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Comorbid Heart Disease in Patients with COPD is Associated with Increased Hospitalization and Mortality – A 15-Year Follow-Up

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Purpose: The aim of this study was to examine the association of comorbid heart disease, defined as chronic heart failure or ischemic heart disease, on all-cause and cause-specific hospitalization and mortality in patients with COPD over a period of nearly 15 years.

Materials and Methods: The cohort study included patients with COPD from primary and secondary care in 2005 with data from questionnaires and medical record reviews. The Swedish Board of Health and Welfare provided hospitalization and mortality data from 2005 through 2019. Cox regression analyses, adjusted for sex, age, educational level, smoking status, BMI, exacerbations, dyspnea score and comorbid diabetes or hypertension, assessed the association of comorbid heart disease with all-cause and cause-specific time to first hospitalization and death. Linear regression analyses, adjusted for the same variables, assessed this association with hospitalization days per year for those patients that had been hospitalized.

Results: Of the 1071 patients, 262 (25%) had heart disease at baseline. Cox regression analysis showed a higher risk of hospitalization for patients with heart disease for all-cause (HR (95% CI) 1.55; 1.32–1.82), cardiovascular (2.14; 1.70–2.70) and other causes (1.27; 1.06–1.52). Patients with heart disease also had an increased risk of all-cause (1.77; 1.48–2.12), cardiovascular (3.40; 2.41–4.78) and other (1.50; 1.09–2.06) mortality. Heart disease was significantly associated with more hospitalization days per year of all-cause (regression coefficient 0.37; 95% CI 0.15–0.59), cardiovascular (0.57; 0.27–0.86) and other (0.37; 0.12–0.62) causes. No significant associations were found between heart disease and respiratory causes of hospitalization and death.

Conclusion: Comorbid heart disease in patients with COPD is associated with an increased risk for all-cause hospitalization and mortality, mainly due to an increase of hospitalization and death of cardiovascular and other causes, but not because of respiratory disease. This finding advocates the need of a strong clinical focus on primary and secondary prevention of cardiovascular disease in patients with COPD.

Keywords: chronic obstructive pulmonary disease, comorbidity, chronic heart failure, ischemic heart disease, hospitalization, mortality

Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease and is now the third cause of death worldwide.[1,2] Patients with COPD often experience periods of acute worsening of symptoms requiring emergency visits and additional medication. In severe cases, these exacerbations require hospitalization. Patients with COPD often have other chronic

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diseases and in particular, they have a two to five times higher risk of developing heart disease.[3] The observed association between COPD and heart disease can partly be explained by shared risk factors such as smoking, age, and inactivity. However, it is also plausible that a systemic inflammatory process related to COPD independently increases the risk of heart disease.[4] Cardiovascular diseases are a major cause of death in patients with COPD.[5,6] Multimorbidity involving COPD and heart disease has been found to lead to a higher risk for hospitalization and mortality.[7–10] COPD has been shown to trigger incident cardiovascular events and worsen existing heart disease.[11,12] Conversely, it has also been shown that heart disease is associated with more COPD exacerbations.[13–15] However, not all studies found an increased risk for hospitalization and mortality in patients with COPD and comorbid heart disease.[16,17] It is still unclear how comorbid heart disease in patients with COPD influences the specific causes of death and hospitalization in an unselected population over a longer period of time.

The aim of this study was to examine the association of comorbid heart disease on all-cause and cause-specific hospitalization and mortality in a cohort of patients with COPD over a period of nearly 15 years.

Materials and Methods

Data Collection

The data was obtained from the PRAXIS study, that is based on data from 14 hospitals and 56 primary health care centers in central-Sweden.[18] In total, 1548 patients were randomly selected from lists with patients aged 34–75 years with an ICD 10 diagnosis code J44 for COPD recorded in their medical records during 2000–2003. The random selection was made from the respective health care unit's diagnosis list by a research nurse, using an internet-based program (https://www.random.org). A questionnaire was sent to these patients between April 2005 and January 2006; 1071 (69%) returned the questionnaire and agreed to a review of their medical records. In Sweden, a personal identity number gives the opportunity to combine study data with the national patient register and mortality register. The Swedish Board of Health and Welfare links the study data with the register data and returns an anonymized dataset. In this way, we obtained hospitalization and mortality data on our participating patients for the period 2005 through 2019. This data included information about the date and underlying cause of death, date(s) and main cause(s) of hospitalization and information about number of days spent in hospital.

Study entry was defined as the date when the patient's questionnaire was sent out. For hospitalization analysis, follow-up time was defined as the time from study entry until the first hospitalization or death or the end of the study 31 December 2019. Follow-up time for mortality analysis was defined as the time from study entrance until death or the end of the study on 31 December 2019.

Patient Characteristics and Measures

The medical records were reviewed for the period 2000–2003. In this study "heart disease" was defined as a doctor's diagnosis of ischemic heart disease and/or heart failure in the medical record. This could be an at least once registered ICD-10 diagnosis code for ischemic heart disease (I20-I25) or heart failure (I50) or mentioning of these diagnoses in the written medical record. The review also gave information on a doctor's diagnosis of hypertension, depression, diabetes, and data on lung function. The study population was divided into two groups: patients with and patients without a comorbid heart disease. In the 542 (51%) patients whose spirometry data were available at baseline, COPD was graded according to the Global initiative for Obstructive Lung Disease (GOLD) criteria, based on forced expiratory volume in one second expressed as a percentage of the predicted values (FEV1%pred).[1,19]

The patient questionnaires that were sent out in 2005 provided information on age, sex, smoking status, level of education, exacerbations in the previous six months, height and weight. Patients rated their level of dyspnea by using the modified Medical Research Council dyspnea scale (mMRC). The mMRC has five points ranging from 0 = I only get breathless with strenuous exercise, to 4 = too breathless to leave the house or breathless when dressing or undressing.[20]

Age at baseline was categorized in three groups: ≤60 years, 61–70 and >70 years. Smoking status was categorized into current daily smoking and not current daily smoking. The latter group included patients that never smoked, had stopped smoking, or smoked occasionally. The dichotomous educational variable identified the most highly educated

group as those who had continued in full-time education for at least 2 years beyond the Swedish compulsory school period of 9 years. An exacerbation of COPD was defined as an emergency visit or need of a course of oral steroids due to worsening of COPD symptoms, during the six months prior to filling out the questionnaire. Self-reported height and weight were used to calculate body mass index (BMI) in kg/m^2. Underweight was defined as a BMI <20, normal weight as a BMI ≥20 and <25, overweight as BMI ≥25 and <30 and obesity as BMI ≥30.

Register data on cause-specific hospitalization and mortality were categorized as "respiratory" (ICD-10 code J XX), "cardiovascular" (ICD-10 code I XX) and "other" causes using the ICD 10 classification of the given main diagnosis in the registers.

Statistical Analysis

Categorical data were expressed by frequencies and percentages and continuous data by means and standard deviations (SD) for normally distributed data or median and interquartile range (IQR) for skewed data. The Chi-square test, Student's *t*-test and Mann Whitney *U*-test were used to analyze the differences between patients with and without heart disease.

Kaplan–Meier (KM) curves indicated that the proportional hazards assumption was justified for mortality data (Figure 1B). Because of convergence of the lines of the KM curve later in the study period, truncation after eight years was used as a sensitivity analysis (Figure 1A). This truncated analysis gave similar results, dismissing the potential violation of the proportional hazards assumption (data not shown). Cox regression was used to assess univariate associations with hospitalization and mortality for baseline data on heart disease, age, sex, smoking status, level of education, a diagnosis of diabetes, depression, hypertension, BMI groups, exacerbations, mMRC and FEV1%pred. All variables significant at $p < 0.05$, except FEV1%pred, were included in a multivariate analysis. This analysis with addition of the FEV1%pred variable was repeated in the subgroup with available spirometry data. Cause-specific hospitalization and mortality associations with comorbid heart disease were assessed by Cox regression analysis with the same variables as in the all-cause mortality and hospitalization analysis. Results were presented as hazard ratios (HR) with 95% confidence intervals (CI). Hospitalization days per year were calculated by dividing the number of days the patient was hospitalized during the study period with the total number of days of the patient's follow-up time and multiply it by 365. Those who had not been hospitalized were excluded from this assessment. Because of skewness, the data were log transformed. Age, BMI and mMRC groups were modeled as series of binary dummy variables. Unadjusted and adjusted linear regression analysis with hospitalization days per year as dependent variable were assessed as described for the Cox regression. Results were presented as regression coefficients with 95% CI.

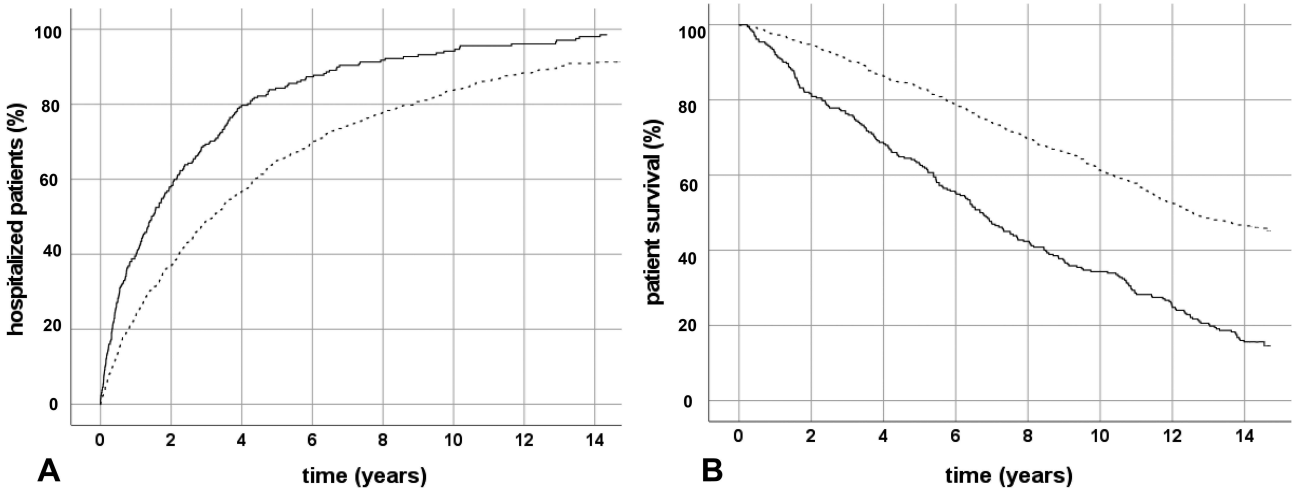

Figure 1 Kaplan Meier curves for patients with COPD with and without comorbid heart disease for all-cause hospitalization (**A**) and mortality (**B**). Solid line: patients with comorbid heart disease, dotted line: patients without comorbid heart disease.

Stratification and multiplicative interaction analyses investigated the potential effect of modification by sex and age for all regression analyses. A dichotomized age variable with age ≤65 and >65 years was used for this purpose.

For all analyses, SPSS version 28 was used. A p value of <0.05 was considered significant.

Ethics

The study was approved by the Regional Ethical Review Board of Uppsala (Dnr 2004:M-445, Dnr 2010/090, Dnr 2011/318, Dnr 2020–00270) and complies with the Declaration of Helsinki. Written informed consents were obtained from all participating patients.

Results

The KM curves for all-cause hospitalization and mortality are given in Figure 1A and B. The flow chart shows the selection procedure and hospitalization and mortality rates till the end of the study (Figure 2). Of the 1071 participating patients, 262 (25%) had heart disease at baseline. More men than women had comorbid heart disease. Patients with comorbid heart disease had a significantly higher mean age, lower level of education, higher BMI and higher mMRC score than patients without comorbid heart disease. They were also more often selected from secondary care, had more exacerbations and additional comorbid diabetes and hypertension (Table 1). Spirometry data were available for 542 (51%) of all the participating patients. These patients were younger, more often selected from hospital care, had a higher education, and less comorbid diabetes or hypertension than those without spirometry data (Supplementary Table 1).

Hospitalization

Patients with comorbid heart disease had more often been hospitalized and had more hospitalization days per year (Table 2). Of the patients without heart disease at baseline, 285 (35%) were hospitalized for a cardiovascular disease during the study period (Table 2). Adjusted Cox regression analysis showed that comorbid heart disease was significantly associated with higher risk for all-cause, cardiovascular, and other causes of hospitalization, but not for respiratory hospitalization (Table 3). These associations were also found for the adjusted linear regression analysis for hospitalization days per year (Table 3).

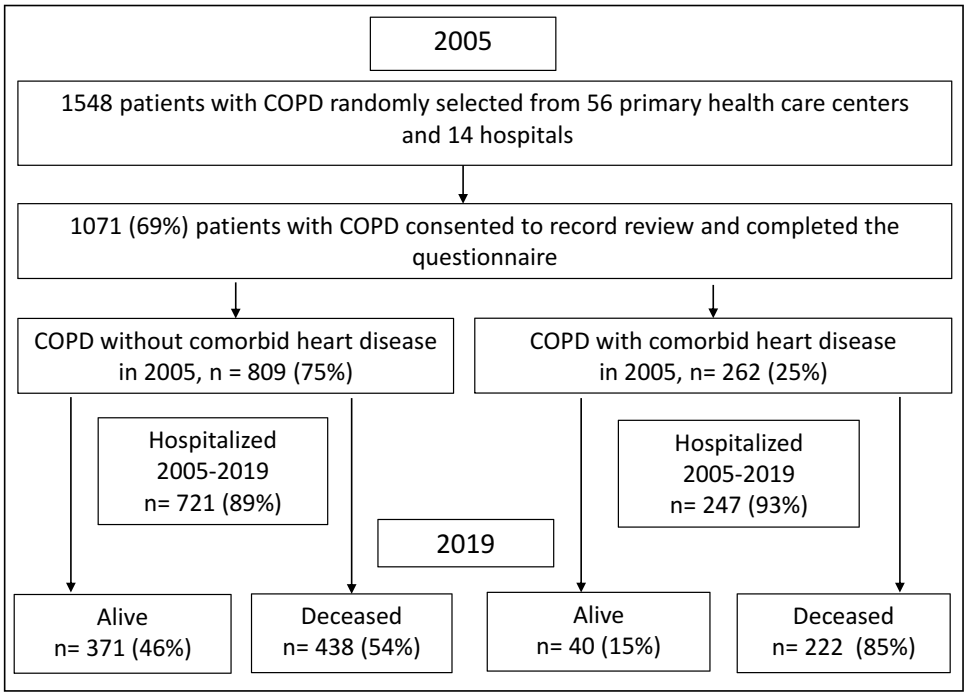

Figure 2 Patient flow chart from 2005 through 2019. Heart disease is defined as a doctor's diagnosis of ischemic heart disease or chronic heart failure.

Table 1 Baseline Characteristics for Patients with COPD without and with a Diagnosis of Heart Disease (n = 1071)

	No Heart Disease n=809 (75%)	Comorbid Heart Disease n=262 (25%)	*p*-value
Sex, n (%)			< 0.001
Men	309 (38)	140 (53)	
Women	500 (62)	122 (47)	
Mean age, years (SD)	64 (8)	67 (6)	< 0.001
Age-groups, n (%)			< 0.001
≤ 60	238 (29)	34 (13)	
61–70	410 (51)	133 (51)	
>70	161 (20)	95 (36)	
Education level (n=1049), n (%)			0.01
Low	522 (66)	198 (77)	
High	271 (34)	58 (23)	
Level of care, n (%)			< 0.001
Hospital care	208 (26)	104 (40)	
Primary care	601 (74)	158 (60)	
Depression, n (%)	98 (12)	29 (11)	0.65
Diabetes, n (%)	66 (8)	36 (14)	0.007
Hypertension, n (%)	201 (25)	93 (36)	0.001
BMI (n=1053), n (%)			0.009
Underweight	93 (12)	22 (9)	
Normal weight	287 (37)	78 (31)	
Overweight	271 (35)	85 (34)	
Obesity	134 (17)	66 (26)	
Current daily smoking (n=1069)	239 (30)	67 (26)	0.23
FEV1%pred (n=542), n (%)			0.30
≥ 80%	85 (21)	18 (14)	
50–79%	175 (42)	55 (42)	
30–49%	111 (27)	42 (32)	
<30%	41 (10)	15 (11)	
Exacerbation in the previous 6 months, n (%)	288 (36)	112 (44)	0.03
mMRC (n=1031), n (%)			< 0.001
0–1	358 (46)	79 (31)	
2	122 (16)	41 (16)	
3	112 (15)	42 (16)	
4	182 (23)	95 (37)	

Note: Exacerbation was defined as an unplanned health care visit or course of oral steroids.
Abbreviations: SD, standard deviation; BMI, body mass index; FEV1%pred, forced expiratory volume in one second as percentage of the predicted value; mMRC, modified Medical Research Council dyspnea score.

In the subgroup with available spirometry data, the same associations were found, except for that there were no significant associations for comorbid heart disease with all-cause hospitalization days, as well as other causes of hospitalization and mortality (Supplementary Table 2). Differences between men and women in HR and statistical significance of association of comorbid heart disease and hospitalization were found. However, interaction analysis was

Table 2 Cause-Specific Hospitalization Days per Year, Hospitalization and Mortality for 2005 Through 2019 for Patients with COPD with and without Comorbid Heart Disease

	No Heart Disease n=809	Comorbid Heart Disease n=262	*p*-value
Hospitalization days per year			
Respiratory, median (IQR)	2.03 (0.68–6.62)	3.39 (0.93–7.66)	0.03
Cardiovascular, median (IQR)	0.69 (0.28–1.72)	1.72 (0.55–4.57)	<0.001
Other, median (IQR)	1.44 (0.54–3.82)	2.79 (1.11–7.63)	<0.001
Hospitalization			
Respiratory, n (%)	403 (53)	153 (58)	0.02
Cardiovascular, n (%)	285 (35)	133 (51)	<0.001
Other, n (%)	543 (67)	207 (79)	<0.001
Mortality			
Respiratory, n (%)	192 (24)	71 (27)	0.003
Cardiovascular, n (%)	83 (10)	85 (32)	<0.001
Other, *n (%)*	163 (20)	66 (25)	0.06

Note: For the calculation of hospitalization days per year, non-hospitalized patients have been excluded.
Abbreviation: IQR, inter quartile range.

not statistically significant (Table 4). The interaction analyses showed no statistically significant effect modification by age for any of the associations (data not shown).

Mortality

The mortality rate was significantly higher in the group with comorbid heart disease (Table 2). Of the patients without heart disease at baseline, 83 (10%) died of a cardiovascular cause (Table 2). Adjusted Cox-regression showed that comorbid heart disease was significantly associated with a higher risk of all-cause, cardiovascular, and other reasons of mortality, but not respiratory mortality (Table 3). In the subgroup with available spirometry data, similar associations were found, except for the association between heart disease and other causes of death (Supplementary Table 2). Differences between men and women in association of comorbid heart disease with mortality were found. However, interaction analysis was not statistically significant (Table 3). The interaction analyses showed no statistically significant effect modification by age for any of the associations (data not shown).

Discussion

The main finding of this multicenter cohort study with nearly 15 years of follow-up period was that comorbid heart disease was associated with increased all-cause hospitalization and mortality in patients with COPD. Our study indicated that this was due to cardiovascular and other causes of hospitalization and mortality. We also found that comorbid heart disease did not increase hospital admission because of respiratory disease and respiratory related mortality.

Our finding that comorbid heart disease predicts all-cause hospitalization and mortality is in line with several other studies.[9,10,21] Our findings are unique as we showed that the associations between baseline heart disease and hospitalization and mortality remained over the long observation time. As 258 of the 809 patients without comorbid heart disease at baseline were later hospitalized for a cardiovascular disease, we estimate that the total number of patients with comorbid

Table 3 Associations of Comorbid Heart Disease in Patients with COPD with All-Cause and Cause-Specific Hospitalization Days per Year, Hospitalization and Mortality

	Unadjusted Regression Coefficient (95% CI) for Comorbid Heart Disease	***p*-value**	**Adjusted Regression Coefficient (95% CI) for Comorbid Heart Disease**	***p*-value**
Hospitalization days per year				
All-cause	0.70 (0.48–0.92)	<0.001	0.37 (0.15–0.59)	0.001
Respiratory	0.36 (0.07–0.65)	0.02	0.14 (−0.14–0.42)	0.33
Cardiovascular	0.80 (0.52–1.08)	<0.001	0.57 (0.27–0.86)	<0.001
Other	0.61 (0.38–0.84)	<0.001	0.37 (0.12–0.62)	0.004
	Unadjusted Hazard Ratio (95% CI) for Comorbid Heart Disease	***p*-value**	**Adjusted Hazard Ratio (95% CI) for Comorbid Heart Disease**	***p*-value**
Hospitalization				
All-cause	1.76 (1.52–2.04)	<0.001	1.55 (1.32–1.82)	<0.001
Respiratory	1.52 (1.27–1.63)	<0.001	1.18 (0.96–1.45)	0.12
Cardiovascular	2.43 (1.98–3.00)	<0.001	2.14 (1.70–2.70)	<0.001
Other	1.39 (1.19–1.64)	<0.001	1.27 (1.06–1.52)	0.009
Mortality				
All-cause	2.37 (2.02–2.79)	<0.001	1,77 (1,48–2,12)	< 0.001
Respiratory	1.71 (1.30–2.24)	<0.001	1.31 (0.97–1.78)	0.08
Cardiovascular	4.69 (3.46–6.37)	<0.001	3.40 (2.41–4.78)	<0.001
Other	1.96 (1.47–2.61)	<0.001	1.50 (1.09–2.06)	0.01

Notes: Results for comorbid heart disease from uni- and multivariate linear regression analysis for all-cause and cause-specific hospitalization days per year and Cox regression analysis for all-cause and cause-specific hospitalization and mortality. Adjusted for age-group, sex, daily smoking, level of education, BMI group, exacerbations in the previous six months, hypertension, diabetes and mMRC at baseline. For the calculation of hospitalization days per year, non-hospitalized patients have been excluded.
Abbreviations: CI, confidence interval; BMI, body mass index; mMRC, medical research council dyspnea score.

heart disease may have doubled in size during the study period. This finding emphasizes the importance of primary and secondary prevention of cardiovascular disease in patients with COPD.

We found that comorbid heart disease did not increase the risk of hospitalization and mortality due to respiratory disease. A significant increase might have been expected, since several studies have found that cardiovascular comorbidity increases the risk of COPD exacerbations.[13–15] However, other researchers have discussed that comorbidity in COPD mainly affects non-COPD related death and hospitalizations.[22,23] The result of our study confirms this finding for comorbid heart disease in patients with COPD.

Additionally, we found that comorbid heart disease at baseline also predicted hospitalization and mortality of other causes. One explanation for this finding is that patients with COPD and heart disease often even have multiple other comorbidities.[24]

The number of hospitalized days per year was significantly higher for patients with comorbid heart disease, which can reflect longer hospital stays or more frequent hospitalizations. Other studies have shown that comorbid heart disease increases both frequency and length of stay similar to the results of this study.[7,9,25,26]

Table 4 Sex-Stratification and Interaction Analysis for Associations of Comorbid Heart Disease with Hospitalization Days per Year, Hospitalization and Mortality

	Men		Women		*p*-value for Interaction Analysis
	Adjusted Regression Coefficient (95% CI)	***p*-value**	**Adjusted Regression Coefficient (95% CI)**	***p*-value**	
Hospitalization days per year					
All-cause	0.28 (−0.02–0.59)	0.07	0.47 (0.15–0.80)	0.003	0.30
Respiratory	0.07 (−0.33–0.46)	0.75	0.24 (−0.16–0.65)	0.21	0.58
Cardiovascular	0.31 (−0.10–0.73)	0.14	0.83 (0.39–1.27)	<0.001	0.06
Other	0.33 (−0.03–0.68)	0.07	0.43 (0.06–0.79)	0.02	0.55
	Adjusted HR (95% CI)	***p*-value**	**Adjusted HR (95% CI)**	***p*-value**	***p*-value for Interaction Analysis**
Hospitalization					
All-cause	1.67 (1.33–2.10)	<0.001	1.54 (1.22–1.94)	<0.001	0.60
Respiratory	1.02 (0.76–1.37)	0.89	1.37 (1.03–1.83)	0.03	0.07
Cardiovascular	1.87 (1.36–2.58)	<0.001	2.71 (1.93–3.80)	0.001	0.24
Other	1.21 (0.94–1.59)	0.13	1.36 (1.04–1.76)	0.02	0.27
Mortality					
All-cause	1.67 (1.29–2.15)	<0.001	2.11 (1.63–2.72)	<0.001	0.11
Respiratory	1.14 (0.72–1.81)	0.57	1.54 (1.02–2.31)	0.04	0.15
Cardiovascular	3.03 (1.90–4.81)	<0.001	5.09 (3.02–8.57)	<0.001	0.15
Other	1.49 (0.96–2.31)	0.08	1.74 (1.08–2.78)	0.02	0.67

Notes: Sex-stratified results for the association of comorbid heart disease in patient with COPD from multivariate linear regression analysis for all-cause and cause-specific hospitalization days per year and Cox regression analysis for all-cause and cause-specific mortality and hospitalization. Including the p-value of interaction analysis for sex and heart disease. Adjusted for age-group, daily smoking, level of education, BMI group, exacerbations in the previous six months, hypertension, diabetes and mMRC at baseline. For the calculation of hospitalization days per year, non-hospitalized patients have been excluded.

Abbreviations: CI, confidence interval; HR, hazard ratio; BMI, body mass index; mMRC, medical research council dyspnea score.

Although not significant at interaction analysis, we found trends in gender differences regarding the association of heart disease with hospitalization and death. Women with comorbid heart disease seemed to have a higher HR for cardiovascular hospitalization and death than men. In line with our study, higher impact of heart disease on mortality in women was also reported by a previous Swedish study.[27] Another study found a stronger association of COPD and hospitalization due to cardiac diseases in younger patients and females, suggesting that cardiovascular disease should be monitored and treated with particular care in younger and female patients with COPD.[26] There are indications that women are at higher risk of death from COPD and cardiovascular disease or not benefiting as much as men from advancements in care.[28,29] It is important to have this in mind in daily clinical practice.

Strengths and Limitations

The strength of this study was the long follow-up time, reflecting the chronic nature of COPD. Also, the multicenter design with an unselected patient population from both primary and secondary care increased the generalizability of the results to clinical practice. However, to enable a long follow-up time, an upper age limit of 75 years was set as

a selection criterion at baseline. This resulted in a lower prevalence of comorbid heart disease at baseline than in previous studies in Sweden.[23,24] Generalization of our finding to the elderly COPD population must thus be done with caution.

Another major strength of this study was the availability of register data in Sweden that could be matched to this cohort, giving detailed information on both all-cause and cause-specific hospitalization and mortality. These registers are compulsory and therefore give a nearly complete account of all hospitalizations and deaths.

A limitation, however, of these registers is that the diagnoses are not validated and can be inaccurate. We also only considered the main cause of hospitalization and death, which not always reflects the complexity of clinical reality. The absence of an association between comorbid heart disease and hospitalization and mortality due to respiratory disease in our study might possibly be explained by this uncertain validity of diagnosis coding. COPD-related mortality and morbidity might be underestimated because it was difficult to attribute death and hospitalization to a single cause in the clinical setting. Cardiovascular disease might be prioritized when choosing the main diagnosis or cause of death. Underreporting of COPD as an underlying cause of death is a known problem especially in patients with mild COPD.[30–32]

Another limitation of this study was that spirometry data was not available in half of the patients, which represents daily practice in the beginning of this millennium. The impact of comorbid heart disease on hospitalization and mortality was, however, mainly the same in this subgroup as in the whole group. The absence of an association of heart disease with hospitalization and mortality of other causes in the spirometry group is probably caused by the fact that this group was younger but also that the group consisted of fewer patients, possibly leading to type II error.

Implications for Further Research

We defined heart disease in our study as having a diagnosis of ischemic heart disease and/or chronic heart failure. There are, however, indications that chronic heart failure has a different impact on the clinical outcomes for patients with COPD than ischemic heart disease.[8–10] Even though ischemic heart disease and chronic heart failure often are comorbid diseases, it is worth investigating these two diseases separately in future research.

The recruitment of patients in this study was based on a diagnosis of COPD between 2000 and 2003. Baseline questionnaire information was gathered in 2005. Since then, the diagnostic procedures and treatment of COPD and cardiovascular diseases have improved. It would be valuable to study whether this has changed morbidity and mortality patterns in patients with COPD and to compare with a reference population.

Conclusions

Comorbid heart disease in patients with COPD is associated with an increased risk for all-cause hospitalization and mortality, mainly due to an increase of hospitalization and death of cardiovascular and other causes, but not of respiratory disease. This finding advocates the need of a strong clinical focus on primary and secondary prevention of cardiovascular disease in patients with COPD.

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Disclosure

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