



# Oxygen desaturation in 6-min walk test is a risk factor for adverse outcomes in COPD

Marie Waatevik<sup>1</sup>, Ane Johannessen<sup>1</sup>, Francisco Gomez Real<sup>2,3</sup>,  
Marianne Aanerud<sup>4</sup>, Jon Andrew Hardie<sup>2</sup>, Per Sigvald Bakke<sup>2</sup> and  
Tomas Mikal Lind Eagan<sup>2,4</sup>

**Affiliations:** <sup>1</sup>Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway. <sup>2</sup>Dept of Clinical Science, University of Bergen, Bergen, Norway. <sup>3</sup>Dept of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway. <sup>4</sup>Dept of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway.

**Correspondence:** Marie Waatevik, Centre for Clinical Research, Haukeland University Hospital, 5021 Bergen, Norway. E-mail: marie.waatevik@helse-bergen.no

**ABSTRACT** The 6-min walk test (6MWT) is an exercise test that measures functional status in chronic obstructive pulmonary disease (COPD) patients and provides information on oxygen desaturation. We investigated oxygen desaturation during 6MWT as a risk factor for important COPD outcomes: mortality, frequency of exacerbations, decline in lung function and decline in lean body mass.

433 COPD patients were included in the Bergen COPD Cohort Study 2006–2009, and followed-up for 3 years. Patients were characterised using spirometry, bioelectrical impedance measurements, Charlson comorbidity score, exacerbation history, smoking and arterial blood gases. 370 patients completed the 6MWT at the baseline of the study. Information on all-cause mortality was collected in 2011.

Patients who experienced oxygen desaturation during the 6MWT had an approximately twofold increased risk of death (hazard ratio 2.4, 95% CI 1.2–5.1), a 50% increased risk for experiencing later COPD exacerbations (incidence rate ratio 1.6, 95% CI 1.1–2.2), double the yearly rate of decline in both forced vital capacity and forced expiratory volume in 1 s (3.2% and 1.7% *versus* 1.7% and 0.9%, respectively) and manifold increased yearly rate of loss of lean body mass (0.18 kg·m<sup>-2</sup> *versus* 0.03 kg·m<sup>-2</sup> among those who did not desaturate).

Desaturating COPD patients had a significantly worse prognosis than non-desaturating COPD patients, for multiple important disease outcomes.



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COPD patients who desaturated in the 6MWT had a significantly increased risk of several adverse disease outcomes <http://ow.ly/YwbSN>

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## Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by persistent and usually progressive airflow limitation. The severity of COPD is traditionally graded using lung function tests, with forced expiratory volume in 1 s (FEV<sub>1</sub>) as a key parameter [1, 2].

The 6-min walk test (6MWT) is a simple exercise test used to measure the functional status of patients with COPD [3]. The 6-min walking distance (6MWD) has been shown in several studies to independently predict mortality in COPD patients and also to be a better predictor of mortality than FEV<sub>1</sub> [4–6].

To date, only three studies have examined whether oxygen desaturation during the 6MWT predicts mortality in COPD patients [7–9]. These three studies included mostly male study subjects, and varied in definition of desaturation and confounders examined. Although all three studies reported higher risk of death in unadjusted analyses, this was not statistically significant after multivariable adjustment in two of the studies [8, 9].

One study on 224 COPD patients, nearly all male, from South Korea, suggested that exertional desaturation may predict a faster decline in FEV<sub>1</sub>; however, change in forced vital capacity (FVC) was not reported [10]. In the same study, rates of later exacerbations were found not to differ between desaturators and non-desaturators [10]. No study to date has examined whether exertional desaturation during the 6MWT predicts loss of lean body mass, an important predictor of development of cachexia.

Thus, there is a paucity of data on the clinical consequences of hypoxaemia during exertion. The aim of the present study was to investigate the effect of oxygen desaturation during the 6MWT in COPD patients on the key longitudinal outcomes mortality, frequency of exacerbations, change in lung function and change in lean body mass.

## Methods

### Study population

In the Bergen COPD Cohort Study, 433 COPD subjects aged 40–76 years were included at baseline in 2006/2007. Participants were recruited from a previously conducted COPD study at Haukeland University Hospital (Bergen, Norway) (GenKOLS, n=232), the outpatient clinic at the Department of Thoracic Medicine, Haukeland University Hospital (n=89), outpatient clinics from other hospitals in Western Norway (n=19) and clinics of private lung specialists practising in Hordaland County (Norway) (n=30). Inclusion and exclusion criteria and the selection of the study population have been described in detail previously [11]. 370 patients completed a 6MWT without using supplementary oxygen.

Informed consent was obtained from each participant. The study was approved by the regional committee of medical research ethics (REK-Vest).

### Data collection

All patients were invited to a clinical examination including an assessment and interview by a study physician every 6 months for 3 years.

### Outcomes

Information on all-cause mortality was collected from the patients' medical records on August 25, 2011, ~5 years after inclusion.

Exacerbations were defined as a worsening of respiratory symptoms that required treatment with oral steroids and/or antibiotics. The study physician recorded exacerbations since last visit at each half-yearly visit. The study physician had the aid of the patient's medical record when taking the history. COPD exacerbations since last visit were classified as moderate if they required treatment with oral steroids and/or antibiotics, or severe if they required hospitalisation. FEV<sub>1</sub> and FVC were measured using a Viasys-Jaeger Masterscope (Viasys, Hoechst, Germany) before and after inhalation of 0.4 mg salbutamol.

Fat mass (kg) and fat-free mass (kg) was determined by bioelectrical impedance using a Bodystat 1500 (Bodystat Ltd, Douglas, UK). Fat mass index (FMI) and fat free mass index (FFMI) were calculated as mass divided by squared height (kg·m<sup>-2</sup>).

### Main exposure

The conduct of the 6MWT has been described in detail [12]. Briefly, walking distance was measured after the subjects had walked as far as possible for 6 min on a 30-m corridor at sea level. Four patients were on long-term oxygen treatment (LTOT), but did not receive supplementary oxygen during the test. Oxygen saturation and pulse rate were measured before and immediately after the 6MWT using a wrist-worn Nonin 3100 pulse oximeter with a finger sensor (Nonin Medical Inc., Plymouth, MN, USA). The expected maximal pulse rate was calculated as 220 – age, and the ratio of end-of-exercise pulse to expected maximal

pulse calculated as an index of effort [13]. Oxygen desaturation was defined according to the Royal College of Physicians' guidelines [14] as >4% reduction between arterial oxygen saturation measured by pulse oximetry pre- and post-test ( $\Delta \text{SpO}_2 \geq 4\%$ ) and post-test  $\text{SpO}_2 < 90\%$ .

### *Covariates*

All patients had a smoking history of >10 pack-years, and patients were categorised as ex-smokers or daily smokers based on their smoking history at baseline. Cachexia was defined as  $\text{FFMI} < 14 \text{ kg}\cdot\text{m}^{-2}$  (females) and  $< 17 \text{ kg}\cdot\text{m}^{-2}$  (males). Obesity was defined as  $\text{FMI} > 13.5 \text{ kg}\cdot\text{m}^{-2}$  (females) and  $> 9.3 \text{ kg}\cdot\text{m}^{-2}$  (males) [15]. Charlson comorbidity score was registered from the physician interview [16]. Arterial oxygen tension was measured in 1.0 mL blood drawn from the radial artery using a radiometer PICO 70 arterial sampler and immediately analysed using an ABL 520 blood gas analyser (Radiometer, Copenhagen, Denmark).

### *Statistical analyses*

All analyses were performed using Stata 13 (StataCorp LP, College Station, TX, USA). *p*-values <0.05 were considered statistically significant.

For comparing baseline differences between desaturating and non-desaturating patients during the 6MWT, Chi-square tests and *t*-tests were used.

Mortality risk (hazard ratios with 95% confidence intervals) was calculated with univariate and multivariable Cox regression analyses. After multivariable analyses, the proportional hazards assumption was tested based on Schoenfeld residuals and found to be unviolated.

Risk for later exacerbations (incidence rate ratios (IRR) with 95% confidence intervals for yearly exacerbations) was analysed using univariate and multivariable negative binomial regression models, which are particularly useful for the analyses of such count variables with a large degree of overdispersion [17].

Changes in FEV<sub>1</sub>, FVC and FFMI require longitudinal modelling, and were thus estimated by generalised estimating equation (GEE) models with robust standard errors, including time by desaturation interaction.

Multivariable adjustment included baseline sex, age, height, weight, body composition, smoking habits, lung function, resting arterial oxygen tension ( $P_{\text{aO}_2}$ ), frequency of exacerbations in the past year, Charlson comorbidity score and 6MWD. The interaction of sex and desaturation was tested in the multivariable models for all outcomes.

In addition to the main analyses we performed sensitivity analyses of all outcomes excluding four participants receiving LTOT. We also performed sensitivity analyses using two different definitions of oxygen desaturation on all outcomes. One definition was stricter than ours, defining desaturation as >6% reduction in  $\text{SpO}_2$  from pre- to post-walk test [7] and one definition was wider than ours, defining desaturation as  $\text{SpO}_2 < 90\%$  post-test or >4% reduction from pre- to post-walk test [8].

## **Results**

The study design is depicted in the Consort flow diagram in figure 1.

The characteristics of the 370 participating COPD patients are shown in table 1. Overall, 23% of the patients desaturated during the 6MWT. Ex-smokers and patients with lower FEV<sub>1</sub>, lower resting arterial oxygen tension or shorter walking distances were more likely to experience desaturation. In addition to the variables shown in table 1, we examined medication use among non-desaturators and desaturators. Desaturators used a mean $\pm$ SD 4.1 $\pm$ 2.3 medications daily compared with 3.7 $\pm$ 2.4 daily among non-desaturators (*p*=0.08 Kruskal–Wallis test). There were no significant differences in the use of typical cardiac medications such as platelet inhibitors, warfarin,  $\beta$ -blockers, calcium channel antagonists or angiotensin converting enzyme inhibitors (data not shown).

Altogether, there were 18 (21%) deaths among desaturators and 32 (11%) deaths among non-desaturators during the 5-year follow-up (*p*=0.02, Chi-squared). The unadjusted and adjusted survival curves according to desaturation status during the 6MWT are shown in figure 2. The hazard ratio (95% CI) for death among desaturators compared to non-desaturators during follow-up was 2.0 (1.2–3.6) unadjusted, and 2.4 (1.2–5.1) after adjustment for sex, age, body composition, smoking habits, FEV<sub>1</sub> % predicted, resting arterial oxygen tension, frequency of exacerbations the year before inclusion, Charlson comorbidity score and the walking distance (table 2).

The mean number of moderate and/or severe exacerbations during the 3-year follow-up period were 4.7 among desaturators and 2.6 among non-desaturators (*p*<0.01 Kruskal–Wallis test). The ratio of severe to moderate exacerbations were not significantly different between groups (0.21 *versus* 0.25, *p*=0.12 Kruskal–Wallis test). The adjusted yearly IRR for moderate and/or severe exacerbations during follow-up are shown

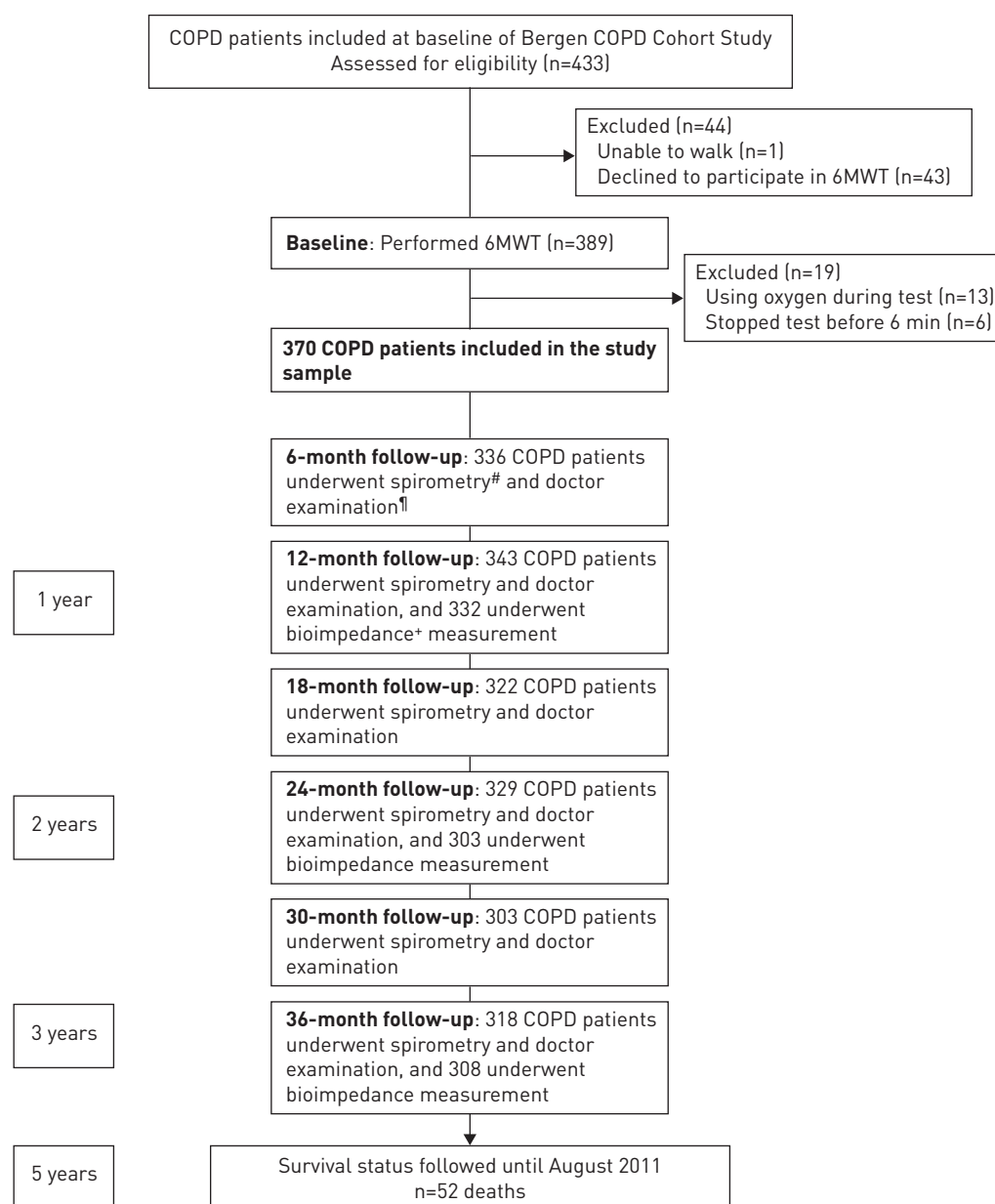


FIGURE 1 Consort flow chart of the study design and the chronic obstructive pulmonary disease (COPD) patients who performed the 6-min walk test (6MWT) at baseline in the Bergen COPD Cohort Study. #: forced expiratory volume in 1 s and forced vital capacity measurement; ¶: history of exacerbations; +: fat-free mass index measurement.

in table 3. COPD patients who desaturated during the 6MWT had an IRR (95% CI) of 1.9 (1.4–2.5) in the unadjusted analyses and 1.6 (1.1–2.2) after adjustment, compared with COPD patients who did not desaturate.

Figure 3 shows the estimated decline in FEV<sub>1</sub> % pred and FVC % pred based on the coefficients from the GEE regression analyses among patients who desaturated during the 6MWT compared with patients who did not desaturate. In both the unadjusted and adjusted analyses, the decline in both FEV<sub>1</sub> and FVC was significantly greater in COPD patients who desaturated compared with patients who did not desaturate during the 6MWT. Whereas the estimated annual decline in FVC and FEV<sub>1</sub> in patients who did not desaturate was 1.7% pred and 0.9% pred, respectively, the annual estimated decline was 3.2% pred and 1.7% pred in patients who did experience desaturation during the test.

Similarly, figure 4 depicts the decline in FFMI according to whether the patients desaturated during testing or not. As with lung function, the decline in fat-free mass was significantly greater in COPD patients who desaturated during the 6MWT than among patients who did not.

TABLE 1 Characteristics of 370 chronic obstructive pulmonary disease (COPD) patients according to whether they experienced oxygen desaturation during the 6 min walk test (6MWT)

	Total	No desaturation	Desaturation	p-value <sup>#</sup>
<b>Subjects</b>	370	284	86	
<b>Sex</b>				0.83
Female	147 (40)	76.2%	23.8%	
Male	223 (60)	77.1%	22.9%	
<b>Age years</b>	63±6.8	63.1±6.9	64.0±6.6	0.31
<b>Body composition</b>				0.08
Normal	215 (58)	80.5%	19.5%	
Cachectic	98 (27)	74.5%	25.5%	
Obese	57 (15)	66.7%	33.3%	
<b>Smoking habits</b>				<0.001
Ex-smoker	205 (55)	69.8%	30.2%	
Daily smoker	165 (45)	85.5%	14.5%	
<b>GOLD (2007) stage</b>				<0.001
II	180 (49)	91.7%	8.3%	
III	160 (43)	66.9%	33.1%	
IV	30 (8)	40.0%	60.0%	
<b>Exacerbations in past 12 months</b>				0.18
0–1	300 (82)	78.1%	21.9%	
≥2	66 (18)	70.0%	30.0%	
<b>PaO<sub>2</sub> at baseline kPa</b>	9.3±1.1	9.5±1.1	8.6±0.9	<0.001
<b>Charlson comorbidity score</b>				0.15
1	220 (59)	76.4%	23.6%	
2	84 (23)	71.4%	28.6%	
3–6	66 (18)	84.8%	15.2%	
<b>Pre-6MWT SpO<sub>2</sub></b>	94±2.6	95±2.4	93±2.7	<0.001
<b>Post-6MWT SpO<sub>2</sub></b>	91±5.6	94±2.7	83±5.5	<0.001
<b>Pre-6MWT pulse</b>	86±15	84±14.5	90±14.6	<0.01
<b>Post-6MWT pulse</b>	110±18	107±16.5	118±1.6	<0.001
<b>Post-6MWT pulse/age-expected maximal pulse ratio</b>	0.7±0.1	0.68±0.1	0.76±0.1	<0.001
<b>6MWD m</b>	432±103.5	440.7±98.8	406.0±114.7	<0.01

Data are presented as n, n (%) or mean±SD, unless otherwise stated. GOLD: Global Initiative for Chronic Obstructive Lung Disease; PaO<sub>2</sub>: arterial oxygen tension; SpO<sub>2</sub>: arterial oxygen saturation measured by pulse oximetry. #: Chi-squared for categorical variables and t-test for continuous variables.

The full analyses with all regression coefficients for the three GEE regression models are presented in online supplementary tables E1 and E2.

For neither of the outcomes was the interaction between sex and desaturation statistically significant.

Sensitivity analyses excluding participants on LTOT did not substantially change the coefficients for any of the outcomes, but for FEV<sub>1</sub> % pred the estimates did not remain statistically significant.

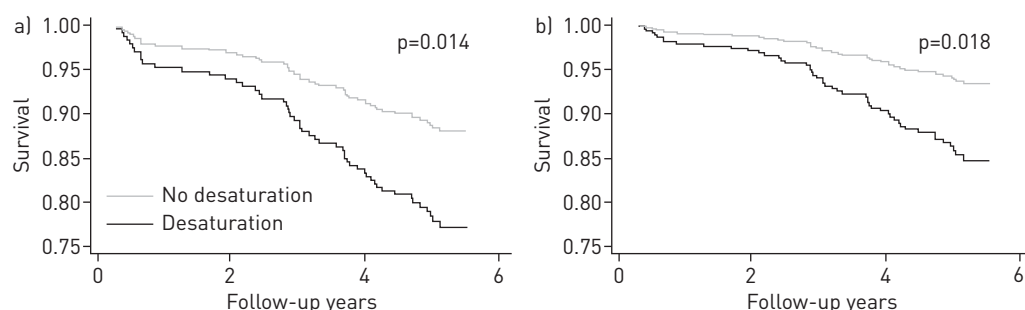


FIGURE 2 Survival curves for the effect of desaturation during the 6-min walk test on 5-year all-cause mortality in chronic obstructive pulmonary disease patients based on Cox regression. a) Unadjusted; b) after adjustment for sex, age, body composition, smoking, forced expiratory volume in 1 s at baseline, exacerbations the past year, resting arterial oxygen tension, Charlson comorbidity score, height, weight and 6-min walking distance.

TABLE 2 Adjusted hazard ratios with 95% confidence intervals calculated in a Cox regression model for all-cause mortality after 5 years of follow-up among chronic obstructive pulmonary disease (COPD) patients in the Bergen COPD Cohort Study

	Hazard ratio (95% CI)	p-value
<b>Desaturation during 6MWT</b>		
No	1	
Yes	2.5 (1.1–5.3)	0.02
<b>Sex</b>		
Female	1	
Male	1.3 (0.5–3.3)	0.49
<b>Age per 10-year increase</b>	1.7 (0.97–2.9)	0.06
<b>Body composition</b>		
Normal	1	
Cachectic	2.7 (1.1–6.9)	0.03
Obese	4.2 (1.2–14.4)	0.02
<b>Smoking habits</b>		
Ex-smoker	1	
Daily smoker	1.1 (0.5–2.1)	0.88
<b>FEV<sub>1</sub> % pred per 10% reduction</b>	0.99 (0.7–1.3)	0.97
<b>Exacerbations in 12 months before inclusion in study</b>		
No	1	
Yes	0.8 (0.4–1.9)	0.68
<b>P<sub>aO<sub>2</sub></sub> at baseline per kPa increase</b>	0.9 (0.7–1.3)	0.57
<b>Charlson comorbidity score</b>		
1	1	
2	0.8 (0.3–1.8)	0.55
3	0.9 (0.4–2.1)	0.76
≥4	4.2 (1.4–13.0)	0.01
<b>6MWD per 10-m increase</b>	0.93 (0.9–0.96)	<0.001
<b>Height per cm increase</b>	1.05 (0.98–1.1)	0.14
<b>Weight per kg increase</b>	0.96 (0.92–0.99)	0.02

6MWT: 6-min walk test; FEV<sub>1</sub>: forced expiratory volume in 1 s; P<sub>aO<sub>2</sub></sub>: arterial oxygen tension; 6MWD: 6-min walking distance.

Sensitivity analyses using different definitions of desaturation are presented in online supplementary table E3. The results remained approximately the same, but for exacerbations, desaturation using both the stricter and wider definition lost significance as a predictor, and for FEV<sub>1</sub> and FVC, using the stricter definition led to loss of significance for desaturation.

## Discussion

This cohort study of 370 COPD patients shows that oxygen desaturation during the 6MWT is an important predictor of several important clinical outcomes, in fact all outcomes examined: mortality, exacerbations, decline in lung function and loss of lean body mass. COPD patients who desaturated during the 6MWT at baseline of the study had an approximately twofold increased risk of death, a 50% increased risk of later moderate or severe COPD exacerbations, double the rate of decline in both FEV<sub>1</sub> and FVC and manifold increased rate of loss of lean body mass. This study had the strength to adjust for important confounders, and is the first study to show a consistent pattern of adverse outcomes among COPD patients who desaturate on exertion and the first study to examine loss of lean body mass among desaturators.

Three previous studies have examined desaturation during the 6MWT as a predictor for mortality [7–9]. In the earliest study from Japan, by TAKIGAWA *et al.* [7], 132 male and 12 female COPD patients were followed for a median 8 years. Desaturation was defined as  $\Delta\text{SpO}_2 \geq 6\%$ . After adjusting for sex, FEV<sub>1</sub>, arterial carbon dioxide tension, lung volume surgery and 6MWD, the risk of death was increased more than twofold among patients who desaturated during testing; comparable to our study. However, the study by TAKIGAWA *et al.* included mostly very severely afflicted COPD patients, with the majority (n=88) having a FEV<sub>1</sub>  $\leq 30\%$  pred [7]. In the two later studies, one a multicentre study from USA and Spain, 236 COPD patients were followed for 3 years [8], and in the other, a single-centre Spanish study, 104 COPD patients were followed from 4 to 34 months [9]. In both studies desaturation was a significant predictor of death in univariate analyses, but not in adjusted analyses. In the case of the study by GOLPE *et al.* [9] this is possibly related to lack of statistical strength due to low mortality and a short follow-up. In the largest study by

TABLE 3 Adjusted yearly incidence rate ratio (IRR) with 95% confidence intervals calculated with negative binomial regression for experiencing moderate and/or severe chronic obstructive pulmonary disease (COPD) exacerbations during follow-up in the Bergen COPD Cohort Study

	IRR (95% CI)	p-value
<b>Desaturation during 6MWT</b>		
No		
Yes	1.6 (1.2–2.2)	<0.01
<b>Sex</b>		
Female	1	
Male	1.0 (0.7–1.4)	0.97
<b>Age per 10-year increase</b>	1.0 (0.8–1.2)	0.85
<b>Body composition</b>		
Normal	1	
Cachectic	0.8 (0.5–1.1)	0.18
Obese	1.7 (1.1–2.8)	0.03
<b>Smoking habits</b>		
Ex-smoker		
Daily smoker	0.9 (0.7–1.2)	0.60
<b>FEV<sub>1</sub> % pred per 10% reduction</b>	1.2 (1.1–1.3)	<0.01
<b>Exacerbations in 12 months before inclusion in study</b>		
No	1	
Yes	2.2 (1.6–3.0)	<0.001
<b>P<sub>aO<sub>2</sub></sub> at baseline per kPa increase</b>	1.0 (0.9–1.1)	0.79
<b>Charlson comorbidity score</b>		
1	1	
2	1.0 (0.7–1.3)	0.94
3	0.9 (0.6–1.3)	0.46
≥4	1.2 (0.7–2.1)	0.54
<b>6MWD per 10-m increase</b>	0.9 (0.7–0.99)	0.03
<b>Height per cm increase</b>	1.0 (0.9–1.0)	0.72
<b>Weight per kg increase</b>	0.98 (0.97–0.99)	<0.01

6MWT: 6-min walk test; FEV<sub>1</sub>: forced expiratory volume in 1 s; P<sub>aO<sub>2</sub></sub>: arterial oxygen tension; 6MWD: 6-min walking distance.

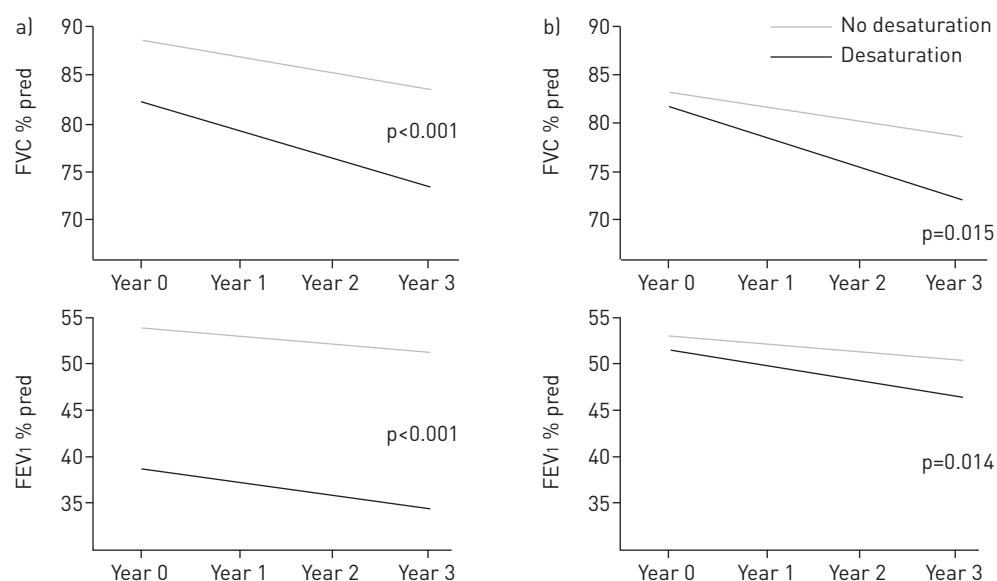


FIGURE 3 The estimated decline in lung function in chronic obstructive pulmonary disease patients over 3 years by desaturation during the 6-min walk test based on the coefficients from generalised estimating equation analyses. a) Unadjusted; b) after adjustments for sex, age, body composition, smoking, forced expiratory volume in 1 s (FEV<sub>1</sub>) or forced vital capacity (FVC) at baseline, exacerbations the last year, resting arterial oxygen tension, Charlson comorbidity score, height, weight and 6-min walking distance.

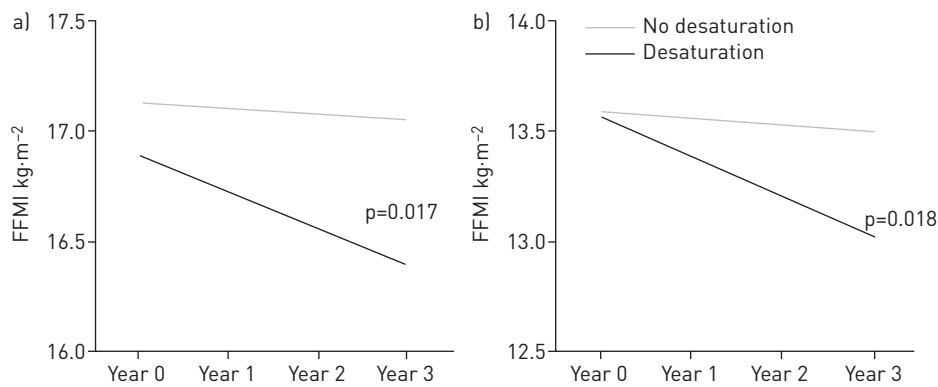


FIGURE 4 The estimated decline in fat-free mass index (FFMI) in chronic obstructive pulmonary disease patients over 3 years by desaturation during the 6-min walk test based on the coefficients from generalised estimating equation analyses. a) Unadjusted; b) after adjustments for sex, age, body composition, smoking, forced expiratory volume in 1 s at baseline, exacerbations in the past year, resting arterial oxygen tension, Charlson comorbidity score, height, weight and 6-min walking distance.

CASANOVA *et al.* [8] desaturation was examined either as a decrease >4% or a fall <90%. The risk of death among patients who desaturated during testing was increased approximately twofold for both definitions of desaturation both in the univariate and multivariable analyses; however, this failed to reach statistical significance ( $p=0.09$ ) after adjustment for the confounders sex, age, body mass index, FEV<sub>1</sub>, Charlson score and 6MWD [8].

We also performed the analyses using desaturation definitions according to the TAKIGAWA and CASANOVA studies (online supplementary table E3). For all definitions, the risk of death is at least doubled in COPD patients who desaturate during the 6MWT, independent of lung function, exacerbation frequency, resting arterial oxygen tension, comorbidities and walking distance measured during the test. However, with a stricter definition, the associations between desaturation and exacerbations and lung function were less significant. With a strict definition, lung function is low to begin with, and unlikely to change as much as with milder cases. In contrast, the wider definition of CASANOVA *et al.* ( $SpO_2 <90\%$  post-test or >4% change) was more in line with our results, except in the analysis of exacerbations where the IRR was lower and not statistically significant.

In the study by CASANOVA *et al.* [8], the increased mortality was primarily seen in patients with FEV<sub>1</sub> <50% pred. We also examined the effect of desaturation on all outcomes in Global Initiative for Chronic Obstructive Lung Disease stage II only. For mortality, risk of exacerbations and change in lung function, the effect estimates were similar to those with more severe COPD; however, with the smaller subsample the estimates did not reach statistical significance. This hints that the effects of desaturation on those three outcomes may be important even in patients with moderate COPD, but larger studies are needed to settle the issue.

A final finding by CASANOVA *et al.* [8] worth mentioning was the finding that resting oxygenation predicted mortality, and to a greater extent than desaturation. Tables 2 and 3 show that baseline  $PaO_2$  predicted neither mortality nor later exacerbations in our study. Furthermore, no effect of baseline  $PaO_2$  was seen on change in lung function or lean body mass (online supplementary tables E1 and E2).

Only one previous study has examined the effect of desaturation during the 6MWT on later change in lung function and risk of exacerbations [10]. In that study, 216 male and eight female COPD patients were examined, and 3 years of follow-up data on FEV<sub>1</sub> were available for 189 patients. The study showed a threefold larger yearly decline in FEV<sub>1</sub> in patients who desaturated during 6MWT. However, the study was restricted by lack of multivariable adjustment and did not examine change in FVC. The study also reported number of exacerbations the first year of follow-up, without finding statistically significant differences [10]. A retrospective analysis by the same author of a smaller patient sample suggested that the nadir desaturation value may be more sensitive to lung function decline [18].

For all studies, including ours, desaturation during testing was associated with more severe disease. Thus, adjustment for important known confounders such as FEV<sub>1</sub> % pred, body composition, resting  $PaO_2$ , exacerbation frequency and 6MWD was important in assessing the effect of desaturation during the 6MWT.

In patients with COPD, desaturation during exertion has been shown primarily to be a consequence of insufficient increase in ventilation due to hyperinflation, and possibly insufficient cardiac output or

increased peripheral oxygen extraction [19–21], factors which are possibly not fully accounted for in our list of predictors.

However, it could be that exertional desaturation in itself is harmful. Persistent hypoxaemia is related to development of adverse sequelae in COPD patients, such as pulmonary hypertension, secondary polycythemia, skeletal muscle dysfunction, systemic inflammation and neurocognitive dysfunction [22]. It could be hypothesised that the on-and-off desaturation that happens when the patient is exercising could lead to the same long-term effects as persistent hypoxaemia, due to possible repeated micro-trauma caused by desaturation. Another possibility is that patients who desaturate during activity have a higher prevalence of nocturnal desaturation, as found in a study by SCOTT *et al.* [23], thus leading to chronic trauma.

The ultimate test of whether exertional desaturation is harmful *per se* would be if oxygen supplementation, either as LTOT or oxygen supply only during exertion, was associated with better outcomes. Very little evidence exists on this subject to date. A 1998 report on ~1400 COPD patients prescribed LTOT outside guidelines (resting  $P_{aO_2} > 8$  kPa), presumably for nocturnal or exertional desaturation, found a similar mortality among this group of patients compared with patients using LTOT for respiratory failure [24]. A meta-analysis of prescribed “short-burst oxygen therapy” found no convincing effect on perceived breathlessness among those treated compared to those not treated [25]. However, on hard outcomes, randomised trials are currently lacking. Given the serious prognosis of COPD, and limited effect of pharmacological treatment, this should be prioritised.

There are some limitations to this study. First, desaturation was measured using pre- and post-test  $SpO_2$  only, thus not using the lowest (nadir)  $SpO_2$  during testing. One previous study found that patients who desaturated early during the 6MWT had a higher probability of desaturating during daily activities and developing severe hypoxaemia [26]. Thus, using nadir  $SpO_2$  could have identified more patients who desaturated. However, if these patients were more likely to develop adverse outcomes and in our study were classified as non-desaturators, it is more likely that this error resulted in less significant coefficients in our regression analyses, rather than leading to false positive results.

Second, only one 6MWT was performed in the study. Studies indicate that walking distance increases when a second test is performed [27–29]. However, previous studies have not investigated whether a second test would have influenced the degree of desaturation.

Third, patients in the study were selected from several different sources, and are not a random sample. The patients selected from specialists and hospital clinics tend to have a more severe or complicated disease than patients undiagnosed or seen by a general practitioner. However, for our study question, it is important to examine an adequate number of severe patients, and to ensure proper adjustment for those variables that are related to severity of COPD, and thus the likelihood for desaturating during the 6MWT. In our study, all multivariable analyses included adjustment for baseline arterial oxygen tension, FEV<sub>1</sub> (or FVC at baseline for change in FVC), exacerbation history, body composition, smoking habits and presence of comorbidities. Thus, we believe our results are relevant for patients with moderate to severe COPD.

In conclusion, this is the largest longitudinal study on the prognostic value of desaturation during the 6MWT in COPD patients to date. With extensive adjustment for important confounders, this study shows a consistent pattern of increased risk among patients who experienced desaturation during the 6MWT for all adverse outcomes examined: mortality, exacerbation frequency, lung function decline and loss of lean body mass.

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