Proportional classifications of COPD phenotypes

S E Marsh,[1] J Travers,[1] M Weatherall,[2] M V Williams,[1] S Aldington,[1] P M Shirtcliffe,[1] A L Hansell,[3] M R Nowitz,[2,4] A A McNaughton,[1] J B Soriano,[5] R W Beasley[1,6]

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[1] Medical Research Institute of New Zealand, Wellington, New Zealand; [2] Wellington School of Medicine and Health Sciences, Wellington, New Zealand; [3] Department of Epidemiology and Public Health, Imperial College London, London, UK; [4] Pacific Radiology Limited, Wellington, New Zealand; [5] Fundació Caubet–CIMERA Illes Balears, Bunyola, Spain; [6] University of Southampton, Southampton, UK

Correspondence to: Professor R Beasley, Medical Research Institute of New Zealand, P O Box 10055, Wellington 6143, New Zealand; richard.beasley@mrinz.ac.nz

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ABSTRACT

Background: Chronic obstructive pulmonary disease (COPD) encompasses a group of disorders characterised by the presence of incompletely reversible airflow obstruction with overlapping subsets of different phenotypes including chronic bronchitis, emphysema or asthma. The aim of this study was to determine the proportion of adult subjects aged >50 years within each phenotypic subgroup of COPD, defined as a post-bronchodilator ratio of forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) <0.7, in accordance with current international guidelines.

Methods: Adults aged >50 years derived from a random population-based survey undertook detailed questionnaires, pulmonary function tests and chest CT scans. The proportion of subjects in each of 16 distinct phenotypes was determined based on combinations of chronic bronchitis, emphysema and asthma, with and without incompletely reversible airflow obstruction defined by a post-bronchodilator FEV_1/FVC ratio of 0.7.

Results: A total of 469 subjects completed the investigative modules, 96 of whom (20.5%) had COPD. Diagrams were constructed to demonstrate the relative proportions of the phenotypic subgroups in subjects with and without COPD. 18/96 subjects with COPD (19%) had the classical phenotypes of chronic bronchitis and/or emphysema but no asthma; asthma was the predominant COPD phenotype, being present in 53/96 (55%). When COPD was defined as a post-bronchodilator FEV_1/FVC less than the lower limit of normal, there were one-third fewer subjects with COPD and a smaller proportion without a defined emphysema, chronic bronchitis or asthma phenotype.

Conclusion: This study provides proportional classifications of the phenotypic subgroups of COPD which can be used as the basis for further research into the pathogenesis and treatment of this heterogeneous disorder.

Current understanding of the epidemiology and pathogenesis of chronic obstructive pulmonary disease (COPD) is limited by difficulties in defining and classifying the different phenotypes that make up this complex group of disorders.[1] Conceptually, since the time of the Ciba symposium in 1959,[2] COPD has been thought of as an overlap between chronic bronchitis, emphysema and subtypes of asthma associated with chronic airflow limitation. This was first represented in a non-proportional Venn diagram by Snider.[3] Subsequently the widely recognised representation of this diagram produced by the American Thoracic Society (ATS) cemented the presence of airflow obstruction into this definition of COPD (fig 1).[4] Current international guidelines propose that the diagnosis of COPD requires the presence of incompletely reversible airflow obstruction to be confirmed by spirometry with a ratio of post-bronchodilator forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) <0.7, in the absence of a defined pathology such as bronchiectasis or tuberculosis to otherwise explain the airflow obstruction.[5 6]

Recognising the different phenotypes within COPD is important for understanding the underlying disease processes. These phenotypes are also clinically relevant due to potential differing responses to therapeutic interventions.[7 8] Previous efforts to quantify the proportion of subjects lying within each of the proposed subsets of the Venn diagram[9 10] have been limited by the lack of post-bronchodilator spirometry to diagnose COPD, the absence of radiological investigations such as chest CT scans to diagnose emphysema, and an over-reliance on non-standardised physician diagnoses.

In this study of a random sample of adults in an urban New Zealand community we have used detailed questionnaire data, pulmonary function tests and chest CT scans to determine the proportion of subjects within each phenotypic subgroup of COPD. Alternative proportional diagrams have been developed to better illustrate the phenotypes making up the spectrum of COPD, and the significance of these findings considered in terms of the pathogenesis of COPD.

METHODS

Subjects

Participants in the Wellington Respiratory Survey (n = 3500) were randomly selected from the electoral register, equally distributed by sex across the five decade age groups from 25 to 75 years.[11] Subjects were sent a simple postal questionnaire seeking demographic, respiratory and smoking history data. All subjects who completed and returned questionnaires were invited to undertake a detailed interviewer-administered questionnaire followed by pulmonary function tests and CT scanning. Subjects aged >50 years who completed satisfactory pulmonary function tests and CT scans were included in the analysis. The survey was approved by the Wellington ethics committee and written informed consent was obtained from each subject.

Pulmonary function testing

Pulmonary function tests in the Wellington Respiratory Survey have been described in detail elsewhere.[11 12] In brief, these were carried out using two whole-body constant-volume plethysmographs with heated pneumotachographs and gas analysers (Masterlab 4.5 and 4.6; Erich-Jaeger, Wurzberg, Germany) according to ATS

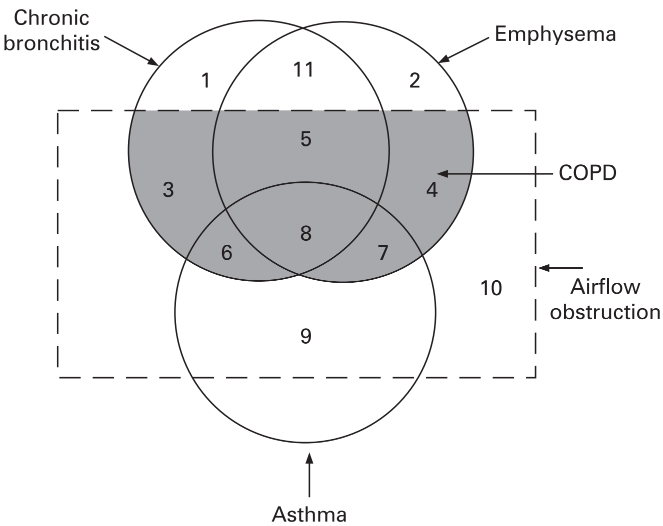

Figure 1 Non-proportional Venn diagram of chronic obstructive pulmonary disease (COPD) produced by the American Thoracic Society.[4] The subsets comprising COPD are shaded. Subset areas are not proportional to the actual relative subset sizes. Asthma is by definition associated with reversible airflow obstruction although, in variant asthma, special manoeuvres may be necessary to make the obstruction evident. Patients with asthma whose airflow obstruction is completely reversible (subset 9) are not considered to have COPD. Because in many cases it is virtually impossible to differentiate patients with asthma whose airflow obstruction does not remit completely from persons with chronic bronchitis and emphysema who have partially reversible airflow obstruction with airway hyperreactivity, patients with unremitting asthma are classified as having COPD (subsets 6, 7 and 8). Chronic bronchitis and emphysema with airflow obstruction usually occur together (subset 5), and some patients may have asthma associated with these two disorders (subset 8). Individuals with asthma who have been exposed to chronic irritation, as from cigarette smoke, may develop chronic productive cough, which is a feature of chronic bronchitis (subset 6). Persons with chronic bronchitis and/or emphysema without airflow obstruction (subsets 1, 2 and 11) are not classified as having COPD. Patients with airway obstruction due to diseases with known aetiology or specific pathology such as cystic fibrosis or obliterative bronchiolitis (subset 10) are not included in this definition.

guidelines.[13 14] Following measurement of static lung volumes, a minimum of three acceptable spirometry manoeuvres were carried out with the best FEV_1 and FVC selected for analysis. A minimum of three measurements of carbon monoxide transfer factor (TLCO) were made at 5 min intervals and the mean of these measurements used in the analysis. Alveolar volume (VA) was simultaneously measured, using helium as a tracer gas, and used to calculate carbon monoxide transfer per unit of alveolar volume (TLCO/VA). A blood sample was taken to adjust results for haemoglobin concentration using the formula recommended by the ATS.[13] Spirometry was carried out before and 45 min after the administration of 400 μg salbutamol inhaled via a spacer device. The subjects measured their peak flow twice daily during a 1-week period and recorded their values in a diary.

CT scanning

CT scans of the chest were undertaken using a single machine (GE Prospeed, General Electric Medical Systems, YMS, Japan) as described previously.[15] In brief, scans were obtained at full inspiration and no intravenous contrast was used. An initial "scout film" was used to identify the levels at which to acquire images. Three images were obtained, one at each of the levels of 1 cm above the aortic arch (level 1), 1 cm below the carina (level 2) and 3 cm above the top of the right hemidiaphragm (level 3) with 1 mm collimation, voltage of 120 kVp, 200 mAs. Scanning occurred in a cranial to caudal direction with each image obtained during a separate breath hold each of 1.5 s duration. The radiological diagnosis of macroscopic emphysema was made if definite centrilobular, panlobular or paraseptal emphysematous changes were visually identified. CT scans were independently examined by two radiologists who were blinded to clinical history and pulmonary function test results. Diagnostic disagreement was resolved by consensus.

Definitions of disease categories

COPD was defined by a post-bronchodilator FEV_1/FVC <0.7 in accordance with current guidelines.[5 6] Subjects who met the criteria for COPD but had a known alternative respiratory disorder (such as bronchiectasis) were not included within the COPD group.[6] The criteria used to identify subjects with chronic bronchitis, emphysema and asthma were:

- Chronic bronchitis: cough and sputum production on most days for a minimum of 3 months per year for at least 2 years.[2]
- Emphysema:
  - Macroscopic emphysema (centrilobular, panlobular or paraseptal) *or*
  - Post-bronchodilator FEV_1/FVC <0.7 *and* TLCO/VA adjusted for haemoglobin less than the lower limit of normal.[12]
- Asthma:
  - Post-bronchodilator increase in FEV_1 ⩾15%[16] *or*
  - Peak flow variability ⩾20% during 1 week of testing[16] *or*
  - Physician diagnosis of asthma in conjunction with current symptoms (wheeze *or* nocturnal shortness of breath and wheeze *or* nocturnal chest tightness in the preceding 12 months) *or* inhaler use in the preceding 12 months.

Subjects could belong to more than one of these categories.

From the questionnaire, subjects were labelled as never, former or current smokers of tobacco (consumed from cigarettes, cigars or pipes). Cumulative tobacco cigarette consumption was calculated in pack-years with 1 pack-year equivalent to 20 cigarettes per day for 1 year.

Data analysis

Comparison of those who completed the screening questionnaire but did not go on to undertake the full investigative modules and those who did was by χ^2 tests for categorical variables and *t* tests or Mann-Whitney tests for continuous variables where appropriate. The number of subjects in each phenotypic category was presented in three forms:

- Table.
- Proportional diagrams constructed by the method of Chow and Ruskey[17] using axis-aligned rectangles to represent phenotypic groups.[18 19]
- Proportional Venn diagrams in which the proportion of subjects with COPD is shown as a clear circle within diagnostic subgroups, as described previously.[9]

The number of subjects in each phenotypic category was also presented, in which COPD was defined as a post-bronchodilator FEV_1/FVC ratio less than the lower limit of normal-derived reference value.[12 20]

Table 1 Initial screening questionnaire responses of subjects aged >50 years who did or did not complete the diagnostic modules

	Screening questionnaire responders only, n (%) (n = 883)	Subjects completing diagnostic modules, n (%) (n = 469)	p Value
Male	422/883 (47.8)	271/469 (57.8)	<0.001
Wheezing in the last 12 months	208/879 (23.7)	116/466 (24.9)	0.62
Cough without cold usually	221/879 (25.1)	125/466 (26.8)	0.50
Cough 3 months each year	118/872 (13.5)	83/457 (18.2)	0.03
Phlegm 3 months each year	89/874 (10.2)	60/459 (13.1)	0.11
Breathing trouble ever	210/878 (23.9)	124/467 (26.6)	0.29
Doctor-diagnosed chronic bronchitis	78/881 (8.9)	45/467 (9.6)	0.64
Doctor-diagnosed emphysema	20/880 (2.3)	8/464 (1.7)	0.50
Doctor-diagnosed asthma	141/881 (16.0)	94/466 (20.2)	0.06
Never smoker	426 (49.8)	210 (46.1)	0.003
Current smoker	98 (11.5)	32 (7.0)	
Former smoker	331 (38.7)	214 (46.9)	
Mean (SD) age (years)	63.1 (8.3)	61.6 (7.3)	<0.001

Age based on age at completion of screening questionnaire. The selection of study participants aged >50 years is based on age at time of pulmonary function tests, which were on average 1.1 years later. As a result, the ages presented in table 1 do not correspond with the ages stated in table 2. Likewise, smoking data presented in table 1 is based on the screening questionnaire and the smoking data presented in table 2 is based on the detailed written questionnaire completed by participants.

RESULTS

Initial recruitment resulted in 2319 responses from 3500 postal questionnaires. With the exclusion of 509 subjects unable to be traced from the address on the electoral register and 13 subjects who had died, this represented a response rate of 2319/2979 (78%). Of those completing the postal questionnaire, 795 completed the detailed written questionnaire and attended for pulmonary function testing. Satisfactory pulmonary function tests and CT scans were completed in 713 subjects who were considered for the analysis. Of these subjects, 469 were aged >50 years at the time of pulmonary function testing. Subjects completing the investigative modules were broadly similar to those completing the screening questionnaire (table 1). The characteristics of the subjects completing the investigative modules are shown in table 2.

Following the exclusion of three subjects with airflow obstruction and prior diagnoses of bronchiectasis (n = 2) or sarcoidosis (n = 1) and two subjects with airflow obstruction and study CT appearances consistent with bronchiectasis, there were 96/469 (20.5%) subjects with a post-bronchodilator FEV_1/FVC <0.7 in the absence of an alternative respiratory disorder, thereby fulfilling the criteria for COPD.[5 6] The number and percentage of these subjects with COPD who met the criteria for mild, moderate, severe and very severe disease, based on post-bronchodilator FEV_1 values ⩾80%, 50–80%, 30–50% and <30% predicted respective,[6] was 40 (41.7%), 48 (50.0%), 6 (6.3%) and 2 (2.1%), respectively.

Among the subjects with COPD, the most common phenotype was asthma (53/96, 55.2%), with chronic bronchitis and emphysema being present in 29/96 (30.2%) and 31/96 (32.3%), respectively (table 3). Of subjects with COPD, 35/96 (37.0%) had only one of the phenotypes, 36/96 (37.5%) had more than one phenotype and 25/96 (26.0%) did not meet criteria for any of asthma, chronic bronchitis or emphysema. Of the subjects with COPD, 50/96 (50%) had chronic bronchitis and/or emphysema; only 18/96 (19%) had the classical phenotypes of incompletely reversible airflow obstruction with either chronic bronchitis and/or emphysema but no diagnostic features of asthma.

Of the subjects with COPD with the asthma phenotype, 27/53 (51%) had FEV_1 bronchodilator reversibility ⩾15%, 26/53 (49%) had peak flow variability ⩾20% and 35/53 (66%) had a physician's diagnosis of asthma and current symptoms or inhaler use. Fourteen of the 53 subjects (26%) had a physician's diagnosis of asthma and current symptoms or inhaler use without either bronchodilator reversibility or peak flow variability; in 13 of these 14 subjects there was a physician's diagnosis of asthma and both current symptoms and inhaler use; 10 of these 14 subjects were former or current smokers. Thirty-nine (74%) of the 53 subjects with COPD with the asthma phenotype had either bronchodilator reversibility or peak flow variability; 21 of these (54%) did not have a physician's diagnosis of asthma and current symptoms or inhaler use.

Table 2 Subject characteristics

Variable	COPD (n = 96)	No COPD (n = 373)*	Total group (n = 469)
Male sex, n (%)	66 (68.8)	205 (55.0)	271 (57.8)
Smokers, n (%)			
Current	21 (21.9)	28 (7.5)	49 (10.5)
Former	40 (41.7)	182 (48.8)	222 (47.3)
FEV_1 bronchodilator reversibility ⩾15%, n (%)	27 (28.1)	8 (2.1)	35 (7.5)
Peak flow variability ⩾20%, n (%)	26 (27.1)	21 (5.6)	47 (10.0)
Mean (SD) age (years)	65.4 (6.8)	62.0 (7.3)	62.7 (7.3)
Mean (SD) post-bronchodilator FEV_1 (l)	2.4 (0.8)	3.2 (0.8)	3.0 (0.9)
Mean (SD) post-bronchodilator FEV_1 (% predicted)	74.0 (17.9)	99.1 (14.4)	94.0 (18.3)
Mean (SD) post-bronchodilator FEV_1/FVC	60.2 (8.6)	78.4 (5.3)	74.7 (9.5)
Mean (SD) T_{LCO}/V_A (mmol/min/kPa/l)	1.21 (0.25)	1.42 (0.18)	1.37 (0.21)
Mean (SD) cigarette pack years (cigarette smokers only)	27.2 (21.6) (n = 60)	14.4 (18.4) (n = 185)	17.6 (20.0) (n = 245)

COPD, chronic obstructive pulmonary disease, FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; T_{LCO}, gas transfer factor, adjusted for haemoglobin; V_A, alveolar volume.
*The "No COPD" group included five subjects who met the spirometric criteria for COPD but had other respiratory disorders (bronchiectasis n = 4, sarcoidosis n = 1).
Note that the age data presented are the age at time of pulmonary function testing and the smoking data presented are derived from the detailed written questionnaire, not the screening questionnaire.

Table 3 Study population distribution across phenotype category

			COPD	No COPD	Total
Asthma*	Chronic bronchitis*	Emphysema*	6	1	7
		No emphysema	15	13	28
	No chronic bronchitis	Emphysema	9	2	11
		No emphysema	23	40	63
No asthma	Chronic bronchitis	Emphysema	6	0	6
		No emphysema	2	17	19
	No chronic bronchitis	Emphysema	10	8	18
		No emphysema	25	292	317
Total			96	373	469

COPD, chronic obstructive pulmonary disease (defined as post-bronchodilator $FEV_1/FVC < 0.7$).
*See text for definitions of these phenotypes.

Among the subjects with COPD, 61/96 (63.5%) were current or former tobacco smokers. The proportion of subjects with COPD with the chronic bronchitis, emphysema or asthma phenotypes who were current or former smokers was 21/29 (72.4%), 27/31 (87.1%) and 33/53 (62.2%), respectively. Among subjects with COPD who did not meet the criteria for chronic bronchitis, emphysema or asthma, the proportion of current or former smokers was 14/25 (56%). Current and former smokers with COPD had about twice the cigarette pack-year history as current and former smokers without COPD (27.2 vs 14.4 pack-years, $p<0.001$). Thirty-five subjects with COPD (36.5%) were never smokers. The mean (SD) age was 65.4 (6.3) years, similar to the total COPD group, and 19/35 (54.3%) were men, a slightly smaller proportion than for the total COPD group. Twenty of these 35 subjects (57%) had asthma (of whom 7 also had chronic bronchitis), 4 (11%) had emphysema (of whom 1 also had chronic bronchitis) and 11 (31%) had no diagnosis of asthma, chronic bronchitis or emphysema.

In the population without COPD, asthma was the most common respiratory disease phenotype (56/373, 15.1%) followed by chronic bronchitis (31/373, 8.3%), while emphysema was uncommon (11/373, 2.9%; table 3).

The conceptual non-proportional Venn diagram produced by the ATS[4] is reproduced in fig 1. Our study identified 16/469 subjects (3.4%) who could not be classified in this Venn diagram by failure to allow the combinations of phenotypes in subjects without airflow obstruction of: asthma and chronic bronchitis (n = 13), asthma and emphysema (n = 2), or asthma, chronic bronchitis and emphysema, (n = 1). The central region of the ATS Venn diagram that defines COPD—namely, that airflow limitation is present together with the phenotypes numbered 3 to 8—accounted for only 48/96 (50%) of our definition of COPD based on the GOLD criteria.[6] Subjects not classified as COPD in the ATS Venn diagram but who were classified as COPD by the GOLD criteria[6] were those with COPD but no asthma, chronic bronchitis or emphysema (n = 25) and those with COPD and asthma alone (n = 23).

In order to include all subjects in one of the 16 potential phenotypes, we constructed a diagram using axis-aligned proportional rectangles in which each phenotype with and without COPD was represented (fig 2). A proportional Venn diagram was also constructed in which the proportion of subjects with COPD was shown as a clear circle within diagnostic subgroups (fig 3).

The use of the lower limit of normal derived post-bronchodilator FEV_1/FVC ratios rather than the fixed ratio of 0.7 resulted in 37 fewer subjects classified as COPD and a smaller proportion of subjects with COPD not meeting the criteria for any of the asthma, chronic bronchitis or emphysema phenotypes (see online supplement).

DISCUSSION

This study reports the relative proportions of phenotypic subgroups of subjects with and without COPD determined by extensive clinical, radiological and physiological measurements in a random sample of an older adult population. Asthma was the predominant phenotype, being present in just over half of the subjects with COPD defined as a post-bronchodilator $FEV_1/FVC < 0.7$, in accordance with current international guidelines.[5,6] The classic phenotype of chronic bronchitis and/or emphysema with no asthma[4] was present in one in five subjects with spirometrically-defined COPD.

The main methodological issue relevant to the interpretation of the findings was the criteria used to define COPD, asthma, chronic bronchitis and emphysema. We used criteria derived from international consensus guidelines. Thus, the criterion for COPD was a post-bronchodilator FEV_1/FVC ratio of <0.7 in the absence of an alternative respiratory disorder.[5,6] Owing to the

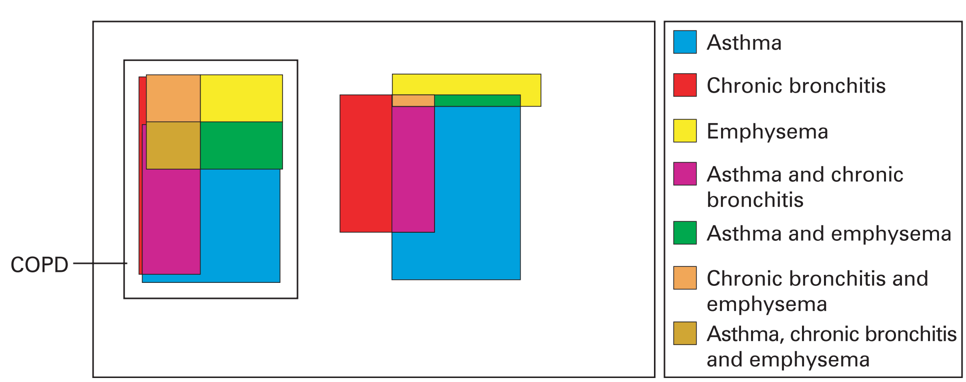

Figure 2 Diagram incorporating axis-aligned proportional rectangles for each of the different phenotypes within the Wellington Respiratory Survey study population. The large black rectangle represents the full study group. The smaller black rectangle represents those with COPD (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity $FEV_1/FVC < 0.7$). The white areas represent those who did not fulfil the criteria for chronic bronchitis, asthma or emphysema. See text for definitions of the individual groups.

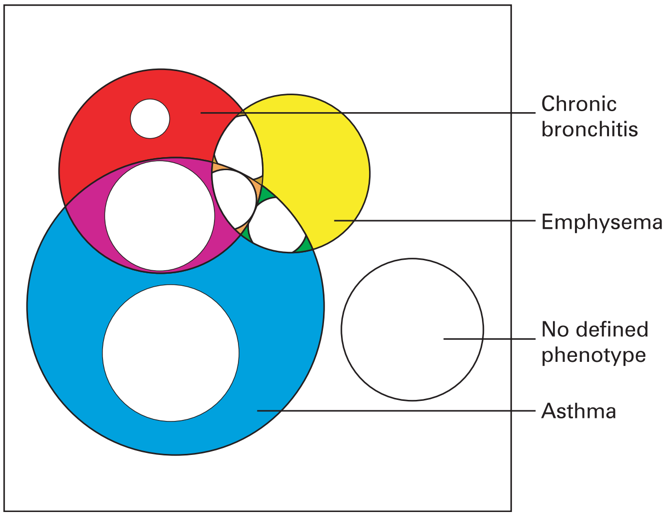

Figure 3 Proportional Venn diagram presenting the different phenotypes within the Wellington Respiratory Survey study population. The large black rectangle represents the full study group. The clear circles within each coloured area represent the proportion of subjects with COPD (post-bronchodilator forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) <0.7). The isolated clear circle represents subjects with COPD who did not have an additional defined phenotype of asthma, chronic bronchitis or emphysema.

decline in the FEV_1/FVC ratio with age, the use of a fixed ratio to define COPD may result in a higher proportion of false positive diagnoses in older adults.[20–22] As a result, use of the alternative criterion of a post-bronchodilator FEV_1/FVC ratio below the lower limit of normal to define COPD was also explored.

The criteria used for chronic bronchitis was the long established symptom complex of chronic cough and mucus production.[2] The definition of emphysema required either definite radiological evidence of macroscopic emphysema on CT scan[23] or a low gas transfer factor in the presence of incompletely reversible airflow obstruction.[20] The use of three slices at specified anatomical levels may have resulted in under-recognition of the presence of macroscopic emphysema, but this approach has been shown to be as informative as 10 slices for the assessment of areas of low attenuation[24] which correspond to tissue loss in emphysema.[23] CT lung density measurements have been proposed as a method to identify and quantitate emphysema;[25] however, this approach was not undertaken as our validation study showed that CT lung density measurements were not able usefully to identify emphysema in a general population setting.[15]

In accordance with internationally accepted guidelines,[16] our criteria for asthma included the presence of either bronchodilator reversibility of $FEV_1 \geqslant 15\%$ of baseline value or peak flow variability of at least 20%. A minority of subjects with asthma will not demonstrate these features at a single time point or over a short period of assessment, so a physician diagnosis of asthma in conjunction with recent symptoms or inhaler use was also employed which identified about a quarter of the subjects with asthma. The baseline characteristics of these subjects did not substantially differ from the other subjects categorised as having asthma.

Our criteria differ from those used in previous studies attempting to quantify the Venn diagram of COPD which have been based primarily on pre-bronchodilator spirometry and non-standardised physician diagnoses derived from computerised databases.[9 10] The limitations of this approach are illustrated in comparisons of figures from USA- and UK-based databases[9] in which the prevalence of chronic bronchitis and/or emphysema defined by physician diagnosis was 4.2% and 0.6%, respectively. These figures suggest that diagnostic labelling was the main determinant of the prevalence of the different COPD phenotypes in these populations. In addition, the use of pre-bronchodilator figures make the separation of reversible and irreversible airflow obstruction impossible.[26 27]

A further methodological issue relates to the generalisability of our findings. Our initial sampling frame was based on the European Community Respiratory Health Survey[28] and the population, which predominantly (90%) comprised subjects of European origin, had a high prevalence of both COPD[11] and asthma.[26] Response bias may have favoured participation of those with existing respiratory symptoms at any age, but is otherwise unlikely to have resulted in preferential selection of one phenotype over another. Since this study was based on a population sample, those with COPD had predominantly mild to moderate airways obstruction. The phenotype proportions in a population with more severe disease, such as patients with a previous hospital admission for COPD, are likely to be different from those presented in our study.

In this study it was possible to determine the proportion of subjects included in the different phenotypes that make up COPD. However, it was not possible to fit these data into the non-proportional Venn diagram proposed by the ATS which assumed that all subjects with COPD have either chronic bronchitis, emphysema, or both. Furthermore, the non-proportional Venn diagram is not consistent with the current definition of COPD which is primarily physiological, requiring the presence of incompletely reversible airflow obstruction confirmed by spirometry, with a post-bronchodilator FEV_1/FVC <0.7. These fundamental design limitations in the non-proportional Venn diagram have led to alternative representations of phenotypic overlap in COPD. For example, Viegi and co-workers proposed paired Venn diagrams with and without airflow obstruction.[10] The single Venn diagram proposed by Soriano *et al*,[9] in which the proportion with incompletely reversible airflow obstruction is shown within each diagnostic subgroup, represents another format. An alternative approach is to use diagrams with area-proportional rectangles which have an enhanced ability to visually convey information about datasets with interacting characteristics.[17–19] In this study we have used diagrams based on axis-aligned proportional rectangles and single proportional Venn diagrams to present the proportions of the different phenotypes. We consider that these may represent the optimal methods by which to present such epidemiological data.

Through these proportional diagrammatic presentations, it is possible to observe one of the important findings of this study—that asthma is the most common phenotype making up spirometrically-defined COPD. This finding is consistent with observations from longitudinal studies that asthma is a major risk factor for subsequent COPD[29 30] and that bronchodilator reversibility, one of the characteristic features of asthma, is commonly present in subjects with COPD.[31 32] The asthma phenotype in COPD is potentially a consequence of accelerated loss of lung function in asthma[33 34] which has been attributed to chronic airways inflammation and remodelling.[35] However, while the physiological manifestations of incompletely reversible airflow obstruction in those with asthma and other forms of COPD may be similar, the pathological characteristics may vary considerably.[36] The observation that most of the subjects with COPD with asthma as well as the other phenotypes were current or former smokers reinforces the importance of tobacco smoking in the pathogenesis of COPD across the different phenotypic groups.

It is recognised that the findings are influenced by the criteria used to define COPD and the different distinct phenotypes as well as the population in which the study was carried out. This was illustrated by the use of the alternative criterion of a post-bronchodilator FEV_1/FVC ratio below the lower limit of normal which has been proposed in recognition that the FEV_1/FVC ratio declines with age.[20–22] This approach resulted in about one-third fewer subjects with COPD and, more importantly, a lower proportion of subjects with COPD without a defined asthma, chronic bronchitis or emphysema phenotype. However, the proportions with asthma, chronic bronchitis or emphysema phenotypes were otherwise similar. Likewise, the use of a pre-bronchodilator FEV_1/FVC ratio of 0.7, which has recently been proposed to facilitate practical implementation of spirometry in general practice,[37] or the British guidelines in which the FEV_1/FVC ratio of 0.7 is recommended without reference to prior bronchodilator use[38] will inevitably result in different proportions of the COPD phenotypes. There is a high prevalence of asthma in New Zealand and it is likely that different proportions would have been observed in populations with lower asthma prevalence rates. Likewise, differing proportions are likely to be observed in developing countries in which there are high rates of COPD in non-smoking women due to indoor air pollution.[39]

We consider that knowledge of the relative proportions of the COPD phenotypes is of more than academic interest, not least because the phenotypic groups may differ in their response to management. An important clinical example which has only recently been recognised is the differential response to inhaled corticosteroid therapy in subjects with asthma, depending on their smoking status.[40 41] Furthermore, the criteria commonly used in randomised controlled trials of therapeutic regimes in COPD have resulted in the exclusion of the vast majority of individuals with COPD treated in the community.[42] A better understanding of the relative proportions of each of the COPD phenotypes and the existence of "overlap" syndromes may allow randomised controlled trials to be designed such that the findings are more generalisable to patients with COPD in the community. In addition, inclusion of other markers such as exhaled nitric oxide or sputum eosinophilia in the criteria defining COPD phenotypes may prove useful in identifying subjects with COPD with distinct therapeutic responses and clinical outcomes.[43 44]

In conclusion, this study provides proportional classifications of the COPD clinical phenotypes based on detailed objective measures. Asthma with incompletely reversible airways obstruction was the dominant COPD phenotype, with the classical phenotypes of chronic bronchitis and/or emphysema but no asthma being less common. Further research is required to determine the optimal management regimes for the different COPD phenotypes.

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Lung alert

‘‘Prognostic pessimism’’ in asthma and COPD

Doctors can be pessimistic—especially when making a prognosis—and this in turn may influence clinical decisions. This study looked at the accuracy of the predicted outcome in patients with chronic obstructive pulmonary disease (COPD) and asthma with regard to admission to the intensive care unit (ITU).

Data were collected over 18 months from nearly half the ITUs involved in the UK Case Mix Program and three high dependency units. Patients aged <45 years and those admitted from other hospitals or within 10 days of surgery were excluded. In the 832 patients who were recruited, the primary outcome analysed was the comparison between the prediction for survival on admission and the actual outcome at 180 days. It was found that, overall, the admitting doctor underestimated the survival potential, especially in patients already in poor health. In fact, 40% of patients with the worst prognosis survived when only 10% had been predicted to do so.

The authors concluded that bias associated with ‘‘prognostic pessimism’’ may deny some patients the benefits of intubation, yet provided no evidence for this. One limitation of this study was that they only looked at patients who had already been admitted into intensive care and high dependency units and not ward-based patients. Also, there were no data as to the seniority or experience level of the clinician admitting to the ITU. However, with increasing pressure for ITU beds and the incidence of COPD increasing, this study provides evidence that this is an important area for further investigation.

- Wildman M, Sanderson C, Groves J, *et al*. Implications of prognostic pessimism in patients with chronic obstructive pulmonary disease (COPD) or asthma admitted to intensive care in the UK within the COPD and Asthma Outcome Study (CAOS): multicenter observational cohort study. *BMJ* 2007;**335**:1132–4.

S McCarthy

Correspondence to: Dr S McCarthy, Foundation Year 2, Queen’s Hospital, Romford, Essex RM7 0AG, UK; smccarthy@doctors.org.uk

Correction

SE Marsh, J Travers, M Weatherall, *et al*. Proportional classifications of COPD phenotypes. *Thorax* 2008;63:761–7. doi:10.1136/thoraxjnl-2007-089193

Figure 3 of this article was published omitting the clear circle in the middle of the emphysema circle as shown in the corrected figure below:

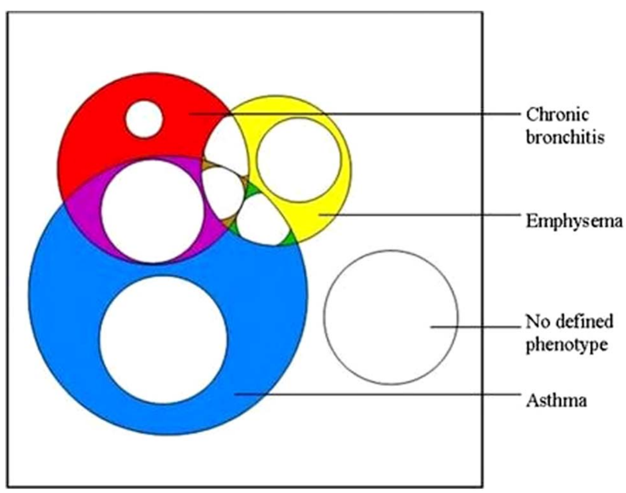

Figure 3

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