

## ORIGINAL ARTICLE

# GOLD classifications and mortality in chronic obstructive pulmonary disease: the HUNT Study, Norway

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/thoraxjnl-2013-203270>).

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Received 16 January 2013

Revised 19 March 2013

Accepted 27 March 2013

Published Online First

23 April 2013



► <http://dx.doi.org/10.1136/thoraxjnl-2013-203595>

**To cite:** Leivseth L, Brumpton BM, Nilsen TIL, et al. *Thorax* 2013;**68**:914–921.

## ABSTRACT

**Background** How different Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications of chronic obstructive pulmonary disease (COPD) predict mortality is unclear.

**Objective** To examine the association of spirometric GOLD grades and the new ABCD groups with mortality, and to compare their informativeness in relation to mortality.

**Methods** We studied 1540 people with post-bronchodilator COPD who participated in the Norwegian Nord-Trøndelag Health Study 1995–1997 and were followed up on all-cause mortality until May 2012. The associations of spirometric GOLD grades and ABCD groups with mortality were estimated by sex specific adjusted HRs from Cox regression and standardised mortality ratios. To assess the informativeness of spirometric GOLD grades and ABCD groups at predicting mortality we used the difference in twice the log-likelihood of a Cox regression model with and without each COPD classification.

**Results** The distribution of participants was 28% in GOLD 1, 57% in GOLD 2, 13% in GOLD 3 and 2% in GOLD 4, in contrast to 61% in group A, 18% in group B, 12% in group C and 10% in group D. During a median of 14.6 years of follow-up, 837 people (54%) died. Mortality increased gradually from GOLD 1 to 4, while it was generally similar in groups A and B, and in groups C and D. Spirometric GOLD grades were substantially more informative than ABCD groups at predicting mortality.

**Conclusions** Spirometric GOLD grades predicted mortality better than the new ABCD groups among people with COPD from a Norwegian general population.

## INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality worldwide<sup>1</sup> and it is estimated to be the fourth leading cause of death by 2030.<sup>2</sup> According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), a diagnosis of COPD should be based on post-bronchodilator spirometric measurements, and the severity should be graded based on per cent predicted forced expiratory volume in 1 s (ppFEV<sub>1</sub>).<sup>3 4</sup>

However, the 2011 revision of the GOLD strategy document presented a new ABCD group classification of COPD which intended to provide a better

## Key messages

### What is the key question?

- Which of the spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades or the new ABCD groups is the better predictor of mortality in chronic obstructive pulmonary disease (COPD)?

### What is the bottom line?

- Spirometric GOLD grades predicted mortality better than the new ABCD groups.

### Why read on?

- This is the first population-based study evaluating which of the spirometric GOLD grades or the new ABCD groups is the better predictor of mortality in people with COPD.

understanding of the impact of the disease on an individual patient than spirometric GOLD grades.<sup>3 4</sup> The ABCD groups combine symptom burden and risk of exacerbations, where the latter is estimated from the spirometric GOLD grades and the number of exacerbations in the last year.<sup>3 4</sup> The association of spirometric GOLD grades and ABCD groups with mortality has been examined in two recent studies.<sup>5 6</sup> In the first study, both pre-bronchodilator spirometric GOLD grades and ABCD groups predicted mortality in a general population in Denmark, but which measure best predicted mortality was not formally tested.<sup>5</sup> In this Danish study, survival was poorer in people with relatively high lung function and dyspnoea compared with people with lower lung function without dyspnoea.<sup>5</sup> In the second study, pooled data from 11 Spanish COPD cohorts showed no difference between post-bronchodilator spirometric GOLD grades and ABCD groups in predicting mortality.<sup>6</sup>

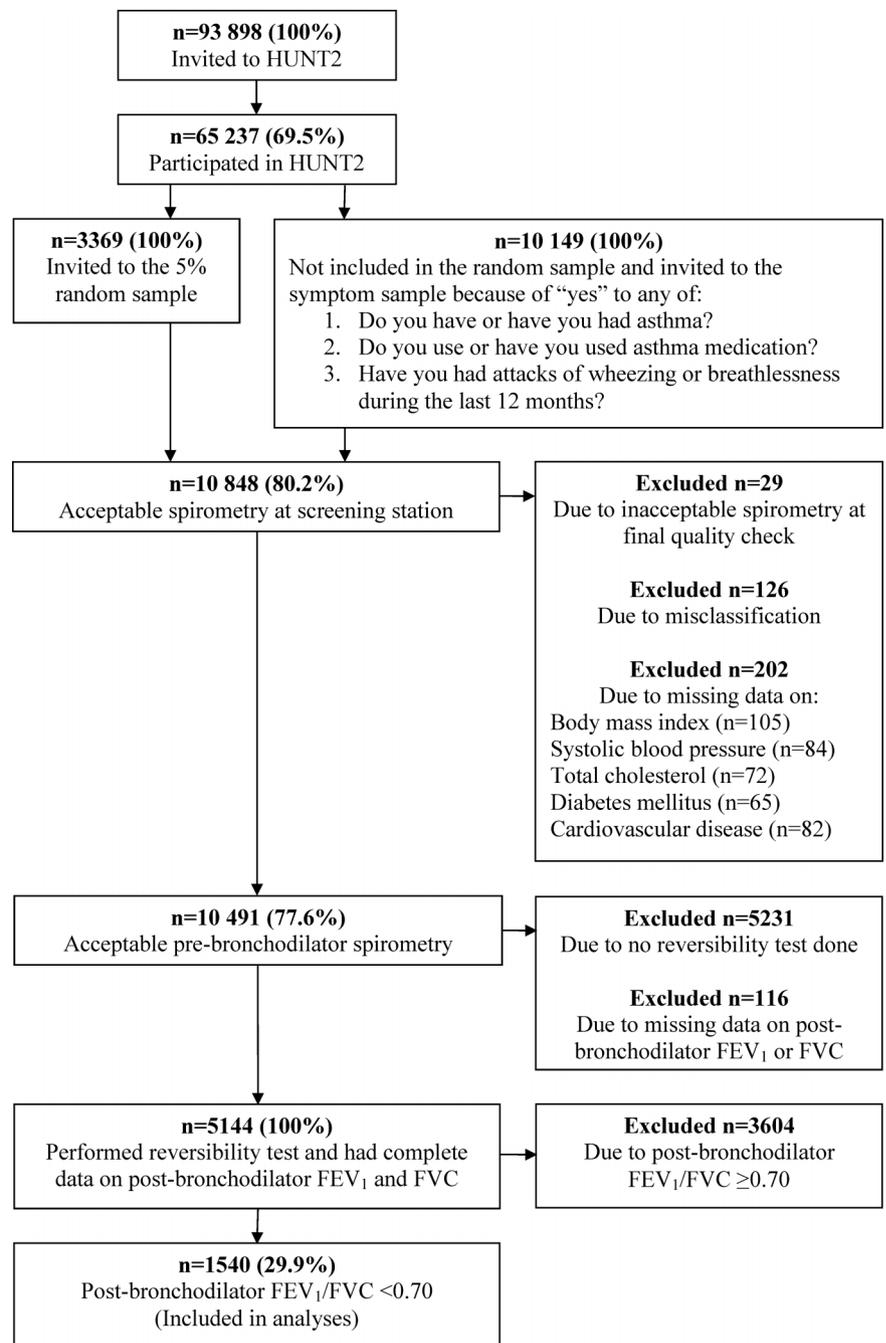
We aimed to examine the association of spirometric GOLD grades and the new ABCD groups with mortality, and to compare their informativeness in relation to mortality.

## METHODS

### Study population

From August 1995 to June 1997, all residents in Nord-Trøndelag County in Norway aged 19 years or older were invited to participate in the second wave of the Nord-Trøndelag Health Study (HUNT2).<sup>7</sup> Among

**Figure 1** Flow chart of inclusion and exclusion in the HUNT2 Lung Study.



the 65 237 participants (69.5% of those invited), a 5% random sample and a symptom sample were invited to participate in the Lung Study.<sup>8-9</sup> Briefly, the symptom sample included participants reporting attacks of wheezing or breathlessness during the last 12 months, having ever had asthma and/or having ever used asthma medication, and who were not included in the random sample. As described elsewhere,<sup>10</sup> a  $\beta_2$ -agonist reversibility test was performed on a subsample of the 10 491 Lung Study participants with acceptable pre-bronchodilator spirometry. Among 5144 participants with complete data on post-bronchodilator FEV<sub>1</sub> and forced vital capacity (FVC), the 1540 participants with post-bronchodilator FEV<sub>1</sub>/FVC <0.70 comprised the study cohort (figure 1).

### Study variables

At participation in HUNT2, questionnaire information was collected on a range of lifestyle and health related factors, and all

participants underwent a clinical examination.<sup>7</sup> The Lung Study participants completed an additional lung specific questionnaire, an interview and flow volume spirometry.<sup>9</sup>

### Lung function and spirometric GOLD grades

Flow volume spirometry was recorded according to the 1994 American Thoracic Society recommendations<sup>11</sup> as described elsewhere.<sup>9</sup> Spirometry was performed before and 30 min after inhalation of 1 mg terbutaline.<sup>10</sup> Pre- and post-bronchodilator FEV<sub>1</sub> and FVC were obtained, and the prediction equations of Langhammer *et al*<sup>9</sup> were used to calculate ppFEV<sub>1</sub>. Post-bronchodilator FEV<sub>1</sub>/FVC <0.70 defined COPD, and airflow limitation was graded according to GOLD criteria as GOLD 1 (ppFEV<sub>1</sub> ≥80), GOLD 2 (50 ≤ ppFEV<sub>1</sub> <80), GOLD 3 (30 ≤ ppFEV<sub>1</sub> <50) and GOLD 4 (ppFEV<sub>1</sub> <30).<sup>3-4</sup>

### ABCD groups

We generated ABCD groups based on symptom burden and exacerbation risk according to the 2011 GOLD strategy document.<sup>3 4</sup> According to GOLD,<sup>3 4</sup> symptom burden should be measured by the modified Medical Research Council (mMRC) dyspnoea scale<sup>12</sup> or the COPD Assessment Test (CAT),<sup>13</sup> and exacerbation risk by the GOLD grades of airflow limitation or exacerbation history. The ABCD group classification is based on a 2×2 table with cells labelled A, B, C and D. Symptom burden is divided into low (A and C) and high (B and D), whereas airflow limitation and/or exacerbation history separates A from C, and B from D. Regarding the latter, patients should be placed in the group that gives the highest exacerbation risk according to airflow limitation (ppFEV<sub>1</sub> <50) or exacerbation history (≥2 last year).<sup>3 4</sup> In the current study, symptom burden was measured by a dyspnoea scale included in the lung specific questionnaire (22% missing data).<sup>8 14 15</sup> We used a cut-off on 'Do you become short of breath when walking on flat ground at a normal pace?' which approximates to dyspnoea grade 2 according to the mMRC dyspnoea scale.<sup>12</sup> Airflow limitation was graded as described above. Exacerbation history (≤1, ≥2 last year) was generated from two questions; 'Have you ever taken cortisone tablets for breathing problems/asthma?' and 'How many cortisone courses have you taken in the last year?' Among participants with data on the dyspnoea scale, four people (0.2%) had missing data on exacerbation history, and these were placed in an exacerbation risk group based on their spirometric GOLD grade.

### Follow-up

The study cohort was followed from the date of attendance in HUNT2 to the date of death or emigration, or the end of follow-up, 24 May 2012, whichever came first. There were no other losses to follow-up. The outcome was all-cause mortality, and date of death was obtained from the Cause of Death Registry in Norway.

### Statistical analyses

Baseline characteristics were presented according to spirometric GOLD grades and ABCD groups. Most statistical analyses were sex specific because women and men differ in many ways including hormonal and immunological determinants,<sup>16</sup> perception and reporting of symptoms,<sup>16 17</sup> and exposure to cigarette smoke or other noxious particles and gasses.<sup>4</sup> Death rates per 1000 person-years were calculated for spirometric GOLD grades and ABCD groups. We also calculated standardised mortality ratios (SMRs) with 95% CIs using the Norwegian population death rates as reference.<sup>18</sup> These death rates were presented separately for women and men, 5-year age bands (20–24, ..., 85–89, ≥90), and 5-year calendar periods (1991–1995, ..., 2006–2010, 2011). By sorting our data in the same way we calculated the expected number of deaths within spirometric GOLD grades and ABCD groups in our study cohort. SMRs were obtained when comparing the observed to the expected number of deaths. Unadjusted Kaplan–Meier curves with time of follow-up as the time scale were generated in order to visualise mortality trends according to spirometric GOLD grades and ABCD groups.

Cox proportional hazard regression was used to compute HRs with 95% CIs for the association of spirometric GOLD grades and ABCD groups with mortality. All associations were adjusted for potential confounding by age (as the time scale),<sup>19</sup> smoking (current, former, never, unknown (4.5%)), and

education (<10, ≥10 years, unknown (8.7%)) as identified through directed acyclic graphs.<sup>20 21</sup> In separate models we also assessed possible confounding by body mass index (BMI) (<18.5, 18.5–24.9, 25.0–29.9, ≥30.0 kg/m<sup>2</sup>), physical activity (inactive, light activity <1 h/week, light activity 1–2 h/week, light activity ≥3 h/week, only vigorous activity, unknown (3.1%)), cardiovascular disease (CVD) (yes, no), diabetes mellitus (DM) (yes, no), total cholesterol (sex specific quartiles; mmol/l), and systolic blood pressure (SBP) (sex specific quartiles; mm Hg). Departures from the proportional hazard assumptions were evaluated by inspecting log-log survival curves for each covariate, calculating Schoenfeld residuals and producing formal tests of interaction with time or log time.

To study how well spirometric GOLD grades and ABCD groups predicted mortality, we estimated their informativeness according to the method described by Peto *et al*<sup>22</sup> and later used by others.<sup>23–25</sup> The informativeness was computed as the difference in twice the log-likelihood between a Cox proportional hazard null model (including age as the time scale, smoking and education) and an alternative model (including spirometric GOLD grades or ABCD groups in addition to all in the null model). This difference approximately follows a  $\chi^2$  distribution. The greater the difference, the more informative is that particular predictor. To help compare models, we set the most informative model to 100% and compared the other model with this reference. Additionally, we analysed the area under the receiver operating characteristic curve (AUC) and the pseudo R<sup>2</sup> from logistic regression models including the same variables as presented above.

In subsequent sensitivity analyses we generated ABCD groups with three alternate measures of symptom burden. First, 'Have you had any kind of attack of wheezing or breathlessness during the last 12 months?' (no missing data). Second, 'Have you at any time in the last 12 months been short of breath when resting during the day?' (0.2% missing data). 'No' was regarded as low and 'yes' as high symptom burden. Third, 'How is your health at the moment?' (0.8% missing data). 'Good/very good' were regarded as low and 'poor/not so good' as high symptom burden.

Statistical analyses were conducted using Stata V.12.1. All statistical tests were two-sided.

### Ethics

The Regional Committee for Medical Research Ethics (reference 4.2008.59) approved the study, and the Norwegian Data Inspectorate licensed the research register (reference 06/00104-39/CGN). All participants signed informed written consents.

## RESULTS

### Baseline characteristics and distribution of participants

In this prospective cohort study of 1540 people with COPD, 837 people (54%) died during a median of 14.6 years (18 150 person-years) of follow-up. Baseline characteristics are presented in table 1. When classified by spirometric GOLD grade, the distribution of participants was 28% in GOLD 1, 57% in GOLD 2, 13% in GOLD 3 and 2% in GOLD 4. In contrast, when classified by ABCD group, the distribution of participants was 61% in group A, 18% in group B, 12% in group C and 10% in group D.

### Spirometric GOLD grades and ABCD groups in association with mortality

Compared to GOLD 1 or the general population, mortality increased with higher spirometric GOLD grade (table 2).

**Table 1** Baseline characteristics according to spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades\* and ABCD group† among participants with chronic obstructive pulmonary disease (COPD) in the HUNT2 Lung Study

	Participants n (%)‡	Ever smokers n (%)§	Education ≥10 years n (%)§	Inactive n (%)§	Cardiovascular disease n (%)§	Body mass index (kg/m <sup>2</sup> ) Mean (SD)	Age (years) Mean (SD)
<b>Women</b>							
GOLD grades (n=584)							
GOLD 1	173 (29.6)	95 (58.6)	51 (32.1)	19 (12.9)	21 (12.1)	26.7 (4.7)	62.4 (15.9)
GOLD 2	338 (57.9)	240 (75.0)	98 (32.1)	43 (16.8)	46 (13.6)	27.1 (5.6)	61.7 (12.0)
GOLD 3	64 (11.0)	49 (83.1)	12 (23.5)	6 (17.6)	10 (15.6)	24.3 (4.4)	63.7 (10.2)
GOLD 4	9 (1.5)	6 (85.7)	3 (37.5)	3 (42.9)	1 (11.1)	23.5 (2.7)	59.6 (8.9)
ABCD groups (n=468)							
Group A	278 (59.4)	179 (69.4)	90 (35.3)	24 (10.8)	31 (11.2)	26.3 (5.0)	61.9 (13.9)
Group B	100 (21.4)	75 (77.3)	25 (26.3)	19 (24.4)	13 (13.0)	29.1 (6.1)	62.3 (12.2)
Group C	42 (9.0)	26 (63.4)	10 (28.6)	1 (3.7)	8 (19.0)	24.3 (3.7)	63.4 (11.3)
Group D	48 (10.3)	33 (78.6)	11 (28.2)	6 (20.0)	7 (14.6)	27.0 (5.0)	64.6 (9.7)
<b>Men</b>							
GOLD grades (n=956)							
GOLD 1	251 (26.3)	197 (83.1)	117 (50.0)	17 (7.8)	44 (17.5)	26.6 (3.6)	61.6 (13.6)
GOLD 2	545 (57.0)	471 (89.0)	216 (44.3)	56 (12.4)	136 (25.0)	26.5 (3.8)	64.5 (12.5)
GOLD 3	140 (14.6)	124 (94.7)	36 (28.8)	17 (15.6)	27 (19.3)	25.1 (3.8)	69.6 (9.5)
GOLD 4	20 (2.1)	20 (100.0)	4 (23.5)	4 (26.7)	4 (20.0)	23.9 (2.8)	67.7 (7.9)
ABCD groups (n=736)							
Group A	453 (61.6)	371 (85.5)	207 (49.5)	29 (7.5)	80 (17.7)	26.2 (3.5)	62.8 (12.9)
Group B	116 (15.8)	109 (95.6)	41 (40.2)	17 (18.3)	41 (35.3)	28.0 (4.4)	66.2 (11.7)
Group C	100 (13.6)	81 (86.2)	38 (40.4)	12 (15.2)	16 (16.0)	25.2 (3.3)	67.5 (11.0)
Group D	67 (9.1)	61 (93.8)	18 (32.7)	13 (24.5)	15 (22.4)	25.3 (4.2)	69.3 (9.5)

\*COPD defined as forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) <0.70 and graded as follows; GOLD 1=per cent predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>) ≥80; GOLD 2=50≤ppFEV<sub>1</sub> <80; GOLD 3=30≤ppFEV<sub>1</sub> <50; GOLD 4=ppFEV<sub>1</sub> <30.

†ABCD groups defined as follows; A=dyspnoea ≤grade 1, GOLD 1 or 2, and ≤1 exacerbation last 12 months; B=dyspnoea ≥grade 2, GOLD 1 or 2, and ≤1 exacerbation last 12 months; C=dyspnoea ≤grade 1, and GOLD 3 or 4 or ≥2 exacerbations last 12 months; D=dyspnoea ≥grade 2, and GOLD 3 or 4 or ≥2 exacerbations last 12 months.

‡% of total.

§% within spirometric GOLD grade or ABCD group, missing excluded.

Compared to group A, women in groups C and D and men in group D had increased mortality. Compared to the general population, women and men in most ABCD groups had increased mortality. In general, mortality did not differ substantially between groups A and B, and between groups C and D. Further adjustments for BMI, physical activity, CVD, DM, total cholesterol and SBP did not materially change the estimates (data not shown). The sensitivity analyses with alternate measures of dyspnoea or health status supported our main findings (see online supplementary table S1 for women and online supplementary table S2 for men).

The unadjusted Kaplan–Meier curves demonstrated large differences in survival between the four spirometric GOLD grades among women and men (figure 2). Among women, there were small differences in survival between groups A and B, and between groups C and D (figure 3). In contrast, survival was lower among men in group B compared to A, and in group D compared to C (figure 3).

### Informativeness

Spirometric GOLD grades were more informative than ABCD groups at predicting mortality (table 3). These findings were supported by the additional analyses of AUC and pseudo R<sup>2</sup> (see online supplementary table S3) and the sensitivity analyses with alternate measures of dyspnoea or health status (see online supplementary tables S4 and S5).

### DISCUSSION

Among participants with COPD in the Norwegian HUNT2 Lung Study, spirometric GOLD grades predicted mortality better than ABCD groups. Mortality increased gradually from GOLD 1 to 4, while it was similar in group A compared to B, and in group C compared to D.

#### Spirometric GOLD grades and ABCD groups in association with mortality

In accordance with other epidemiological studies,<sup>5 26–28</sup> mortality increased with higher spirometric GOLD grade in the current study. In general, our study showed similar mortality in groups A and B, and in groups C and D, which may indicate that symptom burden does not influence mortality substantially. In support of this, we observed that the choice of symptom burden instrument did not affect our findings. The unadjusted Kaplan–Meier curves indicated that reporting dyspnoea when walking might be associated with lower survival in men but not in women. However, these curves must be interpreted with caution since possible confounders like age, smoking and education were more unfavourable among people in group B compared to A, and in group D compared to C.

A likely explanation of the small differences in mortality between groups A and B, and between groups C and D, may be that ppFEV<sub>1</sub> is dichotomised at 50 in the ABCD classification, resulting in less discrimination between people with different lung function. Hence, symptom burden may still be associated

**Table 2** Death rates, adjusted HRs, and standardised mortality ratios (SMRs) with 95% CIs for the associations of spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades and ABCD groups with all-cause mortality among participants with chronic obstructive pulmonary disease (COPD) in the HUNT2 Lung Study

COPD classification	Person-years	Observed deaths	Death rate*	(95% CI)	Age-adjusted HR†	Multi-adjusted HR‡	(95% CI)‡	Expected deaths	SMR§	(95% CI)§
Women										
GOLD grades¶ (n=584)	7393	273	36.93	(32.80 to 41.58)						
GOLD 1	2366	59	24.94	(19.32 to 32.19)	1.00	1.00	(Reference)	79	0.75	(0.59 to 0.95)
GOLD 2	4341	155	35.70	(30.50 to 41.79)	2.32	2.29	(1.66 to 3.16)	91	1.70	(1.46 to 1.99)
GOLD 3	583	52	89.12	(67.91 to 116.96)	6.48	6.23	(4.15 to 9.36)	11	4.72	(3.62 to 6.08)
GOLD 4	102	7	68.55	(32.68 to 143.78)	6.90	6.97	(3.05 to 15.91)	1	5.15	(2.45 to 9.92)
ABCD groups** (n=468)	5918	217	36.67	(32.10 to 41.89)						
Group A	3667	115	31.36	(26.12 to 37.65)	1.00	1.00	(Reference)	96	1.19	(0.99 to 1.44)
Group B	1268	42	33.12	(24.47 to 44.81)	1.22	1.12	(0.78 to 1.62)	27	1.56	(1.18 to 2.08)
Group C	453	28	61.85	(42.70 to 89.58)	2.08	2.47	(1.62 to 3.79)	11	2.55	(1.62 to 3.94)
Group D	530	32	60.41	(42.72 to 85.42)	2.14	2.43	(1.62 to 3.66)	12	2.62	(1.77 to 3.82)
Men										
GOLD grades¶ (n=956)	10 757	564	52.43	(48.28 to 56.94)						
GOLD 1	3259	108	33.14	(27.44 to 40.02)	1.00	1.00	(Reference)	119	0.91	(0.76 to 1.08)
GOLD 2	6142	327	53.24	(47.77 to 59.34)	1.51	1.44	(1.15 to 1.80)	246	1.33	(1.20 to 1.47)
GOLD 3	1189	110	92.51	(76.74 to 111.51)	2.03	2.04	(1.56 to 2.68)	62	1.77	(1.47 to 2.12)
GOLD 4	167	19	113.58	(72.45 to 178.07)	4.28	4.24	(2.57 to 7.00)	5	3.47	(2.70 to 4.39)
ABCD groups** (n=736)	8350	436	52.22	(47.54 to 57.36)						
Group A	5437	242	44.51	(39.24 to 50.49)	1.00	1.00	(Reference)	196	1.24	(1.10 to 1.39)
Group B	1310	72	54.97	(43.63 to 69.25)	0.97	0.89	(0.68 to 1.16)	61	1.18	(0.95 to 1.47)
Group C	1041	69	66.27	(52.34 to 83.90)	1.08	1.10	(0.84 to 1.44)	52	1.32	(1.04 to 1.68)
Group D	562	53	94.38	(72.10 to 123.53)	1.63	1.70	(1.25 to 2.29)	27	1.98	(1.50 to 2.59)

\*Per 1000 person-years.

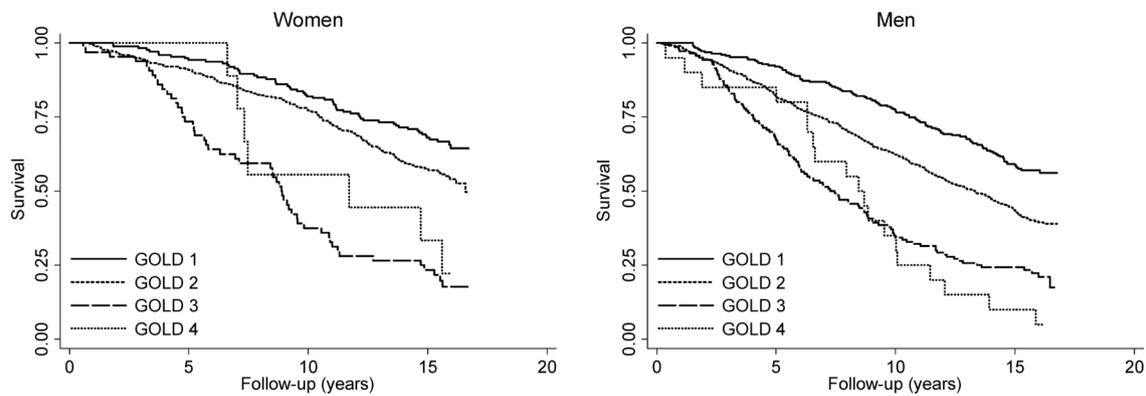
†Adjusted for age (as the time scale).

‡Adjusted for age (as the time scale), smoking (never, former, current, unknown) and education (&lt;10, ≥10 years, unknown).

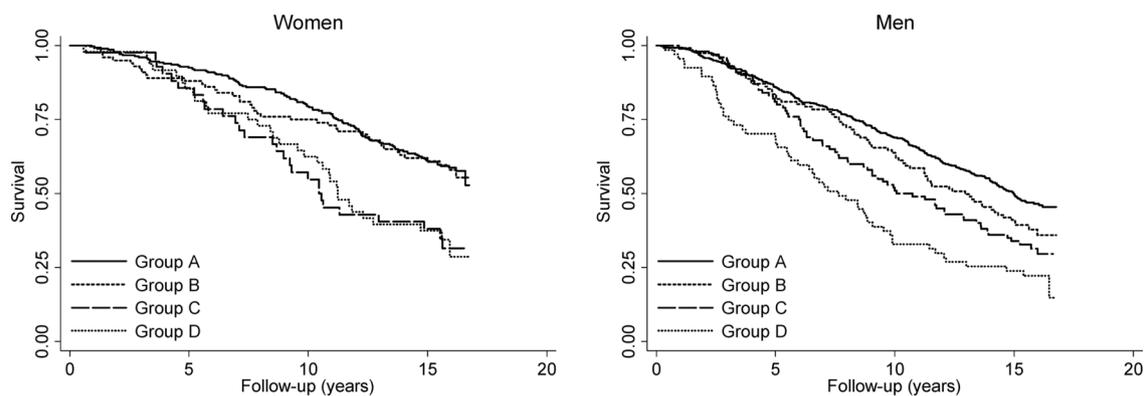
§Standardised according to sex, 5-year age bands and 5-year calendar periods.

¶COPD defined as forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) <0.70 and graded as follows; GOLD 1=per cent predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>) ≥80; GOLD 2=50≤ ppFEV<sub>1</sub> <80; GOLD 3=30≤ ppFEV<sub>1</sub> <50; GOLD 4=ppFEV<sub>1</sub> <30.

\*\*ABCD groups defined as follows; A=dyspnoea ≤grade 1, GOLD 1 or 2, and ≤1 exacerbation last 12 months; B=dyspnoea ≥grade 2, GOLD 1 or 2, and ≤1 exacerbation last 12 months; C=dyspnoea ≤grade 1, and GOLD 3 or 4 or ≥2 exacerbations last 12 months; D=dyspnoea ≥grade 2, and GOLD 3 or 4 or ≥2 exacerbations last 12 months.



**Figure 2** Kaplan–Meier curves according to spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades.



**Figure 3** Kaplan–Meier curves according to ABCD groups.

with mortality despite our findings. Studying over 10 000 people from HUNT2, we recently found dyspnoea to be independently associated with mortality within four levels of pre-bronchodilator ppFEV<sub>1</sub>.<sup>15</sup> In order to add possible predictive value of symptom burden without losing predictive value from lung function, we suggest keeping all four spirometric GOLD grades in the combined COPD assessment in the next revision of the GOLD strategy document.

In contrast to the current study, Lange *et al*<sup>5</sup> found poorer survival in group B compared to group C in people with pre-bronchodilator COPD from the general population of Denmark, and they suggested CVD or cancer as possible explanations. Since

most analyses were unadjusted, their results may have been biased by confounding factors. In addition, the average follow-up was 4.3 years, and it is possible that the associations will change with longer follow-up. In a pooled analysis of 11 COPD cohorts, Soriano *et al*<sup>6</sup> found no difference between post-bronchodilator spirometric GOLD grades and ABCD groups in predicting mortality during almost 16 000 person-years. Neither Lange *et al*<sup>5</sup> nor Soriano *et al*<sup>6</sup> performed sex specific analyses. In the current study, group B consisted of 21% of the women and 16% of the men, while group C consisted of 9% of the women and 14% of the men. This different distribution between sexes may reflect that women tend to report symptoms more often than men.<sup>16 17</sup>

**Table 3** Informativeness\* of spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades and ABCD groups related to all-cause mortality among participants with chronic obstructive pulmonary disease (COPD) in the HUNT2 Lung Study

COPD classification	Women (n=468)†			Men (n=736)†		
	$\chi^2$	(%)	p Value	$\chi^2$	(%)	p Value
GOLD grades‡	62.53	(100)	<0.001	32.47	(100)	<0.001
ABCD groups§	26.28	(42)	<0.001	13.03	(40)	0.046

\*The Cox null model included age (as the time scale), smoking (never, former, current, unknown) and education (<10, ≥10 years, unknown). The Cox alternative models included spirometric GOLD grades or ABCD groups in addition to all in the null model. The  $\chi^2$  shows the difference in twice the log-likelihood between the null model and the alternative model. The most informative model has the highest value of  $\chi^2$  and has been set to 100%.

†People with missing data on dyspnoea were excluded so that the results from the spirometric GOLD grades and the ABCD groups could be compared.

‡COPD defined as forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity (FVC) <0.70 and graded as follows; GOLD 1=per cent predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>) ≥80; GOLD 2=50≤ ppFEV<sub>1</sub> <80; GOLD 3=30≤ ppFEV<sub>1</sub> <50; GOLD 4=ppFEV<sub>1</sub> <30.

§ABCD groups defined as follows; A=dyspnoea ≤grade 1, GOLD 1 or 2, and ≤1 exacerbation last 12 months; B=dyspnoea ≥grade 2, GOLD 1 or 2, and ≤1 exacerbation last 12 months; C=dyspnoea ≤grade 1, and GOLD 3 or 4 or ≥2 exacerbations last 12 months; D=dyspnoea ≥grade 2, and GOLD 3 or 4 or ≥2 exacerbations last 12 months.

**Informativeness**

We observed that spirometric GOLD grades predicted mortality substantially better than ABCD groups, and this reflected the HRs and SMRs from the association analyses discussed above. Although symptom burden and exacerbation history may impact the choice of treatment and quality of life of people with COPD,<sup>3, 4</sup> our results indicate that the prognostic information given by the four spirometric GOLD grades should not be neglected when predicting mortality in people with COPD.

**Methodological considerations**

Since several analytical methods were used to disentangle our data, and they all led to similar interpretations of the results, we considered our findings robust. Our population-based study had a wide age span, and we had sufficient power to do sex specific analyses.<sup>16</sup> Data on mortality were complete due to the unique personal identification number of all inhabitants of Norway, and there were no losses to follow-up. Since we included people based on lung function, both people with and without a physician diagnosis of COPD were included. Han *et al.*<sup>29</sup> recently studied the risk of future exacerbations according to the ABCD groups in 45–80 year-old people with COPD attending clinical centres in the USA. When using the mMRC dyspnoea scale to measure symptom burden, the distribution of participants differed considerably from our post-bronchodilator distribution and from the pre-bronchodilator distribution of the Danish epidemiological study,<sup>5</sup> while the Spanish study of 11 COPD cohorts<sup>6</sup> had a more similar distribution to Han *et al.*<sup>29</sup> This difference in distribution may reflect that patients with a physician diagnosis of COPD got their diagnosis because they experienced symptoms and therefore visited their doctor, although the inclusion criteria differed between these studies.<sup>5, 6, 29</sup>

A limitation of the current study was the lack of data on the mMRC dyspnoea scale<sup>12</sup> or the CAT.<sup>13</sup> However, our dyspnoea cut-off question was not very different from the mMRC dyspnoea scale grade 2 question.<sup>12</sup> Since using alternate measures of dyspnoea or health status did not alter our findings and since the association with mortality seemed to be mostly related to lung function, we assume that using the mMRC dyspnoea scale or the CAT in generating the ABCD groups would not change our findings. Future studies on the association between ABCD groups and mortality using different cut-offs of the mMRC dyspnoea scale,<sup>12</sup> the CAT<sup>13, 30</sup> or other measures of symptom burden in generating the ABCD groups are needed. Further, 22% of our participants had missing data on the dyspnoea scale. However, it is unlikely that this has biased our results since using alternate measures of dyspnoea or health status with little or no missing data did not materially change our results. In addition, we have previously shown that baseline characteristics did not differ materially between people with and without data on the dyspnoea scale.<sup>15</sup>

**CONCLUSIONS**

Spirometric GOLD grades predicted mortality better than the new ABCD groups. In contrast to spirometric GOLD grades where mortality increased with higher grade, there were only minor differences in mortality between groups A and B, and between groups C and D. Our study supports the use of spirometric GOLD grades over the use of the new ABCD groups for predicting mortality.

**Acknowledgements** The second survey of the Nord-Trøndelag Health Study 1995–1997 (HUNT2) was a collaboration between HUNT Research Centre (Faculty of

Medicine, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway Health Authority and the Norwegian Institute of Public Health.

**Contributors** LL and AL planned the study and are guarantors of this paper. LL analysed the data and wrote the paper. BMB and TILN participated in the data analyses. All authors interpreted the results and revised the paper. As project leader for the HUNT2 Lung Study, AL was responsible for planning, data collection and quality assurance of data in the Lung Study.

**Funding** This project was financially supported by the Norwegian ExtraFoundation for Health and Rehabilitation through EXTRA funds (project 2007/2/0214), the Liaison Committee between the Central Norway Regional Health Authority and the Norwegian University of Science and Technology (project 46041600), and the Leif Richard Erichsen and wife Maren Hertzberg Erichsen's fund for Norwegian medical research. The HUNT2 Lung Study received funding without obligation from AstraZeneca. None of the funding sources were involved in any aspect of designing or conducting the study, analysing data, interpreting results or writing the paper.

**Competing interests** LL presented a published paper for GlaxoSmithKline in 2012.

**Ethics approval** The Regional Committee for Medical Research Ethics (Central Norway).

**Provenance and peer review** Not commissioned; internally peer reviewed.

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**Table S1** Sensitivity analyses: Death rates, adjusted hazard ratios (HRs), and standardised mortality ratios (SMRs) with 95% confidence intervals (CIs) for the associations of ABCD groups with all-cause mortality among women in the HUNT2 Lung Study

<b>ABCD groups generated from alternate dyspnoea measures<sup>a</sup></b>	<b>Person-years</b>	<b>Observed deaths</b>	<b>Death rate<sup>b</sup> (95% CI)<sup>b</sup></b>	<b>Age-adjusted HR<sup>c</sup></b>	<b>Multi-adjusted HR<sup>d</sup> (95% CI)<sup>d</sup></b>	<b>Expected deaths</b>	<b>SMR<sup>e</sup> (95% CI)<sup>e</sup></b>
<b><u>Wheeze or dyspnoea (n=584)</u></b>							
Group A	1327	50	37.68 (28.56 to 49.72)	1.00	1.00 (Reference)	43	1.16 (0.86 to 1.55)
Group B	4775	141	29.53 (25.03 to 34.83)	1.06	1.07 (0.77-1.50)	106	1.33 (1.13 to 1.57)
Group C	165	9	54.50 (28.36 to 104.75)	2.06	2.60 (1.26-5.35)	3	2.80 (1.23 to 6.16)
Group D	1126	73	64.85 (51.56 to 81.57)	2.07	2.35 (1.63-3.40)	30	2.48 (1.87 to 3.23)
<b><u>Dyspnoea at rest (n=583)</u></b>							
Group A	4310	139	32.25 (27.31 to 38.09)	1.00	1.00 (Reference)	116	1.20 (1.01 to 1.42)
Group B	1789	51	28.52 (21.67 to 37.52)	1.21	1.42 (1.02-1.97)	33	1.53 (1.18 to 1.98)
Group C	557	37	66.43 (48.13 to 91.68)	2.04	2.28 (1.58-3.30)	15	2.45 (1.68 to 3.51)
Group D	734	45	61.33 (45.79 to 82.14)	2.13	2.69 (1.90-3.82)	18	2.56 (1.75 to 3.66)
<b><u>Health status (n=580)</u></b>							
Group A	2576	59	22.90 (17.74 to 29.56)	1.00	1.00 (Reference)	58	1.02 (0.80 to 1.30)
Group B	3479	131	37.66 (31.73 to 44.69)	1.46	1.42 (1.04 to 1.94)	89	1.48 (1.23 to 1.76)
Group C	228	15	65.93 (39.75 to 109.36)	2.76	3.31 (1.86 to 5.89)	6	2.71 (1.30 to 5.12)
Group D	1063	67	63.01 (49.60 to 80.06)	2.47	2.75 (1.92 to 3.92)	27	2.46 (1.85 to 3.26)

<sup>a</sup> ABCD groups defined as follows; A = Low symptom burden, GOLD 1 or 2, and  $\leq 1$  exacerbation last 12 months; B = High symptom burden, GOLD 1 or 2, and  $\leq 1$  exacerbation last 12 months; C = Low symptom burden, and GOLD 3 or 4 or  $\geq 2$  exacerbations last 12 months; D = High symptom burden, and GOLD 3 or 4 or  $\geq 2$  exacerbations last 12 months.

<sup>b</sup> Per 1000 person-years.

<sup>c</sup> Adjusted for age (as the time scale).

<sup>d</sup> Adjusted for age (as the time scale), smoking (never, former, current, unknown), and education ( $<10$ ,  $\geq 10$  years, unknown).

<sup>e</sup> Standardised according to sex, 5 year age bands, and 5 year calendar periods.

**Table S2** Sensitivity analyses: Death rates, adjusted hazard ratios (HRs), and standardised mortality ratios (SMRs) with 95% confidence intervals (CIs) for the associations of ABCD groups with all-cause mortality among men in the HUNT2 Lung Study

<b>ABCD groups generated from alternate dyspnoea measures<sup>a</sup></b>	<b>Person-years</b>	<b>Observed deaths</b>	<b>Death rate<sup>b</sup> (95% CI)<sup>b</sup></b>	<b>Age-adjusted HR<sup>c</sup></b>	<b>Multi-adjusted HR<sup>d</sup> (95% CI)<sup>d</sup></b>	<b>Expected deaths</b>	<b>SMR<sup>e</sup> (95% CI)<sup>e</sup></b>
<b><u>Wheeze or dyspnoea (n=956)</u></b>							
Group A	2140	92	42.99 (35.04 to 52.73)	1.00	1.00 (Reference)	84	1.10 (0.91 to 1.34)
Group B	6652	314	47.21 (42.26 to 52.73)	1.10	1.00 (0.79-1.26)	255	1.23 (1.11 to 1.37)
Group C	249	16	64.19 (39.33 to 104.78)	1.17	1.18 (0.69-2.01)	12	1.33 (0.80 to 2.17)
Group D	1716	142	82.76 (70.21 to 97.55)	1.57	1.54 (1.18-2.01)	82	1.72 (1.45 to 2.03)
<b><u>Dyspnoea at rest (n=953)</u></b>							
Group A	6335	299	47.20 (42.14 to 52.86)	1.00	1.00 (Reference)	251	1.19 (1.07 to 1.33)
Group B	2433	105	43.17 (35.65 to 52.26)	1.01	1.00 (0.80-1.26)	86	1.22 (1.02 to 1.46)
Group C	1051	97	92.28 (75.63 to 112.60)	1.43	1.54 (1.22-1.94)	58	1.67 (1.35 to 2.07)
Group D	909	60	66.00 (51.25 to 85.01)	1.39	1.44 (1.09-1.90)	36	1.66 (1.31 to 2.08)
<b><u>Health status (n=948)</u></b>							
Group A	4071	150	36.84 (31.39 to 43.24)	1.00	1.00 (Reference)	138	1.09 (0.93 to 1.27)
Group B	4628	253	54.67 (48.33 to 61.84)	1.16	1.07 (0.87 to 1.32)	199	1.27 (1.13 to 1.43)
Group C	463	30	64.79 (45.30 to 92.67)	1.18	1.17 (0.79 to 1.73)	23	1.28 (0.89 to 1.82)
Group D	1486	128	86.14 (72.43 to 102.43)	1.70	1.74 (1.36 to 2.22)	70	1.82 (1.53 to 2.17)

<sup>a</sup> ABCD groups defined as follows; A = Low symptom burden, GOLD 1 or 2, and  $\leq 1$  exacerbation last 12 months; B = High symptom burden, GOLD 1 or 2, and  $\leq 1$  exacerbation last 12 months; C = Low symptom burden, and GOLD 3 or 4 or  $\geq 2$  exacerbations last 12 months; D = High symptom burden, and GOLD 3 or 4 or  $\geq 2$  exacerbations last 12 months.

<sup>b</sup> Per 1000 person-years.

<sup>c</sup> Adjusted for age (as the time scale).

<sup>d</sup> Adjusted for age (as the time scale), smoking (never, former, current, unknown), and education ( $<10$ ,  $\geq 10$  years, unknown).

<sup>e</sup> Standardised according to sex, 5 year age bands, and 5 year calendar periods.

**Table S3** Area under the receiver operating characteristic curve (AUC) and pseudo R<sup>2</sup> from logistic regression models<sup>a</sup> of spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades and ABCD groups related to all-cause mortality among participants with chronic obstructive pulmonary disease (COPD) in the HUNT2 Lung Study

COPD classification	Women (n=468) <sup>b</sup>		Men (n=736) <sup>b</sup>	
	AUC	R <sup>2</sup>	AUC	R <sup>2</sup>
GOLD grades <sup>c</sup>	0.873	0.355	0.889	0.395
ABCD groups <sup>d</sup>	0.847	0.299	0.882	0.384

<sup>a</sup> All models were adjusted for age (continuous), smoking (never, former, current, unknown), and education (<10, ≥10 years, unknown). The most informative model has the highest value of AUC or R<sup>2</sup>.

<sup>b</sup> People with missing data on dyspnoea were excluded so that the results from the spirometric GOLD and the ABCD groups could be compared.

<sup>c</sup> COPD defined as forced expiratory volume in one second (FEV<sub>1</sub>)/ forced vital capacity (FVC) <0.70 and graded as follows; GOLD 1 = % predicted FEV<sub>1</sub> (ppFEV<sub>1</sub>) ≥80; GOLD 2 = 50 ≤ ppFEV<sub>1</sub> <80; GOLD 3 = 30 ≤ ppFEV<sub>1</sub> <50; GOLD 4 = ppFEV<sub>1</sub> <30.

<sup>d</sup> ABCD groups defined as follows; A = Dyspnoea ≤ grade 1, GOLD 1 or 2, and ≤1 exacerbation last 12 months; B = Dyspnoea ≥ grade 2, GOLD 1 or 2, and ≤1 exacerbation last 12 months; C = Dyspnoea ≤ grade 1, and GOLD 3 or 4 or ≥2 exacerbations last 12 months; D = Dyspnoea ≥ grade 2, and GOLD 3 or 4 or ≥2 exacerbations last 12 months.

**Table S4** Sensitivity analyses with alternate measures of symptom burden: Informativeness<sup>a</sup> of spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades and ABCD groups related to all-cause mortality among participants with chronic obstructive pulmonary disease (COPD) in the HUNT2 Lung Study

COPD classification	Women						Men					
	Wheeze or dyspnoea		Dyspnoea at rest		Health status		Wheeze or dyspnoea		Dyspnoea at rest		Health status	
	(n=584)		(n=583) <sup>b</sup>		(n=580) <sup>c</sup>		(n=956)		(n=953) <sup>b</sup>		(n=948) <sup>c</sup>	
	$\chi^2$	(%)	$\chi^2$	(%)	$\chi^2$	(%)	$\chi^2$	(%)	$\chi^2$	(%)	$\chi^2$	(%)
GOLD grades <sup>d</sup>	79.33	(100)	79.33	(100)	78.67	(100)	42.66	(100)	42.17	(100)	44.41	(100)
ABCD groups <sup>e</sup>	32.52	(41)	37.15	(47)	37.65	(48)	18.15	(43)	16.91	(40)	22.33	(50)

<sup>a</sup> The null Cox model included age (as the time scale), smoking (never, former, current, unknown), and education (<10, ≥10 years, unknown). The alternative Cox models included spirometric GOLD grades or ABCD groups in addition to all in the null model. The  $\chi^2$  shows the difference in twice the log-likelihood between the null model and the alternative model. The most informative model has the highest value of  $\chi^2$  and has been set to 100%. All p < 0.001.

<sup>b</sup> One woman and three men were excluded from these models due to missing data on dyspnoea.

<sup>c</sup> Four women and eight men were excluded from these models due to missing data on health status.

<sup>d</sup> COPD defined as forced expiratory volume in one second (FEV<sub>1</sub>)/ forced vital capacity (FVC) < 0.70 and graded as follows; GOLD 1 = % predicted forced expiratory volume in one second (ppFEV<sub>1</sub>) ≥ 80; GOLD 2 = 50 ≤ ppFEV<sub>1</sub> < 80; GOLD 3 = 30 ≤ ppFEV<sub>1</sub> < 50; GOLD 4 = ppFEV<sub>1</sub> < 30.

<sup>e</sup> ABCD groups defined as follows; A = Dyspnoea ≤ grade 1, GOLD 1 or 2, and ≤ 1 exacerbation last 12 months; B = Dyspnoea ≥ grade 2, GOLD 1 or 2, and ≤ 1 exacerbation last 12 months; C = Dyspnoea ≤ grade 1, and GOLD 3 or 4 or ≥ 2 exacerbations last 12 months; D = Dyspnoea ≥ grade 2, and GOLD 3 or 4 or ≥ 2 exacerbations last 12 months.

**Table S5** Sensitivity analyses with alternate measures of symptom burden: Area under the receiver operating characteristic curve (AUC) and pseudo  $R^2$  from logistic regression models<sup>a</sup> of spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades and ABCD groups related to all-cause mortality among participants with chronic obstructive pulmonary disease (COPD) in the HUNT2 Lung Study

COPD classification	Women						Men					
	Wheeze or dyspnoea (n=584)		Dyspnoea at rest (n=583) <sup>b</sup>		Health status (n=580) <sup>c</sup>		Wheeze or dyspnoea (n=956)		Dyspnoea at rest (n=953) <sup>b</sup>		Health status (n=948) <sup>c</sup>	
	AUC	R <sup>2</sup>	AUC	R <sup>2</sup>	AUC	R <sup>2</sup>	AUC	R <sup>2</sup>	AUC	R <sup>2</sup>	AUC	R <sup>2</sup>
GOLD grades <sup>d</sup>	0.881	0.369	0.880	0.369	0.881	0.370	0.885	0.377	0.886	0.379	0.886	0.382
ABCD groups <sup>e</sup>	0.856	0.320	0.858	0.324	0.861	0.329	0.880	0.366	0.881	0.368	0.882	0.370

<sup>a</sup> All models were adjusted for age (continuous), smoking (never, former, current, unknown), and education (<10, ≥10 years, unknown). The most informative model has the highest value of AUC or R<sup>2</sup>.

<sup>b</sup> One woman and three men were excluded from these models due to missing data on dyspnoea.

<sup>c</sup> Four women and eight men were excluded from these models due to missing data on health status.

<sup>d</sup> COPD defined as forced expiratory volume in one second (FEV<sub>1</sub>)/ forced vital capacity (FVC) <0.70 and graded as follows; GOLD 1 = % predicted forced expiratory volume in one second (ppFEV<sub>1</sub>) ≥80; GOLD 2 = 50 ≤ ppFEV<sub>1</sub> <80; GOLD 3 = 30 ≤ ppFEV<sub>1</sub> <50; GOLD 4 = ppFEV<sub>1</sub> <30.

<sup>e</sup> ABCD groups defined as follows; A = Dyspnoea ≤ grade 1, GOLD 1 or 2, and ≤1 exacerbation last 12 months; B = Dyspnoea ≥ grade 2, GOLD 1 or 2, and ≤1 exacerbation last 12 months; C = Dyspnoea ≤ grade 1, and GOLD 3 or 4 or ≥2 exacerbations last 12 months; D = Dyspnoea ≥ grade 2, and GOLD 3 or 4 or ≥2 exacerbations last 12 months.