used to estimate the statistical significance of interaction terms: non-significant terms were excluded, and models refitted with only the main effects.

Fifth, to examine risk factors associated with possible under-diagnosis, a four-category outcome variable was created combining diagnosed COPD and spirometric criteria as follows: (1) neither diagnosed nor spirometrically-defined obstruction; (2) physician-diagnosed COPD but no obstructive spirometry; (3) spirometrically-defined but no diagnosed COPD; and (4) both diagnosed and obstructive spirometry.[41] FT and LLN cut-offs were analysed separately. RRRs generated from multinomial logistic regressions were used to examine associations between the same set of risk factors listed above and the composite dependent variable.

Participants with missing values on covariates were excluded from relevant analyses. Tests of statistical significance were based on two-sided probability (P<0.05). Dataset preparation was performed in SPSS 20.0 (SPSS IBM Inc., Chicago, Illinois, USA), Stata 13.1 (StataCorp, College Station, Texas, USA) and R (version 3.0.3; R Foundation, www.r-project.org). Analysis was conducted in Stata accounting for the complex design of both surveys, using the appropriate weighting variables and Primary Sampling Units. Both datasets are available via the UK Data Service (www.ukdataservice.ac.uk).

Sensitivity analyses

Analyses were initially undertaken excluding participants with reported diagnosed asthma and then repeated including those with asthma. In accordance with the UK National Institute for Health and Care Excellence (NICE) criteria [42], comparisons between FT and LLN were

rerun defining only the subset of FT participants with FEV_1 <80% predicted (i.e., stage II+) as having obstructed airflow.

RESULTS

The analytical sample comprised 7879 participants (5936 and 1943 from UKHLS and HSE respectively) aged 40-95 years, who resided in England and Wales, did not report diagnosed asthma, had valid values of height and ethnicity, and provided good-quality spirometry. Response flowcharts for the UKHLS and HSE are provided in Figures **S1** and **S2** (online supplementary appendix) respectively. Excluded participants were more likely to be older, engaged in routine occupations, and self-report respiratory symptoms (data not shown).

Descriptive characteristics of the analytical sample according to physician-diagnosed COPD, FT, and LLN are shown as supplementary data (Tables **S1-S2**). Overall, 46.8% of participants were male, with mean age 57.6 years (SD 12.3), 16.6% were current smokers, 4.6% had >50 pack-years of cigarette smoking, and 36.5% were engaged in professional occupations. 12 (0.1%) and 265 (3.2%) participants had missing values for pack-years and NS-SEC respectively. The prevalence of reported diagnosed COPD was similar between the sexes (P=0.349), but was higher for men using FT and LLN (both P<0.001). Participants with diagnosed COPD/obstructive spirometry were more likely to be older, currently smoke, have higher pack-years of smoking, and be engaged in routine occupations (all P<0.001). Prevalence of diagnosed COPD was higher in HSE *vs.* UKHLS (P<0.001), but survey-specific prevalence was similar for FT and for LLN. Participants with diagnosed COPD/obstructive spirometry were more likely to report respiratory symptoms and disease, current use of respiratory medications, cardiovascular disease, breathlessness, poor self-rated health and have, on average, lower (percent-of-predicted) values of FEV_1, FVC and FEV_1/FVC. The prevalence of respiratory symptoms was 13.7%, 10.2%, and 11.3% among participants classed as having airflow obstruction according to diagnosed COPD, FT, and LLN respectively; prevalence of having a score of 3+ on the MRC dyspnoea scale was 34.8%, 12.3% and 15.9%.

Prevalence of airflow obstruction

The prevalence of airflow obstruction was 2.8%, 22.2%, and 13.1% using diagnosed COPD, FT, and LLN respectively (**Table 1**). Using FTs, 11.6%, 8.9%, and 1.7% of participants were classed as stage I, stage II, and stage III+ respectively. LLN-derived obstruction was 6.6% (stage I) and 6.4% (stage II). For most subgroups, prevalence was highest for FT and lowest for diagnosed COPD, with LLN falling in-between. The gap in prevalence between FT and LLN increased in older age-groups. Prevalence among participants aged 40-54 years was 11.9% and 10.7% using FT and LLN respectively. Prevalence among participants aged 75-95 years was 45.0% and 17.2%.

Table 2 shows estimates of sensitivity and specificity for FT and LLN, using the alternative spirometric cut-off as the reference standard. When using LLN as reference, specificity - the percentage of participants classed as non-obstructed using LLN identified as non-obstructed using FT – decreased from 94.9% amongst participants aged 40-64 years to 74.4% amongst those aged 65-95 years.

Multivariate analyses of airflow obstruction

Table 3 shows the significant risk factors for diagnosed COPD, and the FT- and LLN-disease stage classifications (non-obstructed as reference category). For diagnosed COPD, the significant interaction between sex and age-group (P=0.022) suggested no difference in odds between the sexes among participants aged 40-64 years, but higher odds among men aged 65-95 years. Using FTs, being male was associated with a significantly increased risk of airflow obstruction: RRR 1.35 (95% CI: 1.16-1.58), RRR 1.35 (1.12-1.63), and RRR 1.72 (1.08-2.76) for stages I, II, and III+ respectively. In contrast, sex differences were not significant using LLN: RRR 1.07 (0.88-1.31) for stage I, and RRR 1.20 (0.96-1.50) for stage II.

Odds of diagnosed COPD increased significantly with age only in men (P=0.022 for the interaction term). Using non-obstruction as reference, RRRs increased significantly with age when using FTs (P<0.001 for each stage). The age-related difference using LLN was more marked for stage II (P=0.492 and P<0.001 for stages I and II, respectively). A dose-related increased risk with pack-years of cigarette smoking was observed across each definition (P<0.001). The difference between NS-SEC levels was more marked with diagnosed COPD (P=0.012) and the most restrictive FT- and LLN-categories (FT: P=0.002 stage III+; LLN: P<0.001 stage II).

Combination of diagnosed COPD and spirometric cut-offs

The significant risk factors for the two four-category outcome variables created as a composite of diagnosed COPD and obstructive spirometry are shown in **Table 4**. Relative to the reference category (neither diagnosed nor spirometrically-defined obstruction), the risk of having obstructed airflow using diagnosed COPD but no obstructive spirometry was significantly lower in men using either spirometric criterion (FT: RRR 0.53 (95% CI: 0.32-0.87); LLN: RRR 0.56 (0.35-0.89)). The risk of having obstructed airflow using spirometry but with no diagnosed COPD – thereby indicating possible under-diagnosis - was significantly higher in men, and in older age-groups, when using FT but not LLN. For both spirometric criterion, increases in risk with increasing pack-years of cigarette smoking, relative to the reference, was consistent across combinations of COPD/obstructive spirometry; the difference between NS-SEC levels was more marked for obstructive spirometry.

Sensitivity analyses

Repeating analyses by including 1183 participants with reported diagnosed asthma increased prevalence of diagnosed COPD, FT and LLN by 2-3 percentage points (Figure **S3**, online

supplementary appendix), but led to similar patterns of association with risk factors. Diagnosed asthma was a strong predictor of diagnosed COPD and obstructive spirometry (P<0.001, data not shown).

Restricting FT-defined obstruction to the subset of FT participants with FEV_1 <80% predicted (i.e., stage II+) more than halved the FT-derived prevalence (22.2% *vs*. 10.6%). Amongst participants aged 65-95 years, specificity using LLN as the reference standard was 74.4% and 91.1% for FT and FT stage II+ respectively (**Table 2**). Patterns of association with risk factors using FT stage II+ was similar to those shown for FT.

DISCUSSION

Consistent estimation of the COPD burden has been hindered by differences in methods, including disagreement among expert groups over the choice of FT-versus-LLN spirometric cut-offs.[5-8] In this study, we combined two nationally-representative general population surveys, with standardised protocols and objective lung function measurements, to evaluate the impact of different definitions on the prevalence of potential airflow obstruction, and its associations with key risk factors. Participants with diagnosed COPD/obstructive spirometry were more likely to be older, currently smoke, have higher pack-years of cigarette smoking, be in lower socioeconomic groups, and report the presence of respiratory symptoms, cardiovascular disease, breathlessness, and poor self-rated health. Among persons aged 40-95 years without physician-diagnosed asthma, prevalence was 2.8%, 22.2%, and 13.1%, according to diagnosed COPD, FT, and LLN respectively. The gap in prevalence between FT and LLN increased in older age-groups. When using LLN as the reference standard, specificity for FT decreased from 94.9% amongst participants aged 40-64 years to 74.4% amongst participants aged 65-95 years, corresponding to false-positive rates of 5.1% and 25.6% respectively. Sex differences in the risk of obstructed airflow, after adjustment for potential confounders, was sensitive to spirometric criteria, being higher in men for FT, compared with no difference using LLN.

Strengths and limitations

Analyses were based on nationally-representative, random samples of the general population, with spirometry conducted by well-trained and supervised nurses using standardised protocols and modern, validated equipment. Combining two datasets ensured a sufficient sample size to estimate prevalence, and infer valid statistical associations. Predicted values and Z-scores were defined using the recently developed European Respiratory Society GLI 2012 reference equations [28], facilitating inclusion of older participants, non-white populations

and comparability with international studies. Our study has a number of limitations. Reversibility in airflow obstruction could not be assessed due to bronchodilators not being used. Spirometry-based prevalence, therefore, may be overestimated. Analysis of the National Health and Nutrition Examination Survey (NHANES) 2007-2010 showed that FT- and LLN-prevalence estimates among US adults aged 40-79 years decreased, in relative terms, by approximately one-third after administration of bronchodilators.[43] Although recent guidelines from the National Institute for Health and Care Excellence [44] and European Respiratory Society [13] recommend use of post-bronchodilator spirometry to confirm the presence of airflow obstruction, debate continues over its use in epidemiological settings, with the arguments against including ethical issues such as possible side-effects and contraindications.[45] Potential misclassification of disease status through bronchodilators not being used was reduced by excluding participants with physician-diagnosed asthma. Some participants in the analytical sample, however, may be undiagnosed asthmatics. On the other hand, the disease burden may be underestimated through excluding participants with poor-quality spirometry. Participation in spirometry, and achievement of good-quality standards among participants with any spirometry data, was higher among participants of younger age, engaged in professional/managerial occupations, non-smokers, and with no self-reported physician-diagnosed chronic bronchitis, emphysema or COPD. Lower survey participation rates amongst socio-demographic groups at higher risk of airflow obstruction (e.g., older persons, lower socioeconomic groups) would also have led to an underestimation of true prevalence. These limitations, however, are unlikely to affect comparisons across definitions, but may have led to an underestimate of risk associations.

Comparisons with previous studies

Earlier analyses of Health Survey for England data [37;39;46] used older sets of reference equations [47;48] applicable only to white and younger populations. Nevertheless, estimates of

prevalence and their substantive conclusions of higher prevalence using FT-versus-LLN, with a widening gap in prevalence in older age-groups, and sex differences when using FT but not LLN were similar to ours: confirming findings reported in the US [43], Europe [49], Korea [16], internationally [12], and in recent literature reviews [6;50]. A further strength of our study was the wide range of clinically-relevant conditions examined in the context of disease staging, with higher prevalence of self-reported respiratory symptoms, respiratory- and cardiovascular-disease, breathlessness, and poor self-rated health among participants in the most restrictive FT- and LLN-categories, confirming similar findings in the US.[51;52] Whilst recent guidelines [13;44;53] recommend adopting multidimensional definitions of respiratory disease, our study outcomes were defined only using spirometry. While we acknowledge the merits of a multidimensional approach, and agree that neither spirometric cut-off is able to fully characterise the complex diagnostic features of COPD [54], our primary aim was to use up-to-date survey data to evaluate differences in prevalence according to FT- and LLN-thresholds, to provide baseline data for monitoring purposes in the UK, and promote comparability with international studies. Current recommendations regarding symptom criteria are less specific than those for spirometry. We chose, therefore, to examine the associations between disease staging assessed only using spirometry and presence of respiratory symptoms, rather than broaden the definition of disease.

Implications

Recent UK studies used administrative primary-care databases to report the number of diagnosed and treated patients, thereby missing undiagnosed cases. Such studies have reported prevalence below 2%.[55;56] The disparity in prevalence from clinical-versus-epidemiological studies led to the development of the COPD prevalence model, with the HSE 2001 used as input data, to more accurately estimate prevalence.[57] In accordance with

National Institute for Health and Care Excellence criteria, COPD is currently defined in the model as FT stage II+ (FEV_1/FVC <0.70 and FEV_1 <80% predicted), with the logistic regression models showing sharp increases with age and a modifying effect of gender.[58;59] Similar to the findings reported by Jordan et al. [37], our study shows that the strength of association between risk factors and airflow obstruction varies according to spirometric criterion, with age- and sex-differences in risk being more marked for FT, and for FT stage II+, than LLN. In the absence of agreement among expert groups, policy-makers, clinicians, and researchers building the COPD epidemiological database, it is important to appreciate the sensitivity of estimates of the disease burden, and its distribution across socio-demographic groups, to differences in methods, including spirometric cut-offs.

The prevalence of reported physician-diagnosed COPD in our study was 2.8%, considerably lower than spirometry-based estimates, possibly indicating considerable under-recognition by both participants and physicians. Using the most restricted definitions, prevalence of reported diagnosed COPD among participants with obstructive spirometry was 30.2% (FT stage III+) and 14.7% (LLN stage II). Similar low rates of physician-diagnosis among participants meeting spirometric criteria have been reported in New Zealand.[60]

Conclusion

In summary, we have enhanced the COPD epidemiological database by evaluating the impact of different definitions on the prevalence of potential airflow obstruction and its associations with key risk factors and comorbidities. With no gold standard currently available, longitudinal studies examining differences in unscheduled hospital admissions and risk of death between FT and LLN may inform the choice as to the best way to include spirometry data in multidimensional assessments of airflow obstruction in both clinical and epidemiological settings.

Abbreviations: COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FT, fixed thresholds; GLI, Global Lungs Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HSE, Health Survey for England; LLN, lower limit of normal; NICE, National Institute for Health and Care Excellence; UKHLS, United Kingdom Household Longitudinal Survey

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Data sharing: Both datasets are available via the UK Data Service (www.ukdataservice.ac.uk). Statistical code is available from the corresponding author at s.scholes@ucl.ac.uk.

Contributors: All authors contributed to the design of the analysis. SS analysed the data and wrote the first draft of the manuscript. All authors contributed to revising the final draft. SS is the study guarantor. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Table 1 Prevalence of Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

		Diagnosed-COPD[b]	Fixed Thresholds[c]				Lower Limit of Normal[d]		
			Obstructed	stage I	stage II	stage III+	Obstructed	stage I	stage II
	n	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
All	7879	2.8 (2.3-3.2)	22.2 (21.2-23.2)	11.6 (10.9-12.4)	8.9 (8.2-9.6)	1.7 (1.3-2.0)	13.1 (12.2-13.9)	6.6 (6.0-7.3)	6.4 (5.8-7.0)
Sex:									
Males	3335	3.0 (2.3-3.6)	26.3 (24.8-27.9)	13.2 (12.1-14.4)	10.7 (9.6-11.8)	2.4 (1.8-3.0)	15.0 (13.7-16.4)	7.2 (6.2-8.1)	7.9 (6.9-8.9)
Females	4544	2.6 (2.0-3.1)	18.6 (17.4-19.9)	10.2 (9.2-11.2)	7.4 (6.5-8.2)	1.0 (0.7-1.4)	11.3 (10.3-12.3)	6.2 (5.4-6.9)	5.1 (4.4-5.9)
Age-group:									
40-54	3472	1.7 (1.3-2.2)	11.9 (10.7-13.1)	7.0 (6.1-7.9)	4.6 (3.8-5.4)	0.3 (0.1-0.6)	10.7 (9.6-11.9)	6.7 (5.7-7.6)	4.1 (3.3-4.9)
55-64	2072	3.4 (2.5-4.2)	24.2 (22.2-26.1)	12.6 (11.1-14.1)	9.5 (8.1-10.9)	2.0 (1.4-2.7)	14.2 (12.6-15.8)	6.5 (5.4-7.7)	7.7 (6.4-8.9)
65-74	1557	3.9 (2.8-5.0)	32.6 (30.1-35.1)	16.5 (14.6-18.5)	12.9 (11.1-14.6)	3.2 (2.1-4.2)	15.0 (13.0-17.0)	6.4 (5.1-7.7)	8.6 (7.0-10.2)
75-95	778	3.9 (2.0-5.8)	45.0 (41.1-48.8)	21.1 (18.0-24.2)	19.6 (16.6-22.6)	4.3 (2.5-6.0)	17.2 (14.2-20.1)	7.2 (5.2-9.2)	9.9 (7.6-12.3)
Smoking status:									
Current	1198	4.7 (3.5-6.0)	37.0 (34.1-39.9)	14.5 (12.3-16.6)	18.2 (15.9-20.6)	4.2 (3.0-5.4)	29.8 (27.0-32.6)	13.5 (11.3-15.7)	16.2 (14.0-18.5)
Ex-regular	2547	3.6 (2.7-4.5)	26.8 (24.9-28.7)	14.1 (12.7-15.6)	10.5 (9.2-11.8)	2.2 (1.5-2.9)	14.5 (13.0-16.1)	7.2 (6.0-8.3)	7.4 (6.2-8.5)
Never	4134	1.6 (1.2-2.0)	14.7 (13.5-15.9)	9.2 (8.2-10.1)	5.0 (4.3-5.7)	0.5 (0.2-0.9)	6.8 (5.9-7.7)	4.1 (3.5-4.8)	2.7 (2.1-3.3)
Pack-years[e]:									
0-0.9	4299	1.6 (1.2-2.0)	14.8 (13.6-16.0)	9.3 (8.4-10.3)	5.0 (4.3-5.7)	0.5 (0.2-0.8)	6.7 (5.9-7.6)	4.1 (3.5-4.7)	2.6 (2.0-3.2)
1-19.9	1905	2.3 (1.5-3.1)	22.3 (20.3-24.3)	12.9 (11.3-14.5)	7.5 (6.2-8.8)	1.9 (1.1-2.6)	13.4 (11.7-15.1)	7.6 (6.3-8.9)	5.8 (4.6-7.0)
20-49.9	1318	5.0 (3.6-6.5)	36.8 (34.0-39.6)	15.7 (13.5-17.9)	18.1 (15.9-20.4)	2.9 (2.0-3.9)	25.4 (22.8-27.9)	11.6 (9.5-13.6)	13.8 (11.8-15.8)
50+	345	10.5 (7.0-14.1)	53.7 (48.0-59.4)	16.0 (12.0-20.1)	28.0 (23.0-32.9)	9.7 (6.2-13.2)	39.3 (33.5-45.0)	12.4 (8.7-16.2)	26.9 (21.6-32.1)
NS-SEC[e]:									
Professional	3050	1.9 (1.4-2.4)	17.1 (15.7-18.5)	10.4 (9.3-11.6)	5.7 (4.9-6.5)	1.0 (0.6-1.4)	9.1 (8.0-10.2)	5.6 (4.6-6.5)	3.6 (2.9-4.3)
Intermediate	1859	2.3 (1.6-3.0)	21.9 (19.9-23.9)	12.5 (10.9-14.1)	8.4 (7.0-9.7)	1.1 (0.5-1.7)	12.0 (10.5-13.5)	6.6 (5.4-7.8)	5.4 (4.3-6.5)
Routine	2705	4.0 (3.1-4.8)	26.6 (24.7-28.5)	11.6 (10.3-12.9)	12.3 (10.9-13.7)	2.7 (2.0-3.5)	17.4 (15.8-19.1)	7.7 (6.6-8.9)	9.7 (8.4-11.0)

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in 1 second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the lower 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts are unweighted; prevalence estimates were weighted.
[b] HSE: reported diagnosed COPD, bronchitis or emphysema; UKHLS: diagnosed bronchitis or emphysema.
[c] FTs: Obstruction (FT): $FEV_1/FVC < 0.70$. Staging classification: stage I ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ of predicted); stage II ($FEV_1/FVC < 0.70$ and FEV_1 50-79% of predicted); stage III+ ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ of predicted).
[d] LLN: Obstruction (LLN): $FEV_1/FVC <$ LLN. Staging classification: stage I ($FEV_1/FVC <$ LLN and $FEV_1 >$ LLN); stage II ($FEV_1/FVC <$ LLN and $FEV_1 <$ LLN).
[e] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table 2 Sensitivity and Specificity of Fixed Thresholds and Lower Limit of Normal Spirometric Criteria by Age-group, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)

	40-64 (*n*=5544)	**65-95** (*n*=2335)	**40-64** (*n*=5544)	**65-95** (*n*=2335)
	FT using LLN as reference standard		**LLN using FT as reference standard**	
False positives, (%)	5.1	25.6	0.4	0.0
False negatives, (%)	2.5	0.0	28.0	57.6
Sensitivity	0.975	1.000	0.720	0.424
Specificity	0.949	0.744	0.996	1.000
PPV	0.720	0.424	0.975	1.000
NPV	0.996	1.000	0.949	0.744
Kappa coefficient	0.801	0.479	0.801	0.479
Likelihood ratio positive	18.98	3.90	200.65	N/A
Likelihood ratio negative	0.027	0.000	0.281	0.576
	FT (stage II+) using LLN as reference standard		**LLN using FT (stage II+) as reference standard**	
False positives, (%)	1.3	8.9	6.3	5.2
False negatives, (%)	49.2	26.7	16.0	39.1
Sensitivity	0.508	0.733	0.840	0.609
Specificity	0.987	0.911	0.937	0.948
PPV	0.840	0.609	0.508	0.733
NPV	0.937	0.948	0.987	0.911
Kappa coefficient	0.597	0.596	0.597	0.596
Likelihood ratio positive	38.82	8.28	13.27	11.67
Likelihood ratio negative	0.499	0.292	0.170	0.412

Abbreviations used: FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NPV, negative predictive value; PPV, positive predictive value; UKHLS, United Kingdom Household Longitudinal Survey.

Table 3 Results of Logistic and Multinomial Logistic Regressions for Reported Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria Among Persons Aged 40-95 years, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

Characteristics		Diagnosed-COPD[b]	Fixed Thresholds[c]			Lower Limit of Normal[d]	
			Non-obstructed as reference			Non-obstructed as reference	
			stage I	stage II	stage III+	stage I	stage II
	N	OR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Sex:							
Females[e]	4372	1.00	1.00	1.00	1.00	1.00	1.00
Males	3231	0.60 (0.34-1.05)	1.35 (1.16-1.58)	1.35 (1.12-1.63)	1.72 (1.08-2.76)	1.07 (0.88-1.31)	1.20 (0.96-1.50)
P-value		*0.075*	*<0.001*	*0.002*	*0.024*	*0.503*	*0.107*
Age-group:							
40-54[e]	3416	1.00	1.00	1.00	1.00	1.00	1.00
55-64	2022	1.66 (1.07-2.58)	2.00 (1.63-2.45)	2.13 (1.65-2.73)	6.05 (2.82-12.99)	0.92 (0.72-1.18)	1.57 (1.20-2.06)
65-74	1451	0.96 (0.54-1.70)	2.85 (2.30-3.53)	3.01 (2.32-3.89)	10.11 (4.55-22.49)	0.83 (0.63-1.09)	1.56 (1.16-2.12)
75+	714	1.20 (0.39-3.70)	4.72 (3.66-6.07)	6.67 (5.00-8.90)	22.26 (9.45-52.44)	1.06 (0.74-1.51)	2.20 (1.52-3.17)
P-value		*0.104*	*<0.001*	*<0.001*	*<0.001*	*0.492*	*<0.001*
Pack-years[f]:							
0-0.9[e]	4165	1.00	1.00	1.00	1.00	1.00	1.00
1-19.9	1835	1.38 (0.88-2.17)	1.61 (1.34-1.93)	1.66 (1.29-2.15)	3.82 (1.80-8.14)	1.94 (1.51-2.49)	2.22 (1.58-3.12)
20-49.9	1269	2.91 (1.91-4.45)	2.30 (1.86-2.85)	4.56 (3.64-5.72)	5.91 (2.81-12.45)	3.39 (2.61-4.41)	5.43 (3.98-7.41)
50+	334	5.64 (3.45-9.22)	2.34 (1.63-3.35)	6.83 (4.85-9.63)	17.27 (7.88-37.84)	4.50 (2.96-6.84)	11.20 (7.59-16.52)
P-value		*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
NS-SEC[f]:							
Professional[e]	3047	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	1855	1.03 (0.68-1.58)	1.18 (0.97-1.45)	1.34 (1.04-1.72)	1.01 (0.51-2.00)	1.14 (0.88-1.48)	1.35 (0.99-1.85)
Routine	2701	1.61 (1.13-2.31)	1.07 (0.89-1.29)	1.82 (1.47-2.26)	2.30 (1.36-3.88)	1.28 (1.01-1.63)	2.18 (1.67-2.85)
P-value		*0.012*	*0.246*	*<0.001*	*0.002*	*0.123*	*<0.001*
Sample:							
UKHLS[e]	5675	1.00	1.00	1.00	1.00	1.00	1.00
HSE	1928	2.22 (1.60-3.07)	0.95 (0.79-1.14)	0.97 (0.79-1.20)	0.99 (0.62-1.59)	1.05 (0.82-1.33)	0.99 (0.77-1.26)
P-value		*<0.001*	*0.587*	*0.798*	*0.967*	*0.716*	*0.913*
Males × age-group:							
40-54[e]	1319	1.00	-	-	-	-	-

55-64	876	1.16 (0.54-2.45)	-	-	-	-	-
65-74	664	3.21 (1.40-7.39)	-	-	-	-	-
75+	372	2.61 (0.67-10.22)	-	-	-	-	-
P-value		*0.022*	-	-	-	-	-

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; OR, odds ratios; RRR; relative risk ratios; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts are unweighted; ORs and RRRs were weighted.
[b] HSE: reported diagnosed COPD, bronchitis or emphysema; UKHLS: diagnosed bronchitis or emphysema.
[c] FTs: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% of predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% of predicted); stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% of predicted). Reference category: FEV_1/FVC ≥0.70.
[d] LLN: stage I (FEV_1/FVC <LLN and FEV_1 >LLN); stage II (FEV_1/FVC <LLN and FEV_1 <LLN). Reference category: FEV_1/FVC ≥LLN.
[e] Reference category.
[f] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table 4 Results of Multinomial Logistic Regressions for Combined Outcome Variable Based on Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria Among Persons aged 40-95 years, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-12)[a]

Characteristics		Fixed Thresholds[b]			Lower Limit of Normal[c]		
		Neither diagnosed nor obstructive spirometry as reference			Neither diagnosed nor obstructive spirometry as reference		
		Diagnosed alone	Obstructive spirometry alone	Diagnosed and obstructive spirometry	Diagnosed alone	Obstructive spirometry alone	Diagnosed and obstructive spirometry
	n	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)	RRR (95% CI)
Sex:							
Females[d]	4372	1.00	1.00	1.00	1.00	1.00	1.00
Males	3231	0.49 (0.31-0.79)	1.31 (1.16-1.49)	2.23 (1.34-3.71)	0.52 (0.34-0.81)	1.05 (0.90-1.23)	2.15 (1.25-3.71)
P-value		*0.003*	*<0.001*	*0.002*	*0.004*	*0.543*	*0.006*
Age-group:							
40-54[d]	3416	1.00	1.00	1.00	1.00	1.00	1.00
55-64	2022	1.26 (0.76-2.09)	2.08 (1.76-2.46)	4.06 (2.11-7.79)	1.34 (0.83-2.16)	1.09 (0.90-1.33)	2.91 (1.49-5.68)
65-74	1451	1.47 (0.84-2.55)	3.05 (2.56-3.63)	4.78 (2.38-9.57)	1.27 (0.74-2.15)	1.02 (0.82-1.27)	3.12 (1.53-6.36)
75+	714	1.95 (0.69-5.51)	5.89 (4.76-7.29)	7.55 (3.35-17.02)	1.60 (0.67-3.81)	1.42 (1.08-1.87)	3.47 (1.43-8.40)
P-value		*0.388*	*<0.001*	*<0.001*	*0.535*	*0.085*	*<0.001*
Pack-years[e]:							
0-0.9[d]	4165	1.00	1.00	1.00	1.00	1.00	1.00
1-19.9	1835	1.08 (0.61-1.92)	1.67 (1.42-1.96)	2.84 (1.30-6.23)	1.16 (0.68-2.00)	2.02 (1.63-2.50)	2.58 (1.10-6.01)
20-49.9	1269	3.05 (1.68-5.54)	3.18 (2.70-3.74)	6.70 (3.35-13.40)	2.98 (1.72-5.16)	4.23 (3.44-5.20)	5.74 (2.70-12.20)
50+	334	3.94 (1.70-9.13)	4.15 (3.13-5.49)	18.50 (8.41-40.70)	3.87 (1.81-8.29)	6.83 (4.98-9.37)	17.23 (7.37-40.28)
P-value		*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
NS-SEC[e]:							
Professional[d]	3047	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	1855	0.76 (0.45-1.30)	1.20 (1.02-1.41)	1.84 (0.87-3.87)	0.83 (0.50-1.40)	1.19 (0.97-1.47)	1.57 (0.72-3.44)
Routine	2701	0.93 (0.59-1.48)	1.31 (1.12-1.53)	3.65 (1.89-7.06)	1.08 (0.70-1.67)	1.54 (1.27-1.87)	3.37 (1.70-6.68)
P-value		*0.612*	*0.002*	*<0.001*	*0.632*	*<0.001*	*<0.001*
Sample:							
UKHLS[d]	5675	1.00	1.00	1.00	1.00	1.00	1.00
HSE	1928	2.38 (1.54-3.69)	0.94 (0.81-1.09)	1.92 (1.21-3.05)	2.21 (1.46-3.35)	0.96 (0.79-1.16)	2.13 (1.31-3.48)
P-value		*<0.001*	*0.420*	*0.006*	*<0.001*	*0.664*	*0.002*

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; OR, odds ratios; RRR; relative risk ratios; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts unweighted; RRRs estimated using survey weights.
[b] FTs: Obstruction (FT): $FEV_1/FVC < 0.70$. Diagnosed COPD: HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[c] LLN: Obstruction (LLN): $FEV_1/FVC <$ LLN. Diagnosed COPD: HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[d] Reference category.
[e] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

SUPPLEMENTARY DATA

Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

Authors: Shaun Scholes *research associate*,[1*] Alison Moody *research associate*,[1] Jennifer S Mindell *clinical senior lecturer* [1]

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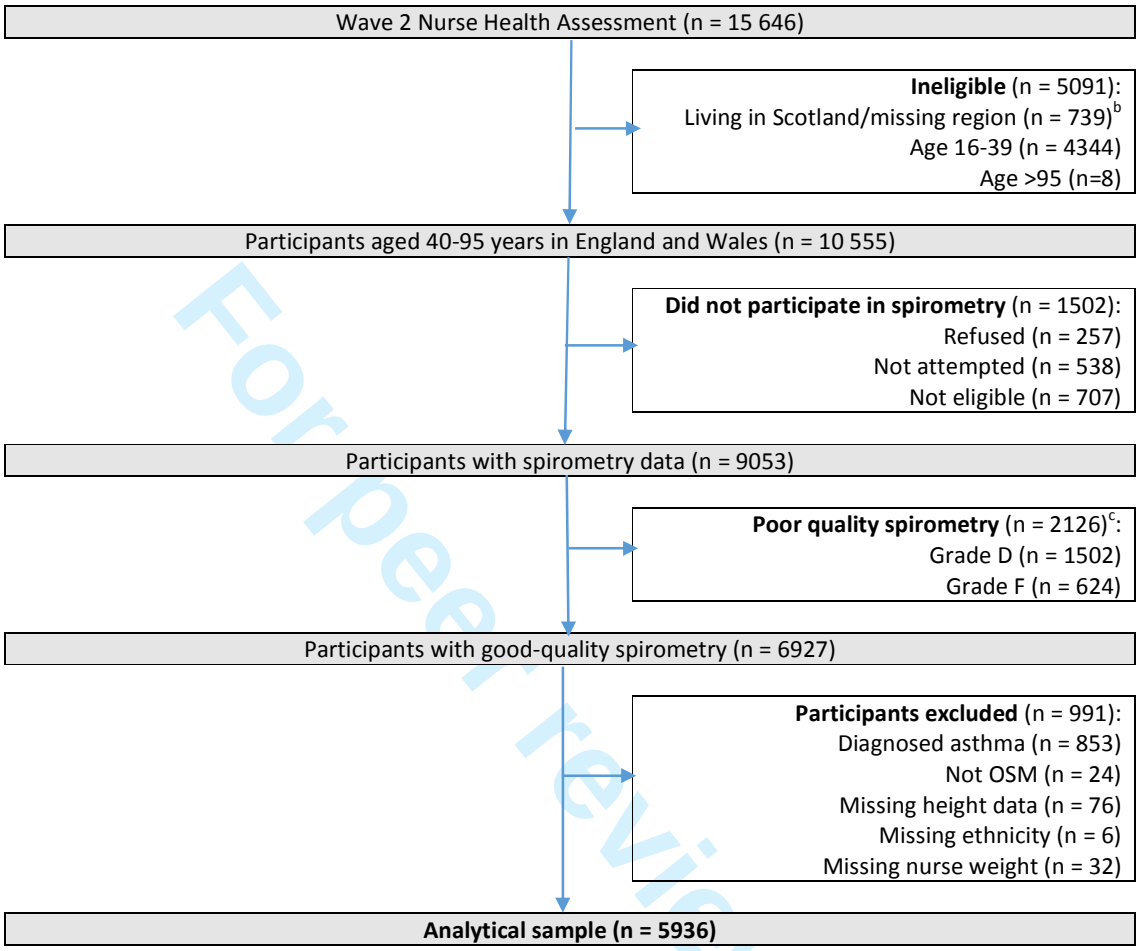
Figure S1 Response Flowchart for Wave 2 of UK Household Longitudinal Survey 2010-2012[a]



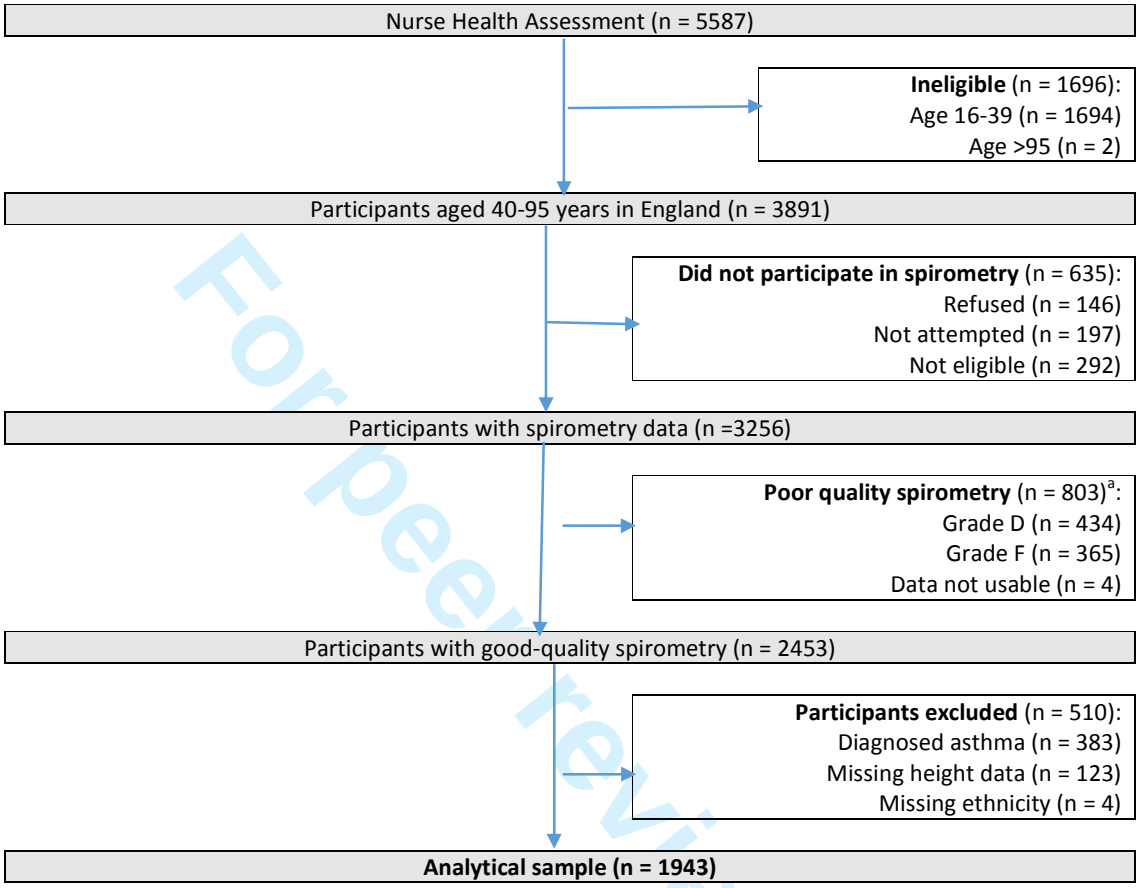
[a] Detailed flow diagram of participation in the Wave 2 Nurse Health Assessment can be found in McFall *et al*.

[b] Lung function measurements in UKHLS were conducted with two different devices: in England and Wales, the electronic NDD Easy on-PCC spirometer (NDD Medical Technologies, Zurich, Switzerland), and in Scotland the Vitalograph Escort (Vitalograph, Buckingham, UK). For this reason, UKHLS residents living in Scotland were excluded from the analytical sample.

[c] Quality criteria for spirometry sessions were as follows (Grades A-C required for inclusion in analytical sample):

Grade	Number of acceptable forced expiratory manoeuvres	Additional criteria
A	At least three	Two highest FVC and FEV_1 within 100 ml
B	At least three	Two highest FVC and FEV_1 within 150 ml
C	At least two	Two highest FVC and FEV_1 within 200 ml
D	Only one	Or best two FEV_1 or FVC were not within 200 ml
F	None	N/A

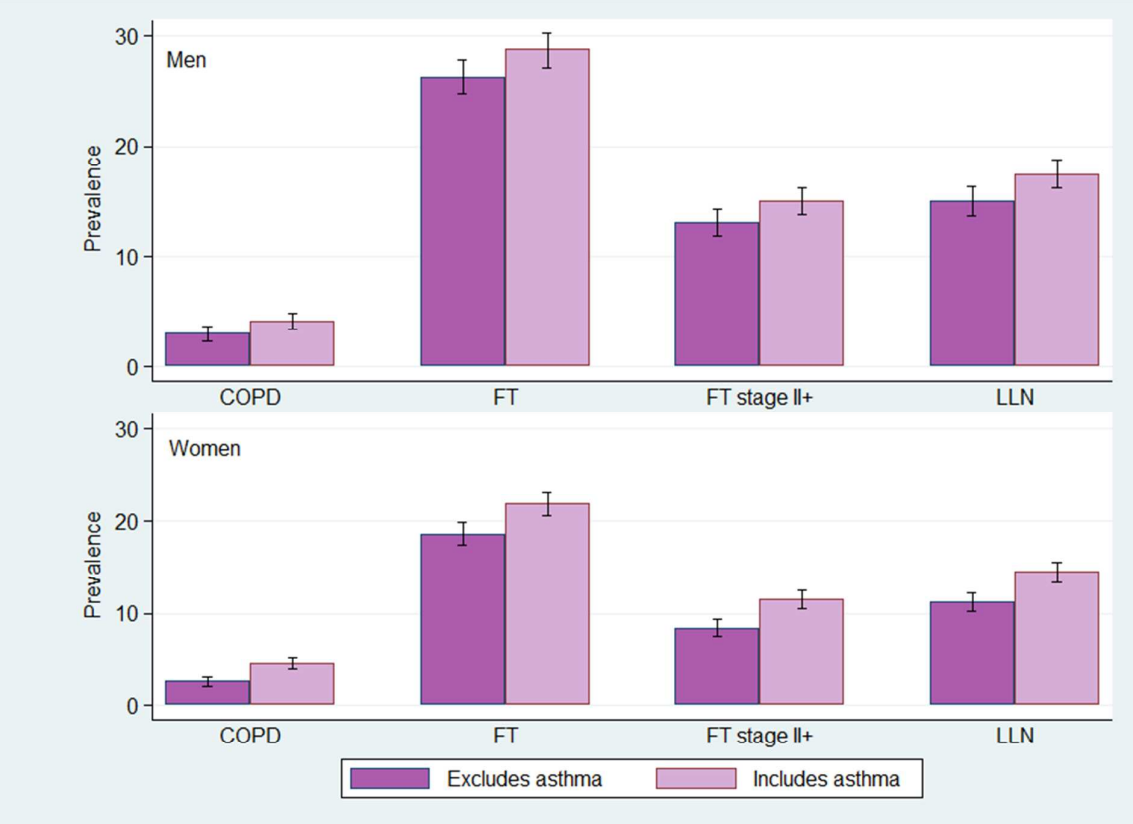
Figure S2 Response Flowchart in Health Survey for England 2010



[a] Quality criteria for spirometry sessions were as follows (Grades A-C required for inclusion in analytical sample):

Grade	Number of acceptable forced expiratory manoeuvres	Additional criteria
A	At least three	Two highest FVC and FEV_1 within 100 ml
B	At least three	Two highest FVC and FEV_1 within 150 ml
C	At least two	Two highest FVC and FEV_1 within 200 ml
D	One	Or best two FEV_1 or FVC were not within 200 ml
F	None	N/A

Figure S3 Prevalence of Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometry-Based Definitions, Persons aged 40-95 years, Including and Excluding Participants With Reported Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)



Abbreviations used: FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); UKHLS, United Kingdom Household Longitudinal Survey.

Table S1 Characteristics of Participants in the Analytical Sample, With Diagnosed COPD, and According to Fixed Thresholds and Lower Limit of Normal Spirometry-based Severity Classifications, Persons aged 40-95 years Without Reported Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

	All participants	Reported diagnosed COPD[b]	P value[c]	Fixed Thresholds[d]			P value[c]	Lower Limit of Normal[e]		P value[c]
				stage I	stage II	stage III+		stage I	stage II	
n	7879	207		926	681	116		503	468	
Diagnosed COPD, n (%)	207 (2.8)	207 (100.0)		17 (2.1)	48 (7.1)	33 (30.2)	*<0.001*	19 (3.9)	65 (14.7)	*<0.001*
Sex, n (%):										
Males	3335 (46.8)	94 (50.4)	*0.349*	461 (53.3)	375 (56.0)	75 (66.9)	*<0.001*	231 (50.5)	255 (57.3)	*<0.001*
Females	4544 (53.3)	113 (49.7)		465 (46.7)	306 (44.0)	41 (33.1)		272 (49.5)	213 (42.7)	
Age-group, n (%):										
40-54	3472 (46.6)	64 (29.3)	*<0.001*	235 (28.1)	144 (23.9)	9 (9.3)	*<0.001*	221 (46.7)	125 (29.8)	*<0.001*
55-64	2072 (24.8)	69 (30.3)		260 (26.9)	191 (26.5)	38 (29.8)		129 (24.4)	156 (29.6)	
65-74	1557 (17.4)	52 (24.7)		262 (24.8)	195 (25.2)	42 (32.7)		98 (16.8)	115 (23.4)	
75-95	778 (11.1)	22 (15.7)		169 (20.2)	151 (24.5)	27 (28.2)		55 (12.1)	72 (17.2)	
Mean age, years (SD)	57.6 (12.3)	61.8 (11.9)	*0.011*	62.9 (12.5)	64.4 (12.2)	67.8 (10.1)	*<0.001*	57.6 (12.1)	61.9 (11.6)	*<0.001*
Smoking status, n (%):										
Current	1198 (16.6)	61 (28.5)	*<0.001*	172 (20.7)	218 (33.9)	49 (41.5)	*<0.001*	156 (33.8)	191 (42.0)	*<0.001*
Ex-regular	2547 (31.7)	80 (41.6)		369 (38.6)	265 (37.2)	51 (41.8)		174 (34.2)	178 (36.5)	
Never	4134 (51.7)	66 (29.9)		385 (40.8)	198 (28.9)	16 (16.7)		173 (32.0)	99 (21.6)	
Pack-years[f], n (%):										
0-0.9	4299 (53.9)	69 (31.2)	*<0.001*	406 (43.2)	207 (30.1)	16 (16.7)	*<0.001*	180 (33.2)	101 (22.1)	*<0.001*
1-19.9	1905 (24.3)	41 (20.1)		252 (27.0)	137 (20.3)	30 (27.1)		138 (27.8)	101 (22.0)	
20-49.9	1318 (17.2)	63 (31.4)		209 (23.2)	241 (34.9)	38 (29.9)		144 (29.9)	180 (36.9)	
50+	345 (4.6)	33 (17.4)		56 (6.3)	94 (14.3)	32 (26.3)		39 (8.5)	86 (19.1)	
NS-SEC[f], n (%):										
Professional	3050 (36.5)	60 (25.4)	*<0.001*	312 (32.7)	180 (23.4)	27 (20.8)	*<0.001*	162 (30.5)	106 (20.3)	*<0.001*
Intermediate	1859 (23.4)	42 (19.4)		242 (25.2)	152 (21.9)	18 (15.1)		126 (23.3)	97 (19.6)	
Routine	2705 (36.9)	100 (53.2)		322 (36.9)	321 (50.9)	65 (59.6)		195 (43.0)	244 (55.9)	

Abbreviations used: COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the lower 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; SD, standard deviation; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts unweighted; means and percentages estimated using survey weights.
[b] HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[c] Within each definition of obstruction, Chi-squared test used to compare categorical variables; ANOVA used to compare mean values of continuous variables.
[d] Staging classification for FTs: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% of predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% of predicted); stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% of predicted).
[e] Staging classification for LLN: stage I (FEV_1/FVC <LLN and FEV_1 >LLN); stage II (FEV_1/FVC <LLN and FEV_1 <LLN).
[f] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table S2 Characteristics of Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometry-based Definitions, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

	All participants	Reported diagnosed COPD[b]	P value[c]	Fixed Thresholds[d]			P value[c]	Lower Limit of Normal[e]		P value[c]
				stage I	stage II	stage III+		stage I	stage II	
n	7879	207		926	681	116		503	468	
UKHLS, n (%)	5936 (75.3)	121 (59.6)	*<0.001*	705 (76.2)	517 (75.6)	87 (74.9)	*0.932*	377 (75.0)	356 (76.1)	*0.922*
HSE, n (%)	1943 (24.7)	86 (40.4)		221 (23.8)	164 (24.4)	29 (25.1)		126 (25.0)	112 (23.9)	
Exposure to passive smoking, hours per week (p/w), n (%)[f]:										
0	1599 (81.1)	64 (74.8)	*0.407*	184 (81.4)	130 (76.7)	20 (69.6)	*0.233*	93 (69.9)	86 (73.7)	*0.007*
1-9	256 (14.1)	16 (19.3)		32 (15.8)	22 (15.0)	6 (24.4)		25 (23.9)	17 (16.8)	
10+	82 (4.8)	4 (6.0)		5 (2.8)	11 (8.3)	2 (6.1)		7 (6.2)	8 (9.5)	
Mean exposure, hours p/w (SD)	1.8 (7.7)	2.4 (10.1)	*0.966*	1.5 (7.3)	3.5 (11.7)	3.3 (13.0)	*0.068*	2.5 (9.2)	3.8 (11.7)	*0.091*
Lung function measurements, percent-of-predicted, mean (SD)[g]:										
FEV_1	92.0 (16.5)	75.0 (23.4)	*<0.001*	92.7 (10.0)	69.0 (7.8)	40.2 (7.2)	*<0.001*	87.2 (8.2)	59.4 (12.9)	*<0.001*
FVC	97.1 (15.0)	88.6 (15.7)	*<0.001*	109.2 (11.5)	87.5 (10.9)	65.4 (12.9)	*<0.001*	108.1 (10.2)	82.5 (14.2)	*<0.001*
FEV_1/FVC	94.2 (9.7)	82.8 (18.2)	*<0.001*	84.6 (4.6)	78.9 (7.9)	62.9 (13.2)	*<0.001*	80.4 (4.5)	71.6 (10.6)	*<0.001*
Comorbidities, n (%):										
Respiratory disease[f, h]	65 (3.8)	33 (42.1)	*<0.001*	6 (3.3)	15 (9.0)	15 (51.5)	*<0.001*	5 (4.2)	24 (21.7)	*<0.001*
Respiratory symptoms[f, i]	69 (4.0)	12 (13.7)	*<0.001*	14 (6.4)	16 (11.7)	8 (27.3)	*<0.001*	7 (5.7)	18 (17.4)	*<0.001*
Respiratory medicine	375 (4.8)	71 (36.1)	*<0.001*	41 (4.3)	70 (9.6)	49 (42.7)	*<0.001*	30 (5.8)	95 (20.2)	*<0.001*
Cardiovascular disease[j]	493 (6.5)	20 (11.5)	*0.012*	84 (9.9)	74 (11.1)	24 (24.1)	*<0.001*	32 (6.8)	49 (12.3)	*<0.001*
Diabetes	543 (7.1)	18 (10.9)	*0.128*	54 (6.3)	67 (9.6)	17 (13.1)	*0.007*	20 (4.4)	39 (7.8)	*0.087*
Poor self-rated health	398 (5.7)	40 (23.4)	*<0.001*	37 (4.9)	58 (9.1)	23 (22.8)	*<0.001*	30 (7.2)	55 (12.6)	*<0.001*
Breathlessness[f, k]	100 (6.7)	23 (34.8)	*<0.001*	10 (6.9)	18 (13.1)	11 (43.9)	*<0.001*	8 (10.5)	21 (21.6)	*<0.001*
Area of residence, n (%):										
Urban	5791 (75.8)	154 (77.2)	*0.654*	656 (72.6)	515 (76.8)	89 (79.3)	*0.125*	372 (75.1)	358 (78.0)	*0.528*
Rural	2087 (24.2)	53 (22.8)		270 (27.4)	166 (23.2)	27 (20.7)		131 (25.0)	110 (22.0)	
BMI:										

Normal	2122 (27.0)	56 (25.7)	*0.751*	347 (38.0)	182 (27.6)	35 (34.7)	*<0.001*	202 (40.6)	147 (32.6)	*<0.001*
Overweight	3235 (41.9)	79 (40.4)		393 (43.4)	298 (44.6)	37 (34.3)		214 (42.8)	177 (38.4)	
Obese	2369 (31.1)	66 (33.8)		165 (18.7)	187 (27.8)	36 (31.0)		77 (16.6)	132 (29.0)	

Abbreviations used: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the lower 5th percentile of Z-scores); MRC, Medical Research Council; NS-SEC, National Statistics Socio-Economic Classification; SD, standard deviation; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts unweighted; means and percentages estimated using survey weights.
[b] HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[c] Within each definition of obstruction, Chi-squared test used to compare categorical variables; ANOVA used to compare mean values of continuous variables.
[d] Staging classification for FTs: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% of predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% of predicted); stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% of predicted).
[e] Staging classification for LLN: stage I (FEV_1/FVC <LLN and FEV_1 >LLN); stage II (FEV_1/FVC <LLN and FEV_1 <LLN).
[f] Measured in HSE 2010 only.
[g] Percent-of-predicted defined as the observed value divided by the predicted value estimated for a person of the same age, gender, ethnicity, and height using the European Respiratory Society Global Lungs Initiative 2012 reference equations [1].
[h] Respiratory disease: ICD-10 codes J00-J99.
[i] Respiratory symptoms: defined as usually coughing first thing in the morning, for at least 3 months a year, and bringing up phlegm from the chest most days for 3 consecutive months in a year. Missing data: 1 case with missing value.
[j] Cardiovascular disease: HSE (longstanding illness): stroke; heart attack/angina; UKHLS (health conditions): coronary heart disease; angina; heart attack/myocardial infarction; stroke.
[k] MRC dyspnoea scale: 63 participants with unspecified shortness of breath excluded. MRC grades as follows: 0, only breathless with strenuous exercise; 1: breathless when hurrying on level or up a slight hill; 2: walk slower than people of same age on the level due to breathlessness or stop for breath when walking on level at own pace; 3: stop for breath after walking 100 yards or a few minutes on the level; 4: too breathless to leave house or breathless when dressing.

Reference List

(1) Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40(6):1324-1343.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

Shaun Scholes, Alison Moody, Jennifer S Mindell

	Item No	Recommendation	Action taken
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, we have used pooled cross-sectional analysis in the title.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured abstract as in BMJ instructions for authors.
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background and rationale reported.
Objectives	3	State specific objectives, including any prespecified hypotheses	Specific objectives of the study reported.
Methods			
Study design	4	Present key elements of study design early in the paper	Key elements presented. We have pooled 2 recent cross-sectional surveys containing lung function data.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Settings, locations, and dates specified.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Eligibility criteria and methods of selection explained. Reason for excluding the Scottish component of UKHLS described in Supplementary data. Response flowcharts for HSE and UKHLS provided as supplementary data.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	All variables in the study clearly described, highlighting, where relevant, differences between the two surveys.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Data sources, including choice of reference equations for predicted values and Z-scores clearly described.

Bias	9	Describe any efforts to address potential sources of bias	We undertook descriptive analysis of participants with and without good-quality spirometry data. Implications of bias are mentioned in the discussion.
Study size	10	Explain how the study size was arrived at	Response flowcharts for HSE and UKHLS provided as supplementary data.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Groupings of quantitative variables clearly set out in the method section.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical methods described in detail.
		(*b*) Describe any methods used to examine subgroups and interactions	Statistical methods described in detail.
		(*c*) Explain how missing data were addressed	Exclusion of participants with missing data for two variables clearly set out in the methods section.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Described in the statistical analyses section. We accounted for the clustering of observations using the svy module in Stata.
		(*e*) Describe any sensitivity analyses	Sensitivity analyses described in detail.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Response flowcharts for HSE and UKHLS provided as supplementary data.
		(b) Give reasons for non-participation at each stage	Response flowcharts for HSE and UKHLS provided as supplementary data.
		(c) Consider use of a flow diagram	Response flowcharts for HSE and UKHLS provided as supplementary data.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Characteristics of study participants (across all variables) are provided as supplementary data.
		(b) Indicate number of participants with missing data for each variable of interest	Numbers with missing data presented as footnote in the tables.

Outcome data	15*	Report numbers of outcome events or summary measures	Outcome data is presented as prevalence.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Both sets of estimates (unadjusted and adjusted) presented.
		(*b*) Report category boundaries when continuous variables were categorized	Details provided.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results of sensitivity analyses provided.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Details provided.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations and potential biases discussed in detail.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Cautious throughout.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Generalisability briefly discussed.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Details provided.

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Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

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Title: Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

Running head: Comparison of different spirometric cut-offs

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Keywords: airflow obstruction; chronic obstructive pulmonary disease; fixed thresholds; Health Survey for England; lower limit of normal; respiratory; sensitivity; specificity; spirometry; United Kingdom Household Longitudinal Survey

ABSTRACT

Objectives: Consistent estimation of the burden of chronic obstructive pulmonary disease (COPD) has been hindered by differences in methods, including different spirometric cut-offs for impaired lung function. The impact of different definitions on the prevalence of potential airflow obstruction, and its associations with key risk factors, is evaluated using cross-sectional data from two nationally-representative population surveys.

Design: Pooled cross-sectional analysis of Wave 2 of the UK Household Longitudinal Survey and the Health Survey for England 2010, including 7879 participants, aged 40-95 years, who lived in England and Wales, without diagnosed asthma, and with good-quality spirometry data. Potential airflow obstruction was defined using self-reported physician-diagnosed COPD; a fixed threshold (FT) forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70; and an age-, sex-, height- and ethnic-specific lower limit of normal (LLN). Standardised questions elicited self-reported information on demography, smoking history, ethnicity, occupation, respiratory symptoms, and cardiovascular disease.

Results: Consistent across definitions, participants classed with obstructed airflow were more likely to be older, currently smoke, have higher pack-years of smoking, and be engaged in routine occupations. The prevalence of airflow obstruction was 2.8% (95% CI 2.3-3.2), 22.2% (21.2-23.2), and 13.1% (12.2-13.9) according to diagnosed COPD, FT and LLN, respectively. The gap in prevalence between FT and LLN increased in older age-groups. Sex differences in the risk of obstruction, after adjustment for key risk factors, was sensitive to the choice of spirometric cut-off, being significantly higher in men when using FT, compared with no significant difference using LLN.

Conclusions: Applying FT or LLN spirometric cut-offs gives a different picture of the size and distribution of the disease burden. Longitudinal studies examining differences in

unscheduled hospital admissions and risk of death between FT and LLN may inform the choice as to the best way to include spirometry in assessments of airflow obstruction.

Word count: 3940

Non-text material: 4 Tables

Strengths and limitations of this study

- Estimates of the burden of chronic obstructive pulmonary disease (COPD) using spirometry data collected in epidemiological studies are inconsistent through differences in methods, including different spirometric cut-offs.
- Our study combined two nationally representative samples of adults living in England and Wales, with standardised protocols and objective measurements of lung function, and a wide-range of clinically-relevant conditions including self-reported respiratory symptoms (chronic cough and phlegm) and breathlessness.
- Consistent definitions and up-to-date reference equations were used, providing baseline data for monitoring purposes in the UK, and for facilitating comparison with international studies.
- Prevalence estimates were based on pre-bronchodilator lung function measurements, and so are likely to overestimate true prevalence.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by a progressive decline in lung function.[1;2] 2.9 million deaths were attributed to COPD in 2010, making it the third leading global cause of death.[3] The National Outcomes Strategy for COPD estimated that 835,000 people living in the UK are currently diagnosed with COPD, with a further 2.2 million being undiagnosed.[4] COPD is the second leading cause of emergency hospital admission and is one of the most costly diseases in terms of acute hospital care in England.[4]

Healthcare budgeting is often contingent upon the estimated burden of disease. Spirometry, the mainstay of lung function assessment, has been used in nationally-representative surveys to estimate the COPD burden in terms of prevalence, associated comorbidities, and mortality. Estimation of the disease burden has been hindered, however, by differences in methods, including spirometric cut-offs.[5-8] Fixed thresholds (FTs) use cut-offs for lung function measurements (e.g., forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70) regardless of age, sex, height, and ethnicity.[9] An additional threshold for percent-of-predicted FEV_1 (expected for persons of a given age, sex, height and ethnicity) is also commonly used for severity classification. In contrast, a lower limit of normal (LLN) cut-off uses a statistical definition of abnormal/normal (e.g., below/above the lower 5th percentile of the distribution of age-, sex-, height-, and ethnic-specific FEV_1/FVC values from a healthy, lifelong non-smoking population).[10]

At present, applying FTs such as FEV_1/FVC <0.70 is the standard approach. However, the European Respiratory Society (ERS) Task Force on epidemiology recently advocated using the LLN in epidemiological studies as FTs both overestimate airflow obstruction in older populations, due to the physiological reduction of FEV_1/FVC with age, and underestimate in

young adults, compared with LLN.[11-16] The controversy over FT-versus-LLN thresholds is well-known with no signs of a consensus among expert groups being agreed.[17-21]

Partly as a result of this controversy, the COPD epidemiological database shows heterogeneity in definitions and consequential estimates of the disease burden.[5;22] Two nationally-representative samples, Wave 2 (2010-2012) of the UK Household Longitudinal Survey (UKHLS, 'Understanding Society') and the Health Survey for England (HSE) 2010, collected lung function data using identical measurement protocols and specialist equipment, providing an opportunity to increase statistical precision by combining both datasets. Therefore, the primary objective of the present study was to compare the prevalence of 'potential' airflow obstruction according to FT- and LLN-thresholds among persons aged 40-95 years living in England and Wales: potential in the sense that the administration of bronchodilators to measure the extent of reversibility in airflow obstruction was not used. As a secondary aim, we compared the sensitivity of associations with risk factors including age, sex, smoking history, and socioeconomic position. Using the same variables, we also examined the characteristics associated with spirometry in connection with self-reported physician-diagnosed COPD.

METHODOLOGY

Study design and setting

Both the UKHLS and HSE selected participants using stratified multi-stage probability sampling designs.[23]Self-reported health information, risk factors and demographics was collected through face-to-face interviews, followed by a visit from a trained nurse during which lung function was measured. Response rates for the Wave 2 interview (among individuals issued) and nurse-visit (among eligible participants in the Wave 2 interview) were 61% and 59% respectively in UKHLS. In HSE 2010, interview (among the estimated total

number of adults in sampled households) and nurse-visit (adults in co-operating households) response rates were 59% and 57%. Sampling methods are described elsewhere.[24-26] Ethical approval was obtained from the Oxfordshire A (UKHLS) and B (HSE 2010) Research Ethics Committees.. Eligible participants gave written consent to participate in spirometry.

Questionnaire and procedures

Participants were excluded from spirometry for the following safety reasons: pregnancy; had in the last 3 months abdominal/chest surgery, a heart attack, detached retina or eye or ear surgery; admitted to hospital with a heart complaint in the preceding month; a resting pulse rate >120 beats/minute; or currently taking medications for the treatment of tuberculosis. Spirometry, without bronchodilator use, was conducted using NDD EasyOne PCC spirometers (NDD Medical Technologies, Zurich, Switzerland). Quality control was summarised in a session grade based on the number of technically acceptable blows and their reproducibility. Grades A (3 acceptable manoeuvres, 2 highest FVC and FEV_1 within 100 ml), B (3 acceptable manoeuvres, 2 highest FVC and FEV_1 within 150 ml), and C (2 or 3 acceptable manoeuvres within 200 ml) were considered good-quality. Full details on measurement procedures are available elsewhere.[25-27]

The highest values for FEV_1 and for FVC, from at least 3 and up to 8 blows, were used. Age-, sex-, height-, and ethnic-specific predicted values and Z-scores (FEV_1, FVC and FEV_1/FVC) were computed using the ERS Global Lungs Initiative (GLI 2012, www.lungfunction.org) reference equations. These have been prepared by an international collaboration based on data spanning 26 countries from >70,000 healthy individuals across four ethnic-groups (Caucasian, African-American, and North- and South-East Asian), valid for persons aged 3-95 years [28;29] and have been shown to fit contemporary Australasian spirometric data.[30]

FT and LLN spirometric cut-offs

Using FTs, we applied the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [31], which was designed for use with post-bronchodilator spirometry: potential airflow obstruction was defined as $FEV_1/FVC < 0.70$ (FT). Disease stage was defined by the reduction in FEV_1 relative to percent-of-predicted values as follows: stage I ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ predicted); stage II ($FEV_1/FVC < 0.70$ and FEV_1 50-79% predicted); and stage III+ ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ predicted).[32] Participants with $FEV_1/FVC \geq 0.70$ were defined as non-obstructed.

Participants with $FEV_1/FVC <$ LLN (below the lower 5th percentile of the distribution of Z-scores) were defined as obstructed (LLN). To examine possible heterogeneity among participants with $FEV_1/FVC <$ LLN, disease stage was defined by FEV_1 relative to LLN as follows: stage I ($FEV_1/FVC <$ LLN and $FEV_1 \geq$ LLN), and stage II ($FEV_1/FVC <$ LLN and $FEV_1 <$ LLN).[33] Participants with $FEV_1/FVC \geq$ LLN were defined as non-obstructed. The 5th percentile was chosen due to its established associations with respiratory symptoms and all-cause mortality.[34]

Physician-diagnosed COPD

In UKHLS, disease status was ascertained through questions asking "*has a doctor or other health professional ever told you that you have [disease]?"* Diagnosed COPD was defined as a positive response to either chronic bronchitis or emphysema. In HSE, diagnosed COPD was defined as a positive response to the question "*did a doctor ever tell you that you had chronic bronchitis, emphysema or COPD?*"

Risk factors, measurements of lung function, and comorbidities

Key subgroups were defined by age (40-54, 55-64, 65-74, 75-95); sex; smoking status (current, former, never); pack-years of cigarette smoking (a cumulative total reflecting the amount and duration of consumption, with 1 pack-year equating to an average of 20

cigarettes smoked/day for 1 year); and socioeconomic position, defined by the National Statistics Socio-Economic Classification (NS-SEC), grouped into professional, intermediate, and routine occupations.

FEV_1, FVC, and FEV_1/FVC, on a continuous scale, were expressed as percent-of-predicted values. Additional variables included current use of respiratory medicine; area of residence (urban/rural); body mass index (BMI: weight in kilograms divided by the square of height in metres), grouped into normal weight (18.5-24.9kg/m^2), overweight (25.0-29.9kg/m^2), and obese (≥30kg/m^2); diagnosed diabetes; poor self-rated health; and reported cardiovascular disease (stroke, angina, myocardial infarction). In HSE, participants were asked to name any long-standing illnesses: respiratory diseases were identified using *International Classification of Diseases, Tenth Revision* codes J00-J99. In the HSE, presence of respiratory symptoms was defined as usually coughing first thing in the morning, for at least 3 months/year, and bringing up phlegm from the chest most days for 3 consecutive months in a year. In the HSE, participants with some limitation of activity due to breathlessness during daily living were identified by a score of 3+ on the Medical Research Council (MRC) dyspnoea scale. Exposure to passive smoking in the HSE was measured by reported number ofhours/week currently exposed to cigarette smoke (0, 1-9, and ≥10 hours).

Statistical analyses

A lower age limit was used of 40 years due to the low prevalence of non-asthma airflow obstruction in the youngest age-groups.[35] As bronchodilators were not used, we excluded participants who reported diagnosed asthma.[34;36-38] Five sets of analyses were conducted across the categories of diagnosed COPD, FT, and LLN. First, participants' characteristics (demographics, risk factors, comorbidities and percent-of-predicted FEV_1, FVC, and FEV_1/FVC) were summarised as means, accompanied by standard deviations, or as counts

accompanied by percentages. Participants were counted under each relevant definition. Participants with/without obstruction were compared using the χ^2 test and analysis of variance for categorical and continuous variables respectively.[39]

Secondly, prevalence estimates were computed for a subset of socio-demographic variables defined by age, sex, smoking status, pack-years of cigarette smoking, and NS-SEC. Thirdly, in the absence of a gold standard, we calculated the sensitivity and specificity of each spirometric criterion, using the alternative cut-off as the reference standard.[40]

Fourth, regression analyses were performed using age, sex, pack-years of smoking, and NS-SEC as independent variables with airflow obstruction as outcome. Current smoking status could not be entered in the same model as pack-years due to significant collinearity. The dependent variable based on FTs had 4 categories: non-obstructed, stage I, stage II, and stage III+. The LLN-derived outcome had 3 categories: non-obstructed, stage I, and stage II. In each case, multinomial logistic regression was used to estimate relative risk ratios (RRRs), with non-obstructed as the reference category. Multinomial logistic regression generalises logistic regression to outcomes with more than two possible discrete outcomes. The RRR is interpreted as the relative risk of one outcome in relation to the reference category for a specified category of an independent variable compared with the reference.[41;42] Diagnosed COPD was analysed as a binary outcome (not reported/reported): logistic regression was therefore used to estimate odds ratios (ORs).[39;41] The overall association for independent variables with >2 categories was computed using the adjusted Wald test. The likelihood-ratio test was used to estimate the statistical significance of interaction terms: non-significant terms were excluded, and models refitted with only the main effects.

Fifth, to examine risk factors associated with possible under-diagnosis, a four-category outcome variable was created combining diagnosed COPD and spirometric criteria as

follows: (1) neither diagnosed nor spirometrically-defined obstruction; (2) physician-diagnosed COPD but no obstructive spirometry; (3) spirometrically-defined but no diagnosed COPD; and (4) both diagnosed and obstructive spirometry.[43] FT and LLN cut-offs were analysed separately. RRRs generated from multinomial logistic regressions were used to examine associations between the same set of risk factors listed above and the composite dependent variable.

Participants with missing values on covariates were excluded from relevant analyses. Tests of statistical significance were based on two-sided probability (P<0.05). Dataset preparation was performed in SPSS 20.0 (SPSS IBM Inc., Chicago, Illinois, USA), Stata 13.1 (StataCorp, College Station, Texas, USA) and R (version 3.0.3; R Foundation, www.r-project.org). Analysis was conducted in Stata accounting for the complex design of both surveys, using the appropriate weighting variables and Primary Sampling Units. Both datasets are available via the UK Data Service (www.ukdataservice.ac.uk).

Sensitivity analyses

Analyses were initially undertaken excluding participants with reported diagnosed asthma and then repeated including those with asthma. In accordance with previous UK National Institute for Health and Care Excellence (NICE) recommendations [44], comparisons between FT and LLN were rerun defining only the subset of FT participants with FEV_1 <80% predicted (i.e., stage II+) as having obstructed airflow.

RESULTS

The analytical sample comprised 7879 participants (5936 and 1943 from UKHLS and HSE respectively) aged 40-95 years, who resided in England and Wales, did not report diagnosed asthma, had valid values of height and ethnicity, and provided good-quality spirometry. Response flowcharts for the UKHLS and HSE are provided in Figures **S1** and **S2** (online supplementary appendix) respectively. Excluded participants were more likely to be older, engaged in routine occupations, and self-report respiratory symptoms (data not shown). Differences between the UKHLS and HSE in terms of sex ratio, age, smoking history, NS-SEC, and objective measurements of lung function were not materially important (see online supplementary Table S1).

Descriptive characteristics of the analytical sample according to physician-diagnosed COPD, FT, and LLN are shown as supplementary data (Tables **S2-S3**). Overall, 46.8% of participants were male, with mean age 57.6 years (SD 12.3), 16.6% were current smokers, 4.6% had >50 pack-years of cigarette smoking, and 36.5% were engaged in professional occupations. 12 (0.1%) and 265 (3.2%) participants had missing values for pack-years and NS-SEC respectively. The prevalence of diagnosed COPD was similar between the sexes (P=0.349), but was higher for men using FT and LLN (both P<0.001). Participants with diagnosed COPD/obstructive spirometry were more likely to be older, currently smoke, have higher pack-years of smoking, and be engaged in routine occupations (all P<0.001). Prevalence of diagnosed COPD was higher in HSE *vs.* UKHLS (P<0.001), but survey-specific prevalence was similar for FT and for LLN. Participants with diagnosed COPD/obstructive spirometry were more likely to report respiratory symptoms (chronic cough and phlegm) and disease, current use of respiratory medications, cardiovascular disease, breathlessness, poor self-rated health and have, on average, lower (percent-of-predicted) values of FEV_1, FVC and FEV_1/FVC. The prevalence of respiratory symptoms

was 13.7%, 10.2%, and 11.3% among participants classed as having airflow obstruction according to diagnosed COPD, FT, and LLN respectively; prevalence of having a score of 3+ on the MRC dyspnoea scale was 34.8%, 12.3% and 15.9%.

Prevalence of airflow obstruction

The prevalence of airflow obstruction was 2.8%, 22.2%, and 13.1% using diagnosed COPD, FT, and LLN respectively (**Table 1**). Using FTs, 11.6%, 8.9%, and 1.7% of participants were classed as stage I, stage II, and stage III+ respectively. LLN-derived obstruction was 6.6% (stage I) and 6.4% (stage II). For most subgroups, prevalence was highest for FT and lowest for diagnosed COPD, with LLN falling in-between. The gap in prevalence between FT and LLN increased in older age-groups. Prevalence among participants aged 40-54 years was 11.9% and 10.7% using FT and LLN respectively. Prevalence among participants aged 75-95 was 45.0% and 17.2%.

Table 2 shows estimates of sensitivity and specificity for FT and LLN, using the alternative spirometric cut-off as the reference standard. When using LLN as reference, specificity - the percentage of participants classed as non-obstructed using LLN identified as non-obstructed using FT – decreased from 94.9% amongst participants aged 40-64 years to 74.4% amongst those aged 65-95.

Multivariate analyses of airflow obstruction

Table 3 shows the significant risk factors for diagnosed COPD, and the FT- and LLN-disease stage classifications (non-obstructed as reference category). For diagnosed COPD, the significant interaction between sex and age-group (P=0.022) suggested no difference in odds between the sexes among participants aged 40-64 years, but higher odds among men aged 65-95. Using FTs, being male was associated with a significantly increased risk of airflow obstruction: RRR 1.35 (95% CI: 1.16-1.58), RRR 1.35 (1.12-1.63), and RRR 1.72 (1.08-2.76)

for stages I, II, and III+ respectively. In contrast, sex differences were not significant using LLN: RRR 1.07 (0.88-1.31) for stage I, and RRR 1.20 (0.96-1.50) for stage II.

Odds of diagnosed COPD increased significantly with age only in men (P=0.022 for the interaction term). Using non-obstruction as reference, RRRs increased significantly with age when using FTs (P<0.001 for each stage). The age-related difference using LLN was more marked for stage II (P=0.492 and P<0.001 for stages I and II, respectively). A dose-related increased risk with pack-years of cigarette smoking was observed across each definition (P<0.001). The difference between NS-SEC levels was more marked with diagnosed COPD (P=0.012) and the tightest FT- and LLN-definitions (FT: P=0.002 stage III+; LLN: P<0.001 stage II).

Combination of diagnosed COPD and spirometric cut-offs

The significant risk factors for the two four-category outcome variables created as a composite of diagnosed COPD and obstructive spirometry are shown in **Table 4**. Relative to the reference category (neither doctor-diagnosed nor spirometrically-defined airflow obstruction), the risk of reporting COPD in the absence of obstructive spirometry was significantly lower in men using either spirometric criterion (FT: RRR 0.53 (95% CI: 0.32-0.87); LLN: RRR 0.56 (0.35-0.89)). The risk of having obstructed airflow using spirometry but with no diagnosed COPD – thereby indicating possible under-diagnosis - was significantly higher in men, and in older age-groups, when using FT but not LLN. For both spirometric criterion, increases in risk with increasing pack-years of cigarette smoking, relative to the reference, was consistent across combinations of COPD/obstructive spirometry; the difference between NS-SEC levels was more marked for obstructive spirometry.

Sensitivity analyses

Repeating analyses by including 1183 participants with reported diagnosed asthma increased prevalence of diagnosed COPD, FT and LLN by 2-3 percentage points (Figure **S3**, online supplementary appendix), but showed similar patterns of association with risk factors. Diagnosed asthma was a strong predictor of diagnosed COPD and obstructive spirometry ($P<0.001$, data not shown). Narrowing FT-defined obstruction to the subset of FT participants with FEV_1 <80% predicted (i.e., stage II+) more than halved the FT-derived prevalence (22.2% *vs*. 10.6%). Amongst participants aged 65-95 years, specificity using LLN as the reference standard was 74.4% and 91.1% for FT and FT stage II+ respectively (**Table 2**). Patterns of association with risk factors using FT stage II+ was similar to those shown for FT.

DISCUSSION

Consistent estimation of the COPD burden has been hindered by differences in methods, including disagreement among experts over the choice of FT-versus-LLN spirometric cut-offs.[5-8] In this study, we combined two nationally-representative surveys, with standardised protocols and objective lung function measurements, to evaluate the impact of different definitions on the prevalence of potential airflow obstruction, and its associations with key risk factors. Participants with diagnosed COPD/obstructive spirometry were more likely to be older, currently smoke, have higher pack-years of cigarette smoking, be in lower socioeconomic groups, and report the presence of respiratory symptoms (chronic cough and phlegm), cardiovascular disease, breathlessness, and poor self-rated health. Among persons aged 40-95 years without physician-diagnosed asthma, prevalence was 2.8%, 22.2%, and 13.1%, according to diagnosed COPD, FT, and LLN respectively. The gap in prevalence between FT and LLN increased in older age-groups. When using LLN as the reference standard, specificity for FT decreased from 94.9% amongst participants aged 40-64 years to 74.4% amongst participants aged 65-95, corresponding to false-positive rates of 5.1% and 25.6% respectively. Sex differences in the risk of obstructed airflow, after adjustment for potential confounders, was sensitive to spirometric criteria, being higher among men for FT, compared with no difference using LLN.

Strengths and limitations

Analyses were based on nationally-representative samples,, with identical measurement protocols and specialist equipment for collecting lung function data. Combining the HSE and UKHLS datasets increased statistical precision for spirometry-based estimates, particularly for population subgroups, and allowed detailed analyses to be conducted. Predicted values and Z-scores were obtained from the ERS GLI 2012 reference equations [28], facilitating inclusion of older participants, non-white populations and comparability with international

studies. Our study has a number of limitations. Reversibility in airflow obstruction could not be assessed due to bronchodilators not being used. Spirometry-based prevalence, therefore, may be overestimated. Analysis of the National Health and Nutrition Examination Survey (NHANES) 2007-2010 showed that FT- and LLN-prevalence estimates among US adults aged 40-79 years decreased, in relative terms, by approximately one-third after administration of bronchodilators.[45] Although recent guidelines from NICE [46] and ERS [13] recommend use of post-bronchodilator spirometry to confirm the presence of airflow obstruction, debate continues over its use in epidemiological settings, with the arguments against including ethical issues such as possible side-effects and contraindications.[47] Potential misclassification of disease status through bronchodilators not being used was reduced by excluding participants with physician-diagnosed asthma. Some participants in the analytical sample, however, may be undiagnosed asthmatics. On the other hand, the disease burden may be underestimated through excluding participants with poor-quality spirometry. Participation in spirometry, and achievement of good-quality standards among participants with any spirometry data, was higher among participants of younger age, engaged in professional/managerial occupations, non-smokers, and with no physician-diagnosed COPD. Lower survey participation rates amongst socio-demographic groups at higher risk of airflow obstruction (e.g., older persons, lower socioeconomic groups) would also have led to an underestimation of true prevalence. These limitations, however, are unlikely to affect comparisons across definitions, but may have led to an underestimate of risk associations. The list of health conditions in the UKHLS interview programme included chronic bronchitis and emphysema but not COPD, leading to potential underestimation of self-reported physician-diagnosed COPD.

Comparisons with previous studies

Earlier analyses of HSE data [36;38;48] used older reference equations [49;50] applicable only to white, younger populations. Nevertheless, estimates of prevalence and their substantive conclusions of higher prevalence using FT-versus-LLN, with a widening gap in prevalence in older age-groups, and sex differences when using FT but not LLN were similar to ours: confirming findings reported in the US [45], Europe [51], Korea [16], internationally [12], and in recent literature reviews.[6;52] A further strength of our study was the wide range of clinically-relevant conditions examined in the context of disease-staging, with higher prevalence of respiratory symptoms, respiratory- and cardiovascular-disease, breathlessness, and poor self-rated health among participants in the tightest definitions of FT- and LLN-obstruction, confirming similar findings in the US.[53;54] Whilst recent guidelines [13;46;55] recommend adopting multidimensional definitions of respiratory disease, our study outcomes were defined only using spirometry. While we acknowledge the merits of a multidimensional approach, and agree that neither spirometric cut-off is able to fully characterise the complex diagnostic features of COPD [56], our primary aim was to use up-to-date survey data to evaluate differences in prevalence according to FT- and LLN-thresholds, to provide baseline data for monitoring purposes in the UK, and promote comparability with international studies. Current recommendations regarding symptom criteria are less specific than those for spirometry. We chose, therefore, to examine the associations between disease-staging assessed only using spirometry and presence of respiratory symptoms, rather than broaden the definition of disease.

Implications

Recent UK studies used administrative primary-care databases to report the number of diagnosed and treated patients, thereby missing undiagnosed cases. Such studies have reported prevalence below 2%.[57;58] The disparity in prevalence from clinical-versus-

epidemiological studies led to the development of the COPD prevalence model, with the HSE 2001 used as input data, to more accurately estimate prevalence.[59] In accordance with previous NICE recommendations [44], COPD is currently defined in the model as FT stage II+ (FEV_1/FVC <0.70 and FEV_1 <80% predicted), with the logistic regression models showing sharp increases with age and a modifying effect of gender.[60;61] Similar to the findings reported by Jordan et al. [36], our study shows that the strength of association between risk factors and airflow obstruction varies according to spirometric criterion, with age- and sex-differences in risk being more marked for FT, and for FT stage II+, than LLN. In the absence of agreement among experts, policy-makers, clinicians, and researchers building the COPD epidemiological database, it is important to appreciate the sensitivity of estimates of the disease burden, and its distribution across socio-demographic groups, to differences in methods, including spirometric cut-offs.

The prevalence of reported physician-diagnosed COPD in our study was 2.8%, considerably lower than spirometry-based estimates, possibly indicating considerable under-recognition by both participants and physicians. Using the tightest definitions, prevalence of physician-diagnosed COPD among participants with obstructive spirometry was 30.2% (FT stage III+) and 14.7% (LLN stage II). Similar low rates of physician-diagnosis among participants meeting spirometric criteria have been reported in New Zealand.[62] Spirometrically-defined airflow obstruction but no diagnosed COPD does not necessarily indicate under-diagnosis. Definitive diagnosis requires further information on all relevant clinical factors, particularly respiratory symptoms and smoking history, as well as post-bronchodilator spirometry.

Conclusion

In summary, we have enhanced the COPD epidemiological database by evaluating the impact of different definitions on the prevalence of potential airflow obstruction and its associations with key risk factors and comorbidities. With no gold standard currently available,

longitudinal studies examining differences in unscheduled hospital admissions and risk of death between FT and LLN may inform the choice as to the best way to include spirometric data in multidimensional assessments of airflow obstruction in both clinical and epidemiological settings.

Abbreviations: COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FT, fixed thresholds; GLI, Global Lungs Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HSE, Health Survey for England; LLN, lower limit of normal; NICE, National Institute for Health and Care Excellence; UKHLS, United Kingdom Household Longitudinal Survey

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Data sharing: Both datasets are available via the UK Data Service (www.ukdataservice.ac.uk). Statistical code is available from the corresponding author at s.scholes@ucl.ac.uk.

Contributors: SS, AM, and JM participated in study concept and design, analysis and interpretation of data. SS performed data acquisition and management. SS participated in drafting of the manuscript. AM and JM aided revision of the manuscript and provided relevant intellectual input. SS is the data guarantor. All authors have approved the final version of the manuscript.

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Table 1 Prevalence of Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

		Diagnosed-COPD[b]	Fixed Thresholds[c]				Lower Limit of Normal[d]		
			Obstructed	stage I	stage II	stage III+	Obstructed	stage I	stage II
	n	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
All	7879	2.8 (2.3-3.2)	22.2 (21.2-23.2)	11.6 (10.9-12.4)	8.9 (8.2-9.6)	1.7 (1.3-2.0)	13.1 (12.2-13.9)	6.6 (6.0-7.3)	6.4 (5.8-7.0)
Sex:									
Males	3335	3.0 (2.3-3.6)	26.3 (24.8-27.9)	13.2 (12.1-14.4)	10.7 (9.6-11.8)	2.4 (1.8-3.0)	15.0 (13.7-16.4)	7.2 (6.2-8.1)	7.9 (6.9-8.9)
Females	4544	2.6 (2.0-3.1)	18.6 (17.4-19.9)	10.2 (9.2-11.2)	7.4 (6.5-8.2)	1.0 (0.7-1.4)	11.3 (10.3-12.3)	6.2 (5.4-6.9)	5.1 (4.4-5.9)
Age-group:									
40-54	3472	1.7 (1.3-2.2)	11.9 (10.7-13.1)	7.0 (6.1-7.9)	4.6 (3.8-5.4)	0.3 (0.1-0.6)	10.7 (9.6-11.9)	6.7 (5.7-7.6)	4.1 (3.3-4.9)
55-64	2072	3.4 (2.5-4.2)	24.2 (22.2-26.1)	12.6 (11.1-14.1)	9.5 (8.1-10.9)	2.0 (1.4-2.7)	14.2 (12.6-15.8)	6.5 (5.4-7.7)	7.7 (6.4-8.9)
65-74	1557	3.9 (2.8-5.0)	32.6 (30.1-35.1)	16.5 (14.6-18.5)	12.9 (11.1-14.6)	3.2 (2.1-4.2)	15.0 (13.0-17.0)	6.4 (5.1-7.7)	8.6 (7.0-10.2)
75-95	778	3.9 (2.0-5.8)	45.0 (41.1-48.8)	21.1 (18.0-24.2)	19.6 (16.6-22.6)	4.3 (2.5-6.0)	17.2 (14.2-20.1)	7.2 (5.2-9.2)	9.9 (7.6-12.3)
Smoking status:									
Current	1198	4.7 (3.5-6.0)	37.0 (34.1-39.9)	14.5 (12.3-16.6)	18.2 (15.9-20.6)	4.2 (3.0-5.4)	29.8 (27.0-32.6)	13.5 (11.3-15.7)	16.2 (14.0-18.5)
Ex-regular	2547	3.6 (2.7-4.5)	26.8 (24.9-28.7)	14.1 (12.7-15.6)	10.5 (9.2-11.8)	2.2 (1.5-2.9)	14.5 (13.0-16.1)	7.2 (6.0-8.3)	7.4 (6.2-8.5)
Never	4134	1.6 (1.2-2.0)	14.7 (13.5-15.9)	9.2 (8.2-10.1)	5.0 (4.3-5.7)	0.5 (0.2-0.9)	6.8 (5.9-7.7)	4.1 (3.5-4.8)	2.7 (2.1-3.3)
Pack-years[e]:									
0-0.9	4299	1.6 (1.2-2.0)	14.8 (13.6-16.0)	9.3 (8.4-10.3)	5.0 (4.3-5.7)	0.5 (0.2-0.8)	6.7 (5.9-7.6)	4.1 (3.5-4.7)	2.6 (2.0-3.2)
1-19.9	1905	2.3 (1.5-3.1)	22.3 (20.3-24.3)	12.9 (11.3-14.5)	7.5 (6.2-8.8)	1.9 (1.1-2.6)	13.4 (11.7-15.1)	7.6 (6.3-8.9)	5.8 (4.6-7.0)
20-49.9	1318	5.0 (3.6-6.5)	36.8 (34.0-39.6)	15.7 (13.5-17.9)	18.1 (15.9-20.4)	2.9 (2.0-3.9)	25.4 (22.8-27.9)	11.6 (9.5-13.6)	13.8 (11.8-15.8)
50+	345	10.5 (7.0-14.1)	53.7 (48.0-59.4)	16.0 (12.0-20.1)	28.0 (23.0-32.9)	9.7 (6.2-13.2)	39.3 (33.5-45.0)	12.4 (8.7-16.2)	26.9 (21.6-32.1)
NS-SEC[e]:									
Professional	3050	1.9 (1.4-2.4)	17.1 (15.7-18.5)	10.4 (9.3-11.6)	5.7 (4.9-6.5)	1.0 (0.6-1.4)	9.1 (8.0-10.2)	5.6 (4.6-6.5)	3.6 (2.9-4.3)
Intermediate	1859	2.3 (1.6-3.0)	21.9 (19.9-23.9)	12.5 (10.9-14.1)	8.4 (7.0-9.7)	1.1 (0.5-1.7)	12.0 (10.5-13.5)	6.6 (5.4-7.8)	5.4 (4.3-6.5)
Routine	2705	4.0 (3.1-4.8)	26.6 (24.7-28.5)	11.6 (10.3-12.9)	12.3 (10.9-13.7)	2.7 (2.0-3.5)	17.4 (15.8-19.1)	7.7 (6.6-8.9)	9.7 (8.4-11.0)

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in 1 second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the lower 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts are unweighted; prevalence estimates were weighted.
[b] HSE: reported diagnosed COPD, bronchitis or emphysema; UKHLS: diagnosed bronchitis or emphysema.
[c] FTs: Obstruction (FT): $FEV_1/FVC < 0.70$. Staging classification: stage I ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ of predicted); stage II ($FEV_1/FVC < 0.70$ and FEV_1 50-79% of predicted); stage III+ ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ of predicted).
[d] LLN: Obstruction (LLN): $FEV_1/FVC <$ LLN. Staging classification: stage I ($FEV_1/FVC <$ LLN and $FEV_1 >$ LLN); stage II ($FEV_1/FVC <$ LLN and $FEV_1 <$ LLN).
[e] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table 2 Sensitivity and Specificity of Fixed Thresholds and Lower Limit of Normal Spirometric Criteria by Age-group, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)

	40-64 (*n*=5544)	**65-95** (*n*=2335)	**40-64** (*n*=5544)	**65-95** (*n*=2335)
	FT using LLN as reference standard		**LLN using FT as reference standard**	
False positives, (%)	5.1	25.6	0.4	0.0
False negatives, (%)	2.5	0.0	28.0	57.6
Sensitivity	0.975	1.000	0.720	0.424
Specificity	0.949	0.744	0.996	1.000
PPV	0.720	0.424	0.975	1.000
NPV	0.996	1.000	0.949	0.744
Kappa coefficient	0.801	0.479	0.801	0.479
Likelihood ratio positive	18.98	3.90	200.65	N/A
Likelihood ratio negative	0.027	0.000	0.281	0.576
	FT (stage II+) using LLN as reference standard		**LLN using FT (stage II+) as reference standard**	
False positives, (%)	1.3	8.9	6.3	5.2
False negatives, (%)	49.2	26.7	16.0	39.1
Sensitivity	0.508	0.733	0.840	0.609
Specificity	0.987	0.911	0.937	0.948
PPV	0.840	0.609	0.508	0.733
NPV	0.937	0.948	0.987	0.911
Kappa coefficient	0.597	0.596	0.597	0.596
Likelihood ratio positive	38.82	8.28	13.27	11.67
Likelihood ratio negative	0.499	0.292	0.170	0.412

Abbreviations used: FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NPV, negative predictive value; PPV, positive predictive value; UKHLS, United Kingdom Household Longitudinal Survey.

Table 3 Results of Logistic and Multinomial Logistic Regressions for Reported Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria Among Persons Aged 40-95 years, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

Characteristics		Diagnosed-COPD[b]	Fixed Thresholds[c]			Lower Limit of Normal[d]	
			Non-obstructed as reference			Non-obstructed as reference	
			stage I	stage II	stage III+	stage I	stage II
	N	OR (95% CI)	RRR (95% CI)[e]	RRR (95% CI)[e]	RRR (95% CI)[e]	RRR (95% CI)[e]	RRR (95% CI)[e]
Sex:							
Females[f]	4372	1.00	1.00	1.00	1.00	1.00	1.00
Males	3231	0.60 (0.34-1.05)	1.35 (1.16-1.58)	1.35 (1.12-1.63)	1.72 (1.08-2.76)	1.07 (0.88-1.31)	1.20 (0.96-1.50)
P-value		*0.075*	*<0.001*	*0.002*	*0.024*	*0.503*	*0.107*
Age-group:							
40-54[f]	3416	1.00	1.00	1.00	1.00	1.00	1.00
55-64	2022	1.66 (1.07-2.58)	2.00 (1.63-2.45)	2.13 (1.65-2.73)	6.05 (2.82-12.99)	0.92 (0.72-1.18)	1.57 (1.20-2.06)
65-74	1451	0.96 (0.54-1.70)	2.85 (2.30-3.53)	3.01 (2.32-3.89)	10.11 (4.55-22.49)	0.83 (0.63-1.09)	1.56 (1.16-2.12)
75+	714	1.20 (0.39-3.70)	4.72 (3.66-6.07)	6.67 (5.00-8.90)	22.26 (9.45-52.44)	1.06 (0.74-1.51)	2.20 (1.52-3.17)
P-value		*0.104*	*<0.001*	*<0.001*	*<0.001*	*0.492*	*<0.001*
Pack-years[g]:							
0-0.9[f]	4165	1.00	1.00	1.00	1.00	1.00	1.00
1-19.9	1835	1.38 (0.88-2.17)	1.61 (1.34-1.93)	1.66 (1.29-2.15)	3.82 (1.80-8.14)	1.94 (1.51-2.49)	2.22 (1.58-3.12)
20-49.9	1269	2.91 (1.91-4.45)	2.30 (1.86-2.85)	4.56 (3.64-5.72)	5.91 (2.81-12.45)	3.39 (2.61-4.41)	5.43 (3.98-7.41)
50+	334	5.64 (3.45-9.22)	2.34 (1.63-3.35)	6.83 (4.85-9.63)	17.27 (7.88-37.84)	4.50 (2.96-6.84)	11.20 (7.59-16.52)
P-value		*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
NS-SEC[g]:							
Professional[f]	3047	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	1855	1.03 (0.68-1.58)	1.18 (0.97-1.45)	1.34 (1.04-1.72)	1.01 (0.51-2.00)	1.14 (0.88-1.48)	1.35 (0.99-1.85)
Routine	2701	1.61 (1.13-2.31)	1.07 (0.89-1.29)	1.82 (1.47-2.26)	2.30 (1.36-3.88)	1.28 (1.01-1.63)	2.18 (1.67-2.85)
P-value		*0.012*	*0.246*	*<0.001*	*0.002*	*0.123*	*<0.001*
Sample:							
UKHLS[f]	5675	1.00	1.00	1.00	1.00	1.00	1.00
HSE	1928	2.22 (1.60-3.07)	0.95 (0.79-1.14)	0.97 (0.79-1.20)	0.99 (0.62-1.59)	1.05 (0.82-1.33)	0.99 (0.77-1.26)
P-value		*<0.001*	*0.587*	*0.798*	*0.967*	*0.716*	*0.913*
Males × age-group:							

40-54[e]	1319	1.00	-	-	-	-	-
55-64	876	1.16 (0.54-2.45)	-	-	-	-	-
65-74	664	3.21 (1.40-7.39)	-	-	-	-	-
75+	372	2.61 (0.67-10.22)	-	-	-	-	-
P-value		*0.022*	-	-	-	-	-

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; OR, odds ratios; RRR; relative risk ratios; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts are unweighted; ORs and RRRs were weighted.

[b] HSE: reported diagnosed COPD, bronchitis or emphysema; UKHLS: diagnosed bronchitis or emphysema.

[c] FTs: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% of predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% of predicted); stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% of predicted). Reference category: FEV_1/FVC ≥0.70.

[d] LLN: stage I (FEV_1/FVC <LLN and FEV_1 >LLN); stage II (FEV_1/FVC <LLN and FEV_1 <LLN). Reference category: FEV_1/FVC ≥LLN.

[e] The RRR is interpreted as the relative risk of one outcome in relation to the reference category for a specified category of an independent variable compared with the reference category for that independent variable. Using FT stage I as an example, the RRR for males *vs.* females is interpreted as the relative risk for FT stage I *vs*. non-obstruction for males compared with the analogous relative risk for females, adjusted for the other variables in the model.

[f] Reference category.

[g] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table 4 Results of Multinomial Logistic Regressions for Combined Outcome Variable Based on Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria Among Persons aged 40-95 years, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-12)[a]

Characteristics		Fixed Thresholds[b]			Lower Limit of Normal[c]		
		Neither diagnosed nor obstructive spirometry as reference			Neither diagnosed nor obstructive spirometry as reference		
		Diagnosed alone	Obstructive spirometry alone	Diagnosed and obstructive spirometry	Diagnosed alone	Obstructive spirometry alone	Diagnosed and obstructive spirometry
	n	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]
Sex:							
Females[e]	4372	1.00	1.00	1.00	1.00	1.00	1.00
Males	3231	0.49 (0.31-0.79)	1.31 (1.16-1.49)	2.23 (1.34-3.71)	0.52 (0.34-0.81)	1.05 (0.90-1.23)	2.15 (1.25-3.71)
P-value		*0.003*	*<0.001*	*0.002*	*0.004*	*0.543*	*0.006*
Age-group:							
40-54[e]	3416	1.00	1.00	1.00	1.00	1.00	1.00
55-64	2022	1.26 (0.76-2.09)	2.08 (1.76-2.46)	4.06 (2.11-7.79)	1.34 (0.83-2.16)	1.09 (0.90-1.33)	2.91 (1.49-5.68)
65-74	1451	1.47 (0.84-2.55)	3.05 (2.56-3.63)	4.78 (2.38-9.57)	1.27 (0.74-2.15)	1.02 (0.82-1.27)	3.12 (1.53-6.36)
75+	714	1.95 (0.69-5.51)	5.89 (4.76-7.29)	7.55 (3.35-17.02)	1.60 (0.67-3.81)	1.42 (1.08-1.87)	3.47 (1.43-8.40)
P-value		*0.388*	*<0.001*	*<0.001*	*0.535*	*0.085*	*<0.001*
Pack-years[f]:							
0-0.9[e]	4165	1.00	1.00	1.00	1.00	1.00	1.00
1-19.9	1835	1.08 (0.61-1.92)	1.67 (1.42-1.96)	2.84 (1.30-6.23)	1.16 (0.68-2.00)	2.02 (1.63-2.50)	2.58 (1.10-6.01)
20-49.9	1269	3.05 (1.68-5.54)	3.18 (2.70-3.74)	6.70 (3.35-13.40)	2.98 (1.72-5.16)	4.23 (3.44-5.20)	5.74 (2.70-12.20)
50+	334	3.94 (1.70-9.13)	4.15 (3.13-5.49)	18.50 (8.41-40.70)	3.87 (1.81-8.29)	6.83 (4.98-9.37)	17.23 (7.37-40.28)
P-value		*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
NS-SEC[f]:							
Professional[e]	3047	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	1855	0.76 (0.45-1.30)	1.20 (1.02-1.41)	1.84 (0.87-3.87)	0.83 (0.50-1.40)	1.19 (0.97-1.47)	1.57 (0.72-3.44)
Routine	2701	0.93 (0.59-1.48)	1.31 (1.12-1.53)	3.65 (1.89-7.06)	1.08 (0.70-1.67)	1.54 (1.27-1.87)	3.37 (1.70-6.68)
P-value		*0.612*	*0.002*	*<0.001*	*0.632*	*<0.001*	*<0.001*
Sample:							
UKHLS[e]	5675	1.00	1.00	1.00	1.00	1.00	1.00
HSE	1928	2.38 (1.54-3.69)	0.94 (0.81-1.09)	1.92 (1.21-3.05)	2.21 (1.46-3.35)	0.96 (0.79-1.16)	2.13 (1.31-3.48)

P-value	*<0.001*	*0.420*	*0.006*	*<0.001*	*0.664*	*0.002*

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; OR, odds ratios; RRR; relative risk ratios; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts unweighted; RRRs estimated using survey weights.
[b] FTs: Obstruction (FT): FEV_1/FVC <0.70. Diagnosed COPD: HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[c] LLN: Obstruction (LLN): FEV_1/FVC <LLN. Diagnosed COPD: HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[d] The RRR is interpreted as the relative risk of one outcome in relation to the reference category for a specified category of an independent variable compared with the reference category for that independent variable. Using diagnosed alone as an example, the RRR for males *vs.* females is interpreted as the relative risk for diagnosed alone *vs*. neither diagnosed nor objective spirometry for males compared with the analogous relative risk for females, adjusted for the other variables in the model.
[e] Reference category.
[f] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Title: Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

Running head: Comparison of different spirometric cut-offs

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ABSTRACT

Objectives: Consistent estimation of the burden of chronic obstructive pulmonary disease (COPD) has been hindered by differences in methods, including different spirometric cut-offs for impaired lung function. The impact of different definitions on the prevalence of potential airflow obstruction, and its associations with key risk factors, is evaluated using cross-sectional data from two nationally-representative~~general~~ population surveys.

Design: Pooled cross-sectional analysis of Wave 2 of the UK Household Longitudinal Survey and the Health Survey for England 2010, including 7879 participants, aged 40-95 years, who lived in England and Wales, without diagnosed asthma, and with good-quality spirometry data. Potential airflow obstruction was defined using self-reported physician-diagnosed COPD; a fixed threshold (FT) forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70; and an age-, sex-, height- and ethnic-specific lower limit of normal (LLN). Standardised questions elicited self-reported information on demography, smoking history, ethnicity, occupation, respiratory symptoms, and cardiovascular disease.

Results: Consistent across definitions, participants classed with obstructed airflow were more likely to be older, currently smoke, have higher pack-years of smoking, and be engaged in routine occupations. The prevalence of airflow obstruction was 2.8% (95% CI 2.3-3.2), 22.2% (21.2-23.2), and 13.1% (12.2-13.9) according to diagnosed COPD, FT and LLN, respectively. The gap in prevalence between FT and LLN increased in older age-groups. Sex differences in the risk of obstruction, after adjustment for key risk factors, was sensitive to the choice of spirometric cut-off, being significantly higher in men when using FT, compared with no significant difference using LLN.

Conclusions: Applying FT or LLN spirometric cut-offs gives a different picture of the size and distribution of the disease burden. Longitudinal studies examining differences in

unscheduled hospital admissions and risk of death between FT and LLN may inform the choice as to the best way to include spirometry in assessments of airflow obstruction.

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Non-text material: 4 Tables

Keywords: airflow obstruction; chronic obstructive pulmonary disease; fixed thresholds; Health Survey for England; lower limit of normal; respiratory; sensitivity; specificity; spirometry; United Kingdom Household Longitudinal Survey

Strengths and limitations of this study

- Estimates of the burden of chronic obstructive pulmonary disease (COPD) using spirometry data collected in epidemiological studies are inconsistent through differences in methods, including different spirometric cut-offs.
- Our study combined two nationally representative samples of adults living in England and Wales, with standardised protocols and objective measurements of lung function, and a wide-range of clinically-relevant conditions including self-reported respiratory symptoms (chronic cough and phlegm) and breathlessness.
- Consistent definitions and up-to-date reference equations were used, providing baseline data for monitoring purposes in the UK, and for facilitating comparison with international studies.
- Prevalence estimates were based on pre-bronchodilator lung function measurements, and so are likely to overestimate true prevalence.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterised by a progressive decline in lung function.[1;2] 2.9 million deaths were attributed to COPD in 2010, making it the third leading global cause of death.[3] The National Outcomes Strategy for COPD estimated that 835,000 people living in the UK are currently diagnosed with COPD, with a further 2.2 million being undiagnosed.[4] COPD is the second leading ~~most common~~ cause of emergency hospital admission and is one of the most costly diseases in terms of acute hospital care in England.[4]

Healthcare budgeting~~Budgeting of healthcare~~ is often contingent upon the estimated burden of disease. Spirometry, the mainstay of lung function assessment, has been used in nationally-representative surveys to estimate the COPD burden in terms of prevalence, associated comorbidities, and mortality. Estimation of the disease burden has been hindered, however, by differences in methods, including ~~different~~ spirometric cut-offs.[5-8] Fixed thresholds (FTs) use cut-offs for lung function measurements (e.g., forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70) regardless of age, sex, height, and ethnicity.[9] An additional threshold for percent-of-predicted FEV_1 (expected for persons of a given age, sex, height and ethnicity) is also commonly used for severity classification. In contrast, a lower limit of normal (LLN) cut-off uses a statistical definition of abnormal/normal (e.g., below/above the lower 5th percentile of the distribution of age-, sex-, height-, and ethnic-specific FEV_1/FVC values from a healthy, lifelong non-smoking population).[10]

At present, applying FTs such as FEV_1/FVC <0.70 is the standard approach. However, the European Respiratory Society (ERS) Task Force on epidemiology recently advocated using the LLN in epidemiological studies as FTs both overestimate airflow obstruction in older

populations, due to the physiological reduction of FEV_1/FVC with age, and underestimate in young adults, compared with LLN.[11-16] The controversy over FT-versus-LLN thresholds is well-known ~~and has been fiercely debated~~ with no signs of a consensus among expert groups being agreed.[17-21]

Partly as a result of this controversy, the COPD epidemiological database~~, within and across countries,~~ shows heterogeneity in ~~both~~ definitions and consequential estimates of the disease burden.[5;22] Two nationally-representative samples, Wave 2 (2010-2012) of the UK Household Longitudinal Survey (UKHLS, 'Understanding Society') and the Health Survey for England (HSE) 2010, collected lung function data using identical measurement protocols and specialist equipment, providing an opportunity to increase statistical precision by combining both datasets. Therefore, the primary objective of the present study was to compare the prevalence of 'potential' airflow obstruction according to FT- and LLN-thresholds among~~in a representative sample of~~ persons aged 40-95 years living in England and Wales: potential in the sense that the administration of bronchodilators to measure the extent of reversibility in airflow obstruction was not used. As a secondary aim, we compared the sensitivity of associations with risk factors including age, sex, smoking history, and socioeconomic position. Using the same variables, we also examined the characteristics associated with spirometry in connection with self-reported physician-diagnosed COPD.

METHODOLOGY

Study design and setting

~~Two nationally-representative samples, Wave 2 (2010-2012) of the UK Household Longitudinal Survey (UKHLS, 'Understanding Society') and the Health Survey for England (HSE) 2010, were pooled to increase sample size.~~ Both the UKHLS and HSE~~surveys~~ selected

participants using stratified multi-stage probability sampling designs.[23] , with similar measurement protocols and specialist equipment for collecting spirometry.

Self-reported health information, risk factors and demographics was collected through face-to-face interviews, followed by a visit from a trained nurse during which lung function was measured. Response rates for the Wave 2 interview (among individuals issued) and nurse-visit (among eligible participants in the Wave 2 interview) were 61% and 59% respectively in UKHLS. In HSE 2010, interview (among the estimated total number of adults in sampled households) and nurse-visit (adults in co-operating households) response rates were 59% and 57%. Sampling methods are described in detail elsewhere.[24-26] Ethical approval was obtained from the Oxfordshire A (UKHLS) and B (HSE 2010) Research Ethics Committees. Ethical approval for the UKHLS was obtained from the Oxfordshire A Research Ethics Committee (10/H0604/2); approval for HSE 2010 was obtained from the Oxfordshire B Research Ethics Committee (09/H0605/73). Eligible participants gave written consent to participate in spirometry.

Questionnaire and procedures

Participants were excluded from spirometry for the following safety reasons: pregnancy; had in the last 3 months abdominal/ or chest surgery, a heart attack, detached retina or eye or ear surgery; admitted to hospital with a heart complaint in the preceding month; a resting pulse rate >120 beats/minute; or currently taking medications for the treatment of tuberculosis. Spirometry, without bronchodilator use, was conducted using NDD EasyOne PCC spirometers (NDD Medical Technologies, Zurich, Switzerland). , a hand-held, battery-operated device that uses an ultrasonic sensor to measure airflow. Calibration of spirometers was checked with a 3l syringe prior to use the following day. Participants performed the manoeuvre in a sitting position wearing a nose-clip to prevent air leaks during testing.

~~Systematic quality control procedures were used,~~ Quality control was summarised in a session grade based on the number of technically acceptable blows and their reproducibility. ~~Sessions G~~gradesd A (3 acceptable manoeuvres, 2 highest FVC and FEV_1 within 100 ml), B (3 acceptable manoeuvres, 2 highest FVC and FEV_1 within 150 ml), and C (2 or 3 acceptable manoeuvres within 200 ml) were considered good-quality. ~~In HSE, 1 in 4 spirometry sessions were over read by an experienced respiratory physiology consultant.~~ Full details on measurement procedures are available elsewhere.[25-27]

The highest values for FEV_1 and for FVC, from at least 3 and up to 8 blows, were used. Age-, sex-, height-, and ethnic-specific predicted values and Z-scores (FEV_1, FVC and FEV_1/FVC) were computed using the ERS~~European Respiratory Society~~ Global Lungs Initiative (GLI 2012, www.lungfunction.org) reference equations. These have been prepared by an international collaboration based on data spanning 26 countries from ≥~~over~~ 70,000 healthy individuals across four ethnic-groups (Caucasian, African-American, and North- and South-East Asian), valid for persons aged 3-95 years [28;29] and have been shown to fit contemporary Australasian spirometric data.[30]

FT and LLN spirometric cut-offs

Using FTs, we applied the 2007 Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [31], which was designed for use with post-bronchodilator spirometry: potential airflow obstruction was defined as FEV_1/FVC <0.70 (FT). Disease stage was defined by the reduction in FEV_1 relative to percent-of-predicted values as follows: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% predicted); and stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% predicted).[32] Participants with FEV_1/FVC ≥0.70 were defined as non-obstructed.

~~Using the lambda-mu-sigma method (33),~~ ~~P~~participants with FEV_1/FVC <LLN (below the lower 5th percentile of the distribution of Z-scores) were defined as obstructed (LLN). To examine possible heterogeneity among participants with FEV_1/FVC < LLN, ~~d~~Disease stage was defined by FEV_1 relative to LLN as follows: stage I (FEV_1/FVC <LLN and FEV_1 ≥LLN), and stage II (FEV_1/FVC <LLN and FEV_1 <LLN).[33] Participants with FEV_1/FVC ≥LLN were defined as non-obstructed. The 5th percentile was chosen due to its established associations with respiratory symptoms and all-cause mortality.[34]

Physician-diagnosed COPD

In UKHLS, disease status was ascertained through questions asking "*has a doctor or other health professional ever told you that you have [disease]?"* Diagnosed COPD was defined as a positive response to either chronic bronchitis or emphysema. In HSE, diagnosed COPD was defined as a positive response to the question "*did a doctor ever tell you that you had chronic bronchitis, emphysema or COPD?*"

Risk factors, measurements of lung function, and comorbidities

Key subgroups were defined by age (40-54, 55-64, 65-74, 75-95); sex; smoking status (current, former, never); pack-years of cigarette smoking (a cumulative total reflecting the amount and duration of consumption, with 1 pack-year equating to an average of 20 cigarettes smoked/day for 1 year); and socioeconomic position, defined by the National Statistics Socio-Economic Classification (NS-SEC), grouped into professional, intermediate, and routine occupations.

~~Three lung function measurements (~~FEV_1, FVC, and FEV_1/FVC~~,)~~ on a continuous scale, were expressed as percent-of-predicted values. Additional variables included current use of respiratory medicine; area of residence ~~, defined as (~~urban ~~or~~ /rural~~), used as a possible proxy for traffic-related air pollution~~; body mass index (BMI: weight in kilograms divided by the

square of height in metres), grouped into normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obese (≥30 kg/m^2); diagnosed diabetes; poor self-rated health; and reported cardiovascular disease (stroke, angina, myocardial infarction). In HSE, participants were asked to name any long-standing illnesses: respiratory diseases were identified using *International Classification of Diseases, Tenth Revision* codes J00 to J99. Standard questions in the HSE covered a range of respiratory symptoms including wheeze, dyspnoea, chronic cough, and phlegm. In the HSE, presence of respiratory symptoms was defined as usually coughing first thing in the morning, for at least 3 months/year a year, and bringing up phlegm from the chest most days for 3 consecutive months in a year. In the HSE, participants with some limitation of activity due to breathlessness during daily living were identified by a score of 3+ on the Medical Research Council (MRC) dyspnoea scale, a validated method of categorising patients with COPD in terms of their disability (35). Exposure to passive smoking in the HSE was measured by reported number of weekly hours/week currently exposed to cigarette smoke (0, 1-9, and ≥10 hours).

Statistical analyses

A lower age limit was used of 40 years was used due to the low prevalence of non-asthma airflow obstruction in the youngest age-groups.[35] As bronchodilators were not used, we excluded participants who reported diagnosed asthma.[34;36-38] Five sets of analyses were conducted across the categories of diagnosed COPD, FT, and LLN. First, participants' characteristics (demographics, health information, risk factors, comorbidities and percent-of-predicted FEV_1, FVC, and FEV_1/FVC) were summarised as means, accompanied by standard deviations, or as counts accompanied by percentages. Participants were counted under each relevant definition. Participants with/without obstruction were compared using the χ^2 test and analysis of variance for categorical and continuous variables respectively.[39]

Secondly, prevalence estimates were computed for a subset of socio-demographic variables defined by age, sex, smoking status, pack-years of cigarette smoking, and NS-SEC. Thirdly, in the absence of a gold standard, we calculated the sensitivity and specificity of each spirometric criterion, using the alternative cut-off as the reference standard.[40]

Fourth, regression analyses were performed using age, sex, pack-years of smoking, and NS-SEC as independent variables with airflow obstruction as outcome. Current smoking status could not be entered in the same model as pack-years due to significant collinearity. The dependent variable based on FTs had 4 categories: non-obstructed, stage I, stage II, and stage III+. The LLN-derived outcome had 3 categories: non-obstructed, stage I, and stage II. In each case, multinomial logistic regression~~s~~ was~~ere~~ used to estimate relative risk ratios (RRRs), with non-obstructed as the reference category. Multinomial logistic regression generalises logistic regression to outcomes with more than two possible discrete outcomes. The RRR is interpreted as the relative risk of one outcome in relation to the reference category for a specified category of an independent variable compared with the reference.[41;42] Diagnosed COPD was analysed as a binary outcome~~dependent variable~~ (not reported/reported): logistic regression was therefore used to estimate odds ratios (ORs).[39;41] The overall association for~~with categorical~~ independent variables with >2 categories was computed using the adjusted Wald test. The likelihood-ratio test was used to estimate the statistical significance of interaction terms: non-significant terms were excluded, and models refitted with only the main effects.

Fifth, to examine risk factors associated with possible under-diagnosis, a four-category outcome variable was created combining diagnosed COPD and spirometric criteria as follows: (1) neither diagnosed nor spirometrically-defined obstruction; (2) physician-diagnosed COPD but no obstructive spirometry; (3) spirometrically-defined but no diagnosed

COPD; and (4) both diagnosed and obstructive spirometry.[43] FT and LLN cut-offs were analysed separately. RRRs generated from multinomial logistic regressions were used to examine associations between the same set of risk factors listed above and the composite dependent variable.

Participants with missing values on covariates were excluded from relevant analyses. Tests of statistical significance were based on two-sided probability (P<0.05). Dataset preparation was performed in SPSS 20.0 (SPSS IBM Inc., Chicago, Illinois, USA), Stata 13.1 (StataCorp, College Station, Texas, USA) and R (version 3.0.3; R Foundation, www.r-project.org). Analysis was conducted in Stata accounting for the complex design of both surveys, using the appropriate weighting variables and Primary Sampling Units. Both datasets are available via the UK Data Service (www.ukdataservice.ac.uk).

Sensitivity analyses

Analyses were initially undertaken excluding participants with reported diagnosed asthma and then repeated including those with asthma. In accordance with previous~~the~~ UK National Institute for Health and Care Excellence (NICE) recommendations~~criteria~~ [44], comparisons between FT and LLN were rerun defining only the subset of FT participants with FEV_1 <80% predicted (i.e., stage II+) as having obstructed airflow.

RESULTS

The analytical sample comprised 7879 participants (5936 and 1943 from UKHLS and HSE respectively) aged 40-95 years, who resided in England and Wales, did not report diagnosed asthma, had valid values of height and ethnicity, and provided good-quality spirometry. Response flowcharts for the UKHLS and HSE are provided in Figures **S1** and **S2** (online supplementary appendix) respectively. Excluded participants were more likely to be older, engaged in routine occupations, and self-report respiratory symptoms (data not shown). Differences between the UKHLS and HSE in terms of sex ratio, age, smoking history, NS-SEC, and objective measurements of lung function were not materially important (see online supplementary Table S1).

Descriptive characteristics of the analytical sample according to physician-diagnosed COPD, FT, and LLN are shown as supplementary data (Tables **S2-S3**). Overall, 46.8% of participants were male, with mean age 57.6 years (SD 12.3), 16.6% were current smokers, 4.6% had >50 pack-years of cigarette smoking, and 36.5% were engaged in professional occupations. 12 (0.1%) and 265 (3.2%) participants had missing values for pack-years and NS-SEC respectively. The prevalence of ~~reported~~ diagnosed COPD was similar between the sexes (P=0.349), but was higher for men using FT and LLN (both P<0.001). Participants with diagnosed COPD/obstructive spirometry were more likely to be older, currently smoke, have higher pack-years of smoking, and be engaged in routine occupations (all P<0.001). Prevalence of diagnosed COPD was higher in HSE *vs.* UKHLS (P<0.001), but survey-specific prevalence was similar for FT and for LLN. Participants with diagnosed COPD/obstructive spirometry were more likely to report respiratory symptoms (chronic cough and phlegm) and disease, current use of respiratory medications, cardiovascular disease, breathlessness, poor self-rated health and have, on average, lower (percent-of-predicted) values of FEV_1, FVC and FEV_1/FVC. The prevalence of respiratory symptoms

was 13.7%, 10.2%, and 11.3% among participants classed as having airflow obstruction according to diagnosed COPD, FT, and LLN respectively; prevalence of having a score of 3+ on the MRC dyspnoea scale was 34.8%, 12.3% and 15.9%.

Prevalence of airflow obstruction

The prevalence of airflow obstruction was 2.8%, 22.2%, and 13.1% using diagnosed COPD, FT, and LLN respectively (**Table 1**). Using FTs, 11.6%, 8.9%, and 1.7% of participants were classed as stage I, stage II, and stage III+ respectively. LLN-derived obstruction was 6.6% (stage I) and 6.4% (stage II). For most subgroups, prevalence was highest for FT and lowest for diagnosed COPD, with LLN falling in-between. The gap in prevalence between FT and LLN increased in older age-groups. Prevalence among participants aged 40-54 years was 11.9% and 10.7% using FT and LLN respectively. Prevalence among participants aged 75-95 ~~years~~ was 45.0% and 17.2%.

Table 2 shows estimates of sensitivity and specificity for FT and LLN, using the alternative spirometric cut-off as the reference standard. When using LLN as reference, specificity - the percentage of participants classed as non-obstructed using LLN identified as non-obstructed using FT – decreased from 94.9% amongst participants aged 40-64 years to 74.4% amongst those aged 65-95 ~~years~~.

Multivariate analyses of airflow obstruction

Table 3 shows the significant risk factors for diagnosed COPD, and the FT- and LLN-disease stage classifications (non-obstructed as reference category). For diagnosed COPD, the significant interaction between sex and age-group (P=0.022) suggested no difference in odds between the sexes among participants aged 40-64 years, but higher odds among men aged 65-95 ~~years~~. Using FTs, being male was associated with a significantly increased risk of airflow obstruction: RRR 1.35 (95% CI: 1.16-1.58), RRR 1.35 (1.12-1.63), and RRR 1.72 (1.08-2.76)

for stages I, II, and III+ respectively. In contrast, sex differences were not significant using LLN: RRR 1.07 (0.88-1.31) for stage I, and RRR 1.20 (0.96-1.50) for stage II.

Odds of diagnosed COPD increased significantly with age only in men (P=0.022 for the interaction term). Using non-obstruction as reference, RRRs increased significantly with age when using FTs (P<0.001 for each stage). The age-related difference using LLN was more marked for stage II (P=0.492 and P<0.001 for stages I and II, respectively). A dose-related increased risk with pack-years of cigarette smoking was observed across each definition (P<0.001). The difference between NS-SEC levels was more marked with diagnosed COPD (P=0.012) and the tightest ~~most restrictive~~ FT- and LLN-definitions~~categories~~ (FT: P=0.002 stage III+; LLN: P<0.001 stage II).

Combination of diagnosed COPD and spirometric cut-offs

The significant risk factors for the two four-category outcome variables created as a composite of diagnosed COPD and obstructive spirometry are shown in **Table 4**. Relative to the reference category (neither doctor-diagnosed nor spirometrically-defined airflow obstruction), the risk of reporting~~having obstructed airflow using diagnosed~~ COPD in the absence of~~but no~~ obstructive spirometry was significantly lower in men using either spirometric criterion (FT: RRR 0.53 (95% CI: 0.32-0.87); LLN: RRR 0.56 (0.35-0.89)). The risk of having obstructed airflow using spirometry but with no diagnosed COPD – thereby indicating possible under-diagnosis - was significantly higher in men, and in older age-groups, when using FT but not LLN. For both spirometric criterion, increases in risk with increasing pack-years of cigarette smoking, relative to the reference, was consistent across combinations of COPD/obstructive spirometry; the difference between NS-SEC levels was more marked for obstructive spirometry.

Sensitivity analyses

Repeating analyses by including 1183 participants with reported diagnosed asthma increased prevalence of diagnosed COPD, FT and LLN by 2-3 percentage points (Figure **S3**, online supplementary appendix), but showed~~led to~~ similar patterns of association with risk factors. Diagnosed asthma was a strong predictor of diagnosed COPD and obstructive spirometry (P<0.001, data not shown).

Narrowing~~Restricting~~ FT-defined obstruction to the subset of FT participants with FEV_1 <80% predicted (i.e., stage II+) more than halved the FT-derived prevalence (22.2% *vs*. 10.6%). Amongst participants aged 65-95 years, specificity using LLN as the reference standard was 74.4% and 91.1% for FT and FT stage II+ respectively (**Table 2**). Patterns of association with risk factors using FT stage II+ was similar to those shown for FT.

DISCUSSION

Consistent estimation of the COPD burden has been hindered by differences in methods, including disagreement among experts ~~groups~~ over the choice of FT-versus-LLN spirometric cut-offs.[5-8] In this study, we combined two nationally-representative ~~general population~~ surveys, with standardised protocols and objective lung function measurements, to evaluate the impact of different definitions on the prevalence of potential airflow obstruction, and its associations with key risk factors. Participants with diagnosed COPD/obstructive spirometry were more likely to be older, currently smoke, have higher pack-years of cigarette smoking, be in lower socioeconomic groups, and report the presence of respiratory symptoms (chronic cough and phlegm), cardiovascular disease, breathlessness, and poor self-rated health. Among persons aged 40-95 years without physician-diagnosed asthma, prevalence was 2.8%, 22.2%, and 13.1%, according to diagnosed COPD, FT, and LLN respectively. The gap in prevalence between FT and LLN increased in older age-groups. When using LLN as the reference standard, specificity for FT decreased from 94.9% amongst participants aged 40-64 years to 74.4% amongst participants aged 65-95 ~~years~~, corresponding to false-positive rates of 5.1% and 25.6% respectively. Sex differences in the risk of obstructed airflow, after adjustment for potential confounders, was sensitive to spirometric criteria, being higher among~~in~~ men for FT, compared with no difference using LLN.

Strengths and limitations

Analyses were based on nationally-representative samples, ~~random samples of the general population~~, with identical measurement protocols and specialist equipment for collecting lung function data. ~~spirometry conducted by well-trained and supervised nurses using standardised protocols and modern, validated equipment.~~ ~~Combining two datasets ensured a sufficient sample size to estimate prevalence, and infer valid statistical associations.~~ Combining the HSE and UKHLS datasets increased statistical precision for spirometry-based estimates,

particularly for population subgroups, and allowed detailed analyses to be conducted.

Predicted values and Z-scores were obtained from~~defined using~~ the ERS~~recently developed European Respiratory Society~~ GLI 2012 reference equations [28], facilitating inclusion of older participants, non-white populations and comparability with international studies. Our study has a number of limitations. Reversibility in airflow obstruction could not be assessed due to bronchodilators not being used. Spirometry-based prevalence, therefore, may be overestimated. Analysis of the National Health and Nutrition Examination Survey (NHANES) 2007-2010 showed that FT- and LLN-prevalence estimates among US adults aged 40-79 years decreased, in relative terms, by approximately one-third after administration of bronchodilators.[45] Although recent guidelines from NICE~~the National Institute for Health and Care Excellence~~ [46] and ERS~~European Respiratory Society~~ [13] recommend use of post-bronchodilator spirometry to confirm the presence of airflow obstruction, debate continues over its use in epidemiological settings, with the arguments against including ethical issues such as possible side-effects and contraindications.[47] Potential misclassification of disease status through bronchodilators not being used was reduced by excluding participants with physician-diagnosed asthma. Some participants in the analytical sample, however, may be undiagnosed asthmatics. On the other hand, the disease burden may be underestimated through excluding participants with poor-quality spirometry. Participation in spirometry, and achievement of good-quality standards among participants with any spirometry data, was higher among participants of younger age, engaged in professional/managerial occupations, non-smokers, and with no ~~self-reported~~ physician-diagnosed ~~chronic bronchitis, emphysema or~~ COPD. Lower survey participation rates amongst socio-demographic groups at higher risk of airflow obstruction (e.g., older persons, lower socioeconomic groups) would also have led to an underestimation of true prevalence. These limitations, however, are unlikely to affect comparisons across definitions, but may have led to an underestimate of risk associations.

The list of health conditions in the UKHLS interview programme included chronic bronchitis and emphysema but not COPD, leading to potential underestimation of self-reported physician-diagnosed COPD.

Comparisons with previous studies

Earlier analyses of HSE~~ealth Survey for England~~ data [36;38;48] used older ~~sets of~~ reference equations [49;50] applicable only to white~~, and~~ younger populations. Nevertheless, estimates of prevalence and their substantive conclusions of higher prevalence using FT-versus-LLN, with a widening gap in prevalence in older age-groups, and sex differences when using FT but not LLN were similar to ours: confirming findings reported in the US [45], Europe [51], Korea [16], internationally [12], and in recent literature reviews.[6;52] A further strength of our study was the wide range of clinically-relevant conditions examined in the context of disease-staging, with higher prevalence of ~~self-reported~~ respiratory symptoms, respiratory- and cardiovascular-disease, breathlessness, and poor self-rated health among participants in the tightest definitions of~~most restrictive~~ FT- and LLN-obstruction~~categories~~, confirming similar findings in the US.[53;54] Whilst recent guidelines [13;46;55] recommend adopting multidimensional definitions of respiratory disease, our study outcomes were defined only using spirometry. While we acknowledge the merits of a multidimensional approach, and agree that neither spirometric cut-off is able to fully characterise the complex diagnostic features of COPD [56], our primary aim was to use up-to-date survey data to evaluate differences in prevalence according to FT- and LLN-thresholds, to provide baseline data for monitoring purposes in the UK, and promote comparability with international studies. Current recommendations regarding symptom criteria are less specific than those for spirometry. We chose, therefore, to examine the associations between disease-staging assessed only using spirometry and presence of respiratory symptoms, rather than broaden the definition of disease.

Implications

Recent UK studies used administrative primary-care databases to report the number of diagnosed and treated patients, thereby missing undiagnosed cases. Such studies have reported prevalence below 2%.[57;58] The disparity in prevalence from clinical-versus-epidemiological studies led to the development of the COPD prevalence model, with the HSE 2001 used as input data, to more accurately estimate prevalence.[59] In accordance with previous NICE~~National Institute for Health and Care Excellence~~ recommendations ~~criteria~~[44], COPD is currently defined in the model as FT stage II+ (FEV_1/FVC <0.70 and FEV_1 <80% predicted), with the logistic regression models showing sharp increases with age and a modifying effect of gender.[60;61] Similar to the findings reported by Jordan et al. [36], our study shows that the strength of association between risk factors and airflow obstruction varies according to spirometric criterion, with age- and sex-differences in risk being more marked for FT, and for FT stage II+, than LLN. In the absence of agreement among expert ~~group~~s, policy-makers, clinicians, and researchers building the COPD epidemiological database, it is important to appreciate the sensitivity of estimates of the disease burden, and its distribution across socio-demographic groups, to differences in methods, including spirometric cut-offs.

The prevalence of reported physician-diagnosed COPD in our study was 2.8%, considerably lower than spirometry-based estimates, possibly indicating considerable under-recognition by both participants and physicians. Using the tightest ~~most restricted~~ definitions, prevalence of physician-diagnosed COPD among participants with obstructive spirometry was 30.2% (FT stage III+) and 14.7% (LLN stage II). Similar low rates of physician-diagnosis among participants meeting spirometric criteria have been reported in New Zealand.[62]

Spirometrically-defined airflow obstruction but no diagnosed COPD does not necessarily indicate under-diagnosis. Definitive diagnosis requires further information on all relevant clinical factors, particularly respiratory symptoms and smoking history, as well as post-bronchodilator spirometry.

Conclusion

In summary, we have enhanced the COPD epidemiological database by evaluating the impact of different definitions on the prevalence of potential airflow obstruction and its associations with key risk factors and comorbidities. With no gold standard currently available, longitudinal studies examining differences in unscheduled hospital admissions and risk of death between FT and LLN may inform the choice as to the best way to include spirometricy data in multidimensional assessments of airflow obstruction in both clinical and epidemiological settings.

Abbreviations: COPD, chronic obstructive pulmonary disease; ERS, European Respiratory Society; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FT, fixed thresholds; GLI, Global Lungs Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HSE, Health Survey for England; LLN, lower limit of normal; NICE, National Institute for Health and Care Excellence; UKHLS, United Kingdom Household Longitudinal Survey

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Data sharing: Both datasets are available via the UK Data Service (www.ukdataservice.ac.uk). Statistical code is available from the corresponding author at s.scholes@ucl.ac.uk.

Contributors: SS, AM, and JM participated in study concept and design, analysis and interpretation of data. SS performed data acquisition and management. SS participated in drafting of the manuscript. AM and JM aided revision of the manuscript and provided relevant intellectual input. SS is the data guarantor. All authors have approved the final version of the manuscript.

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Table 1 Prevalence of Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

		Diagnosed-COPD[b]	Fixed Thresholds[c]				Lower Limit of Normal[d]		
			Obstructed	stage I	stage II	stage III+	Obstructed	stage I	stage II
	n	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
All	7879	2.8 (2.3-3.2)	22.2 (21.2-23.2)	11.6 (10.9-12.4)	8.9 (8.2-9.6)	1.7 (1.3-2.0)	13.1 (12.2-13.9)	6.6 (6.0-7.3)	6.4 (5.8-7.0)
Sex:									
Males	3335	3.0 (2.3-3.6)	26.3 (24.8-27.9)	13.2 (12.1-14.4)	10.7 (9.6-11.8)	2.4 (1.8-3.0)	15.0 (13.7-16.4)	7.2 (6.2-8.1)	7.9 (6.9-8.9)
Females	4544	2.6 (2.0-3.1)	18.6 (17.4-19.9)	10.2 (9.2-11.2)	7.4 (6.5-8.2)	1.0 (0.7-1.4)	11.3 (10.3-12.3)	6.2 (5.4-6.9)	5.1 (4.4-5.9)
Age-group:									
40-54	3472	1.7 (1.3-2.2)	11.9 (10.7-13.1)	7.0 (6.1-7.9)	4.6 (3.8-5.4)	0.3 (0.1-0.6)	10.7 (9.6-11.9)	6.7 (5.7-7.6)	4.1 (3.3-4.9)
55-64	2072	3.4 (2.5-4.2)	24.2 (22.2-26.1)	12.6 (11.1-14.1)	9.5 (8.1-10.9)	2.0 (1.4-2.7)	14.2 (12.6-15.8)	6.5 (5.4-7.7)	7.7 (6.4-8.9)
65-74	1557	3.9 (2.8-5.0)	32.6 (30.1-35.1)	16.5 (14.6-18.5)	12.9 (11.1-14.6)	3.2 (2.1-4.2)	15.0 (13.0-17.0)	6.4 (5.1-7.7)	8.6 (7.0-10.2)
75-95	778	3.9 (2.0-5.8)	45.0 (41.1-48.8)	21.1 (18.0-24.2)	19.6 (16.6-22.6)	4.3 (2.5-6.0)	17.2 (14.2-20.1)	7.2 (5.2-9.2)	9.9 (7.6-12.3)
Smoking status:									
Current	1198	4.7 (3.5-6.0)	37.0 (34.1-39.9)	14.5 (12.3-16.6)	18.2 (15.9-20.6)	4.2 (3.0-5.4)	29.8 (27.0-32.6)	13.5 (11.3-15.7)	16.2 (14.0-18.5)
Ex-regular	2547	3.6 (2.7-4.5)	26.8 (24.9-28.7)	14.1 (12.7-15.6)	10.5 (9.2-11.8)	2.2 (1.5-2.9)	14.5 (13.0-16.1)	7.2 (6.0-8.3)	7.4 (6.2-8.5)
Never	4134	1.6 (1.2-2.0)	14.7 (13.5-15.9)	9.2 (8.2-10.1)	5.0 (4.3-5.7)	0.5 (0.2-0.9)	6.8 (5.9-7.7)	4.1 (3.5-4.8)	2.7 (2.1-3.3)
Pack-years[e]:									
0-0.9	4299	1.6 (1.2-2.0)	14.8 (13.6-16.0)	9.3 (8.4-10.3)	5.0 (4.3-5.7)	0.5 (0.2-0.8)	6.7 (5.9-7.6)	4.1 (3.5-4.7)	2.6 (2.0-3.2)
1-19.9	1905	2.3 (1.5-3.1)	22.3 (20.3-24.3)	12.9 (11.3-14.5)	7.5 (6.2-8.8)	1.9 (1.1-2.6)	13.4 (11.7-15.1)	7.6 (6.3-8.9)	5.8 (4.6-7.0)
20-49.9	1318	5.0 (3.6-6.5)	36.8 (34.0-39.6)	15.7 (13.5-17.9)	18.1 (15.9-20.4)	2.9 (2.0-3.9)	25.4 (22.8-27.9)	11.6 (9.5-13.6)	13.8 (11.8-15.8)
50+	345	10.5 (7.0-14.1)	53.7 (48.0-59.4)	16.0 (12.0-20.1)	28.0 (23.0-32.9)	9.7 (6.2-13.2)	39.3 (33.5-45.0)	12.4 (8.7-16.2)	26.9 (21.6-32.1)
NS-SEC[e]:									
Professional	3050	1.9 (1.4-2.4)	17.1 (15.7-18.5)	10.4 (9.3-11.6)	5.7 (4.9-6.5)	1.0 (0.6-1.4)	9.1 (8.0-10.2)	5.6 (4.6-6.5)	3.6 (2.9-4.3)
Intermediate	1859	2.3 (1.6-3.0)	21.9 (19.9-23.9)	12.5 (10.9-14.1)	8.4 (7.0-9.7)	1.1 (0.5-1.7)	12.0 (10.5-13.5)	6.6 (5.4-7.8)	5.4 (4.3-6.5)
Routine	2705	4.0 (3.1-4.8)	26.6 (24.7-28.5)	11.6 (10.3-12.9)	12.3 (10.9-13.7)	2.7 (2.0-3.5)	17.4 (15.8-19.1)	7.7 (6.6-8.9)	9.7 (8.4-11.0)

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in 1 second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the lower 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts are unweighted; prevalence estimates were weighted.
[b] HSE: reported diagnosed COPD, bronchitis or emphysema; UKHLS: diagnosed bronchitis or emphysema.
[c] FTs: Obstruction (FT): $FEV_1/FVC < 0.70$. Staging classification: stage I ($FEV_1/FVC < 0.70$ and $FEV_1 \geq 80\%$ of predicted); stage II ($FEV_1/FVC < 0.70$ and FEV_1 50-79% of predicted); stage III+ ($FEV_1/FVC < 0.70$ and $FEV_1 < 50\%$ of predicted).
[d] LLN: Obstruction (LLN): $FEV_1/FVC <$ LLN. Staging classification: stage I ($FEV_1/FVC <$ LLN and $FEV_1 >$ LLN); stage II ($FEV_1/FVC <$ LLN and $FEV_1 <$ LLN).
[e] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table 2 Sensitivity and Specificity of Fixed Thresholds and Lower Limit of Normal Spirometric Criteria by Age-group, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)

	40-64 (*n*=5544)	**65-95** (*n*=2335)	**40-64** (*n*=5544)	**65-95** (*n*=2335)
	FT using LLN as reference standard		**LLN using FT as reference standard**	
False positives, (%)	5.1	25.6	0.4	0.0
False negatives, (%)	2.5	0.0	28.0	57.6
Sensitivity	0.975	1.000	0.720	0.424
Specificity	0.949	0.744	0.996	1.000
PPV	0.720	0.424	0.975	1.000
NPV	0.996	1.000	0.949	0.744
Kappa coefficient	0.801	0.479	0.801	0.479
Likelihood ratio positive	18.98	3.90	200.65	N/A
Likelihood ratio negative	0.027	0.000	0.281	0.576
	FT (stage II+) using LLN as reference standard		**LLN using FT (stage II+) as reference standard**	
False positives, (%)	1.3	8.9	6.3	5.2
False negatives, (%)	49.2	26.7	16.0	39.1
Sensitivity	0.508	0.733	0.840	0.609
Specificity	0.987	0.911	0.937	0.948
PPV	0.840	0.609	0.508	0.733
NPV	0.937	0.948	0.987	0.911
Kappa coefficient	0.597	0.596	0.597	0.596
Likelihood ratio positive	38.82	8.28	13.27	11.67
Likelihood ratio negative	0.499	0.292	0.170	0.412

Abbreviations used: FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NPV, negative predictive value; PPV, positive predictive value; UKHLS, United Kingdom Household Longitudinal Survey.

Table 3 Results of Logistic and Multinomial Logistic Regressions for Reported Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria Among Persons Aged 40-95 years, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

Characteristics		Diagnosed-COPD[b]	Fixed Thresholds[c]			Lower Limit of Normal[d]	
			Non-obstructed as reference			Non-obstructed as reference	
			stage I	stage II	stage III+	stage I	stage II
	N	OR (95% CI)	RRR (95% CI)[e]	RRR (95% CI)[e]	RRR (95% CI)[e]	RRR (95% CI)[e]	RRR (95% CI)[e]
Sex:							
Females[f]	4372	1.00	1.00	1.00	1.00	1.00	1.00
Males	3231	0.60 (0.34-1.05)	1.35 (1.16-1.58)	1.35 (1.12-1.63)	1.72 (1.08-2.76)	1.07 (0.88-1.31)	1.20 (0.96-1.50)
P-value		*0.075*	*<0.001*	*0.002*	*0.024*	*0.503*	*0.107*
Age-group:							
40-54[f]	3416	1.00	1.00	1.00	1.00	1.00	1.00
55-64	2022	1.66 (1.07-2.58)	2.00 (1.63-2.45)	2.13 (1.65-2.73)	6.05 (2.82-12.99)	0.92 (0.72-1.18)	1.57 (1.20-2.06)
65-74	1451	0.96 (0.54-1.70)	2.85 (2.30-3.53)	3.01 (2.32-3.89)	10.11 (4.55-22.49)	0.83 (0.63-1.09)	1.56 (1.16-2.12)
75+	714	1.20 (0.39-3.70)	4.72 (3.66-6.07)	6.67 (5.00-8.90)	22.26 (9.45-52.44)	1.06 (0.74-1.51)	2.20 (1.52-3.17)
P-value		*0.104*	*<0.001*	*<0.001*	*<0.001*	*0.492*	*<0.001*
Pack-years[g]:							
0-0.9[f]	4165	1.00	1.00	1.00	1.00	1.00	1.00
1-19.9	1835	1.38 (0.88-2.17)	1.61 (1.34-1.93)	1.66 (1.29-2.15)	3.82 (1.80-8.14)	1.94 (1.51-2.49)	2.22 (1.58-3.12)
20-49.9	1269	2.91 (1.91-4.45)	2.30 (1.86-2.85)	4.56 (3.64-5.72)	5.91 (2.81-12.45)	3.39 (2.61-4.41)	5.43 (3.98-7.41)
50+	334	5.64 (3.45-9.22)	2.34 (1.63-3.35)	6.83 (4.85-9.63)	17.27 (7.88-37.84)	4.50 (2.96-6.84)	11.20 (7.59-16.52)
P-value		*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
NS-SEC[g]:							
Professional[f]	3047	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	1855	1.03 (0.68-1.58)	1.18 (0.97-1.45)	1.34 (1.04-1.72)	1.01 (0.51-2.00)	1.14 (0.88-1.48)	1.35 (0.99-1.85)
Routine	2701	1.61 (1.13-2.31)	1.07 (0.89-1.29)	1.82 (1.47-2.26)	2.30 (1.36-3.88)	1.28 (1.01-1.63)	2.18 (1.67-2.85)
P-value		*0.012*	*0.246*	*<0.001*	*0.002*	*0.123*	*<0.001*
Sample:							
UKHLS[f]	5675	1.00	1.00	1.00	1.00	1.00	1.00
HSE	1928	2.22 (1.60-3.07)	0.95 (0.79-1.14)	0.97 (0.79-1.20)	0.99 (0.62-1.59)	1.05 (0.82-1.33)	0.99 (0.77-1.26)
P-value		*<0.001*	*0.587*	*0.798*	*0.967*	*0.716*	*0.913*
Males × age-group:							

40-54[e]	1319	1.00	-	-	-	-	-
55-64	876	1.16 (0.54-2.45)	-	-	-	-	-
65-74	664	3.21 (1.40-7.39)	-	-	-	-	-
75+	372	2.61 (0.67-10.22)	-	-	-	-	-
P-value		*0.022*	-	-	-	-	-

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; OR, odds ratios; RRR; relative risk ratios; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts are unweighted; ORs and RRRs were weighted.

[b] HSE: reported diagnosed COPD, bronchitis or emphysema; UKHLS: diagnosed bronchitis or emphysema.

[c] FTs: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% of predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% of predicted); stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% of predicted). Reference category: FEV_1/FVC ≥0.70.

[d] LLN: stage I (FEV_1/FVC <LLN and FEV_1 >LLN); stage II (FEV_1/FVC <LLN and FEV_1 <LLN). Reference category: FEV_1/FVC ≥LLN.

[e] The RRR is interpreted as the relative risk of one outcome in relation to the reference category for a specified category of an independent variable compared with the reference category for that independent variable. Using FT stage I as an example, the RRR for males *vs.* females is interpreted as the relative risk for FT stage I *vs.* non-obstruction for males compared with the analogous relative risk for females, adjusted for the other variables in the model.

[f] Reference category.

[g] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table 4 Results of Multinomial Logistic Regressions for Combined Outcome Variable Based on Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometric Criteria Among Persons aged 40-95 years, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-12)[a]

Characteristics		Fixed Thresholds[b]			Lower Limit of Normal[c]		
		Neither diagnosed nor obstructive spirometry as reference			Neither diagnosed nor obstructive spirometry as reference		
		Diagnosed alone	Obstructive spirometry alone	Diagnosed and obstructive spirometry	Diagnosed alone	Obstructive spirometry alone	Diagnosed and obstructive spirometry
	n	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]	RRR (95% CI)[d]
Sex:							
Females[e]	4372	1.00	1.00	1.00	1.00	1.00	1.00
Males	3231	0.49 (0.31-0.79)	1.31 (1.16-1.49)	2.23 (1.34-3.71)	0.52 (0.34-0.81)	1.05 (0.90-1.23)	2.15 (1.25-3.71)
P-value		*0.003*	*<0.001*	*0.002*	*0.004*	*0.543*	*0.006*
Age-group:							
40-54[e]	3416	1.00	1.00	1.00	1.00	1.00	1.00
55-64	2022	1.26 (0.76-2.09)	2.08 (1.76-2.46)	4.06 (2.11-7.79)	1.34 (0.83-2.16)	1.09 (0.90-1.33)	2.91 (1.49-5.68)
65-74	1451	1.47 (0.84-2.55)	3.05 (2.56-3.63)	4.78 (2.38-9.57)	1.27 (0.74-2.15)	1.02 (0.82-1.27)	3.12 (1.53-6.36)
75+	714	1.95 (0.69-5.51)	5.89 (4.76-7.29)	7.55 (3.35-17.02)	1.60 (0.67-3.81)	1.42 (1.08-1.87)	3.47 (1.43-8.40)
P-value		*0.388*	*<0.001*	*<0.001*	*0.535*	*0.085*	*<0.001*
Pack-years[f]:							
0-0.9[e]	4165	1.00	1.00	1.00	1.00	1.00	1.00
1-19.9	1835	1.08 (0.61-1.92)	1.67 (1.42-1.96)	2.84 (1.30-6.23)	1.16 (0.68-2.00)	2.02 (1.63-2.50)	2.58 (1.10-6.01)
20-49.9	1269	3.05 (1.68-5.54)	3.18 (2.70-3.74)	6.70 (3.35-13.40)	2.98 (1.72-5.16)	4.23 (3.44-5.20)	5.74 (2.70-12.20)
50+	334	3.94 (1.70-9.13)	4.15 (3.13-5.49)	18.50 (8.41-40.70)	3.87 (1.81-8.29)	6.83 (4.98-9.37)	17.23 (7.37-40.28)
P-value		*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*	*<0.001*
NS-SEC[f]:							
Professional[e]	3047	1.00	1.00	1.00	1.00	1.00	1.00
Intermediate	1855	0.76 (0.45-1.30)	1.20 (1.02-1.41)	1.84 (0.87-3.87)	0.83 (0.50-1.40)	1.19 (0.97-1.47)	1.57 (0.72-3.44)
Routine	2701	0.93 (0.59-1.48)	1.31 (1.12-1.53)	3.65 (1.89-7.06)	1.08 (0.70-1.67)	1.54 (1.27-1.87)	3.37 (1.70-6.68)
P-value		*0.612*	*0.002*	*<0.001*	*0.632*	*<0.001*	*<0.001*
Sample:							
UKHLS[e]	5675	1.00	1.00	1.00	1.00	1.00	1.00
HSE	1928	2.38 (1.54-3.69)	0.94 (0.81-1.09)	1.92 (1.21-3.05)	2.21 (1.46-3.35)	0.96 (0.79-1.16)	2.13 (1.31-3.48)

P-value	*<0.001*	*0.420*	*0.006*	*<0.001*	*0.664*	*0.002*

Abbreviations used: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); NS-SEC, National Statistics Socio-Economic Classification; OR, odds ratios; RRR; relative risk ratios; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts unweighted; RRRs estimated using survey weights.

[b] FTs: Obstruction (FT): FEV_1/FVC <0.70. Diagnosed COPD: HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.

[c] LLN: Obstruction (LLN): FEV_1/FVC <LLN. Diagnosed COPD: HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.

[d] The RRR is interpreted as the relative risk of one outcome in relation to the reference category for a specified category of an independent variable compared with the reference category for that independent variable. Using diagnosed alone as an example, the RRR for males *vs.* females is interpreted as the relative risk for diagnosed alone *vs.* neither diagnosed nor objective spirometry for males compared with the analogous relative risk for females, adjusted for the other variables in the model.

[e] Reference category.

[f] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

SUPPLEMENTARY DATA

Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

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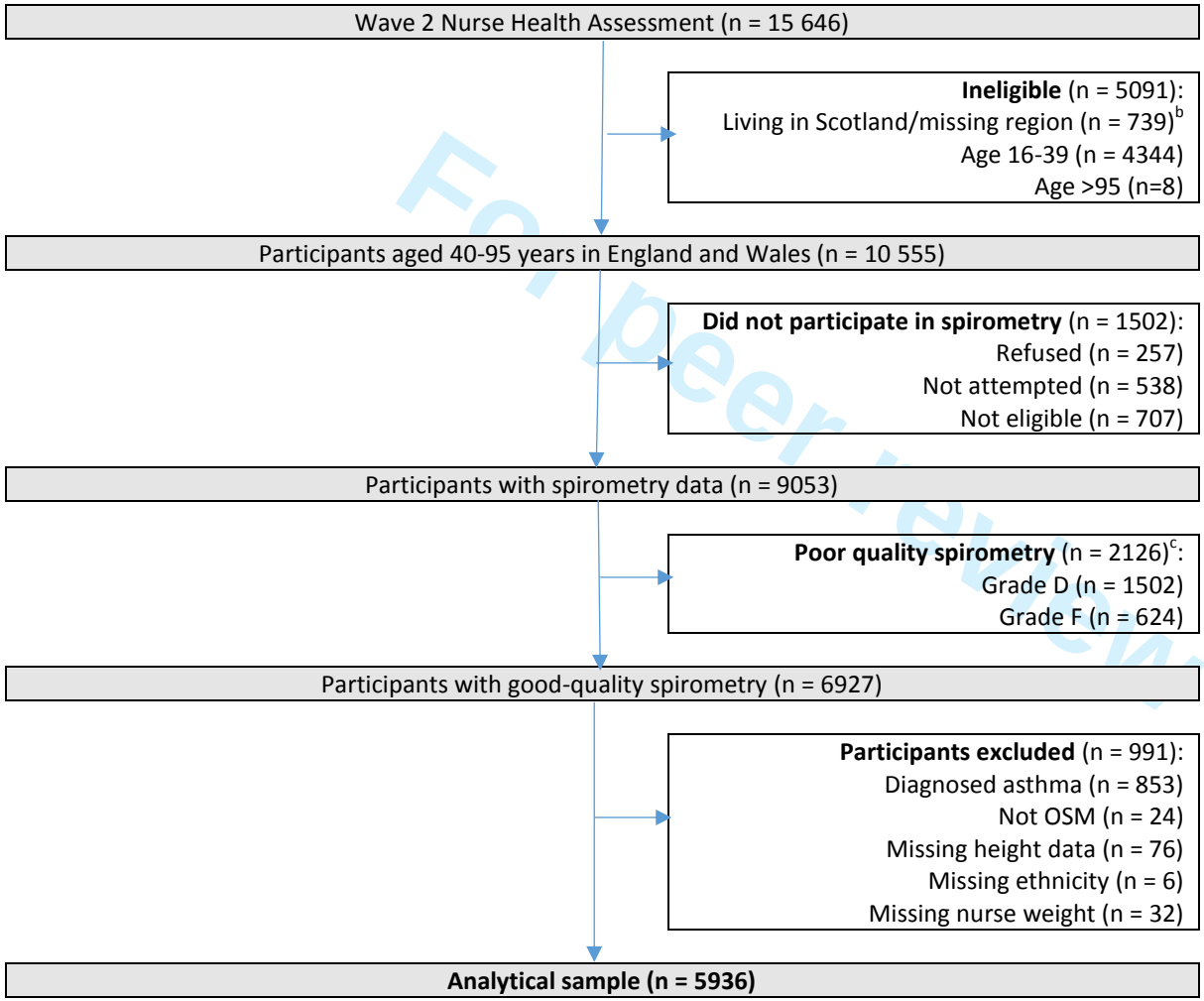
Figure S1 Response Flowchart for Wave 2 of UK Household Longitudinal Survey 2010-2012[a]

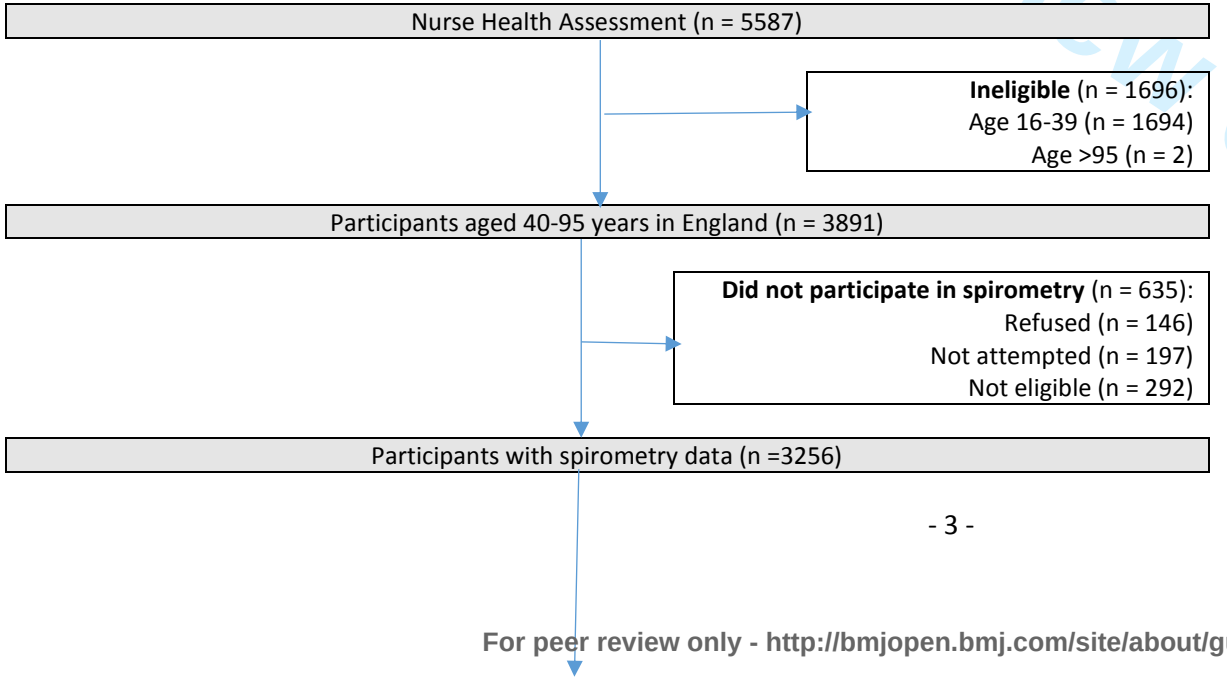


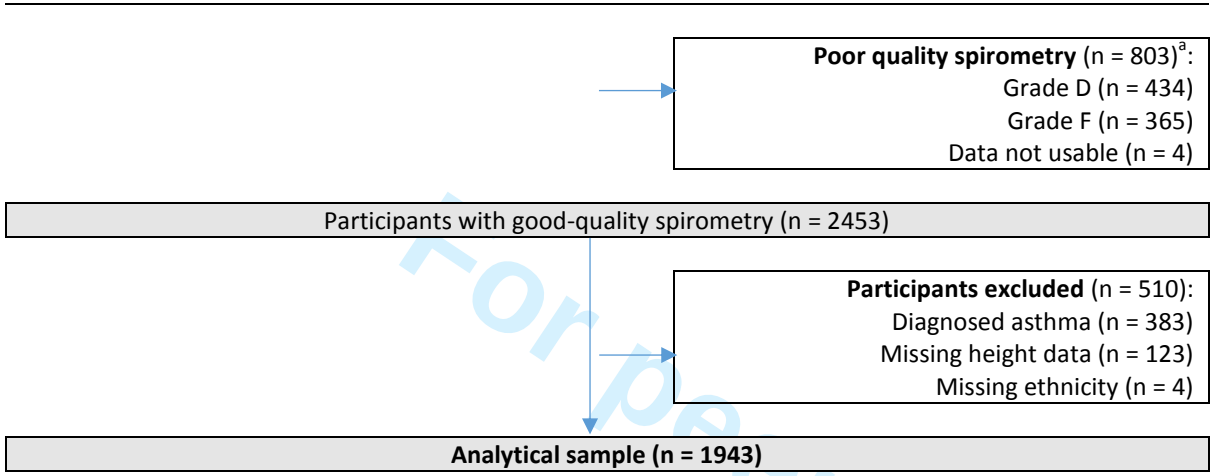
[a] Detailed flow diagram of participation in the Wave 2 Nurse Health Assessment can be found in McFall *et al*.

[b] Lung function measurements in UKHLS were conducted with two different devices: in England and Wales, the electronic NDD Easy on-PCC spirometer (NDD Medical Technologies, Zurich, Switzerland), and in Scotland the Vitalograph Escort (Vitalograph, Buckingham, UK). For this reason, UKHLS residents living in Scotland were excluded from the analytical sample.
[c] Quality criteria for spirometry sessions were as follows (Grades A-C required for inclusion in analytical sample):

Grade	Number of acceptable forced expiratory manoeuvres	Additional criteria
A	At least three	Two highest FVC and FEV_1 within 100 ml
B	At least three	Two highest FVC and FEV_1 within 150 ml
C	At least two	Two highest FVC and FEV_1 within 200 ml
D	Only one	Or best two FEV_1 or FVC were not within 200 ml
F	None	N/A

Figure S2 Response Flowchart in Health Survey for England 2010

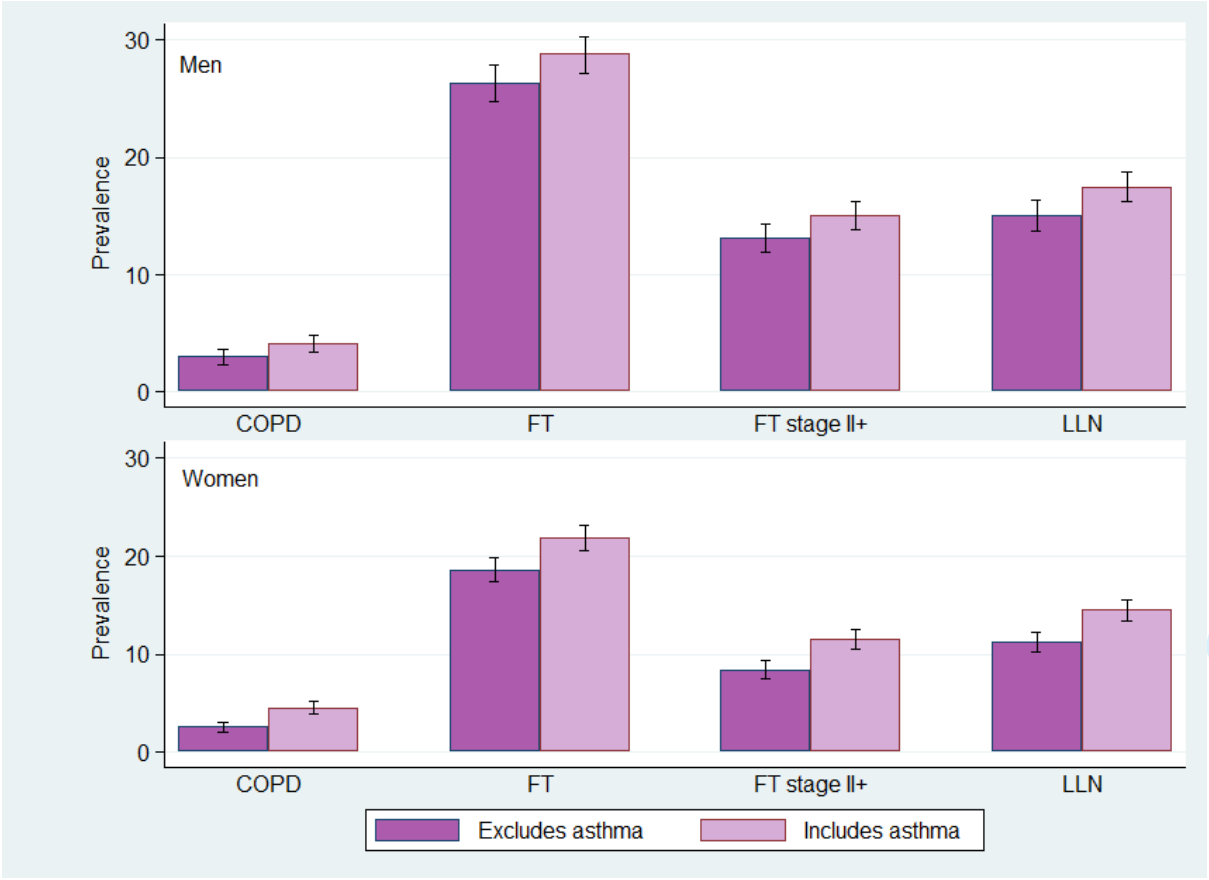




[a] Quality criteria for spirometry sessions were as follows (Grades A-C required for inclusion in analytical sample):

Grade	Number of acceptable forced expiratory manoeuvres	Additional criteria
A	At least three	Two highest FVC and FEV_1 within 100 ml
B	At least three	Two highest FVC and FEV_1 within 150 ml
C	At least two	Two highest FVC and FEV_1 within 200 ml
D	One	Or best two FEV_1 or FVC were not within 200 ml
F	None	N/A

Figure S3 Prevalence of Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometry-Based Definitions, Persons aged 40-95 years, Including and Excluding Participants With Reported Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)



Abbreviations used: FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the 5th percentile of Z-scores); UKHLS, United Kingdom Household Longitudinal Survey.

Table S1 Participant characteristics for the analytical sample and by survey

	HSE and UKHLS	HSE	UKHLS
N	7,879	1,943	5,936
Male, n (%)	3335 (46.8)	824 (48.4)	2511 (46.2)
Age-group, n (%):			
40-54	3472 (46.6)	868 (45.8)	2604 (46.9)
55-64	2072 (24.8)	497 (24.2)	1575 (25.0)
65-74	1557 (17.4)	369 (17.3)	1188 (17.5)
75-95	778 (11.1)	209 (12.6)	569 (10.6)
Mean age, years (SD)	57.6 (12.3)	57.9 (12.5)	57.5 (12.2)
Smoking status, n (%):			
Current	1198 (16.6)	254 (14.5)	944 (17.3)
Ex-regular	2547 (31.7)	659 (33.1)	1888 (31.3)
Never	4134 (51.7)	1030 (52.4)	3104 (51.5)
Pack-years, n (%):			
0-0.9	4299 (53.9)	1082 (55.0)	3217 (53.5)
1-19.9	1905 (24.3)	493 (25.1)	1412 (24.0)
20-49.9	1318 (17.2)	283 (15.0)	1035 (17.9)
50+	345 (4.6)	80 (4.7)	265 (4.5)
NS-SEC, n (%):			
Professional	3050 (36.5)	772 (36.1)	2278 (36.6)
Intermediate	1859 (23.4)	452 (23.6)	1407 (23.3)
Routine	2705 (36.9)	709 (39.8)	1996 (36.0)
Missing	265 (3.2)	10 (0.5)	255 (4.1)
Lung function (%-of-predicted), mean (SD):			
FEV_1	92.0 (16.5)	91.9 (16.4)	92.0 (16.5)
FVC	97.1 (15.0)	97.2 (15.0)	97.1 (15.1)
FEV_1/FVC	94.2 (9.7)	94.0 (9.9)	94.3 (9.7)

Abbreviations: FEV_1 = forced expiratory volume in one second; FVC, forced vital capacity; HSE = Health Survey for England; NS-SEC = National Statistics Socio-Economic Classification; SD = standard deviation; UKHLS = United Kingdom Household Longitudinal Study

Table S2 Characteristics of Participants in the Analytical Sample, With Diagnosed COPD, and According to Fixed Thresholds and Lower Limit of Normal Spirometry-based Severity Classifications, Persons aged 40-95 years Without Reported Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

	All participants	Reported diagnosed COPD[b]	P value[c]	Fixed Thresholds[d]			P value[c]	Lower Limit of Normal[e]		P value[c]
				stage I	stage II	stage III+		stage I	stage II	
n	7879	207		926	681	116		503	468	
Diagnosed COPD, n (%)	207 (2.8)	207 (100.0)		17 (2.1)	48 (7.1)	33 (30.2)	*<0.001*	19 (3.9)	65 (14.7)	*<0.001*
Sex, n (%):										
Males	3335 (46.8)	94 (50.4)	*0.349*	461 (53.3)	375 (56.0)	75 (66.9)	*<0.001*	231 (50.5)	255 (57.3)	*<0.001*
Females	4544 (53.3)	113 (49.7)		465 (46.7)	306 (44.0)	41 (33.1)		272 (49.5)	213 (42.7)	
Age-group, n (%):										
40-54	3472 (46.6)	64 (29.3)	*<0.001*	235 (28.1)	144 (23.9)	9 (9.3)	*<0.001*	221 (46.7)	125 (29.8)	*<0.001*
55-64	2072 (24.8)	69 (30.3)		260 (26.9)	191 (26.5)	38 (29.8)		129 (24.4)	156 (29.6)	
65-74	1557 (17.4)	52 (24.7)		262 (24.8)	195 (25.2)	42 (32.7)		98 (16.8)	115 (23.4)	
75-95	778 (11.1)	22 (15.7)		169 (20.2)	151 (24.5)	27 (28.2)		55 (12.1)	72 (17.2)	
Mean age, years (SD)	57.6 (12.3)	61.8 (11.9)	*0.011*	62.9 (12.5)	64.4 (12.2)	67.8 (10.1)	*<0.001*	57.6 (12.1)	61.9 (11.6)	*<0.001*
Smoking status, n (%):										
Current	1198 (16.6)	61 (28.5)	*<0.001*	172 (20.7)	218 (33.9)	49 (41.5)	*<0.001*	156 (33.8)	191 (42.0)	*<0.001*
Ex-regular	2547 (31.7)	80 (41.6)		369 (38.6)	265 (37.2)	51 (41.8)		174 (34.2)	178 (36.5)	
Never	4134 (51.7)	66 (29.9)		385 (40.8)	198 (28.9)	16 (16.7)		173 (32.0)	99 (21.6)	
Pack-years[f], n (%):										
0-0.9	4299 (53.9)	69 (31.2)	*<0.001*	406 (43.2)	207 (30.1)	16 (16.7)	*<0.001*	180 (33.2)	101 (22.1)	*<0.001*
1-19.9	1905 (24.3)	41 (20.1)		252 (27.0)	137 (20.3)	30 (27.1)		138 (27.8)	101 (22.0)	
20-49.9	1318 (17.2)	63 (31.4)		209 (23.2)	241 (34.9)	38 (29.9)		144 (29.9)	180 (36.9)	
50+	345 (4.6)	33 (17.4)		56 (6.3)	94 (14.3)	32 (26.3)		39 (8.5)	86 (19.1)	
NS-SEC[f], n (%):										
Professional	3050 (36.5)	60 (25.4)	*<0.001*	312 (32.7)	180 (23.4)	27 (20.8)	*<0.001*	162 (30.5)	106 (20.3)	*<0.001*
Intermediate	1859 (23.4)	42 (19.4)		242 (25.2)	152 (21.9)	18 (15.1)		126 (23.3)	97 (19.6)	
Routine	2705 (36.9)	100 (53.2)		322 (36.9)	321 (50.9)	65 (59.6)		195 (43.0)	244 (55.9)	

Abbreviations used: COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the lower 5th percentile of

Z-scores); NS-SEC, National Statistics Socio-Economic Classification; SD, standard deviation; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts unweighted; means and percentages estimated using survey weights.
[b] HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[c] Within each definition of obstruction, Chi-squared test used to compare categorical variables; ANOVA used to compare mean values of continuous variables.
[d] Staging classification for FTs: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% of predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% of predicted); stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% of predicted).
[e] Staging classification for LLN: stage I (FEV_1/FVC <LLN and FEV_1 >LLN); stage II (FEV_1/FVC <LLN and FEV_1 <LLN).
[f] Missing data: 12/7879 (0.2%) pack-years of cigarette smoking; 265/7879 (3.4%) NS-SEC.

Table S3 Characteristics of Diagnosed COPD and Potential Airflow Obstruction Using Fixed Thresholds and Lower Limit of Normal Spirometry-based Definitions, Persons aged 40-95 years Without Diagnosed Asthma, Health Survey for England 2010 and UK Household Longitudinal Survey Wave 2 (2010-2012)[a]

	All participants	Reported diagnosed COPD[b]	P value[c]	Fixed Thresholds[d]			P value[c]	Lower Limit of Normal[e]		P value[c]
				stage I	stage II	stage III+		stage I	stage II	
n	7879	207		926	681	116		503	468	
UKHLS, n (%)	5936 (75.3)	121 (59.6)	*<0.001*	705 (76.2)	517 (75.6)	87 (74.9)	*0.932*	377 (75.0)	356 (76.1)	*0.922*
HSE, n (%)	1943 (24.7)	86 (40.4)		221 (23.8)	164 (24.4)	29 (25.1)		126 (25.0)	112 (23.9)	
Exposure to passive smoking, hours per week (p/w), n (%)[f]:										
0	1599 (81.1)	64 (74.8)	*0.407*	184 (81.4)	130 (76.7)	20 (69.6)	*0.233*	93 (69.9)	86 (73.7)	*0.007*
1-9	256 (14.1)	16 (19.3)		32 (15.8)	22 (15.0)	6 (24.4)		25 (23.9)	17 (16.8)	
10+	82 (4.8)	4 (6.0)		5 (2.8)	11 (8.3)	2 (6.1)		7 (6.2)	8 (9.5)	
Mean exposure, hours p/w (SD)	1.8 (7.7)	2.4 (10.1)	*0.966*	1.5 (7.3)	3.5 (11.7)	3.3 (13.0)	*0.068*	2.5 (9.2)	3.8 (11.7)	*0.091*
Lung function measurements, percent-of-predicted, mean (SD)[g]:										
FEV_1	92.0 (16.5)	75.0 (23.4)	*<0.001*	92.7 (10.0)	69.0 (7.8)	40.2 (7.2)	*<0.001*	87.2 (8.2)	59.4 (12.9)	*<0.001*
FVC	97.1 (15.0)	88.6 (15.7)	*<0.001*	109.2 (11.5)	87.5 (10.9)	65.4 (12.9)	*<0.001*	108.1 (10.2)	82.5 (14.2)	*<0.001*
FEV_1/FVC	94.2 (9.7)	82.8 (18.2)	*<0.001*	84.6 (4.6)	78.9 (7.9)	62.9 (13.2)	*<0.001*	80.4 (4.5)	71.6 (10.6)	*<0.001*
Comorbidities, n (%):										
Respiratory disease[f, h]	65 (3.8)	33 (42.1)	*<0.001*	6 (3.3)	15 (9.0)	15 (51.5)	*<0.001*	5 (4.2)	24 (21.7)	*<0.001*
Respiratory symptoms[f, i]	69 (4.0)	12 (13.7)	*<0.001*	14 (6.4)	16 (11.7)	8 (27.3)	*<0.001*	7 (5.7)	18 (17.4)	*<0.001*
Respiratory medicine	375 (4.8)	71 (36.1)	*<0.001*	41 (4.3)	70 (9.6)	49 (42.7)	*<0.001*	30 (5.8)	95 (20.2)	*<0.001*
Cardiovascular disease[j]	493 (6.5)	20 (11.5)	*0.012*	84 (9.9)	74 (11.1)	24 (24.1)	*<0.001*	32 (6.8)	49 (12.3)	*<0.001*
Diabetes	543 (7.1)	18 (10.9)	*0.128*	54 (6.3)	67 (9.6)	17 (13.1)	*0.007*	20 (4.4)	39 (7.8)	*0.087*
Poor self-rated health	398 (5.7)	40 (23.4)	*<0.001*	37 (4.9)	58 (9.1)	23 (22.8)	*<0.001*	30 (7.2)	55 (12.6)	*<0.001*
Breathlessness[f, k]	100 (6.7)	23 (34.8)	*<0.001*	10 (6.9)	18 (13.1)	11 (43.9)	*<0.001*	8 (10.5)	21 (21.6)	*<0.001*
Area of residence, n (%):										
Urban	5791 (75.8)	154 (77.2)	*0.654*	656 (72.6)	515 (76.8)	89 (79.3)	*0.125*	372 (75.1)	358 (78.0)	*0.528*
Rural	2087 (24.2)	53 (22.8)		270 (27.4)	166 (23.2)	27 (20.7)		131 (25.0)	110 (22.0)	
BMI:										
Normal	2122 (27.0)	56 (25.7)	*0.751*	347 (38.0)	182 (27.6)	35 (34.7)	*<0.001*	202 (40.6)	147 (32.6)	*<0.001*
Overweight	3235 (41.9)	79 (40.4)		393 (43.4)	298 (44.6)	37 (34.3)		214 (42.8)	177 (38.4)	

Obese	2369 (31.1)	66 (33.8)	165 (18.7)	187 (27.8)	36 (31.0)	77 (16.6)	132 (29.0)

Abbreviations used: BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV_1, maximum expiratory volume in one second; FVC, forced vital capacity; FTs, fixed thresholds; HSE, Health Survey for England; LLN, lower limit of normal (below the lower 5th percentile of Z-scores); MRC, Medical Research Council; NS-SEC, National Statistics Socio-Economic Classification; SD, standard deviation; UKHLS, United Kingdom Household Longitudinal Survey.

[a] Participants were included under each relevant definition. Bronchodilators were not used. Cell counts unweighted; means and percentages estimated using survey weights.
[b] HSE: reported diagnosed chronic bronchitis, emphysema, or COPD; UKHLS: diagnosed bronchitis or emphysema.
[c] Within each definition of obstruction, Chi-squared test used to compare categorical variables; ANOVA used to compare mean values of continuous variables.
[d] Staging classification for FTs: stage I (FEV_1/FVC <0.70 and FEV_1 ≥80% of predicted); stage II (FEV_1/FVC <0.70 and FEV_1 50-79% of predicted); stage III+ (FEV_1/FVC <0.70 and FEV_1 <50% of predicted).
[e] Staging classification for LLN: stage I (FEV_1/FVC <LLN and FEV_1 >LLN); stage II (FEV_1/FVC <LLN and FEV_1 <LLN).
[f] Measured in HSE 2010 only.
[g] Percent-of-predicted defined as the observed value divided by the predicted value estimated for a person of the same age, gender, ethnicity, and height using the European Respiratory Society Global Lungs Initiative 2012 reference equations [1].
[h] Respiratory disease: ICD-10 codes J00-J99.
[i] Respiratory symptoms: defined as usually coughing first thing in the morning, for at least 3 months a year, and bringing up phlegm from the chest most days for 3 consecutive months in a year. Missing data: 1 case with missing value.
[j] Cardiovascular disease: HSE (longstanding illness): stroke; heart attack/angina; UKHLS (health conditions): coronary heart disease; angina; heart attack/myocardial infarction; stroke.
[k] MRC dyspnoea scale: 63 participants with unspecified shortness of breath excluded. MRC grades as follows: 0, only breathless with strenuous exercise; 1: breathless when hurrying on level or up a slight hill; 2: walk slower than people of same age on the level due to breathlessness or stop for breath when walking on level at own pace; 3: stop for breath after walking 100 yards or a few minutes on the level; 4: too breathless to leave house or breathless when dressing.

Reference List

(1) Quanjer PH, Stanojevic S, Cole TJ, Baur X, Hall GL, Culver BH et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J* 2012; 40(6):1324-1343.

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Estimating population prevalence of potential airflow obstruction using different spirometric criteria: a pooled cross-sectional analysis of persons aged 40-95 years in England and Wales

Shaun Scholes, Alison Moody, Jennifer S Mindell

	Item No	Recommendation	Action taken
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes, we have used pooled cross-sectional analysis in the title.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Structured abstract as in BMJ instructions for authors.
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Background and rationale reported.
Objectives	3	State specific objectives, including any prespecified hypotheses	Specific objectives of the study reported.
Methods			
Study design	4	Present key elements of study design early in the paper	Key elements presented. We have pooled 2 recent cross-sectional surveys containing lung function data.
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Settings, locations, and dates specified.
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Eligibility criteria and methods of selection explained. Reason for excluding the Scottish component of UKHLS described in Supplementary data. Response flowcharts for HSE and UKHLS provided as supplementary data.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	All variables in the study clearly described, highlighting, where relevant, differences between the two surveys.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Data sources, including choice of reference equations for predicted values and Z-scores clearly described.

Bias	9	Describe any efforts to address potential sources of bias	We undertook descriptive analysis of participants with and without good-quality spirometry data. Implications of bias are mentioned in the discussion.
Study size	10	Explain how the study size was arrived at	Response flowcharts for HSE and UKHLS provided as supplementary data.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Groupings of quantitative variables clearly set out in the method section.
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Statistical methods described in detail.
		(*b*) Describe any methods used to examine subgroups and interactions	Statistical methods described in detail.
		(*c*) Explain how missing data were addressed	Exclusion of participants with missing data for two variables clearly set out in the methods section.
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Described in the statistical analyses section. We accounted for the clustering of observations using the svy module in Stata.
		(*e*) Describe any sensitivity analyses	Sensitivity analyses described in detail.
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Response flowcharts for HSE and UKHLS provided as supplementary data.
		(b) Give reasons for non-participation at each stage	Response flowcharts for HSE and UKHLS provided as supplementary data.
		(c) Consider use of a flow diagram	Response flowcharts for HSE and UKHLS provided as supplementary data.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Characteristics of study participants (across all variables) are provided as supplementary data.
		(b) Indicate number of participants with missing data for each variable of interest	Numbers with missing data presented as footnote in the tables.

Outcome data	15*	Report numbers of outcome events or summary measures	Outcome data is presented as prevalence.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Both sets of estimates (unadjusted and adjusted) presented.
		(*b*) Report category boundaries when continuous variables were categorized	Details provided.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Results of sensitivity analyses provided.
Discussion			
Key results	18	Summarise key results with reference to study objectives	Details provided.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Limitations and potential biases discussed in detail.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Cautious throughout.
Generalisability	21	Discuss the generalisability (external validity) of the study results	Generalisability briefly discussed.
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Details provided.