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ORIGINAL ARTICLE

Comparison of pre- and post-bronchodilator lung function as predictors of mortality: The HUNT Study

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ABSTRACT

Background and objective: **Post-bronchodilator (BD) lung function is recommended for the diagnosis of chronic obstructive pulmonary disease (COPD). However, often only pre-BD lung function is used in clinical practice or epidemiological studies. We aimed to compare the discrimination ability of pre-BD and post-BD lung function to predict all-cause mortality.**

Methods: **Participants aged ≥40 years with airflow limitation (n = 2538) and COPD (n = 1262) in the second survey of the Nord-Trøndelag Health Study (HUNT2, 1995–1997) were followed up until 31 December 2015. Survival analysis and time-dependent area under the receiver operating characteristic curves (AUC) were used to compare the discrimination ability of pre-BD and post-BD lung function (percent-predicted forced expiratory volume in the first second (FEV_1) ($ppFEV_1$), FEV_1 z-score, FEV_1 quotient (FEV_1Q), modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories or GOLD grades).**

Results: **Among 2538 participants, 1387 died. The AUC for pre-BD and post-BD $ppFEV_1$ to predict mortality were 60.8 and 61.8 (P = 0.005), respectively, at 20 years' follow-up. The corresponding AUC for FEV_1 z-score were 58.5 and 60.4 (P < 0.001), for FEV_1Q were 68.7 and 70.1 (P = 0.002) and for modified GOLD categories were 62.3 and 64.5 (P < 0.001). Among participants with COPD, the AUC for pre-BD and post-BD $ppFEV_1$ were 57.0 and 58.8 (P < 0.001), respectively. The corresponding AUC for FEV_1 z-score were 53.1 and 55.8 (P < 0.001), for FEV_1Q were 63.6 and 65.1 (P = 0.037) and for GOLD grades were 56.0 and 57.0 (P = 0.268).**

Conclusion: **Mortality was better predicted by post-BD than by pre-BD lung function; however, they differed only by a small margin. The discrimination ability using GOLD grades among COPD participants was similar.**

SUMMARY AT A GLANCE

Few previous studies have compared the discrimination ability of pre-BD and post-BD lung function in predicting mortality. We found post-BD is slightly better than pre-BD to predict mortality using percent-predicted forced expiratory volume in the first second (FEV_1), FEV_1 z-score, FEV_1 quotient (FEV_1Q) or modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories. However, among people with chronic obstructive pulmonary disease (COPD), mortality was similarly predicted using GOLD grades.

Key words: area under the curve, mortality, post-bronchodilator, pre-bronchodilator, prediction.

INTRODUCTION

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), diagnosis and classification of chronic obstructive pulmonary disease (COPD) should be based on post-bronchodilator (BD) spirometric measurements.[1] However, post-BD tests are time-consuming and not performed as frequently as recommended.[2,3] Often, only pre-BD lung function is used in clinical practice or in epidemiological studies. Additionally, only a few studies have

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compared mortality associated with both pre-BD and post-BD lung function.[4–6] Mannino *et al.*[6] found similar mortality prediction for pre-BD and post-BD lung function in the general population. However, the area under the receiver operating characteristic curve (AUC) from logistic models was used to compare models, and this approach ignores important information about time-to-event concerning mortality. In contrast to Mannino *et al.*,[6] Chen *et al.*[4] and Fortis *et al.*[5] found post-BD to be better than pre-BD percent-predicted forced expiratory volume in the first second ($ppFEV_1$) in predicting mortality. However, the study by Chen *et al.*[4] included only a limited number of COPD patients (n = 300) from a pulmonary department and follow-up in both studies was limited to approximately 5 years.

We aimed to compare the discrimination ability of pre-BD and post-BD lung function to predict all-cause mortality in participants with airflow limitation or COPD selected from a large population-based study with over 20 years' follow-up.

METHODS

Study population

The second survey of the Nord-Trøndelag Health Study (HUNT2, 1995–1997) invited the entire adult population (≥20 years old) of northern Trøndelag, Norway, to attend clinical examinations and answer questionnaires.[7]

The current study included participants aged ≥40 years in the HUNT2 Study (n = 44 384)[7] with airflow limitation (pre-BD FEV_1/forced vital capacity (FVC) < 0.75 or FEV_1 < 80% of predicted using the European Coal and Steel Community (ECSC) equations[8]) and acceptable pre-BD and post-BD spirometry manoeuvres (n = 2538) (Fig. S1, Appendix S1 in Supplementary Information).

Ethical approval was obtained from the Regional Committee for Medical Research Ethics (2015/1461/REK midt). All participants gave informed written consent.

Spirometry and lung function classification

Participants performed pre-BD and post-BD (30 min after inhalation of 1 mg terbutaline) spirometry according to the 1994 American Thoracic Society (ATS) guidelines with a heated pneumotachograph spirometer.[9,10] Quality assurance of spirometric measurements is described in detail elsewhere.[9,11]

The Global Lung Function Initiative (GLI)-2012 reference equation was used to calculate $ppFEV_1$, percent-predicted FVC (ppFVC) and to derive FEV_1 z-scores based on lambda–mu–sigma (LMS) methods.[9,12] In the LMS method, the median (Mu) represents how FEV_1 changes with age, sex, height and ethnicity; the coefficient of variation (Sigma) models the spread of reference values; and the skewness (Lambda) models departure from normality.[12,13] FEV_1 was standardized by sex-specific lowest first percentile (0.5 L for men and 0.4 L for women) of FEV_1 distribution to calculate the FEV_1 quotient (FEV_1Q).[14] Pre-BD and post-BD lung function were classified into modified GOLD categories as follows: normal (FEV_1/FVC ≥ 0.70 and ppFVC ≥ 80), preserved ratio impaired spirometry (FEV_1/FVC ≥ 0.70 and ppFVC < 80), mild obstruction (FEV_1/FVC < 0.70 and $ppFEV_1$ ≥ 80), moderate obstruction (FEV_1/FVC < 0.70 and 80 > $ppFEV_1$ ≥ 50), severe obstruction (FEV_1/FVC < 0.70 and 50 > $ppFEV_1$ ≥ 30) and very severe obstruction (FEV_1/FVC < 0.70 and $ppFEV_1$ < 30).[1,15]

Additionally, a COPD cohort (n = 1262) was defined as having persistent airflow limitation (pre-BD and post-BD FEV_1/FVC < 0.70) concurrent with respiratory symptoms or self-reported doctor-diagnosed COPD.[1] Respiratory symptoms included daily cough in periods, cough with phlegm, wheezing and dyspnoea. GOLD grades were defined as GOLD1 ($ppFEV_1$ ≥ 80), GOLD2 (80 > $ppFEV_1$ ≥ 50), GOLD3 (50 > $ppFEV_1$ ≥ 30) and GOLD4 ($ppFEV_1$ < 30) in the COPD cohort.[1]

Clinical examination and questionnaires

Information on age (years), sex, body mass index (BMI, kg/m^2), smoking status, smoking pack-years, physical activity, education, diabetes ever, asthma ever, cardiovascular disease, systolic blood pressure (mm Hg) and non-fasting total serum cholesterol (mmol/L) was ascertained from clinical examination and questionnaires.

Age was recorded to one decimal place. Height and weight were measured with light clothing and without shoes, and rounded to the nearest centimetre or half kilogram, respectively.[16,17] Cardiovascular disease included self-reported angina pectoris, myocardial infarction and stroke. Systolic blood pressure was measured three times and the mean of the last two measurements was used.[17]

Follow-up and outcome

HUNT2 participants (1995–1997) were followed up until death, emigration (n = 6) or 31 December 2015. The Norwegian Cause of Death Registry provided information on date of death.

Statistical analysis

Mortality rates per 1000 person-years with 95% CI were calculated. We used log-rank test of Kaplan–Meier estimates for mortality.

Cox proportional hazard models were used to calculate hazard ratios (HR) and 95% CI for the associations of pre-BD and post-BD lung function with mortality. We presented crude HR (Model 1) and adjusted HR (Model 2). Model 2 accounted for age (as a continuous variable), sex (women and men), smoking (never, former (<10, 10–19 and ≥20 pack-years), current (<10, 10–19 and ≥20 pack-years) and unknown), BMI (<25.0, 25.0–29.9, ≥30.0 and unknown) and education (<10, ≥10 years and unknown). In supplementary analyses, we additionally adjusted for physical activity (none, light exercise, hard exercise and unknown), cardiovascular diseases (no, yes and unknown), asthma ever (no, yes and unknown), diabetes ever (no, yes and unknown), systolic blood pressure (sex-specific

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Table 1 Characteristics of participants aged ≥40 years with airflow limitation stratified by modified GOLD categories in the HUNT2 Study (1995–1997)

	Pre-BD[†]						Post-BD[†]					
Characteristic (n = 2538)	Normal (n = 709)	PRISm (n = 177)	Mild obstructive (n = 501)	Moderate obstructive (n = 858)	Severe obstructive (n = 248)	Very severe obstructive (n = 45)	Normal (n = 946)	PRISm (n = 167)	Mild obstructive (n = 474)	Moderate obstructive (n = 762)	Severe obstructive (n = 170)	Very severe obstructive (n = 19)
Participants (%)	27.9	7.0	19.7	33.8	9.8	1.8	37.3	6.6	18.7	30.0	6.7	0.7
Age (years) (mean ± SD)	58.4 ± 11.9	61.8 ± 11.5	62.8 ± 11.8	64.5 ± 10.9	67.9 ± 10.2	65.4 ± 9.2	58.2 ± 11.8	62.2 ± 11.8	64.9 ± 11.3	65.5 ± 10.4	68.0 ± 9.5	64.7 ± 10.4
BMI (mean ± SD)	26.9 ± 4.0	29.5 ± 6.4	26.8 ± 3.8	27.0 ± 4.6	25.4 ± 4.5	23.6 ± 3.5	27.2 ± 4.2	29.6 ± 6.3	26.7 ± 3.9	26.7 ± 4.6	24.6 ± 4.0	23.2 ± 2.6
Smoking pack-years (mean ± SD)	17.8 ± 12.3	20.9 ± 14.5	20.8 ± 13.5	24.6 ± 14.9	25.2 ± 16.3	33.2 ± 19.0	18.1 ± 12.2	20.8 ± 14.2	22.6 ± 14.6	24.9 ± 15.1	27.5 ± 16.5	28.9 ± 24.5
Current smoker (%)	34.3	35.6	37.7	49.1	46.6	38.6	33.8	35.6	42.8	50.3	46.3	26.3
Physically inactive (%)	7.1	11.5	8.0	11.1	10.7	13.5	7.0	11.9	10.4	10.9	9.7	18.8
Education ≥10 years (%)	51.9	40.0	47.0	36.6	29.8	26.3	52.1	37.4	40.8	35.5	28.3	31.3
Cardiovascular disease (%)	13.3	19.8	15.8	21.5	19.8	13.9	12.6	19.2	19.0	21.8	21.3	22.2
Asthma ever (%)	45.8	54.8	47.7	59.0	77.4	93.3	47.6	50.9	52.1	61.4	78.2	94.7
Diabetes ever (%)	4.2	10.9	4.8	4.9	3.6	6.8	3.6	11.0	5.3	5.5	4.1	5.3
SBP (mean ± SD)	141.1 ± 20.7	146.3 ± 23.3	145.5 ± 23.5	146.8 ± 22.2	149.9 ± 24.4	143.5 ± 19.7	141.2 ± 21.2	145.8 ± 24.1	147.1 ± 23.2	147.9 ± 22.1	149.7 ± 24.8	136.9 ± 19.8
Cholesterol (mean ± SD)	6.2 ± 1.2	6.4 ± 1.2	6.2 ± 1.2	6.3 ± 1.2	6.3 ± 1.2	6.3 ± 1.0	6.2 ± 1.2	6.4 ± 1.3	6.3 ± 1.2	6.3 ± 1.2	6.2 ± 1.2	6.3 ± 1.0

[†]Normal: $FEV_1/FVC \geq 0.70$ and $ppFVC \geq 80$; PRISm: $FEV_1/FVC \geq 0.70$ and $ppFVC < 80$; mild obstructive: $FEV_1/FVC < 0.70$ and $ppFEV_1 \geq 80$; moderate obstructive: $FEV_1/FVC < 0.70$ and $80 > ppFEV_1 \geq 50$; severe obstructive, $FEV_1/FVC < 0.70$ and $50 > ppFEV_1 \geq 30$; very severe obstructive: $FEV_1/FVC < 0.70$ and $ppFEV_1 < 30$.

BD, bronchodilator; BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HUNT2, the second survey of the Nord-Trøndelag Health Study (1995–1997); $ppFEV_1$, percent-predicted FEV_1; ppFVC, percent-predicted FVC; PRISm, preserved ratio impaired spirometry.

quartiles and unknown) and cholesterol (sex-specific quartiles and unknown) (Model 3).

Multicollinearity was tested where the variance inflation factor (VIF) was less than 1.5 in all models.[18,19] Proportional hazard assumptions were evaluated using log–log survival curves and Schoenfeld residual test.[20] As a measure of goodness of fit, we estimated the Akaike information criteria (AIC) and performed Gronnesby and Borgan tests for each model (Table S1 in Supplementary Information).[21,22]

We calculated time-dependent AUC to compare the discrimination ability of pre-BD and post-BD lung function to predict mortality.[23–26] The incident/dynamic (I/D) AUC models account for incident cases at time t and dynamic controls, which means it characterizes the time-varying performance without selecting a particular timeframe over which cases accrue, whereas cumulative/dynamic (C/D) AUC models account for cumulative cases at time t and dynamic controls.[25,27] We compared the AUC for crude models because the clinical decision usually does not explicitly take other factors into account.[14,28] Additionally, as a global measure of informativeness, we calculated concordance index (C-index).[25] We used 10 000 bootstrap iterations to calculate 95% CI for I/D AUC and C-index.[27] A general bootstrap algorithm (gBA) was applied to compare the I/D AUC and C-index.[29]

We performed all the analyses both among participants with airflow limitation and among participants with COPD. Statistical analysis was performed using R 3.5.0 (http://www.r-project.org) and Stata 15.1 (StataCorp., College Station, TX, USA).

RESULTS

In the cohort of participants with airflow limitation, the median and maximum follow-up times were 17.8 and 20.4 years, respectively. Based on pre-BD lung function at baseline, 27.9% had normal lung function and 1.8% had very severe obstruction. Corresponding proportions for post-BD lung function were 37.3% and 0.7%, respectively (Table 1). The distribution of participants between pre-BD and post-BD modified GOLD categories is presented in Table S2 in Supplementary Information.

A trend for increasing age, smoking pack-years, physical inactivity and mortality rates, and decreasing education and BMI with worsening modified GOLD categories was observed for both pre-BD and post-BD lung function (Table 1, Table S3 in Supplementary Information). We observed a similar increasing trend of mortality in unadjusted cumulative incidence curves (Fig. S2 in Supplementary Information).

A 10% reduction in $ppFEV_1$ and 1-unit reduction in FEV_1 z-score and FEV_1Q were associated with 19%, 36% and 33% increased risk of death, respectively, using pre-BD lung function. Similarly, worsening modified GOLD categories were associated with increased risk of death. Results were similar for post-BD lung function (Table 2, Model 2), in Model 3 (Table S4 in Supplementary Information) and among participants with COPD (Table S5 in Supplementary information).

The I/D AUC (95% CI) for pre-BD and post-BD $ppFEV_1$ were 60.8 (59.3–62.2) and 61.8 (60.2–63.4), respectively, for mortality at 20 years' follow-up

Table 2 HR for pre-BD and post-BD lung function among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997)

		Pre-BD		Post-BD	
Lung function[†,‡,§,¶] (*n* = 2538)		Model 1 HR (95% CI)[††]	Model 2 HR (95% CI)[‡‡]	Model 1 HR (95% CI)[††]	Model 2 HR (95% CI)[‡‡]
$ppFEV_1$[¶]		1.28 (1.24–1.31)	1.19 (1.16–1.22)	1.31 (1.27–1.34)	1.22 (1.19–1.25)
FEV_1 z-score[§]		1.31 (1.26–1.37)	1.36 (1.30–1.42)	1.40 (1.34–1.45)	1.41 (1.35–1.48)
FEV_1Q[‡]		1.67 (1.61–1.73)	1.33 (1.27–1.39)	1.72 (1.66–1.78)	1.38 (1.32–1.44)
Modified GOLD categories[†]	Normal	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
	PRISm	2.33 (1.85–2.94)	1.79 (1.41–2.26)	2.59 (2.08–3.24)	1.95 (1.56–2.45)
	Mild obstructive	1.77 (1.47–2.12)	1.17 (0.98–1.41)	2.12 (1.80–2.50)	1.16 (0.98–1.37)
	Moderate obstructive	2.78 (2.38–3.25)	1.78 (1.52–2.08)	3.20 (2.78–3.69)	1.86 (1.60–2.15)
	Severe obstructive	5.23 (4.32–6.33)	2.77 (2.27–3.37)	6.59 (5.41–8.02)	3.44 (2.80–4.23)
	Very severe obstructive	7.00 (5.02–9.75)	5.03 (3.57–7.08)	6.00 (3.73–9.67)	4.68 (2.89–7.59)

[†]Normal: $FEV_1/FVC \geq 0.70$ and $ppFVC \geq 80$; PRISm: $FEV_1/FVC \geq 0.70$ and $ppFVC < 80$; mild obstructive: $FEV_1/FVC < 0.70$ and $ppFEV_1 \geq 80$; moderate obstructive: $FEV_1/FVC < 0.70$ and $80 > ppFEV_1 \geq 50$; severe obstructive: $FEV_1/FVC < 0.70$ and $50 > ppFEV_1 \geq 30$; very severe obstructive: $FEV_1/FVC < 0.70$ and $ppFEV_1 < 30$.

[‡]FEV_1 standardized by sex-specific lowest first percentile (0.5 L for men and 0.4 L for women) of FEV_1 distribution. HR were for a 1-unit reduction in FEV_1Q.

[§]FEV_1 z-score based on GLI-2012 equation. HR were for a 1-unit reduction in FEV_1 z-score.

[¶]$ppFEV_1$ based on GLI-2012 equation. HR were for a 10% reduction in $ppFEV_1$.

[††]Crude model.

[‡‡]Adjusted for age, sex, smoking, body mass index and education.

BD, bronchodilator; FEV_1, forced expiratory volume in the first second; FEV_1Q, FEV_1 quotient; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; HUNT2, the second survey of the Nord-Trøndelag Health Study (1995–1997); $ppFEV_1$, percent-predicted FEV_1; ppFVC, percent-predicted FVC; PRISm, preserved ratio impaired spirometry.

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(P = 0.005) (Table 3, Fig. 1, Fig. S3 in Supplementary Information). A similar pattern was observed over time (Fig. 1). Corresponding estimates for FEV_1 z-score were 58.5 (57.0–59.9) and 60.4 (58.8–62.0) (P < 0.001), for FEV_1Q were 68.7 (66.8–70.5) and 70.1 (68.1–72.1) (P = 0.002) and for modified GOLD categories were 62.3 (60.6–63.8) and 64.5 (62.9–66.1) (P < 0.001) (Table 3,Fig. 1,Fig. S3 in Supplementary Information).

Among participants with COPD, the I/D AUC (95% CI) for pre-BD and post-BD $ppFEV_1$ were 57.0 (55.1–58.8) and 58.8 (56.7–60.8), respectively, for predicting mortality at 20 years' follow-up (P < 0.001) and results were similar over time (Fig. 2, Table S6 in Supplementary Information). Corresponding estimates for FEV_1 z-score were 53.1 (95% CI: 51.5–54.8) and 55.8 (95% CI: 53.9–57.7) (P < 0.001), for FEV_1Q were 63.6 (95% CI: 60.9–65.9) and 65.1 (95% CI: 62.0–67.9) (P = 0.037) and for GOLD grades were 56.0 (95% CI: 53.9–57.9) and 57.0 (95% CI: 54.6–59.2) (P = 0.268) (Fig. 2, Table S6 in Supplementary Information).

The results from C-index and C/D AUC (Tables S6, S7, Figs S4, S5 in Supplementary Information) were generally in agreement with I/D AUC.

Table 3 I/D time-dependent AUC for pre-BD and post-BD lung function at 20 years of follow-up among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997)

Lung function[†,‡,§,¶] (n = 2538)	Pre-BD Model 1 I/D AUC (95% CI)[††]	Post-BD Model 1 I/D AUC (95% CI)[††]	P-value
$ppFEV_1$[¶]	60.8 (59.3–62.2)	61.8 (60.2–63.4)	0.005
FEV_1 z-score[§]	58.5 (57.0–59.9)	60.4 (58.8–62.0)	<0.001
FEV_1Q[‡]	68.7 (66.8–70.5)	70.1 (68.1–72.1)	0.002
Modified GOLD categories[†]	62.3 (60.6–63.8)	64.5 (62.9–66.1)	<0.001

[†]Normal: $FEV_1/FVC \geq 0.70$ and $ppFVC \geq 80$; PRISm: $FEV_1/FVC \geq 0.70$ and $ppFVC < 80$; mild obstructive: $FEV_1/FVC < 0.70$ and $ppFEV_1 \geq 80$; moderate obstructive: $FEV_1/FVC < 0.70$ and $80 > ppFEV_1 \geq 50$; severe obstructive: $FEV_1/FVC < 0.70$ and $50 > ppFEV_1 \geq 30$; very severe obstructive: $FEV_1/FVC < 0.70$ and $ppFEV_1 < 30$.

[‡]FEV_1 standardized by sex-specific lowest first percentile (0.5 L for men and 0.4 L for women) of FEV_1 distribution.

[§]FEV_1 z-score based on GLI-2012 equation.

[¶]$ppFEV_1$ based on GLI-2012 equation.

[††]The Cox model included pre-BD or post-BD lung function.

AUC, area under the receiver operating characteristic curve; BD, bronchodilator; FEV_1, forced expiratory volume in the first second; FEV_1Q, FEV_1 quotient; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HUNT2, the second survey of the Nord-Trøndelag Health Study (1995–1997); I/D, incident/dynamic; $ppFEV_1$, percent-predicted FEV_1; ppFVC, percent-predicted FVC; PRISm, preserved ratio impaired spirometry.

DISCUSSION

In this large population-based study of participants with airflow limitation, mortality was slightly better predicted by post-BD than by pre-BD lung function whether using $ppFEV_1$, FEV_1 z-score, FEV_1Q or modified GOLD categories. Among participants with COPD, the discrimination ability of post-BD was slightly higher than pre-BD to predict mortality using $ppFEV_1$, FEV_1 z-score or FEV_1Q but the discrimination ability using GOLD grades was similar.

Similar to our study, other studies have found that decreased $ppFEV_1$, FEV_1 z-score or FEV_1Q are associated with an increased risk of death.[6,14,30,31] Furthermore, a study by Mannino *et al.*[32] found that the risk of death increased with worsening GOLD-defined airflow limitation, where participants with severe or very severe obstruction were associated with 4.5 times higher risk of dying compared to participants with normal lung function. HR were slightly higher than in our study, likely due to the exclusion of participants with respiratory symptoms from their reference population.[32]

The discrimination ability of pre-BD and post-BD lung function to predict mortality was generally poor except for FEV_1Q which had fair discrimination ability.[33] Nevertheless, we found that mortality was better predicted by post-BD than by pre-BD lung function at 20 years' follow-up, and this was consistent over time in models using $ppFEV_1$, FEV_1 z-score, FEV_1Q or modified GOLD categories. There are no previous studies directly comparing the discrimination ability of pre-BD and post-BD lung function as a predictive marker of mortality when other predictors are not taken into consideration and no studies have included measurements of FEV_1 z-score and FEV_1Q. However, in a study by Fortis *et al.*[5] that followed up 8221 adults for approximately 6.5 years, post-BD was a stronger predictor for mortality than pre-BD lung function in models adjusted with covariates. We found similar results in our study at 6.5 years' follow-up for mortality in both crude and adjusted models (P < 0.001 for both, results not shown). Additionally, one study investigated 5887 adults from the general population participating in NHANES and compared the predictive ability of pre-BD and post-BD lung function for mortality after 20 years.[6] In this study, Mannino *et al.*[6] found that pre-BD and post-BD lung function similarly predicted mortality where the AUC for pre-BD and post-BD $ppFEV_1$ were 69.2 and 69.4, respectively, and for pre-BD and post-BD modified GOLD categories the AUC were 69.2 and 69.6, respectively. Compared to our study, this study included other predictors of mortality and AUC were calculated from logistic regression models, which do not take account of time-to-event.[6] However, at 20 years' follow-up, when we included other predictors of mortality in our models the results were similar to Mannino *et al.*[6] (Table S8 in Supplementary Information). This suggests that when other factors are considered, including post-BD lung function in models might not be more informative than pre-BD lung function at predicting long-term mortality.

Among participants with COPD, mortality was better predicted by post-BD $ppFEV_1$, FEV_1 z-score and FEV_1Q

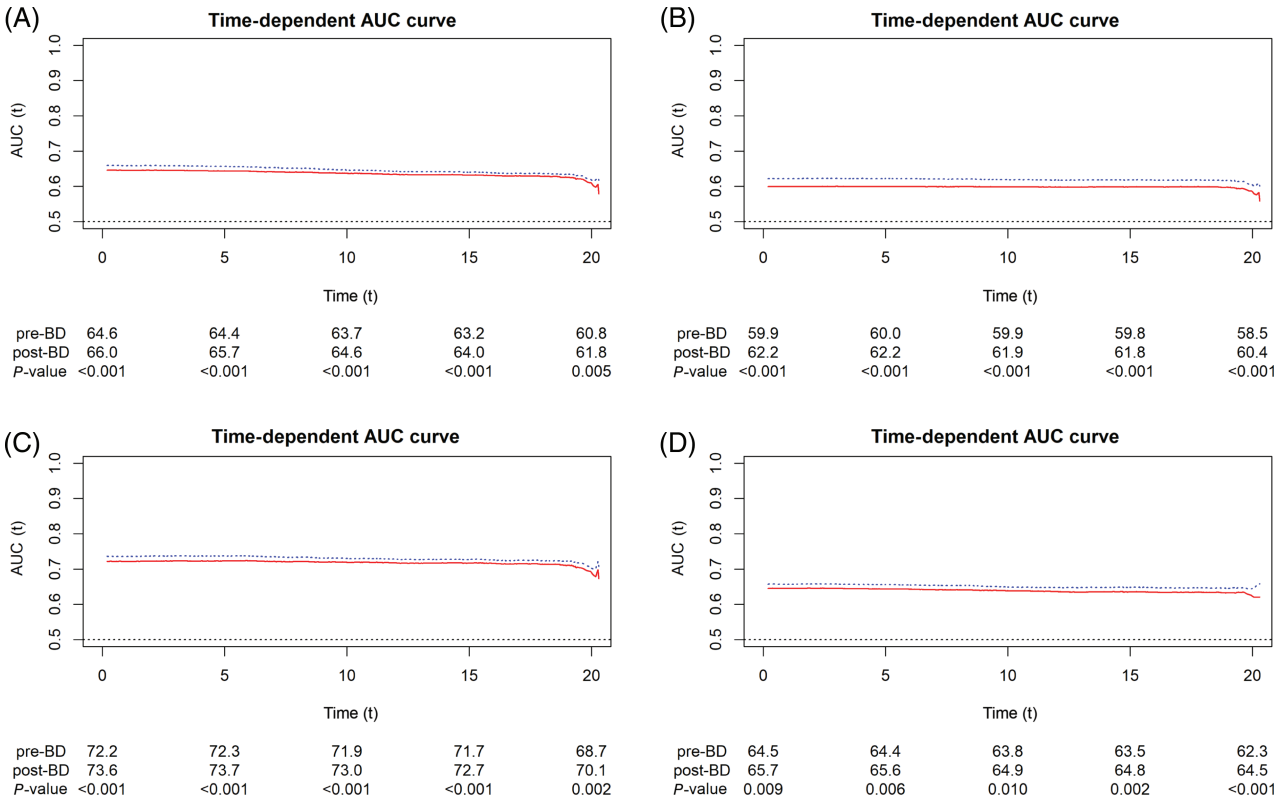

Figure 1 Incident/dynamic time-dependent area under the receiver operating characteristic curve (AUC) for pre-bronchodilator (BD) (——) and post-BD (------) (A) percent-predicted forced expiratory volume in the first second (FEV_1), (B) FEV_1 z-score, (C) FEV_1 quotient (FEV_1Q) and (D) modified Global Initiative for Chronic Obstructive Lung Disease (GOLD) categories for all-cause mortality change over follow-up time (years) among participants aged ≥40 years with airflow limitation in the second survey of the Nord-Trøndelag Health Study (HUNT2, 1995–1997).

than by pre-BD $ppFEV_1$, FEV_1 z-score and FEV_1Q, respectively, at 20 years' follow-up. Over time, the difference was constant for pre-BD and post-BD $ppFEV_1$, post-BD FEV_1 z-score or post-BD FEV_1Q. However, for GOLD grades, the discrimination ability was similar at 20 years' follow-up and this pattern was constant over time. To our knowledge, no other studies have compared pre-BD and post-BD lung function using FEV_1 z-score or FEV_1Q, and only one study has compared pre-BD- and post-BD-defined GOLD grades in predicting mortality among participants with COPD.[4] In contrast to our study, Chen *et al.*[4] found that mortality was better predicted by post-BD than by pre-BD lung function after 51 months (approximately 4 years) of follow-up among 300 COPD patients from a pulmonary department. The discrimination ability for mortality was compared between pre-BD and post-BD GOLD grades using log-rank tests (Kaplan–Meier estimates) where respective models had $P = 0.131$ and $P = 0.009$.[4] The disagreement between Chen *et al.*[4] and our study might be due to methodological differences between studies (log-rank method vs time-dependent AUC used in our study).

BD dilate bronchi and bronchioles to reverse the airflow limitation. In COPD, airflow limitation is variable and primarily irreversible where use of BD features small reversible components.[34] GOLD guidelines recommend post-BD spirometry for the classification of COPD.[1] It is also reported that lung function reference values for post-BD differ from pre-BD spirometry in the general population.[35] However, often, only pre-BD lung function is used in clinical practice or in epidemiological studies. Therefore, to compare which measure best predicts mortality is an important question for respiratory medicine. In our study, we observed that mortality was better predicted by post-BD than by pre-BD lung function among participants with airflow limitation, by a margin of approximately 2%. This potential gain in discrimination ability, if replicated in other studies, should be evaluated against the cost and clinical significance of such measurements in this subgroup of individuals. Among participants with COPD, mortality did not seem to be better predicted by post-BD-defined GOLD grades than by pre-BD. This study could have clinical implications as to how procedures might be prioritized in different subgroups.

This study had several strengths. It is the first study to investigate the discrimination ability of pre-BD and post-BD lung function over a 20-year period to predict mortality using FEV_1 z-score and FEV_1Q. The study is based on the HUNT2 Lung Study which had a reasonably high level of participation (76.0% of invited Lung Study population), which limits potential selection bias. We had complete information on mortality and there

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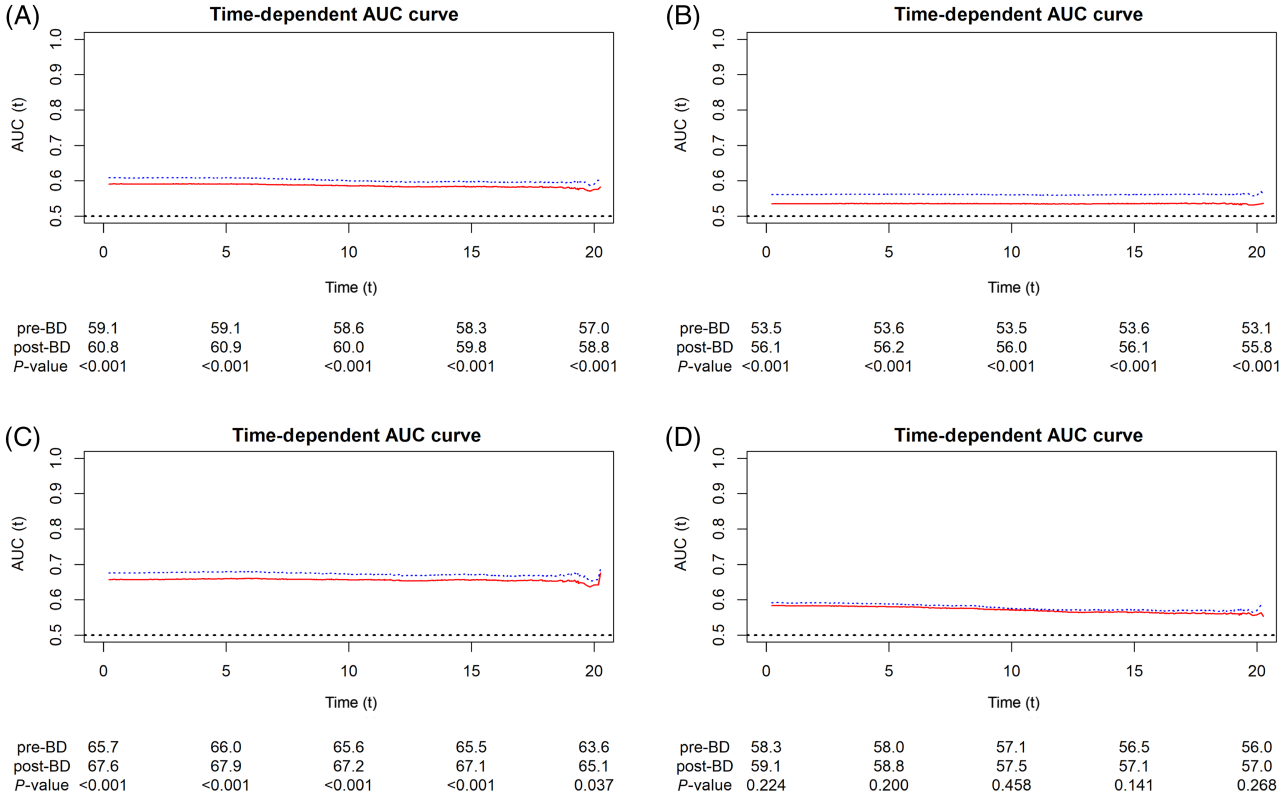

Figure 2 Incident/dynamic time-dependent area under the receiver operating characteristic curve (AUC) for pre-bronchodilator (BD) (——) and post-BD (------) (A) percent-predicted forced expiratory volume in the first second (FEV_1), (B) FEV_1 z-score, (C) FEV_1 quotient (FEV_1Q) and (D) Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades for all-cause mortality change over follow-up time (years) among participants aged ≥40 years with chronic obstructive pulmonary disease (COPD) in the second survey of the Nord-Trøndelag Health Study (HUNT2, 1995–1997).

was no loss to follow-up other than very few emigrations (6 out of 2538 participants). To reduce measurement error, quality assurance of spirometry curves was performed.[9,11]

This study however had certain limitations. Participants with airflow limitation from the HUNT2 Lung Study were included; therefore, these findings may not necessarily apply to the general population. Additionally, there was missing information on some covariates; therefore, to avoid sample loss in adjusted models, a missing indicator variable (missing information as unknown category) was used which might bias the association between lung function and mortality. The HUNT population is homogeneous; therefore, generalizability of findings outside a non-Caucasian population might be limited.

In summary, we found that mortality was better predicted by post-BD than by pre-BD lung function; however, they differed only by a small margin. The discrimination ability using GOLD grades among COPD participants was similar. The clinical significance of the findings in daily handling of patients should be studied further.

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Author contributions: Conceptualization: L.B., L.L., A.L., B.M.B. Data curation: A.L. Formal analysis: L.B. Funding acquisition: B.M.B., L.L. Investigation: L.B., B.M.B. Methodology: L.B., B.M.B. Project administration: B.M.B., L.B. Supervision: B.M.B., L.L., D.C., A.L., X.-M.M., Y.C., A.H.H. Validation: L.B.,

B.M.B. Visualization: L.B. Writing—original draft: L.B. Writing—review and editing: L.B., L.L., D.C., A.L., X.-M.M., Y.C., A.H.H., B.M.B.

Abbreviations: AUC, area under the receiver operating characteristic curve; BD, bronchodilator; C/D, cumulative/dynamic; C-index, concordance index; FEV_1, forced expiratory volume in the first second; FEV_1Q, FEV_1 quotient; FVC, forced vital capacity; GLI, Global Lung Function Initiative; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; HUNT2, the second survey of the Nord-Trøndelag Health Study (1995–1997); I/D, incident/dynamic; LMS, lambda–mu–sigma; $ppFEV_1$, percent-predicted FEV_1; ppFVC, percent-predicted FVC; PRISm, preserved ratio impaired spirometry.

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Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 Study population.
Figure S1 Flow chart: pre-bronchodilator (BD) and post-BD spirometry among people aged ≥40 years in the HUNT2 Study.
Figure S2 Cumulative incidence curves of all-cause mortality for pre-bronchodilator (BD) and post-BD modified GOLD categories among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997).
Figure S3 Incident/dynamic time-dependent ROC curve (Model 1) for pre-bronchodilator (BD) and post-BD (A) percent-predicted forced expiratory volume in the first second (FEV_1), (B) FEV_1 z-score, (C) FEV_1Q and (D) modified GOLD categories for all-cause mortality at 20 years' follow-up time among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995–1997).
Figure S4 Cumulative/dynamic time-dependent AUC (Model 1) for pre-bronchodilator (BD) and post-BD (A) percent-predicted forced expiratory volume in the first second (FEV_1), (B) FEV_1 z-score, (C) FEV_1Q and (D) modified GOLD categories for all-cause mortality change over follow-up time (years) among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997).
Figure S5 Cumulative/dynamic time-dependent AUC (Model 1) for pre-bronchodilator (BD) and post-BD (A) percent-predicted forced expiratory volume in the first second (FEV_1), (B) FEV_1 z-score, (C) FEV_1Q and (D) GOLD grades for all-cause mortality change over follow-up time (years) among participants aged ≥40 years with COPD in the HUNT2 Study (1995–1997).
Table S1 Akaike information criteria and Gronnesby and Borgan goodness-of-fit test (χ^2) of pre-bronchodilator (BD) and post-BD lung function among participants aged ≥40 years with airflow limitation or COPD in the HUNT2 Study (1995–1997).
Table S2 Pre-bronchodilator (BD) and post-BD modified GOLD categories of participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997).
Table S3 Mortality rate for pre-bronchodilator (BD) and post-BD modified GOLD categories among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997).
Table S4 Hazard ratios for pre-bronchodilator (BD) and post-BD lung function among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997).
Table S5 Hazard ratios for pre-bronchodilator (BD) and post-BD lung function among participants aged ≥40 years with COPD in the HUNT2 Study (1995–1997).
Table S6 Incident/dynamic time-dependent area under the receiver operating characteristic curve (AUC), C-index and cumulative/dynamic time-dependent AUC for pre-bronchodilator (BD) and post-BD lung function at 20 years of follow-up among participants aged ≥40 years with COPD in the HUNT2 Study (1995–1997).
Table S7 C-index and cumulative/dynamic time-dependent AUC for pre-bronchodilator (BD) and post-BD lung function at 20 years of follow-up among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997).
Table S8 Incident/dynamic time-dependent AUC for pre-bronchodilator (BD) and post-BD lung function at 20 years of follow-up among participants aged ≥40 years with airflow limitation in the HUNT2 Study (1995–1997).

Supplementary Information

Comparison of pre- and post-bronchodilator lung function as predictors of mortality: The HUNT Study

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Appendix S1. STUDY POPULATION

The Nord-Trøndelag Health Study (HUNT) invited the entire adult population (≥20 years) of northern Trøndelag to attend clinical examinations and answer questionnaires in 1984-1986 (HUNT1), 1995-1997 (HUNT2), and 2006-2008 (HUNT3) [1].

The current study included people aged ≥40 years who participated in HUNT2 (n=44384, 75.2% participation). A 5% random sample and persons reporting asthma related symptoms, diagnosis or use of medication were invited to perform spirometry [2]. At pre-BD screening stations, 7512

(79.7% of invitees) participated where 7158 (95.3% of participants) had acceptable spirometry manoeuvres. Participants having an airflow limitation (pre-BD FEV_1/FVC <0.75 or FEV_1<80% of predicted using the European Coal and Steel Community [ECSC] equations [3]) from the 5 urban municipalities and all participants from 19 rural municipalities were invited to attend post-BD spirometry screening stations. We used airflow limitation criteria to allow for future changes to the GOLD guidelines definition of COPD. At the post-BD screening stations, among the 4178 participants (73.6% of invitees), 3840 (91.9% of participants) had acceptable spirometry manoeuvres. Participants with airflow limitation from both the urban and rural municipalities with acceptable pre-BD and post-BD lung function were included in the analysis (n=2538).

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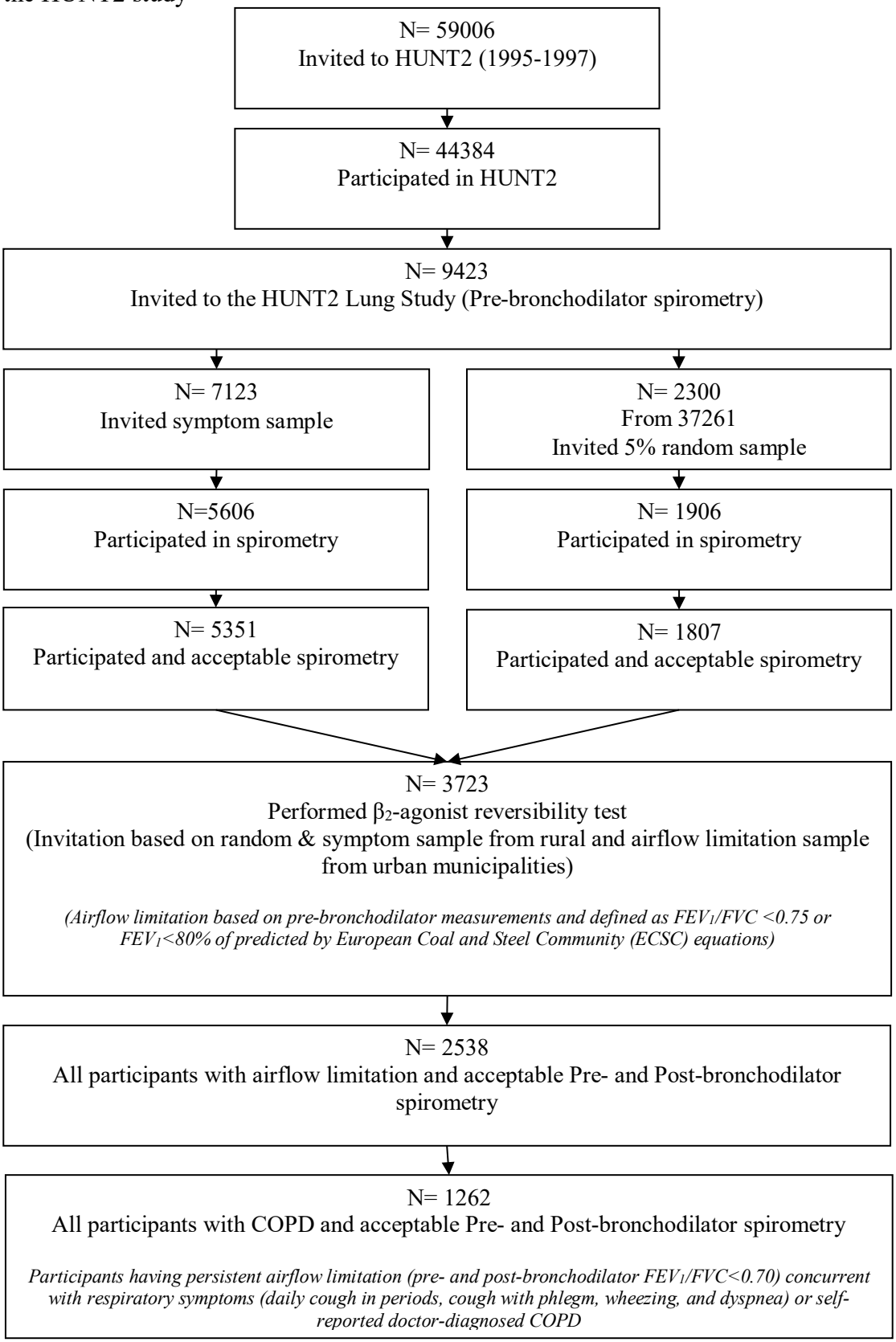
Figure S1. Flow chart - Pre- and Post-bronchodilator spirometry among people aged ≥40 years in the HUNT2 study



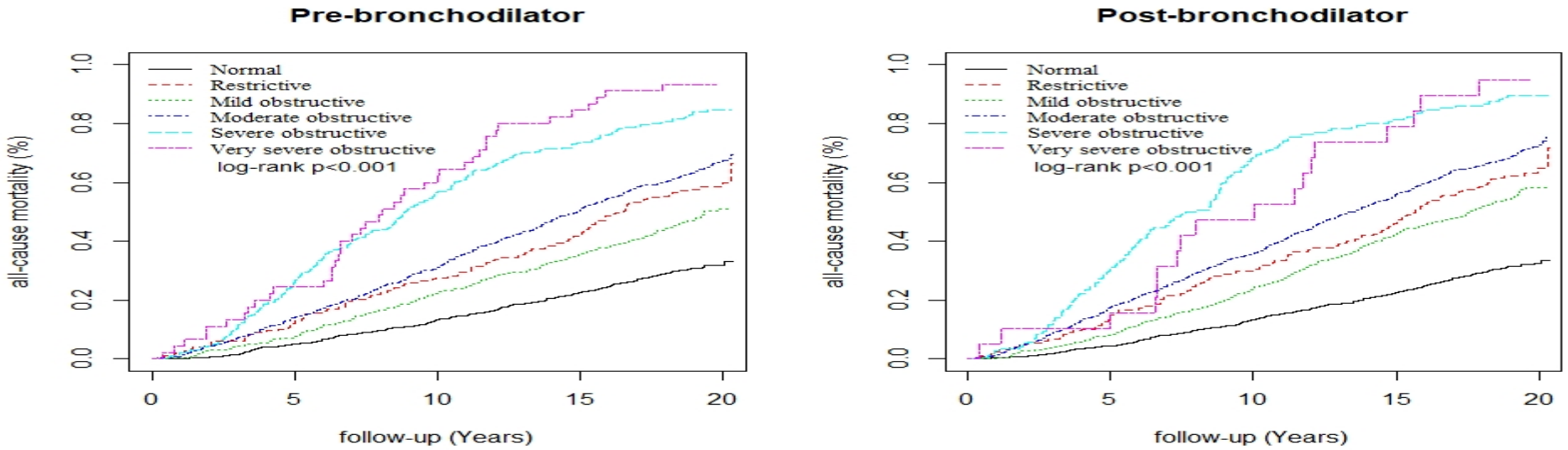


Figure S2. Cumulative incidence curves of all-cause mortality for pre-BD and post-BD modified-GOLD categories among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

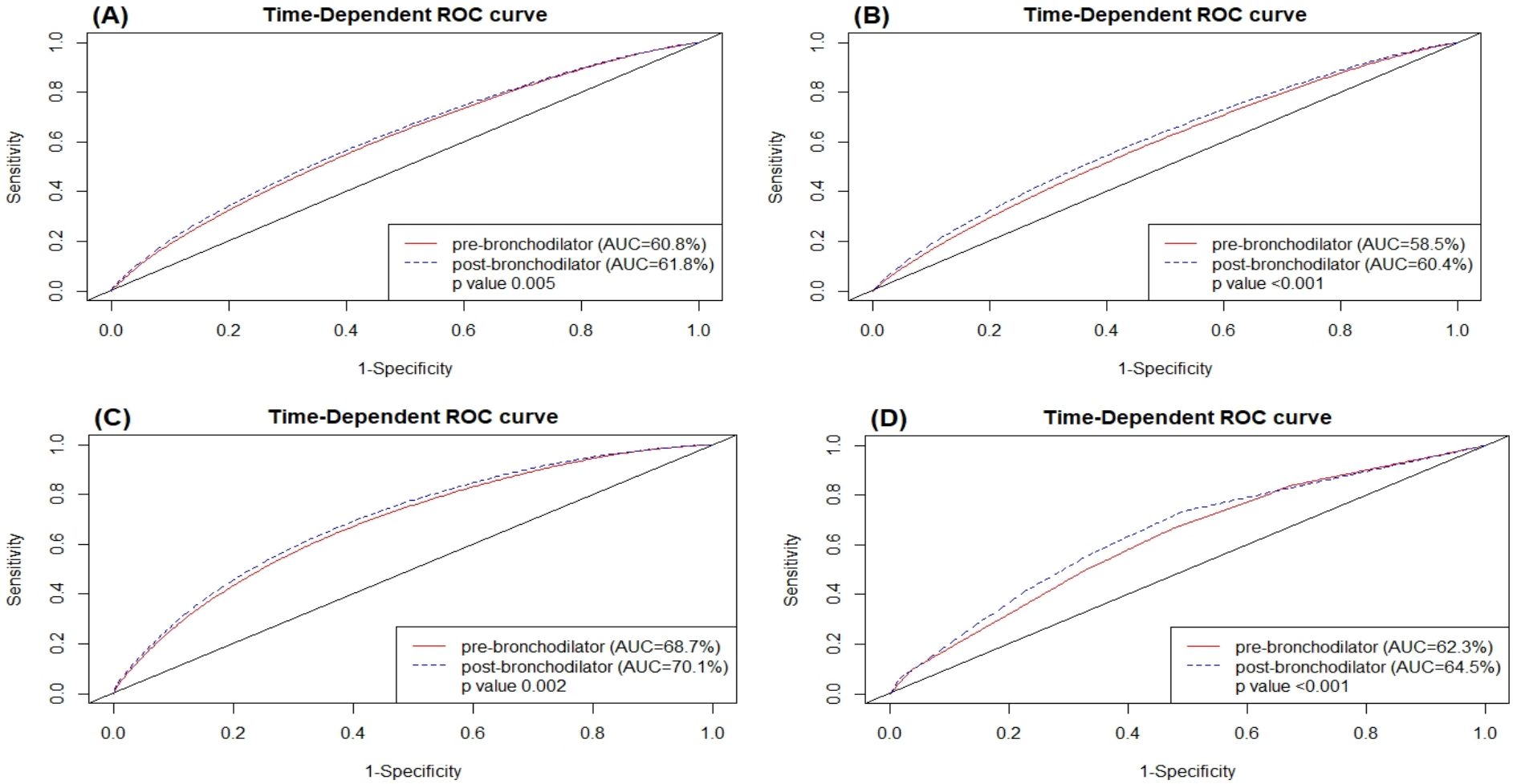


Figure S3. Incident/Dynamic time-dependent ROC curve (Model 1) for pre-BD and post-BD (A) percent-predicted FEV_1, (B) FEV_1 z-score, (C) FEV_1Q, and (D) modified-GOLD categories for all-cause mortality at 20 years' follow-up time among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

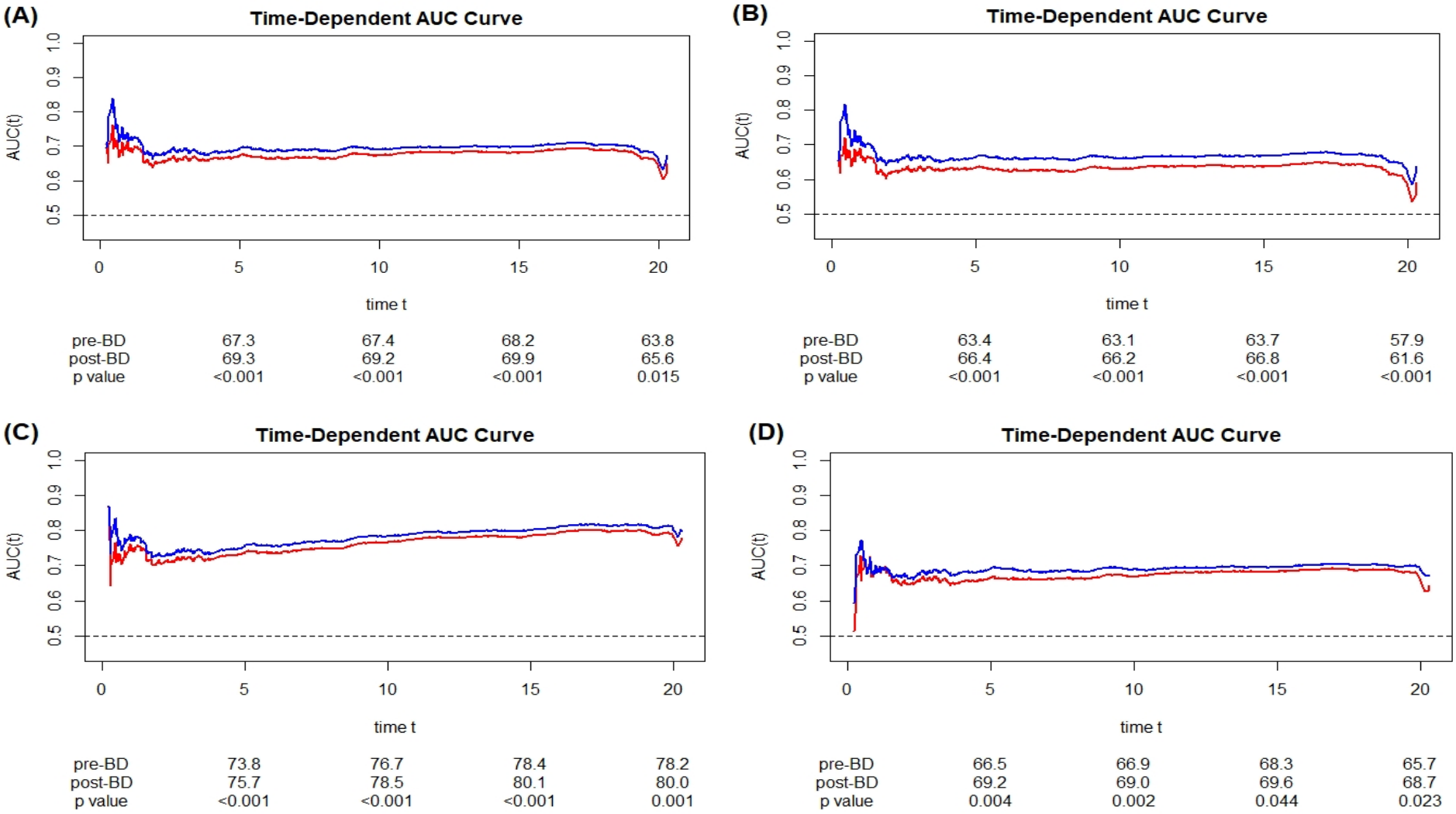


Figure S4. Cumulative/Dynamic time-dependent AUC curve (Model 1) for pre-BD (___) and post-BD (___) (A) percent-predicted FEV_1, (B) FEV_1 z-score, (C) FEV_1Q, and (D) modified-GOLD categories for all-cause mortality change over follow-up time (years) among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

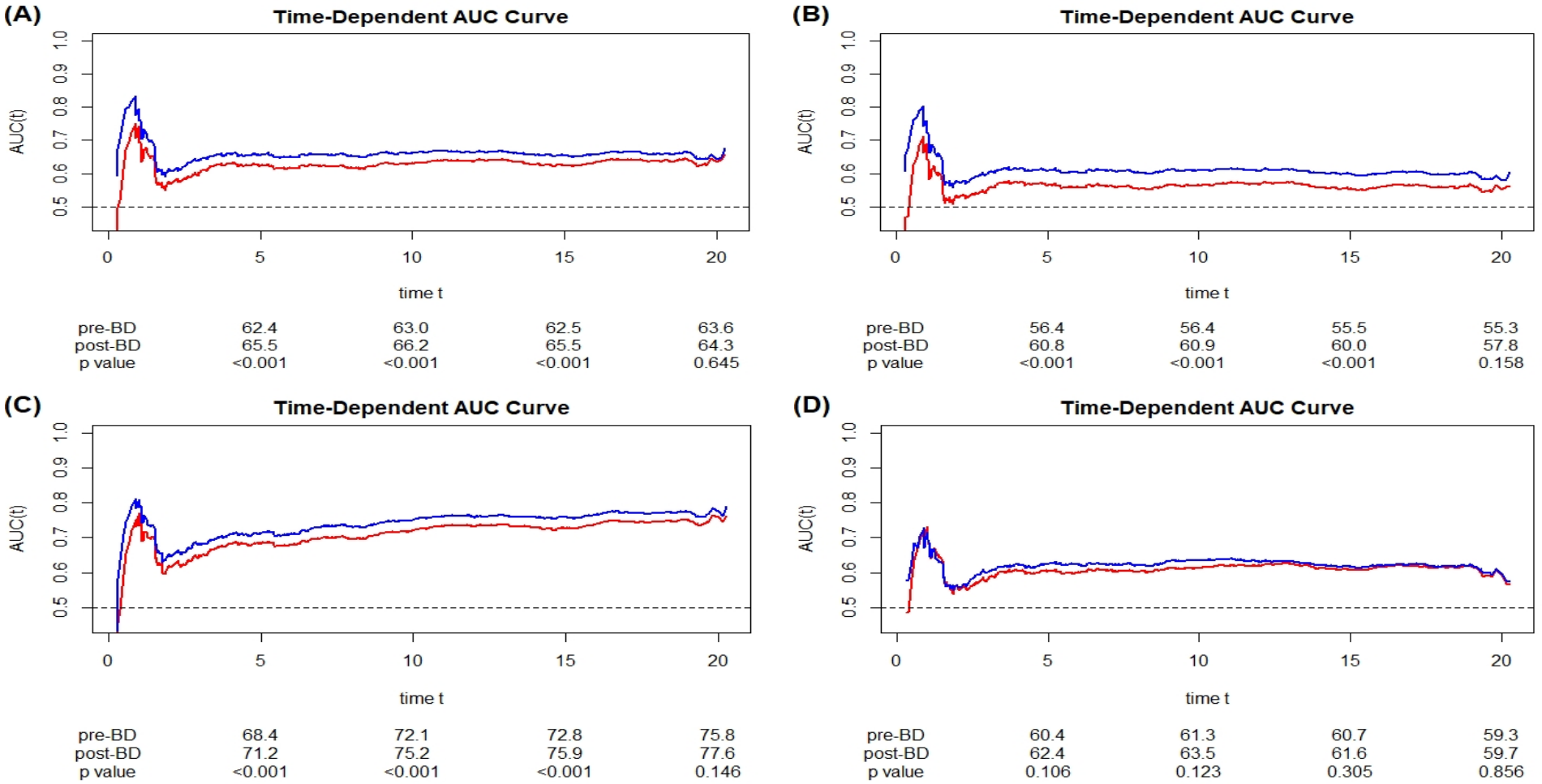


Figure S5. Cumulative/Dynamic time-dependent AUC curve (Model 1) for pre-BD (——) and post-BD (——) (A) percent-predicted FEV_1, (B) FEV_1 z-score, (C) FEV_1Q, and (D) GOLD grades for all-cause mortality change over follow-up time (years) among participants aged ≥40 years with COPD in the HUNT2 study (1995-1997).

Table S1. Akaike Information Criteria (AIC) and Gronnesby and Borgan goodness of fit test (χ^2) of pre-BD and post-BD lung function among participants aged ≥40 years with airflow limitation or COPD in the HUNT2 study (1995-1997).

Lung function ¶,¥,†,§		Pre-BD	Post-BD	Pre-BD	Post-BD	Pre-BD	Post-BD
		AIC *	AIC *	AIC #	AIC #	AIC €	AIC €
Airflow limitation (N=2538)	$ppFEV_1$ §	20382	20318	18942	18903	18914	18880
	FEV_1 z-score †	20549	20463	18935	18895	18908	18873
	FEV_1Q ¥	19844	19727	18936	18901	18909	18878
	modified-GOLD categories ¶	20354	20279	18952	18933	18918	18905
COPD (N=1262)	$ppFEV_1$ §	11678	11642	10997	10962	10998	10964
	FEV_1 z-score †	11748	11720	10995	10959	10997	10962
	FEV_1Q ¥	11486	11415	10996	10965	10999	10969
	GOLD grades ¶	11684	11668	11011	10994	11009	10998
		χ^2 (*p* value) *	χ^2 (*p* value) *	χ^2 (*p* value) #	χ^2 (*p* value) #	χ^2 (*p* value) €	χ^2 (*p* value) €
Airflow limitation (N=2538)	$ppFEV_1$ §	9.1 (0.427)	13.8 (0.128)	13.0 (0.162)	10.5 (0.315)	13.7 (0.135)	13.6 (0.138)
	FEV_1 z-score †	13.1 (0.159)	10.4 (0.322)	10.9 (0.281)	13.0 (0.162)	6.7 (0.664)	8.2 (0.511)
	FEV_1Q ¥	8.6 (0.475)	11.7 (0.229)	10.5 (0.309)	10.0 (0.349)	8.1 (0.523)	10.6 (0.304)
	modified-GOLD categories ¶	10.7 (0.299)	13.6 (0.138)	9.2 (0.418)	18.8 (0.027)	12.7 (0.178)	15.6 (0.076)
COPD (N=1262)	$ppFEV_1$ §	16.5 (0.057)	13.6 (0.139)	7.7 (0.567)	10.9 (0.285)	12.6 (0.180)	5.7 (0.765)
	FEV_1 z-score †	3.6 (0.933)	8.5 (0.489)	11.7 (0.228)	7.8 (0.558)	9.6 (0.387)	6.4 (0.700)
	FEV_1Q ¥	3.0 (0.963)	2.9 (0.969)	12.3 (0.196)	6.4 (0.700)	12.8 (0.172)	14.4 (0.109)
	GOLD grades ¶	9.5 (0.395)	8.1 (0.523)	7.3 (0.604)	17.0 (0.048)	8.4 (0.497)	10.5 (0.309)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GLI (Global Lung Function Initiative), AIC (Akaike Information Criteria), BD (bronchodilator), PRISm (preserved ratio impaired spirometry), χ^2 (chi-square with degree of freedom=9)

*- crude #- adjusted for age, sex, smoking, body mass index, education €- adjusted for age, sex, smoking, body mass index, education, physical activity, cardiovascular diseases, asthma ever, diabetes ever, systolic blood pressure, and cholesterol. § – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation. †- forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation. ¥ - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution. ¶- normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC \geq 0.70$ & $ppFVC < 80$; mild obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; moderate obstructive – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; severe obstructive – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; very severe obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$

Table S2. Pre-BD and post-BD modified-GOLD categories of participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

Characteristic (N=2538)		Post-BD ¶					
		Normal n (%)	PRISm n (%)	Mild obstructive n (%)	Moderate obstructive n (%)	Severe obstructive n (%)	Very severe obstructive n (%)
Pre-BD ¶	Normal, n (%)	644 (25.4)	7 (0.3)	41 (1.6)	17 (0.7)	0	0
	PRISm, n (%)	32 (1.3)	124 (4.9)	0	19 (0.8)	2 (0.1)	0
	Mild obstructive, n (%)	200 (7.9)	2 (0.1)	281 (11.1)	18 (0.7)	0	0
	Moderate obstructive, n (%)	70 (2.8)	33 (1.3)	152 (6.0)	597 (23.5)	6 (0.2)	0
	Severe obstructive, n (%)	0	1 (0.04)	0	111 (4.4)	134 (5.3)	2 (0.1)
	Very severe obstructive, n (%)	0	0	0	0	28 (1.1)	17 (0.7)

BD (bronchodilator), PRISm (preserved ratio impaired spirometry), Cell percentage of total participants,
¶- normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC \geq 0.70$ & ppFVC<80; mild obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; moderate obstructive – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; severe obstructive – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; very severe obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$

Table S3. Mortality rate for pre-BD and post-BD modified-GOLD categories among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

Lung function ¶		Pre-BD			Post-BD		
		Person-years	Observed deaths	Mortality rate (95% CI) *	Person-years	Observed deaths	Mortality rate (95% CI) *
modified-GOLD categories ¶	Normal	11911	223	18.7(16.4-21.3)	15886	302	19.0(17.0-21.3)
	PRISm	2505	105	41.9(34.6-50.7)	2285	107	46.8(38.7-56.6)
	Mild obstructive	7620	246	32.3(28.5-36.6)	6944	268	38.6(34.2-43.5)
	Moderate obstructive	11497	563	49.0(45.1-53.2)	9612	540	56.2(51.6-61.1)
	Severe obstructive	2483	208	83.8(73.1-96.0)	1499	152	101.4(86.5-118.9)
	Very severe obstructive	399	42	105.3(77.8-142.5)	190	18	94.6(59.6-150.1)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GOLD (global initiative for chronic obstructive lung disease), CI (confidence interval), BD (bronchodilator), PRISm (preserved ratio impaired spirometry)
*- per 1000 person-years. ¶- normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC \geq 0.70$ & ppFVC<80; mild obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; moderate obstructive – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; severe obstructive – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; very severe obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$

Table S4. Hazard ratios for pre-BD and post-BD lung function among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

Lung function ¶,¥,†,§ (N=2538)		Pre-BD	Post-BD
		Model 3	Model 3
		HR (95% CI) €	HR (95% CI) €
$ppFEV_1$ §		1.18 (1.15-1.21)	1.21 (1.17-1.24)
FEV_1 z-score †		1.34 (1.27-1.40)	1.39 (1.32-1.46)
FEV1Q ¥		1.31 (1.25-1.37)	1.35 (1.29-1.42)
modified-GOLD categories ¶	Normal	1.00 (Reference)	1.00 (Reference)
	PRISm	1.67 (1.31-2.12)	1.82 (1.45-2.29)
	Mild obstructive	1.16 (0.97-1.40)	1.12 (0.95-1.33)
	Moderate obstructive	1.70 (1.44-2.00)	1.76 (1.52-2.05)
	Severe obstructive	2.59 (2.11-3.18)	3.13 (2.53-3.87)
	Very severe obstructive	5.09 (3.55-7.28)	4.35 (2.58-7.31)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GOLD (global initiative for chronic obstructive lung disease), HR (Hazard ratio), CI (confidence interval), BD (bronchodilator), PRISm (preserved ratio impaired spirometry)

€- adjusted for age, sex, smoking, body mass index, education, physical activity, cardiovascular diseases, asthma ever, diabetes ever, systolic blood pressure, and cholesterol

§ – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation. HRs were for a 10% reduction in $ppFEV_1$. † – forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation. HRs were for a 1-unit reduction in FEV_1 z-score. ¥ - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution. HRs were for a 1-unit reduction in FEV_1Q. ¶- normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC \geq 0.70$ & $ppFVC < 80$; mild obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; moderate obstructive – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; severe obstructive – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; very severe obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$

Table S5. Hazard ratios for pre-BD and post-BD lung function among participants aged ≥40 years with COPD in the HUNT2 study (1995-1997).

Lung function ¶,¥,†,§ (N=1262)		Pre-BD			Post-BD		
		Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
		HR (95% CI) *	HR (95% CI) #	HR (95% CI) €	HR (95% CI) *	HR (95% CI) #	HR (95% CI) €
$ppFEV_1$ §		1.19 (1.15-1.24)	1.23 (1.18-1.27)	1.19 (1.15-1.24)	1.23 (1.19-1.28)	1.20 (1.15-1.25)	1.24 (1.19-1.29)
FEV_1 z-score †		1.12 (1.06-1.19)	1.34 (1.26-1.44)	1.36 (1.27-1.46)	1.21 (1.15-1.29)	1.42 (1.33-1.51)	1.44 (1.34-1.54)
FEV_1Q ¥		1.55 (1.47-1.64)	1.34 (1.26-1.42)	1.35 (1.26-1.44)	1.62 (1.54-1.71)	1.40 (1.32-1.49)	1.41 (1.32-1.51)
GOLD grades ¶	GOLD 1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
	GOLD 2	1.30 (1.08-1.57)	1.38 (1.15-1.66)	1.37 (1.13-1.65)	1.46 (1.25-1.71)	1.52 (1.30-1.79)	1.51 (1.29-1.78)
	GOLD 3	2.30 (1.86-2.84)	2.09 (1.68-2.60)	2.08 (1.65-2.61)	2.94 (2.39-3.62)	2.82 (2.27-3.51)	2.74 (2.20-3.45)
	GOLD 4	3.04 (2.16-4.29)	3.55 (2.48-5.09)	4.11 (2.82-5.99)	2.67 (1.65-4.32)	3.37 (2.06-5.52)	3.96 (2.36-6.64)

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GLI (Global Lung Function Initiative), GOLD (global initiative for chronic obstructive lung disease), HR (Hazard ratio), CI (confidence interval), BD (bronchodilator)

*- crude #- adjusted for age (as a continuous variable), sex, smoking, body mass index, education €- adjusted for age (as a continuous variable), sex, smoking, body mass index, education, physical activity, cardiovascular diseases, asthma ever, diabetes ever, systolic blood pressure, and cholesterol. § – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation. HRs were for a 10% reduction in $ppFEV_1$. †- forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation. HRs were for a 1-unit reduction in FEV_1 z-score. ¥ - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution. HRs were for a 1-unit reduction in FEV_1Q. ¶- GOLD grades: GOLD1 – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; GOLD2 – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; GOLD3 – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; GOLD4 – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$

Table S6. Incident/Dynamic time-dependent AUC, C-index, and Cumulative/Dynamic time-dependent AUC for pre-BD and post-BD lung function at 20 years of follow-up among participants aged ≥40 years with COPD in the HUNT2 study (1995-1997).

Lung function ¶,¥,†,§ (N=1262)	Pre-BD	Post-BD	p value	Pre-BD	Post-BD	p value	Pre-BD	Post-BD	p value
	Model 1	Model 1		Model 1	Model 1		Model 1	Model 1	
	I/D AUC (95% CI) *	I/D AUC (95% CI) *		C-index (95% CI) *	C-index (95% CI) *		C/D AUC (95% CI) *	C/DAUC (95% CI) *	
$ppFEV_1$ §	57.0 (55.1-58.8)	58.8 (56.7-60.8)	<0.001	58.8 (57.0-60.6)	60.4 (58.6-62.2)	<0.001	63.6 (57.6-69.6)	64.3 (58.1-70.6)	0.645
FEV_1 z-score †	53.1 (51.5-54.8)	55.8 (53.9-57.7)	<0.001	53.5 (51.7-55.4)	56.1 (54.4-58.0)	<0.001	55.3 (48.5-62.1)	57.8 (50.7-64.9)	0.158
FEV_1Q ¥	63.6 (60.9-65.9)	65.1 (62.0-67.9)	0.037	65.7 (64.0-67.4)	67.5 (65.8-69.2)	<0.001	75.8 (70.5-81.1)	77.6 (72.5-82.7)	0.146
GOLD grades ¶	56.0 (53.9-57.9)	57.0 (54.6-59.2)	0.268	57.5 (55.9-59.0)	58.2 (56.6-59.8)	0.184	59.3 (53.7-65.0)	59.7 (53.8-65.6)	0.856

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GLI (Global Lung Function Initiative), AUC (area under receiver operating characteristics curves), BD (bronchodilator), C-index (Concordance index)

*- the Cox model included pre-BD or post-BD lung function. § – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation. †- forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation. ¥ - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution. ¶- GOLD grades: GOLD1 – $FEV_1/FVC<0.70$ & $ppFEV_1\geq80$; GOLD2 – $FEV_1/FVC<0.70$ & $80>ppFEV_1\geq50$; GOLD3 – $FEV_1/FVC<0.70$ & $50>ppFEV_1\geq30$; GOLD4 – $FEV_1/FVC<0.70$ & $ppFEV_1<30$

Table S7. C-index and Cumulative/Dynamic time-dependent AUC for pre-BD and post-BD lung function at 20 years of follow-up among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

Lung function ¶,¥,†,§ (N=2538)	Pre-BD	Post-BD	p value	Pre-BD	Post-BD	p value
	Model 1	Model 1		Model 1	Model 1	
	C-index (95%CI) *	C-index (95%CI) *		C/D AUC (95%CI) *	C/D AUC (95%CI) *	
$ppFEV_1$ §	63.8 (62.4-65.2)	64.9 (63.5-66.2)	<0.001	63.8 (60.3-67.3)	65.3 (62.2-69.1)	0.015
FEV_1 z-score †	59.9 (58.5-61.3)	62.0 (60.6-63.4)	<0.001	57.9 (54.0-61.7)	61.6 (57.8-65.4)	<0.001
FEV_1Q ¥	71.9 (70.8-73.2)	73.2 (72.0-74.4)	<0.001	78.2 (75.1-81.2)	80.0 (77.1-83.0)	0.001
modified-GOLD categories ¶	64.0 (62.6-65.3)	65.2 (63.9-66.5)	0.003	65.7 (62.1-69.2)	68.7 (65.1-72.3)	0.023

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GLI (Global Lung Function Initiative), AUC (area under receiver operating characteristics curves), BD (bronchodilator), C-index (Concordance index), PRISm (preserved ratio impaired spirometry)

*- the Cox model included pre-BD or post-BD lung function. § – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation. †- forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation. ¥ - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution. ¶- normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC\geq0.70$ & $ppFVC<80$; mild obstructive – $FEV_1/FVC<0.70$ & $ppFEV_1\geq80$; moderate obstructive – $FEV_1/FVC<0.70$ & $80>ppFEV_1\geq50$; severe obstructive – $FEV_1/FVC<0.70$ & $50>ppFEV_1\geq30$; very severe obstructive – $FEV_1/FVC<0.70$ & $ppFEV_1<30$

Table S8. Incident/Dynamic time-dependent AUC for pre-BD and post-BD lung function at 20 years of follow-up among participants aged ≥40 years with airflow limitation in the HUNT2 study (1995-1997).

Lung function ¶,¥,†,§ (N=2538)	Pre-BD Model 2 I/D AUC (95% CI) #	Post-BD Model 2 I/D AUC (95% CI) #	p value	Pre-BD Model 3 I/D AUC (95% CI) €	Post-BD Model 3 I/D AUC (95% CI) €	p value
$ppFEV_1$ §	76.9 (74.7-78.9)	77.0 (74.8-78.9)	0.768	77.1 (74.7-79.1)	77.2 (74.8-79.1)	0.852
FEV_1 z-score †	77.2 (74.9-79.2)	77.5 (75.2-79.3)	0.437	77.4 (75.0-79.4)	77.5 (75.2-79.5)	0.501
FEV_1Q ¥	77.4 (75.1-79.4)	77.6 (75.3-79.5)	0.512	77.5 (75.1-79.1)	77.6 (75.3-79.6)	0.586
modified-GOLD categories ¶	76.8 (74.6-78.7)	77.2 (74.8-79.2)	0.303	76.9 (74.5-79.0)	77.3 (74.7-79.4)	0.379

Abbreviations: HUNT2 (Nord-Trøndelag Health Study 1995-1997), GLI (Global Lung Function Initiative), AUC (area under receiver operating characteristics curves), BD (bronchodilator), PRISm (preserved ratio impaired spirometry)

#- the Cox model included age, sex, smoking, body mass index, education, and pre-BD or post-BD lung function. € - the Cox model included age, sex, smoking, body mass index, education, physical activity, cardiovascular diseases, asthma ever, diabetes ever, systolic blood pressure, and cholesterol, and pre-BD or post-BD lung function. § – percent-predicted Forced expiratory volume in first second ($ppFEV_1$) based on GLI-2012 equation. †- forced expiratory volume in first second (FEV_1) z-score based on GLI-2012 equation. ¥ - FEV_1 standardized by sex-specific lowest first percentile (0.5L for men and 0.4L for women) of FEV_1 distribution.

¶- normal – forced expiratory volume in first second (FEV_1)/forced vital capacity (FVC) ≥0.70 & percent predicted FVC (ppFVC) ≥80; PRISm - $FEV_1/FVC \geq 0.70$ & $ppFVC < 80$; mild obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 \geq 80$; moderate obstructive – $FEV_1/FVC < 0.70$ & $80 > ppFEV_1 \geq 50$; severe obstructive – $FEV_1/FVC < 0.70$ & $50 > ppFEV_1 \geq 30$; very severe obstructive – $FEV_1/FVC < 0.70$ & $ppFEV_1 < 30$