Proportional classifications of COPD phenotypes

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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 subgroups 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 (FEV1/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 FEV1/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 FEV1/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 (FEV1/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 diagram9–11 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 = 5500) 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...
Chronic obstructive pulmonary disease

Figure 1  Non-proportional Venn diagram of chronic obstructive pulmonary disease (COPD) produced by the American Thoracic Society. 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 airflow 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.

Definitions of disease categories
COPD was defined by a post-bronchodilator FEV\textsubscript{1}/FVC <0.7 in accordance with current guidelines.\textsuperscript{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.\textsuperscript{7} 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.\textsuperscript{2}
- Emphysema:
  - Macroscopic emphysema (centrilobular, panlobular or paraseptal) or
  - Post-bronchodilator FEV\textsubscript{1}/FVC <0.7 and TLCO/VA adjusted for haemoglobin less than the lower limit of normal.\textsuperscript{12}
- Asthma:
  - Post-bronchodilator increase in FEV\textsubscript{1} \(\geq 15\%\textsuperscript{16} or
  - Peak flow variability \(\geq 20\%\textsuperscript{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 \(\chi^2\) 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\textsuperscript{17} using axis-aligned rectangles to represent phenotypic groups.\textsuperscript{13,19}
- Proportional Venn diagrams in which the proportion of subjects with COPD is shown as a clear circle within diagnostic subgroups, as described previously.\textsuperscript{7}

The number of subjects in each phenotypic category was also presented, in which COPD was defined as a post-bronchodilator FEV\textsubscript{1}/FVC ratio less than the lower limit of normal-derived reference value.\textsuperscript{13,20}

CT scanning
CT scans of the chest were undertaken using a single machine (GE Prospeed, General Electric Medical Systems, YMS, Japan) as described previously.\textsuperscript{13} 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.

Guidelines.\textsuperscript{13,14} Following measurement of static lung volumes, a minimum of three acceptable spirometry manoeuvres were carried out with the best FEV\textsubscript{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.\textsuperscript{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.
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 who had died, this represented a response rate of 2319/2979 (78%). Of those completing the postal questionnaire, 795 responders only, n (%)

<table>
<thead>
<tr>
<th>Variable</th>
<th>COPD (n = 96)</th>
<th>No COPD (n = 373)*</th>
<th>Total group (n = 469)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex, n (%)</td>
<td>66 (68.8)</td>
<td>205 (55.0)</td>
<td>271 (57.8)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>21 (21.9)</td>
<td>28 (7.5)</td>
<td>49 (10.5)</td>
</tr>
<tr>
<td>Former</td>
<td>40 (41.7)</td>
<td>192 (48.8)</td>
<td>222 (47.3)</td>
</tr>
<tr>
<td>FEV1, bronchodilator reversibility ≥15%, n (%)</td>
<td>27 (28.1)</td>
<td>8 (2.1)</td>
<td>35 (7.5)</td>
</tr>
<tr>
<td>Peak flow variability ≥20%, n (%)</td>
<td>26 (27.1)</td>
<td>21 (5.6)</td>
<td>47 (10.0)</td>
</tr>
<tr>
<td>Mean (SD) age (years)</td>
<td>65.4 (6.8)</td>
<td>62.0 (7.3)</td>
<td>62.7 (7.3)</td>
</tr>
<tr>
<td>Mean (SD) post-bronchodilator FEV1 (l)</td>
<td>2.4 (0.8)</td>
<td>3.2 (0.8)</td>
<td>3.0 (0.9)</td>
</tr>
<tr>
<td>Mean (SD) post-bronchodilator FEV1 (% predicted)</td>
<td>74.0 (17.9)</td>
<td>99.1 (14.4)</td>
<td>94.0 (18.3)</td>
</tr>
<tr>
<td>Mean (SD) post-bronchodilator FEV1/FVC</td>
<td>60.2 (8.6)</td>
<td>78.4 (5.3)</td>
<td>74.7 (9.5)</td>
</tr>
<tr>
<td>Mean (SD) TcO2/Va (mmol/min/kPa/l)</td>
<td>1.21 (0.25)</td>
<td>1.42 (0.18)</td>
<td>1.37 (0.21)</td>
</tr>
<tr>
<td>Mean (SD) cigarette pack years (cigarette smokers only)</td>
<td>27.2 (21.6)</td>
<td>14.4 (18.4)</td>
<td>17.6 (20.0)</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease, FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TcO2, gas transfer factor, adjusted for haemoglobin; Va, 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.
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 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. Subjects not classified as COPD in the ATS Venn diagram but who were classified as COPD by the GOLD criteria were those with COPD but no asthma, chronic bronchitis or emphysema (n = 25) and those with COPD and asthma alone (n = 25).

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 FEV1/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 spirometrically-defined COPD, in accordance with current international guidelines. The classic phenotype of chronic bronchitis and/or emphysema with no asthma 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 FEV1/FVC ratio of <0.7 in the absence of an alternative respiratory disorder. Owing to the

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**Table 3** Study population distribution across phenotype category

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>COPD</th>
<th>No COPD</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma*</td>
<td>6</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Chronic bronchitis*</td>
<td>15</td>
<td>13</td>
<td>28</td>
</tr>
<tr>
<td>No emphysema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chronic bronchitis</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Emphysema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No emphysema</td>
<td>23</td>
<td>40</td>
<td>63</td>
</tr>
<tr>
<td>No asthma</td>
<td>6</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>Chronic bronchitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No emphysema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No chronic bronchitis</td>
<td>10</td>
<td>8</td>
<td>18</td>
</tr>
<tr>
<td>Emphysema</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No emphysema</td>
<td>25</td>
<td>292</td>
<td>317</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>373</td>
<td>469</td>
</tr>
</tbody>
</table>

*COPD, chronic obstructive pulmonary disease (defined as post-bronchodilator FEV1/FVC <0.7). *See text for definitions of these phenotypes.

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**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 FEV1/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.
The assessment of areas of low attenuation which correspond to tissue loss in emphysema. The definition of emphysema required either definite radiological evidence of macroscopic emphysema on CT scan or a low gas transfer factor in the presence of incompletely reversible airflow obstruction. The use of three slices at specified anatomical levels may have resulted in under-representation of subjects with COPD who did not have a defined phenotype of asthma, chronic bronchitis or emphysema.

In accordance with internationally accepted guidelines, our criteria for asthma included the presence of either bronchodilator reversibility of FEV₁ ≥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 in conjunction with recent symptoms or inhaler use. This approach has been shown to be as informative as 10 slices for recognition of the presence of macroscopic emphysema, but this was not useful to identify emphysema in a validation study showed that CT lung density measurements were not able to identify emphysema in a general population setting.

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 FEV₁/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. The single Venn diagram proposed by Soriano et al., 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. 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 and that bronchodilator reversibility, one of the characteristic features of asthma, is commonly present in subjects with COPD. The asthma phenotype in COPD is potentially a consequence of accelerated loss of lung function in asthma which has been attributed to chronic airways inflammation and remodelling. 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. The observation that most of the subjects experienced a decline in the FEV₁/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. A further methodological issue relates to the generalisability of our findings. Our initial sampling frame was based on the European Community Respiratory Health Survey and the population, which predominantly (90%) comprised subjects of European origin, had a high prevalence of both COPD and asthma. 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.

Figure 3 Proportional Venn diagram presenting the different phenotypes within the Wellington Respiratory Survey study population.

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Chronic obstructive pulmonary disease

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 FEV1/FVC ratio below the lower limit of normal which has been proposed in recognition that the FEV1/FVC ratio declines with age.20–22 This approach resulted in about one-third which has been proposed in recognition that the FEV1/FVC ratio written informed consent was obtained from each subject.

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Competing interests: None.

Ethics approval: The survey was approved by the Wellington ethics committee and written informed consent was obtained from each subject.

REFERENCES


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 852 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.

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Correction


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:

![Corrected Figure 3](image)

Figure 3

*Thorax* 2015;70:905. doi:10.1136/thx.2007.089193corr2