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The impact of comorbidities on mortality among men and women with COPD: report from the OLIN COPD study

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Abstract

Background: Comorbidities probably contribute to the increased mortality observed among subjects with chronic obstructive pulmonary disease (COPD), but sex differences in the prognostic impact of comorbidities have rarely been evaluated in population-based studies. The aim of this study was to evaluate the impact of common comorbidities, cardiovascular disease (CVD), diabetes mellitus (DM), and anxiety/depression (A/D), on mortality among men and women with and without airway obstruction in a population-based study.

Methods: All subjects with airway obstruction [forced expiratory volume in 1 second (FEV_1)/ (forced) vital capacity ((F)VC) <0.70, $n = 993$] were, together with age- and sex-matched referents, identified after examinations of population-based cohorts in 2002–2004. Spirometric groups: normal lung function (NLF) and COPD (post-bronchodilator FEV_1/(F)VC <0.70) and additionally, LLN-COPD (FEV_1/(F)VC $<$lower limit of normal). Mortality data was collected until December 2015.

Results: In COPD, the prevalence of CVD and DM was higher in men, whereas the prevalence of A/D was higher in women. The cumulative mortality was significantly higher in COPD than NLF, and higher in men than women in both groups. Among women with COPD, CVD and A/D but not DM increased the risk of death independent of age, body mass index, smoking habits, and disease severity, whereas among men DM and A/D but not CVD increased the risk for death. When the LLN criterion was applied, the pattern was similar.

Conclusion: There were sex-dependent differences regarding the impact of comorbidities on prognosis in COPD. Even though the prevalence of CVD was higher in men, the impact of CVD on mortality was higher in women, and despite higher prevalence of A/D in women, the impact on mortality was similar in both sexes.

The reviews of this paper are available via the supplemental material section.

Keywords: chronic airflow obstruction, co-morbidity, epidemiology, mortality, sex

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Introduction

Among individuals with chronic obstructive pulmonary disease (COPD), multimorbidity is common. In addition to the most common comorbidity, cardiovascular disease (CVD), diabetes mellitus (DM), and anxiety/depression (A/D) are also more common among subjects with than without COPD,[1–3] and population-based studies have shown a higher mortality among individuals with than without COPD,[4,5] but the known under-diagnosis of COPD[6,7] contributes to an underestimation of the mortality among subjects with COPD in register-based studies. Even though respiratory failure is common in severe COPD,[8] comorbidities probably contribute to the increased mortality observed among individuals with mild-to-moderate COPD.[8,9]

COPD has historically been more prevalent among men, 'the smoking mans' disease'. Owing to an increased smoking prevalence among women during the last century, in combination with high vulnerability to tobacco smoke exposure among women,[10] the sex difference in the prevalence of COPD has diminished. In Sweden, the smoking prevalence has decreased over the last several decades to around 10%, and epidemiologic data indicate that the prevalence of COPD has also decreased.[11] However, despite a decreased smoking prevalence in Sweden, the overall pattern with increased cardiovascular comorbidities among individuals with than without COPD seems to remain.[12] In addition to changes in smoking habits, sex-dependent differences with regards to COPD are indeed multifaceted.[10] CVD is more common among men,[13,14] and depression is more common among women,[13,15] whereas the previously higher mortality among men with COPD has decreased and the number of COPD deaths is now comparable or even higher among women.[13] Still, it has not been established whether the impact of comorbidities on mortality is similar among men and women with COPD.

The aim of this population-based study was to investigate the impact of CVD, DM, and A/D on mortality among men and women with COPD, compared with those with normal lung function (NLF).

Material and methods

Study design and study population
The study design has been described in detail previously.[16] In short, within the epidemiological research program Obstructive Lung Disease in Northern Sweden (OLIN) studies, all subjects with airway obstruction [forced expiratory volume in 1 second (FEV_1)/(forced) vital capacity ((F)VC) <0.70, $n = 993$] were, together with age- and sex-matched referents without obstructive lung function impairment (FEV_1/(F)VC ≥ 0.70, $n = 993$), identified from examinations of four population-based cohorts in 2002–2004. The examinations included spirometry and a structured interview following a questionnaire with well-validated questions regarding respiratory symptoms and conditions,[17,18] and in addition questions on smoking habits and comorbidities. This paper includes data from the individuals at recruitment and mortality (data from the Swedish Tax Agency) from the date of examination during 2002–2004 until 31 December 2015. The study was approved by the Regional Ethical Review Board at Umeå University, Sweden.

Spirometry and spirometric classification
Lung function testing was performed using a dry volume spirometer, the Mijnhardt Vicatest 5, following the American Thoracic Society (ATS) guidelines.[19] Vital capacity (VC) was defined as the best of FVC and slow vital capacity (SVC). Reversibility testing was performed if FEV_1/VC <0.70 or FEV_1 $<90\%$ of predicted, using 4×0.2 mg Ventoline Discus® (salbutamol). The non-obstructive referents, FEV_1/VC ≥ 0.70, were divided into restrictive pattern, FEV_1/VC ≥ 0.70 & VC $<80\%$ predicted, and NLF, FEV_1/VC ≥ 0.70 and VC $\geq 80\%$ predicted. Airway obstruction, FEV_1/VC <0.70, was divided into pre- but not post-bronchodilator airway obstruction and post-bronchodilator airway obstruction (post-BD obstruction). Post-BD obstruction, FEV_1/VC <0.70, corresponds to the spirometric criteria for COPD according to GOLD[20] and will hereafter be labeled as COPD. Among those with post-BD obstruction (COPD) the lower fifth percentile of the reference value for FEV_1/VC was used to identify LLN-COPD. Locally derived reference values were used.[21] The study population is illustrated by spirometric classification in Figure 1, including number of subjects in each group.

Definitions
Body mass index (BMI) is defined as weight in kilograms/height in meters squared, divided into the categories underweight, normal weight, and overweight/obesity according to the WHO.[22] Smoking habits were classified into nonsmokers, exsmokers (quit at least 1 year previous), and current smokers. Dyspnea was classified according to the modified Medical Research Council dyspnea scale (mMRC, grade 0–4).[23] Any respiratory symptom was defined as at least one of longstanding cough, productive cough, wheeze, or mMRC score ≥ 2. Heart disease was defined as any of angina pectoris, previous coronary artery bypass surgery, previous percutaneous coronary intervention, myocardial infarction, or heart failure. CVD was defined as any of heart disease, claudication, or stroke. DM and A/D were based on report of having or having had either of the conditions.
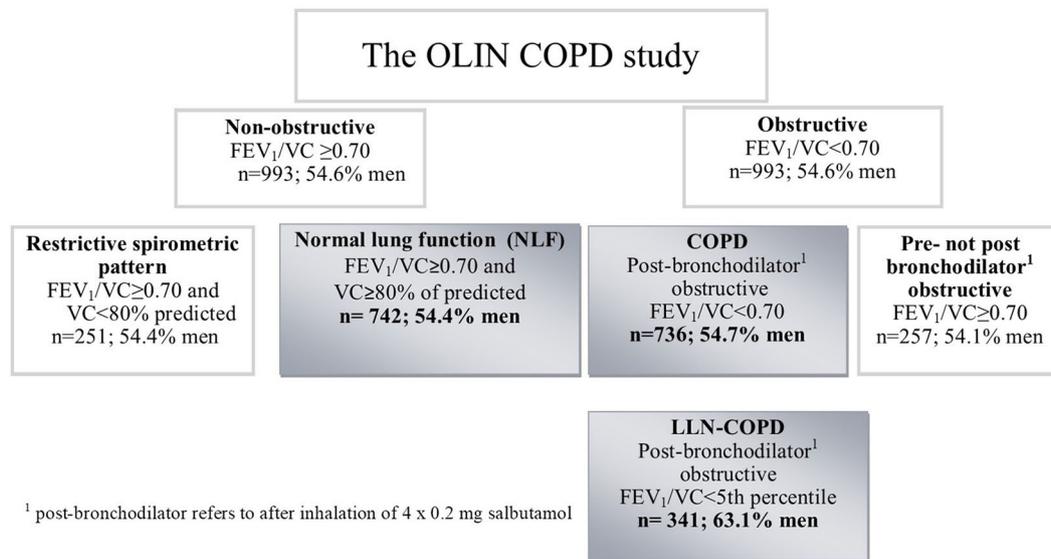
Figure 1. Flow chart of the study population by spirometric classification.

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) software version 25 was used for statistical analyses. A *p* value <0.05 was considered statistically significant. The chi-squared and test for trend were used for comparisons of proportions, and Student's *t* test for comparing means. Missing answers in individual questions were uncommon, <0.5%, except for the questions regarding A/D, DM, and claudication, *n* (%): 206 (13.9), 170 (11.5), 176 (11.9), and in these cases missing was recoded as no. Mortality data was collected over at least 10 years observation time, from date of examination at recruitment during 2002–2004 until 31 December 2015. To analyze the comorbidities (CVD, DM, and A/D) as risk factors for death, Cox's regression models were used and the results were expressed as hazard ratios (HRs) using 95% confidence intervals (95% CI) for statistical significance. Covariates included in the model were age, sex, BMI categories, and smoking habits. The proportional hazards assumption for the Cox regression was met when checked by log–log plots. The analyses in the Cox regression model were performed by spirometric groups (COPD and NLF) as well as stratified for sex. In a similar model, including the same covariates and comorbidities, COPD was analyzed as a risk factor for death in comparison with NLF. Corresponding analyses were also performed by applying the LLN-COPD criterion.

Results

Clinical characteristics by sex in NLF and COPD

Table 1 shows basic characteristics by sex and by NLF and COPD, respectively. Men had a higher prevalence of CVD and DM than women in COPD but not in NLF, whereas A/D was more common among women in both spirometric groups. Among men, but not women, the prevalence of CVD and A/D was higher in COPD than in NLF.

Mortality among men and women with NLF and COPD

In total 485 (295 men, 190 women) died between recruitment and 31 December 2015. The cumulative mortality was higher in COPD than in NLF in both sexes and higher among men than women with COPD (Table 1). The mean age at death (±SD) among men with NLF and COPD was 72.3 (8.9) and 72.4 (8.3) years, whereas the corresponding among women was 75.2 (8.8) and 72.8 (9.3) years. The cohort generated a total of 15,853 person-years, and the mortality rates per 1000 person-years in NLF and COPD, respectively, were estimated as 25.0 and 45.7 among men and 19.6 and 32.4 among women.

Comorbidities as risk factors for death in NLF and COPD and by sex

Analyses of associations between comorbidities and death after adjustment for age, sex, smoking habits, and BMI categories showed that CVD,

Table 1. Clinical characteristics at recruitment in 2002–2004 and cumulative mortality during the observation time (until December 2015); comparing men and women within the groups NLF and COPD and, in analyses stratified for sex also comparing NLF and COPD, respectively. Data presented as *n* (%) unless stated otherwise, significant *p* values are given in bold.

	NLF		P^a	COPD		P^a	P^b	P^c
	Men	Women		Men	Women			
Variables	*n* = 404	*n* = 338		*n* = 403	*n* = 333			
Age, mean (±SD)	62.8 (11.2)	64.3 (11.5)	0.069	65.5 (10.7)	65.4 (11.3)	0.889	< **0.001**	0.883
BMI, mean (±SD)	26.4 (3.3)	26.4 (4.1)	0.952	25.9 (3.5)	25.5 (4.33)	0.138	**0.033**	**0.004**
BMI categories								
Underweight	0	4 (1.2)		4 (1.0)	7 (2.1)			
Normal weight	142 (35.1)	134 (39.6)		164 (40.7)	166 (49.8)			
Overweight/obesity	262 (64.9)	200 (59.2)		235 (58.3)	160 (48.0)			
Smoking habits			< **0.001**			< **0.001**	< **0.001**	< **0.001**
Nonsmoker	154 (38.1)	191 (26.9)		68 (16.9)	98 (29.4)			
Exsmoker	200 (49.5)	91 (26.9)		189 (46.9)	102 (30.6)			
Current smoker	50 (12.4)	56 (16.6)		146 (36.2)	133 (39.9)			
FEV$_1$ % of predicted, mean (±SD)	97.2 (10.6)	97.8 (10.9)	0.419	72.8 (17.6)	73.9 (17.3)	0.389	< **0.001**	< **0.001**
Respiratory symptoms								
Any respiratory symptoms	154 (38.2)	149 (44.1)	0.106	302 (74.9)	249 (75.0)	0.985	< **0.001**	< **0.001**
Productive cough	92 (22.8)	64 (18.9)	0.201	205 (50.9)	133 (39.9)	**0.003**	< **0.001**	< **0.001**
mMRC ⩾2	17 (4.2)	38 (11.2)	< **0.001**	94 (23.3)	115 (34.5)	**0.001**	< **0.001**	< **0.001**
Comorbidities								
Cardiovascular disease	84 (20.8)	61 (18.0)	0.348	128 (31.8)	64 (19.2)	< **0.001**	< **0.001**	0.697
Diabetes mellitus	37 (9.2)	21 (6.2)	0.137	45 (11.2)	21 (6.3)	**0.022**	0.345	0.960
Anxiety/depression	31 (7.7)	71 (21.0)	< **0.001**	51 (12.7)	85 (25.5)	< **0.001**	**0.019**	0.166
Cumulative mortality	111 (27.5)	75 (22.2)	0.098	184 (45.7)	115 (34.5)	**0.002**	< **0.001**	< **0.001**

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FEV$_1$, forced expiratory volume in 1 second; mMRC, modified Medical Research Council dyspnea scale; NLF, normal lung function; P^a comparing men and women in NLF and COPD, respectively; P^b comparing NLF and COPD among men; P^c comparing NLF and COPD among women; SD, standard deviation.

DM, and A/D independently increased the risk of death among subjects with COPD, and the pattern was fairly similar in NLF with regard to DM and A/D, whereas the results indicate that the risk of death associated with CVD was less pronounced (Table 2). When FEV$_1$ % of predicted was included in the model, the increased risk of death associated with these comorbidities persisted with a similar pattern (Table 2).

Sex stratified analyses were performed with corresponding adjustment and are illustrated in Figure 2; among those with COPD the pattern indicate that CVD is of greater importance for

Table 2. Comorbidities analyzed as risk factors for death, expressed as HR, 95% CI among subjects with NLF, COPD, and LLN-COPD. The Cox regression models are adjusted for age, body mass index categories, and smoking habits, additionally in models marked as * also for FEV$_1$ % of predicted. Significant HRs are shown in bold.

	NLF	COPD	LLN-COPD
	$n = 742$	$n = 736$	$n = 341$
Variables	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cardiovascular disease	1.20 (0.87–1.65)	**1.58 (1.23–2.02)**	**1.56 (1.09–2.22)**
Diabetes mellitus	1.46 (0.95–2.26)	**1.50 (1.07–2.10)**	1.65 (0.99–2.73)
Anxiety/depression	**1.54 (1.03–2.30)**	**1.59 (1.20–2.11)**	**1.51 (1.02–2.23)**
	NLF*	COPD*	LLN-COPD*
Cardiovascular disease	1.16 (0.85–1.60)	**1.50 (1.17–1.92)**	**1.62 (1.14–2.29)**
Diabetes mellitus	1.43 (0.92–2.22)	**1.40 (1.00–1.97)**	1.44 (0.87–2.40)
Anxiety/depression	**1.60 (1.07–2.39)**	**1.54 (1.16–2.04)**	**1.53 (1.03–2.28)**

CI, confidence interval; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; FEV$_1$, forced expiratory volume in 1 second; LLN, lower limit of normal; NLF, normal lung function.
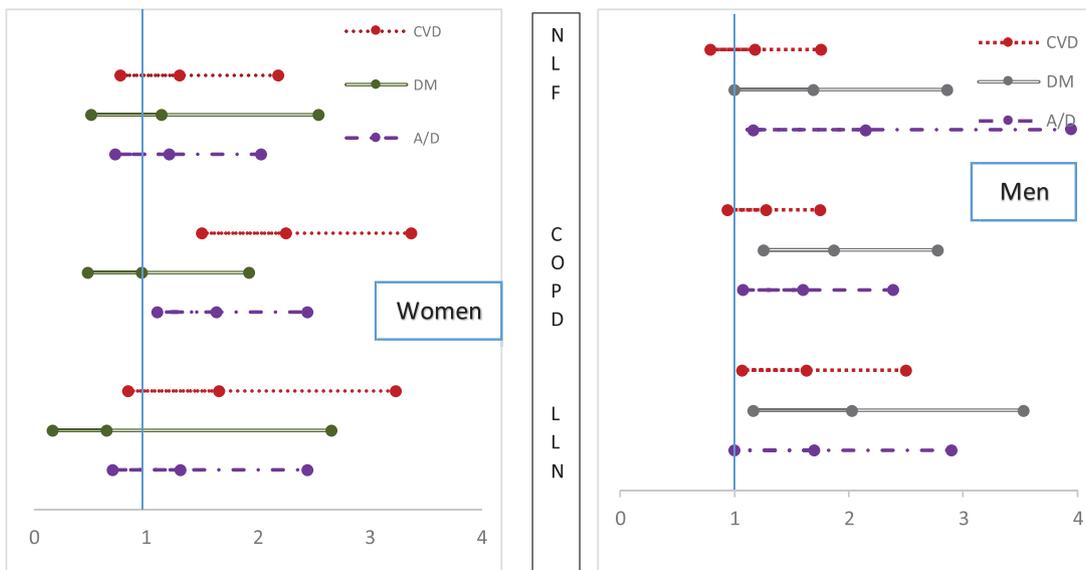

Figure 2. Cardiovascular disease (CVD), diabetes mellitus (DM), and anxiety/depression (A/D) analyzed as risk factors for death, expressed as hazard ratio (HR) and 95% confidence interval (CI), in a Cox regression model adjusting for age, smoking habits, and body mass index categories; analyses stratified for sex and spirometric groups, normal lung function (NLF), chronic obstructive pulmonary disease (COPD), and lower limit of normal (LLN)-COPD.

mortality among women than men, and DM of greater importance among men, whereas A/D increase the risk for death in both sexes. Among those with NLF, all comorbidities seem to be of low importance as risk factors for death among women, whereas DM and A/D may be of greater importance than CVD among men. These results persisted with a similar pattern in additional analyses additionally adjusted for FEV$_1$ % of predicted.
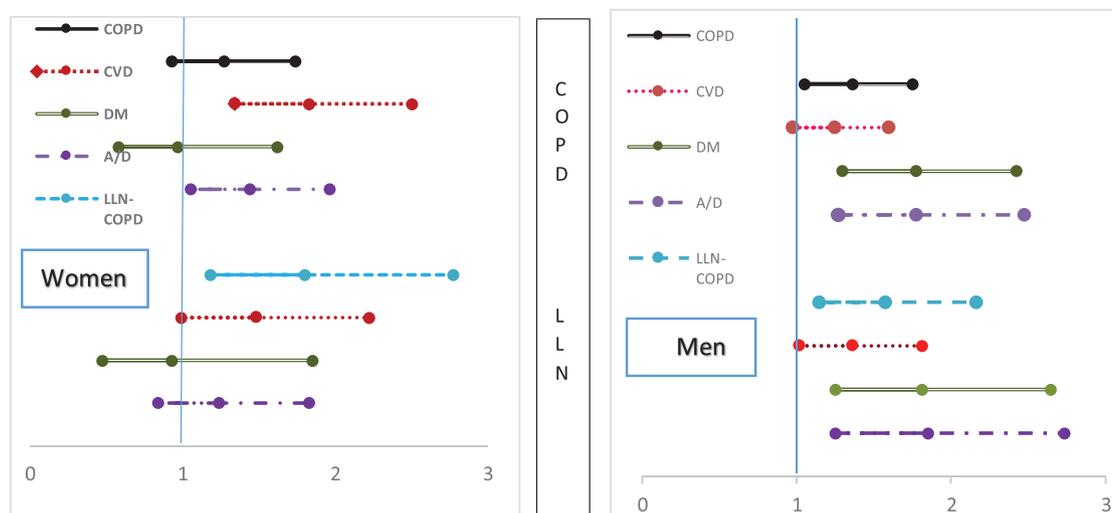
Figure 3. Chronic obstructive pulmonary disease (COPD) and lower limit of normal (LLN)-COPD, respectively, analyzed as risk factors for death compared with normal lung function (NLF) in the presence of the comorbidities under study [cardiovascular disease (CVD), diabetes mellitus (DM), and anxiety/depression (A/D)], expressed as hazard ratio (HR), 95% confidence interval (CI), among men and women in a Cox regression model adjusting for age, smoking habits, and body mass index (BMI) categories.

Analyses using the LLN-COPD criterion

Among those with COPD 341 individuals (46.3%) fulfilled the LLN-COPD criterion, whereof 126 (37.0%) were women. Comparing comorbidities by sex in LLN-COPD confirmed the pattern observed for fixed ratio defined COPD, and the cumulative mortality among those with LLN-COPD was also higher than in NLF in both sexes, although not significantly so (Supplementary Table S1). The mortality rate per 1000 person-years was 44.0 among men and 38.7 among women with LLN-COPD. As in COPD, each of the comorbidities independently increased the risk for death among subjects with LLN-COPD (Table 2). In analyses stratified for sex, each of the comorbidities increased the risk of death among men with LLN-COPD, whereas the pattern among women with LLN-COPD indicates that merely CVD was a risk factor for death, however nonsignificantly so (Figure 2).

COPD and LLN-COPD as risk factors for death when compared with NLF

Among women, LLN-COPD, but not COPD, was associated with an increased risk of death independent of comorbidities when compared with NLF. In corresponding analyses performed among men, both COPD and LLN-COPD were, independent of comorbidities, associated with an increased risk of death when compared with NLF (Figure 3).

Discussion

In this population-based study, the cumulative mortality was, as expected, higher among men than women, and higher among those with COPD than among those with NLF. However, there was a discrepancy between the prevalence of comorbidities and the impact on mortality among men and women with COPD. Although men had a higher prevalence of CVD than women, CVD was more strongly related to mortality among women than among men. A/D seems to be of similar importance for mortality in both sexes, even though the prevalence was twice as high among women.

Comorbidities are common in COPD, however, the prevalence of comorbidities varies strongly between studies, mainly dependent on the selection of the study population, definition of airway obstruction, and age.[9,24,25] In a French study, in which COPD was identified by prescription of inhalation drugs, up to 68.4% had any of the major comorbidities CVD, DM, or depression.[26] In our study just over 40% of those with COPD reported any of these comorbidities. The differences are probably related to the dominance of

mild-to-moderate COPD in population-based studies, these subjects are, owing to the known underdiagnosis of COPD, less represented in register-based studies. Our study confirms that A/D is more common among women,[3,13,14] and that CVD is more common among men.[13,14] According to register based studies, the results are more contradictory with regard to DM,[14,26] whereas in our population-based study DM was more common among men than women with COPD.

The global burden of COPD is high[27] and it is well known that COPD is associated with increased mortality.[4,5,28] The major comorbidities under study have each in different studies been associated with increased mortality in subjects with COPD: CVD,[29,30] DM,[31] and depression.[32,33] The question regarding comorbidities and the impact on mortality among individuals with COPD has more often been addressed in cohorts with COPD patients,[34,35] whereas few studies evaluate the prognostic impact of common comorbidities at the same time in population-based studies. One large population-based US study included evaluation of CVD, DM, and/or hypertension, and the risk of death increased by number of comorbidities, and also by COPD severity.[1] However, COPD was defined by pre-bronchodilator spirometry, hypertension but not anxiety/depression was included as a comorbid condition, and no sex-specific data was reported. Still, in contrast with the US study,[1] the increased risk for death associated with comorbidities in our study was independent of COPD severity, when assessed as FEV_1 % of predicted.

The analyses stratified for sex indicate that the prognostic impact of the studied comorbidities differs between sexes among those with COPD. Even though CVD was more common among men with COPD, it may be of greater importance as a risk factor for death among women. CVD is under-recognized and undertreated among women,[36] and a possible explanation for our results may be that self-reported CVD among women represents a more severe and poorly treated disease. Even though A/D was twice as common among women with COPD, the impact on mortality was similar, the risk for death increased by around 60% in both sexes. These results could, in turn, possibly relate to underreporting or under-recognition of A/D among men. In a large-scale study based on the UK General Practice Research Database,[37] the incidence of depression was higher in women than in men with COPD, but the 1 year mortality among incident cases was higher in men. DM was more common among men than women with COPD and was also associated with increased mortality among men but not women. For comparison, the previously referred French study based on data from the national register of beneficiaries (patients) covered by the French health system, CVD, DM, and depression increased the risk of death similarly in men and women with COPD by 20%, 20%, and 40%, respectively.[26] Still, in this register-based study, most likely more severe cases of COPD were included among which a respiratory cause of death is more common.

When the LLN-COPD spirometric criterion was applied, the different pattern among men and women was similar as observed when using the GOLD fixed ratio criterion. Despite low statistical power in these subanalyses, it seemed useful to proceed with further analyses regarding the potential impact of spirometric criteria. Women with LLN-COPD, in contrast to those with fixed ratio COPD, had an increased risk of death when compared with NLF, independent of comorbidities. These results indicate that the LLN criterion identifies a population among women where the studied comorbidities seem to be of less importance than the respiratory condition. Men had a different pattern: both COPD and LLN-COPD increased the risk of death when compared with NLF independent of comorbidities.

The strength of this study is the population-based study design, including a large cohort of subjects fulfilling post-bronchodilator spirometric criteria for COPD, thus the results are generalizable to the general population. The reference values are locally derived, which should minimize the risk for misclassification when applying the LLN criterion. Most clinical guidelines for diagnostics and treatment of COPD are based on the fixed ratio (GOLD) criterion,[38] whereas the LLN criterion is recommended for epidemiological studies.[39] As a consequence, there is a need to understand the outcome of both criteria and the potential differences between them in addition to those related to age. Furthermore, stratified analyses are needed to understand sex-dependent differences in risk factor pattern, and the statistical power was large enough to demonstrate such differences.

However, there are some important limitations of in the current study that merit discussion. Information regarding comorbidities was based on interview data and not verified by medical records. Still, there is fairly good agreement between self-reported data on comorbidities and medical records, even though A/D seems to be less studied in this regard.[40–43] The study was designed shortly after the shift of the millennium when the fixed ratio was generally accepted after the launch of the GOLD document, and in our study subjects fulfilling the spirometric criterion for COPD according to GOLD were labeled COPD. However, fulfilling the spirometric criterion for COPD is not synonymous with the disease COPD, and it is, for example, well known that the fixed ratio criterion will overestimate COPD among the elderly.[44] Furthermore, when applying the LLN criterion in a population identified by the fixed ratio criterion, a few cases, especially among younger people, will be missing compared with when applying the LLN criterion in a general population. In addition, the number of missing answers for DM, A/D, and claudication were rather high, 11.5–13.9%, however, missing was recoded as negative answer, meaning that the observed relationships with regard to these comorbidities most probably were underestimated.

In conclusion, there was a sex-dependent discrepancy regarding the prevalence of CVD and A/D and the observed pattern of impact on mortality among individuals with COPD. Although the prevalence of CVD was higher in men, the impact on mortality appeared to be greater among women, and although the prevalence of A/D was twice as high in women, the impact on mortality was similar in both sexes. Our study highlights new aspects on possible sex-dependent differences regarding the association between comorbidities and mortality in COPD. A sex-specific risk assessment could be a step towards optimized preventive measures and treatment of comorbidities in COPD.

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Supplemental material
Supplemental material for this article is available online.

References
1. Mannino DM, Thorn D, Swensen A, *et al*. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32: 962–969.

2. Lin CS, Liu CC, Yeh CC, *et al*. Diabetes risks and outcomes in chronic obstructive pulmonary disease patients: two nationwide population-based retrospective cohort studies. *PLoS One* 2017; 12: e0181815.

3. Hanania NA, Mullerova H, Locantore NW, *et al*. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort. *Am J Respir Crit Care Med* 2011; 183: 604–611.

4. Lindberg A, Larsson LG, Muellerova H, *et al*. Up-to-date on mortality in COPD - report from the OLIN COPD study. *BMC Pulm Med* 2012; 12: 1.

5. Gayle AV, Axson EL, Bloom CI, *et al*. Changing causes of death for patients with chronic respiratory disease in England, 2005–2015. *Thorax* 2019; 74: 483–491.

6. Lamprecht B, Soriano BJ, Studnicka M, *et al*.; Buist S for the BOLD Collaborative Research Group, the EPI-SCAN Team, the PLATINO Team, and the PREPOCOL Study Group. Determinants of underdiagnosis of COPD in national and international surveys. *Chest* 2015; 148: 971–985.

7. Lindberg A, Bjerg A, Ronmark E, *et al*. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking report from the Obstructive Lung disease In Northern Sweden studies. *Respir Med* 2006; 100: 264–272.

8. Sin DD, Anthonisen NR, Soriano JB, *et al.* Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; 28: 1245–1257.

9. Marcon A, Saugo M and Fedeli U. COPD-related mortality and co-morbidities in northeastern Italy, 2008–2012: a multiple causes of death analysis. *COPD* 2016; 13: 35–41.

10. Sørheim IC, Johannessen A, Gulsvik A, *et al.* Gender differences in COPD: are women more susceptible to smoking effects than men? *Thorax* 2010; 65: 480–485.

11. Backman H, Eriksson B, Rönmark E, *et al.* Decreased prevalence of moderate to severe COPD over 15 years in northern Sweden. *Respir Med* 2016; 114: 103–110.

12. Eriksson B, Backman H, Ekerljung L, *et al.* Pattern of cardiovascular comorbidity in COPD in a country with low-smoking prevalence: results from two-population-based cohorts from Sweden. *COPD* 2018; 26: 1–10.

13. Aryal S, Diaz-Guzman E and Mannino DM. Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. *Int J Chron Obstruct Pulmon Dis* 2014; 9: 1145–1154.

14. Agusti A, Calverley PM, Celli B, *et al.* Characterisation of COPD heterogeneity in the ECLIPSE cohort. *Respir Res* 2010; 11: 122.

15. Di Marco F, Verga M, Reggente M, *et al.* Anxiety and depression in COPD patients: the roles of gender and disease severity. *Respir Med* 2006; 100: 1767–1774.

16. Lindberg A and Lundback B. The obstructive lung disease in northern Sweden chronic obstructive pulmonary disease study: design, the first year participation and mortality. *Clin Respir J* 2008; 2(Suppl. 1): 64–71.

17. Lundback B, Stjernberg N, Nystrom L, *et al.* An interview study to estimate prevalence of asthma and chronic bronchitis. The obstructive lung disease in northern Sweden study. *Eur J Epidemiol* 1993; 9: 123–133.

18. Lundbäck B, Stjernberg N, Nyström L, *et al.* Epidemiology of respiratory symptoms, lung function and important determinants: report from the Obstructive Lung disease In Northern Sweden project. *Tubercle Lung Dis* 1994; 75: 116–126.

19. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152: 1107–1136.

20. Vogelmeier CF, Criner GJ, Martinez FJ, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Eur Respir J* 2017; 49: 1700214.

21. Backman H, Lindberg A, Oden A, *et al.* Reference values for spirometry - report from the obstructive lung disease in northern Sweden studies. *Eur Clin Respir J* 2015; 2: 26375.

22. World Health Organization. *Physical status: the use and interpretation of anthropometry*. Report of a WHO Expert Committee. WHO Technical Report Series 854. Geneva: World Health Organization, 1995.

23. Bestall JC, Paul EA, Garrod R, *et al.* Usefulness of the Medical Research Council (MRC) dyspnoea scales a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax* 1999; 54: 581–586.

24. Chatila WM, Thomashow BM, Minai OA, *et al.* Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5: 549–555.

25. Mattila T, Vasankari T, Kanervisto M, *et al.* Association between all-cause and cause-specific mortality and the GOLD stages 1-4: a 30-year follow-up among Finnish adults. *Respir Med* 2015; 109: 1012–1018.

26. Laforest L, Roche N, Devouassoux G, *et al.* Frequency of comorbidities in chronic obstructive pulmonary disease, and impact on all-cause mortality: a population-based cohort study. *Respir Med* 2016; 117: 33–39.

27. López-Campos JL, Tan W and Soriano JB. Global burden of COPD. *Respirology* 2016; 21: 14–23.

28. Burney PG, Patel J, Newson R, *et al.* Global and regional trends in COPD mortality, 1990-2010. *Eur Respir J* 2015; 45: 1239–1247.

29. Nilsson U, Blomberg A, Johansson B, *et al.* Ischemic ECG abnormalities are associated with an increased risk for death among subjects with COPD, also among those without known heart disease. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 2507–2514.

30. Zhang J, Rutten FH, Cramer MJ, *et al.* The importance of cardiovascular disease for mortality in patients with COPD: a prognostic cohort study. *Fam Pract* 2011; 28: 474–481.

31. Ho TW, Huang CT, Ruan SY, *et al.* Diabetes mellitus in patients with chronic obstructive pulmonary disease-the impact on mortality. *PLoS One* 2017; 12: e0175794.

32. de Voogd JN, Wempe JB, Koeter GH, *et al.* Depressive symptoms as predictors of mortality in patients with COPD. *Chest* 2009; 135: 619–625.

33. Lou P, Zhu Y, Chen P, *et al*. Interaction of depressive and anxiety symptoms on the mortality of patients with COPD: a preliminary study. *COPD* 2014; 11: 444–450.

34. Divo M, Cote C, de Torres JP, *et al*.; BODE Collaborative Group. Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 186: 155–161.

35. Holguin F, Folch E, Redd SC, *et al*. Comorbidity and mortality in COPD-related hospitalizations in the United States, 1979 to 2001. *Chest* 2005; 128: 2005–2011.

36. Maas AH, van der Schouw YT, Regitz-Zagrosek V, *et al*. Red alert for women's heart: the urgent need for more research and knowledge on cardio-vascular disease in women: proceedings of the workshop held in Brussels on gender differences in cardiovascular disease, 29 September 2010. *Eur Heart J* 2011; 32: 1362–1368.

37. Schneider C, Jick SS, Bothner U, *et al*. COPD and the risk of depression. *Chest* 2010; 137: 341–347.

38. Miravitlles M, Vogelmeier C, Roche N, *et al*. A review of national guidelines for management of COPD in Europe. *Eur Respir J* 2016; 47: 625–637.

39. Bakke PS, Rönmark E, Eagan T, *et al*.; European Respiratory Society Task Force. Recommendations for epidemiological studies on COPD. *Eur Respir J* 2011; 38: 1261–1277.

40. Okura Y, Urban LH, Mahoney DW, *et al*. Agreement between self-report questionnaires and medical record data was substantial for diabetes, hypertension, myocardial infarction and stroke but not for heart failure. *J Clin Epidemiol* 2004; 57: 1096–1103.

41. Machon M, Arriola L, Larranaga N, *et al*. Validity of self-reported prevalent cases of stroke and acute myocardial infarction in the Spanish cohort of the EPIC study. *J Epidemiol Community Health* 2013; 67: 71–75.

42. Klungel OH, de Boer A, Paes AH, *et al*. Cardiovascular diseases and risk factors in a population-based study in the Netherlands: agreement between questionnaire information and medical records. *Neth J Med* 1999; 55: 177–183.

43. Sanchez-Villegas A, Schlatter J, Ortuno F, *et al*. Validity of a self-reported diagnosis of depression among participants in a cohort study using the structured clinical interview for DSM-IV (SCID-I). *BMC Psychiatry* 2008; 8: 43-244X-8-43.

44. Hardie JA, Buist AS, Vollmer WM, *et al*. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002; 20: 1117–1122.