International Journal of Chronic Obstructive Pulmonary Disease Dovepress
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ORIGINAL RESEARCH

The Increased Burden of Morbidity Over the Life-Course Among Patients with COPD: A Register-Based Cohort Study in Sweden

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Purpose: Patients with a diagnosis of chronic obstructive pulmonary disease (COPD) often have other chronic disorders. This study aims to describe the life-course pattern of morbidity in patients with COPD.

Patients and Methods: Among all residents aged 50–90 years in Sweden in 1997, people with a hospital COPD diagnosis were identified using Swedish national registers (1997–2018). Each patient with COPD was matched by sex, birthyear and county of residency with up to five COPD-free controls. Other chronic disease diagnoses were identified during 1987–2018. Conditional logistic regression calculated risk of diseases diagnosed prior to first COPD diagnosis, producing odds ratios (OR) and 95% confidence intervals (95% CI). Cox regression estimated risk of diagnoses after first COPD diagnosis, producing hazard ratios (HR) and 95% CI.

Results: Among 2,706,814 individuals, 225,159 (8.3%) had COPD. The nested case–control sample included 223,945 COPD-cases with 1,062,731 controls. Prior to first COPD diagnosis, future COPD patients had higher risks than controls for most examined conditions. Highest risks were seen for chronic heart failure (OR = 3.25, 3.20–3.30), peripheral arterial disease (OR = 3.12, 3.06–3.18) and lung cancer (OR = 12.73, 12.12–13.37). Following the COPD diagnosis, individuals with COPD had higher risks of most conditions than individuals without COPD. Chronic heart failure (HR = 3.50, 3.46–3.53), osteoporosis (HR = 3.35, 3.30–3.42), depression (HR = 2.58, 2.53–2.64) and lung cancer (HR = 6.04, 5.90–6.18) predominated. The risk of vascular dementia was increased after COPD diagnosis (HR = 1.53, 1.48–1.58) but not Alzheimer's disease.

Conclusion: Accumulation of chronic morbidity may precede COPD. Following the diagnosis, an increased burden of cardiovascular disease and cancer is to be expected, but subsequent depression, osteoporosis, and vascular dementia should also be noted. Management strategies for patients with COPD should consider the higher-than-average risk of multimorbidity.

Keywords: COPD, multimorbidity, register-study

Introduction

The majority of patients with chronic obstructive pulmonary disease (COPD) have at least one other coexisting chronic disease.[1] Some comorbid disorders have shared pathophysiology like systemic inflammation, and others have shared risk factors like older age and smoking.[2] Comorbidity in COPD is associated with worsened health status and an increased risk of exacerbations and mortality.[3,4]

A recent Swedish cohort study from primary care reported a higher prevalence of several comorbid conditions in COPD patients two years prior to the COPD diagnosis and two years subsequently, compared to an age and sex matched

Received: 22 February 2024
Accepted: 7 May 2024
Published: 19 June 2024

reference population without COPD.[5] The prevalence of diseases two years post-diagnosis increased in both groups, but the increase was significantly higher in COPD patients, especially regarding cardiovascular diseases, diabetes, and depression.

However, the extent to which this increased risk of morbidity is present years earlier than the first hospital COPD diagnosis and possibly before the typical ages of clinical COPD onset, is not clear. Information about this and the long-term development of comorbidity in COPD patients could improve our understanding of multimorbidity in COPD and potentially help clinicians provide these patients with optimal holistic care.

This study aims to describe the life-course burden of morbidity in patients with COPD compared to those without COPD in a general population cohort using Swedish national registers.

Materials and Methods

Study Population and Design

The initial data included all residents in Sweden 25 years of age or older and identified in the Swedish Total Population Register from 1990 to 2019. The register includes information on birth, death, and migration of all residents in Sweden. The study population was limited to all individuals who were alive and between 50 and 90 years in 1997. Individuals immigrating to Sweden after 1987 were not included due to incomplete health data.

We used two study designs. First, we used a nested case–control study design to investigate the risk of various disease diagnoses over time for future COPD patients and their matched comparators (controls). Patients with COPD were identified using hospital inpatient or outpatient diagnosis from 1997 to the end of 2018. For both COPD patients and their controls, we identified disease diagnoses from 1st January 1987 to the day of COPD diagnosis (or the date of matching for controls). The date of first COPD diagnosis was used as the index date, and for each case of COPD, we sampled five individuals (controls) who did not have COPD by the index date from the study population. The controls were matched by birthyear, sex, and county of residence at the index date. A control could only serve as a control once, and controls who later became a case only served as case. The majority had five controls per case, but 33% had fewer.

Second, we used a cohort study design to investigate the risk of morbidity subsequent to the COPD diagnosis. Follow-up time started on 1st January 1997 and ended with death, emigration, age 90 years, date of first diagnosis of the outcome, or on 31st December 2018, whichever occurred first. COPD diagnosis was modelled as a time-varying variable.

In both studies, individuals with missing data on covariates were excluded from the analysis.

Variables in the Study

COPD Diagnosis

We identified patients with COPD from the National Patient Register using the ICD-10 code J44 from 1997 and onwards. The register contains information on diagnoses from inpatient care with complete national coverage since 1987, and of hospital-based outpatient care from 2001.[6] We used both primary and secondary hospital diagnoses for the identification of COPD. We identified COPD from age 50 years. Median and mean age at diagnosis have been found to be 68 years in previous studies.[7,8]

Other Morbidity

We used the National Patient Register and the Cancer Register between 1987 and 2018 (see Supplemental Table 1 for full list) to obtain data on other morbidity and defined the first recorded date of diagnosis as the incidence date.[9] The diseases were selected based on previous literature and with consideration to the Patient register not containing data from primary care.[1,3–6] Data on underlying and contributing causes of death were obtained from the National Cause of Death Register and we considered them together in three main categories not mutually exclusive: cardiovascular, respiratory and cancers (see Supplemental Table 1 for ICD-codes).[10]

Covariates

Highest attained level of education was used as a marker of socioeconomic characteristics and was obtained from the Longitudinal Integrated Database for Health Insurance and Labour Market Studies in 1997.[11] Data on county of residence

and date of birth, death, and emigration were extracted from the Total Population Register. The county of residence was defined at the year of matching in the nested case–control study and in 1997 in the cohort study.

Statistical Analysis

For descriptive data, categorical variables were summarised using frequencies and percentages. Continuous variables were summarised by median and interquartile range (IQR) given their distributions. The Chi-square test was used to compare differences between the COPD and non-COPD group in attained level of education.

Nested Case–Control Study

To examine the risk of pre-COPD morbidity, we analysed the matched case–control data using conditional logistic regression models. Odds ratios (OR) with 95% confidence intervals (CI) were calculated. The analyses were adjusted for level of attained education in 1997 and stratified by sex. For assessment of the accumulating burden of comorbidity, and to identify possible age patterns, we repeated the analysis focusing on pre-COPD morbidity occurring before 50 years of age. The analysis was further repeated to include pre-COPD morbidity occurring up to ages 65 years and 75 years.

Cohort Study

We performed Cox regression analyses to assess risk of comorbid disease and cause of death following the first COPD diagnosis. Each comorbid disease was analysed separately. Age was the underlying timescale. Hazard ratios (HR) with 95% CI were calculated. COPD diagnosis was modelled as a time-varying covariate, where COPD status changed from "no" to "yes" at date of first COPD diagnosis. The proportional hazards assumption was tested graphically using Kaplan-Meier, smooth hazard function, and log-minus-log curves. For melanoma and brain tumours, the proportional hazards assumption appeared violated towards older ages, so right truncation at age 80 years (melanoma) and 70 years (brain tumour) was implemented. The analyses were performed unadjusted and adjusted for sex, level of attained education, and county of residence in 1997. Analyses were also performed stratified by sex. We assessed the accumulation of comorbidity by age, by repeating the Cox regression analyses and ending follow-up at 65 years and 75 years.

Sensitivity Analyses

We performed two sensitivity analyses. First, to examine the effect of missing data, we compared HRs obtained from unadjusted analyses with and without excluding individuals with missing data. Second, to examine possible surveillance bias, we defined COPD only using primary diagnoses and refitted models for both nested case-control and cohort studies.

Data management was performed using SPSS version 28 and Stata version 17. Statistical analysis was performed using Stata version 17.

Ethics

Following approval by the national Swedish Ethical Review Authority for this study (2019–04755 and 2023–03585-02), the organisations responsible for the data approved and supplied the variables. The National Board of Health and Welfare provided data from the following registers: the National Patient Register, the Cancer Register, and the National Cause of Death Register.

Statistics Sweden provided data from the following registers: the Total Population Register and the Longitudinal Integrated Database for Health Insurance and Labour Market Studies. All data received from the registers are pseudonymised.

Results

Participants Characteristics

In the nested case–control study, there were 223945 individuals with COPD (cases) and 1062731 individuals without COPD (controls). Cases without information on county of residence in the year of COPD diagnosis or with no available matched controls were excluded prior to analysis (n = 1214). The median age at COPD diagnosis was 76 years and 50.2% were female (see Supplemental Table 2).

In total, 2966804 individuals were alive and between ages 50 and 90 years in 1997. Some 2% (n=70,647) had immigrated to Sweden after 1987 and were not included in the analysis due to incomplete health data. After exclusion due to lack of data on attained level of education or county of residence (n=189,343), the cohort study included the remaining 2706 814 individuals with complete data. Of these, 225159 had a diagnosis of COPD sometime during follow-up (1997–2018). Median age at the start of follow-up (1997) was 64 years for both the COPD and the non-COPD group. The non-COPD group had higher attained level of education (P <0.001). In the COPD group 50.1% were female, compared with 53.5% in the non-COPD group.

Diagnoses Prior to First Hospital COPD Diagnosis: Nested Case–Control Study

The results of the nested case–control study investigating the risk of comorbid diseases prior to the first COPD diagnosis are shown in Table 1. Individuals with a future diagnosis of COPD showed higher risks of having most of the studied

Table 1 Risk of Diseases Prior to COPD Diagnosis

	COPD	Non-COPD	Unadjusted	Adjusted		
	n=223 945	n=1062 731			Males	Females
Outcome	**n (%)**	**n (%)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Cardiovascular						
Atrial fibrillation	35,676 (15.9)	108 734 (10.2)	1.72 (1.70–1.74)	1.72 (1.70–1.75)	1.67 (1.65–1.70)	1.79 (1.76–1.83)
Cerebrovascular disease	27,130 (12.1)	96,787 (9.1)	1.40 (1.38–1.42)	1.37 (1.35–1.40)	1.31 (1.29–1.34)	1.46 (1.43–1.50)
Chronic heart failure	40,031 (17.9)	69,506 (6.5)	3.32 (3.27–3.37)	3.25 (3.20–3.30)	3.03 (2.97–3.08)	3.57 (3.50–3.65)
Ischemic heart disease	54,915 (24.5)	169 397 (15.9)	1.77 (1.75–1.79)	1.73 (1.71–1.75)	1.59 (1.57–1.61)	1.95 (1.92–1.99)
Peripheral arterial disease	22,157 (9.9)	36,179 (3.4)	3.19 (3.13–3.25)	3.12 (3.06–3.18)	2.84 (2.78–2.91)	3.59 (3.49–3.69)
Endocrine						
Diabetes	27,363 (12.2)	95,926 (9.0)	1.42 (1.40–1.44)	1.37 (1.35–1.39)	1.33 (1.31–1.36)	1.42 (1.38–1.45)
Osteoporosis	9340 (4.2)	23,955 (2.3)	1.96 (1.91–2.01)	1.99 (1.94–2.04)	2.48 (2.32–2.64)	1.92 (1.86–1.97)
Gastrointestinal						
Crohn's disease	1432 (0.6)	3628 (0.3)	1.88 (1.77–2.00)	1.86 (1.75–1.98)	1.58 (1.43–1.73)	2.13 (1.96–2.31)
Ulcerative colitis	1692 (0.8)	6257 (0.6)	1.29 (1.22–1.36)	1.29 (1.22–1.36)	1.24 (1.15–1.33)	1.36 (1.25–1.47)
Liver diseases	3898 (1.7)	8861 (0.8)	2.11 (2.03–2.19)	2.07 (2.00–2.16)	2.07 (1.96–2.19)	2.08 (1.97–2.20)
Malabsorptive disorders	861 (0.4)	2976 (0.3)	1.38 (1.28–1.49)	1.40 (1.29–1.51)	1.43 (1.27–1.62)	1.37 (1.24–1.51)
Psychiatric						
Bipolar disorder	2031 (0.9)	5514 (0.5)	1.76 (1.68–1.86)	1.80 (1.71–1.90)	1.65 (1.52–1.80)	1.90 (1.78–2.03)
Depression	12,422 (5.6)	33,547 (3.2)	1.82 (1.78–1.86)	1.82 (1.78–1.86)	1.72 (1.66–1.78)	1.88 (1.83–1.93)
Psychosis	3406 (1.5)	8358 (0.8)	1.95 (1.87–2.03)	1.89 (1.81–1.96)	1.82 (1.70–1.94)	1.93 (1.83–2.03)
Neurological						
Dementia	5207 (2.3)	30,323 (2.9)	0.81 (0.79–0.84)	0.81 (0.78–0.83)	0.85 (0.81–0.88)	0.77 (0.74–0.81)
Epilepsy	4210 (1.9)	13,396 (1.3)	1.50 (1.44–1.55)	1.47 (1.42–1.52)	1.50 (1.44–1.58)	1.42 (1.35–1.50)
Parkinson's disease	1455 (0.7)	9787 (0.9)	0.71 (0.67–0.75)	0.72 (0.68–0.76)	0.71 (0.66–0.76)	0.73 (0.67–0.79)

(*Continued*)

Table 1 (Continued).

	COPD	Non-COPD	Unadjusted	Adjusted		
	n=223 945	n=1062 731			Males	Females
Outcome	n (%)	n (%)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Respiratory						
Asthma	33,561 (15.0)	22,172 (2.1)	8.33 (8.18–8.49)	8.31 (8.15–8.46)	8.74 (8.49–9.00)	8.02 (7.82–8.21)
Others						
Chronic kidney disease	6757 (3.0)	14,801 (1.4)	2.26 (2.20–2.33)	2.21 (2.14–2.28)	2.12 (2.04–2.20)	2.40 (2.28–2.52)
Psoriasis	5938 (2.7)	15,866 (1.5)	1.82 (1.77–1.88)	1.81 (1.76–1.87)	1.70 (1.63–1.79)	1.91 (1.83–1.99)
Rheumatic disease	11,105 (5.0)	32,913 (3.1)	1.65 (1.61–1.69)	1.63 (1.60–1.67)	1.70 (1.64–1.77)	1.60 (1.56–1.64)
Cancers						
Bladder	4186 (1.9)	9535 (0.9)	2.11 (2.04–2.19)	2.12 (2.04–2.20)	1.96 (1.88–2.05)	2.74 (2.54–2.96)
Brain	516 (0.2)	2904 (0.3)	0.85 (0.77–0.93)	0.85 (0.77–0.93)	0.89 (0.77–1.04)	0.82 (0.73–0.93)
Breast[a]	6071 (5.4)	25,337 (4.8)	1.15 (1.11–1.18)	1.18 (1.15–1.22)		1.18 (1.15–1.22)
Cervical[a]	269 (0.2)	817 (0.2)	1.59 (1.38–1.82)	1.56 (1.35–1.79)		1.56 (1.35–1.79)
Colorectal	4938 (2.2)	19,540 (1.8)	1.21 (1.17–1.25)	1.21 (1.18–1.25)	1.22 (1.17–1.28)	1.20 (1.14–1.26)
Endometrial[a]	1079 (1.0)	7413 (1.4)	0.69 (0.65–0.74)	0.70 (0.65–0.74)		0.70 (0.65–0.74)
Kidney	1090 (0.5)	3532 (0.3)	1.47 (1.38–1.58)	1.47 (1.38–1.58)	1.49 (1.36–1.63)	1.45 (1.30–1.62)
Leukaemia	1871 (0.8)	6110 (0.6)	1.47 (1.39–1.54)	1.48 (1.41–1.56)	1.55 (1.45–1.66)	1.39 (1.28–1.51)
Liver	172 (0.1)	294 (<0.1)	2.76 (2.28–3.34)	2.77 (2.29–3.36)	2.84 (2.23–3.60)	2.65 (1.92–3.66)
Lung	6242 (2.8)	2354 (0.2)	13.00 (12.38–13.65)	12.73 (12.12–13.37)	11.81 (11.03–12.63)	13.80 (12.84–14.82)
Lymphoma	1239 (0.6)	4546 (0.4)	1.30 (1.22–1.39)	1.31 (1.23–1.40)	1.29 (1.18–1.40)	1.34 (1.22–1.48)
Melanoma	1244 (0.6)	8538 (0.8)	0.69 (0.65–0.73)	0.72 (0.68–0.77)	0.69 (0.64–0.75)	0.76 (0.70–0.83)
Oesophagus	369 (0.2)	352 (<0.1)	4.90 (4.23–5.68)	4.80 (4.14–5.58)	4.67 (3.92–5.57)	5.16 (3.89–6.84)
Oral	1414 (0.6)	3114 (0.3)	2.18 (2.04–2.32)	2.16 (2.02–2.30)	2.20 (2.03–2.37)	2.07 (1.84–2.32)
Ovarian[a]	365 (0.3)	1878 (0.4)	0.92 (0.82–1.03)	0.92 (0.82–1.03)		0.92 (0.82–1.03)
Pancreas	190 (0.1)	439 (<0.1)	2.05 (1.73–2.43)	2.06 (1.73–2.45)	1.87 (1.44–2.42)	2.24 (1.77–2.82)
Prostate[b]	8805 (7.9)	42,368 (8.0)	0.99 (0.97–1.01)	1.01 (0.99–1.04)	1.01 (0.99–1.04)	
Stomach	565 (0.3)	1383 (0.1)	1.96 (1.78–2.16)	1.91 (1.73–2.11)	1.89 (1.67–2.14)	1.95 (1.64–2.31)

Notes: ORs were calculated using conditional logistic regression models, controlling for matched variables (birthyear, sex and county of residence in matching year). In the adjusted analyses, highest attained level of education was included as covariate. [a]Only female cases and controls. [b]Only male cases and controls.
Abbreviations: OR, odds ratio; CI, confidence interval.

conditions. Exceptions were dementia, Parkinson's disease, melanoma and cancer in the brain and endometrium, where we instead found statistically significantly lower risks for future COPD patients. Among the cardiovascular diseases, highest risks were found for chronic heart failure and peripheral arterial disease. When data were stratified by sex, the ORs differed by sex for several conditions. For osteoporosis, men had OR 2.48 (95% CI 2.32–2.64) and women OR 1.92 (95% CI 1.86–1.97).

The results were consistent when only primary diagnoses of COPD were used (data not shown).

Risk of Pre-COPD Morbidity by Age

When the analysis focused on morbidity identified by age 50 years, future COPD patients had an increased risk of having almost all studied conditions, except for most cancers (Table 2). High magnitude associations were seen for lung cancer and chronic heart failure. For most diseases, ORs decreased with increasing age, as the occurrence of the diseases increased among non-COPD individuals. Dementia had a positive association prior to age 50 years, shifting towards an inverse association by age 75 years.

Diagnoses Subsequent to First Hospital COPD Diagnosis: Cohort Study

After the first hospital COPD diagnosis, individuals with COPD showed a higher risk of being diagnosed with most comorbid conditions including dementia (Table 3). When looking separately at vascular dementia and Alzheimer's, the risk of vascular dementia was increased with HR 1.53 (95% CI 1.48–1.58), while the hazard ratio for Alzheimer's was not significantly different from the non-COPD population (HR 1.02, 95% CI 0.98–1.05). The risk of Parkinson's disease was lower, while the risk of subsequent depression was increased. Except for melanoma, endometrial and prostate cancer, there were positive associations for all cancers. Lung cancer had the highest estimated relative risk. The results for melanoma were truncated at age 80 years, and for brain cancer at age 70 years due to violation of the proportional hazard assumption. The three examined causes of death showed positive associations, the highest magnitude HR found for respiratory causes. The sex-stratified analyses showed higher risks for women than men for all cardiovascular diseases, with statistically significant interaction terms ($P < 0.001$). For osteoporosis, the sex-stratified analysis showed a higher risk for men than women ($P < 0.001$).

Results were consistent when only primary COPD diagnoses were used and when sample with complete data was compared with all available sample (data not shown).

Risk of Post-COPD Morbidity by Age

When follow-up was truncated up until 65 years and 75 years (see Table 4), there was a pattern of decreasing relative risks with increasing age for most conditions.

Discussion

The first main finding of this nationwide study in Sweden was that individuals with a future inpatient or outpatient hospital diagnosis of COPD, already by 50 years of age, had a higher risk of chronic morbidity than individuals who remained COPD-free until the study end. Second, both prior to and following the first COPD diagnosis, patients with COPD had a higher risk of cardiovascular, endocrine, gastrointestinal, psychiatric, and respiratory diseases, than non-COPD controls.

This study aimed to describe the life-course patterns of disease accumulation, both the expected and possibly unexpected, and not causation. Smoking induces systemic inflammation and is a known risk factor for cardiovascular diseases and cancers, as well as COPD.[12,13] A Danish study of never-smokers with COPD found that they had less severe disease, limited to the lungs, while smokers and ex-smokers with COPD had an increased risk of cardiovascular comorbidity.[14] A previous study reported that the current smoking rate in Swedish COPD patients was 34% in 2004.[15] Some 42% were reported ex-smokers. For participants without COPD, the rates were 13% and 40%, respectively. Thus, the non-COPD population in this study is likely to have a lower rate of both current smokers and ex-smokers than the population with COPD. Our findings may reflect the systemic nature of COPD, as well as shared risks, such as tobacco smoking.

Previous research has indicated that age-related chronic disorders occur at younger ages in COPD patients than others and our results are consistent with this.[16] We found a pattern of decreasing relative risks with increasing age for most diagnoses, as disease prevalence increased with increasing age in the non-COPD controls. Interestingly, even prior to the COPD diagnosis, the risk of other chronic morbidity was increased. Since COPD was defined by the earliest diagnosis registered at hospital in our study, it is likely that the onset of COPD was at least some years earlier, and possibly already diagnosed in primary care. In Sweden, 59% of COPD patients were first diagnosed in primary care in 1999, which increased to 81% in 2009.[8] The average age at diagnosis in primary care was 73 years in 1999, and 66 years in 2009.[8] In

Table 2 Risk of Diseases Prior to COPD Diagnosis by Age

Outcome	Diseases Prior to Age 50 Years			Diseases Prior to Age 65 Years			Diseases Prior to Age 75 Years		
	COPD n (%)	Non-COPD n (%)	Adjusted OR (95% CI)	COPD n (%)	Non-COPD n (%)	Adjusted OR (95% CI)	COPD n (%)	Non-COPD n (%)	Adjusted OR (95% CI)
Cardiovascular									
Atrial fibrillation	258 (0.1)	655 (0.1)	1.92 (1.65–2.22)	6427 (2.9)	17,251 (1.6)	1.80 (1.75–1.86)	20,995 (9.4)	60,349 (5.7)	1.75 (1.72–1.77)
Cerebrovascular disease	383 (0.2)	835 (0.1)	2.11 (1.86–2.38)	6862 (3.1)	17,665 (1.7)	1.83 (1.78–1.89)	17,951 (8.0)	55,586 (5.2)	1.56 (1.53–1.58)
Chronic heart failure	178 (0.1)	155 (<0.1)	5.20 (4.17–6.49)	6330 (2.8)	7356 (0.7)	4.07 (3.92–4.21)	21,486 (9.6)	30,972 (2.9)	3.49 (3.43–3.56)
Ischemic heart disease	1359 (0.6)	2364 (0.2)	2.66 (2.49–2.85)	18,775 (8.4)	49,024 (4.6)	1.87 (1.84–1.91)	40,676 (18.2)	120 143 (11.3)	1.73 (1.71–1.75)
Peripheral arterial disease	245 (0.1)	253 (<0.1)	4.44 (3.71–5.32)	4943 (2.2)	6128 (0.6)	3.78 (3.64–3.93)	15,016 (6.7)	21,186 (2.0)	3.50 (3.42–3.58)
Endocrine									
Diabetes	711 (0.3)	1534 (0.1)	2.10 (1.92–2.30)	9065 (4.1)	25,368 (2.4)	1.67 (1.63–1.72)	20,325 (9.1)	66,164 (6.2)	1.46 (1.44–1.49)
Osteoporosis	16 (<0.1)	22 (<0.1)	3.40 (1.76–6.58)	1367 (0.6)	2888 (0.3)	2.31 (2.16–2.46)	5200 (2.3)	11,945 (1.1)	2.17 (2.10–2.25)
Gastrointestinal									
Crohn's disease	166 (0.1)	352 (<0.1)	2.17 (1.80–2.62)	795 (0.4)	1897 (0.2)	1.96 (1.80–2.13)	1253 (0.6)	3039 (0.3)	1.93 (1.81–2.07)
Ulcerative colitis	127 (0.1)	491 (0.1)	1.26 (1.03–1.53)	737 (0.3)	2908 (0.3)	1.21 (1.11–1.31)	1382 (0.6)	5170 (0.5)	1.27 (1.19–1.35)
Liver diseases	270 (0.1)	446 (<0.1)	2.79 (2.39–3.26)	1980 (0.9)	3874 (0.4)	2.38 (2.25–2.51)	3360 (1.5)	7160 (0.7)	2.20 (2.11–2.30)
Malabsorptive disorders	38 (<0.1)	93 (<0.1)	1.97 (1.35–2.89)	367 (0.2)	1123 (0.1)	1.56 (1.38–1.76)	703 (0.3)	2346 (0.2)	1.45 (1.33–1.58)
Psychiatric									
Bipolar disorder	434 (0.2)	688 (0.1)	3.00 (2.65–3.39)	1387 (0.6)	3091 (0.3)	2.18 (2.04–2.32)	1879 (0.8)	4779 (0.5)	1.92 (1.82–2.03)
Depression	929 (0.4)	1384 (0.1)	3.18 (2.92–3.46)	5323 (2.4)	11,258 (1.1)	2.29 (2.22–2.37)	9388 (4.2)	22,876 (2.2)	2.00 (1.95–2.05)
Psychosis	798 (0.4)	1118 (0.1)	3.31 (3.01–3.63)	2295 (1.0)	4340 (0.4)	2.43 (2.30–2.55)	3029 (1.4)	6626 (0.6)	2.10 (2.01–2.19)
Neurological									
Dementia	9 (<0.1)	17 (<0.1)	2.57 (1.12–5.91)	344 (0.2)	955 (0.1)	1.64 (1.44–1.86)	1648 (0.7)	8195 (0.8)	0.93 (0.88–0.99)
Epilepsy	346 (0.2)	584 (0.1)	2.56 (2.24–2.93)	1997 (0.9)	4498 (0.4)	2.02 (1.91–2.13)	3352 (1.5)	9432 (0.9)	1.64 (1.58–1.71)
Parkinson's disease	6 (<0.1)	28 (<0.1)	1.15 (0.47–2.83)	179 (0.1)	1213 (0.1)	0.69 (0.59–0.81)	798 (0.4)	5329 (0.5)	0.72 (0.67–0.77)

(*Continued*)

https://doi.org/10.2147/COPD.S459784 DovePress

Table 2 (Continued).

Outcome	Diseases Prior to Age 50 Years			Diseases Prior to Age 65 Years			Diseases Prior to Age 75 Years		
	COPD n (%)	Non-COPD n (%)	Adjusted OR (95% CI)	COPD n (%)	Non-COPD n (%)	Adjusted OR (95% CI)	COPD n (%)	Non-COPD n (%)	Adjusted OR (95% CI)
Respiratory									
Asthma	1373 (0.6)	767 (0.1)	8.10 (7.40–8.87)	11,623 (5.2)	7350 (0.7)	7.80 (7.56–8.04)	24,467 (10.9)	16,259 (1.5)	7.90 (7.73–8.07)
Others									
Chronic kidney disease	29 (<0.1)	45 (<0.1)	2.90 (1.80–4.66)	691 (0.3)	1361 (0.1)	2.33 (2.12–2.56)	3116 (1.4)	6088 (0.6)	2.40 (2.30–2.51)
Psoriasis	147 (0.1)	235 (<0.1)	2.69 (2.18–3.31)	2206 (1.0)	5514 (0.5)	1.89 (1.80–1.99)	4811 (2.2)	12,428 (1.2)	1.86 (1.80–1.93)
Rheumatic disease	427 (0.2)	819 (0.1)	2.43 (2.16–2.74)	4011 (1.8)	9791 (0.9)	1.94 (1.86–2.01)	8124 (3.6)	22,358 (2.1)	1.74 (1.70–1.79)
Cancers									
Bladder	43 (<0.1)	100 (<0.1)	2.06 (1.43–2.97)	930 (0.4)	2089 (0.2)	2.09 (1.94–2.27)	2740 (1.2)	6058 (0.6)	2.14 (2.05–2.24)
Brain	33 (<0.1)	141 (<0.1)	1.12 (0.76–1.64)	235 (0.1)	1333 (0.1)	0.84 (0.73–0.97)	439 (0.2)	2489 (0.2)	0.84 (0.76–0.93)
Breast [a]	258 (0.2)	1025 (0.2)	1.22 (1.06–1.40)	2561 (2.3)	11,021 (2.1)	1.14 (1.09–1.19)	4952 (4.4)	21,103 (4.0)	1.15 (1.12–1.19)
Cervical [a]	27 (<0.1)	105 (<0.1)	1.17 (0.76–1.79)	129 (0.1)	408 (0.1)	1.48 (1.21–1.80)	219 (0.2)	665 (0.1)	1.55 (1.33–1.81)
Colorectal	41 (<0.1)	152 (<0.1)	1.29 (0.91–1.84)	911 (0.4)	3960 (0.4)	1.10 (1.03–1.19)	3040 (1.4)	12,236 (1.2)	1.18 (1.14–1.23)
Endometrial [a]	26 (<0.1)	144 (<0.1)	0.86 (0.57–1.32)	396 (0.4)	2770 (0.5)	0.68 (0.61–0.76)	849 (0.8)	5821 (1.1)	0.70 (0.65–0.75)
Kidney	12 (<0.1)	60 (<0.1)	0.96 (0.51–1.81)	276 (0.1)	986 (0.1)	1.31 (1.14–1.50)	787 (0.4)	2530 (0.2)	1.48 (1.36–1.60)
Leukaemia	20 (<0.1)	64 (<0.1)	1.57 (0.94–2.61)	424 (0.2)	1231 (0.1)	1.69 (1.51–1.89)	1219 (0.5)	3772 (0.4)	1.57 (1.47–1.68)
Liver	0 (0)	0 (0)	-	17 (<0.1)	36 (<0.1)	2.14 (1.19–3.85)	109 (0.1)	155 (<0.1)	3.24 (2.52–4.15)
Lung	27 (<0.1)	15 (<0.1)	9.63 (4.83–19.20)	1049 (0.5)	453 (<0.1)	10.52 (9.39–11.78)	4162 (1.9)	1548 (0.2)	12.73 (11.98–13.52)
Lymphoma	35 (<0.1)	85 (<0.1)	1.98 (1.33–2.96)	377 (0.2)	1240 (0.1)	1.44 (1.28–1.62)	895 (0.4)	3115 (0.3)	1.37 (1.27–1.48)
Melanoma	42 (<0.1)	348 (<0.1)	0.60 (0.43–0.83)	387 (0.2)	2931 (0.3)	0.65 (0.59–0.73)	857 (0.4)	6271 (0.6)	0.67 (0.63–0.72)
Oesophagus	2 (<0.1)	0 (0)	-	66 (<0.1)	59 (<0.1)	5.29 (3.67–7.61)	253 (0.1)	228 (<0.1)	5.00 (4.16–6.01)
Oral	29 (<0.1)	47 (<0.1)	2.83 (1.76–4.54)	439 (0.2)	910 (0.1)	2.28 (2.03–2.56)	1075 (0.5)	2239 (0.2)	2.27 (2.11–2.44)
Ovarian[a]	21 (<0.1)	98 (<0.1)	1.05 (0.65–1.69)	164 (0.2)	810 (0.2)	0.94 (0.79–1.11)	303 (0.3)	1543 (0.3)	0.92 (0.81–1.04)
Pancreas	0 (0)	4 (<0.1)	-	24 (<0.1)	69 (<0.1)	1.61 (1.00–2.57)	115 (0.1)	276 (<0.1)	1.99 (1.59–2.48)
Prostate[b]	0 (0)	7 (<0.1)	-	1356 (1.2)	6628 (1.3)	1.02 (0.96–1.08)	5727 (5.1)	27,985 (5.3)	1.00 (0.97–1.03)
Stomach	6 (<0.1)	14 (<0.1)	1.91 (0.73–5.04)	107 (0.1)	299 (<0.1)	1.60 (1.28–2.00)	353 (0.2)	858 (0.1)	1.90 (1.67–2.15)

Notes: ORs were calculated using conditional logistic regression models, controlling for matched variables (birthyear, sex and county of residence in matching year) and adjusted for highest attained level of education. Only morbidity occurring prior to index date and prior to age 50, 65 or 75 years respectively was included in analyses. [a]Only female cases and controls. [b]Only male cases and controls.

Abbreviations: OR, odds ratio; CI, confidence interval.

Table 3 Risk of Comorbid Disease After COPD Diagnosis

	No of Outcome Events	No of Individuals[a]	Unadjusted	Adjusted		
					Males	Females
Outcome	**n**	**n**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Cardiovascular						
Atrial fibrillation	506 790	2626 114	1.95 (1.93–1.98)	1.90 (1.88–1.93)	1.83 (1.80–1.86)	2.02 (1.99–2.06)
Cerebrovascular disease	445 626	2615 538	1.46 (1.44–1.48)	1.42 (1.40–1.44)	1.33 (1.30–1.35)	1.56 (1.53–1.59)
Chronic heart failure	472 598	2635 423	3.63 (3.60–3.67)	3.50 (3.46–3.53)	3.13 (3.09–3.18)	4.02 (3.97–4.08)
Ischemic heart disease	520 916	2510 244	2.08 (2.05–2.10)	2.02 (2.00–2.05)	1.82 (1.79–1.86)	2.32 (2.28–2.36)
Peripheral arterial disease	199 246	2676 447	2.87 (2.82–2.91)	2.75 (2.70–2.79)	2.47 (2.41–2.52)	3.19 (3.12–3.27)
Endocrine						
Diabetes	366 794	2623 067	1.44 (1.41–1.46)	1.39 (1.37–1.42)	1.35 (1.31–1.38)	1.48 (1.44–1.51)
Osteoporosis	143 938	2697 832	3.15 (3.09–3.20)	3.35 (3.30–3.42)	4.41 (4.24–4.59)	3.14 (3.08–3.20)
Gastrointestinal						
Crohn's disease	10,061	2702 662	2.54 (2.34–2.76)	2.48 (2.28–2.70)	2.08 (1.83–2.38)	2.83 (2.54–3.16)
Ulcerative colitis	17,507	2701 214	2.01 (1.88–2.16)	2.01 (1.87–2.15)	1.84 (1.66–2.04)	2.17 (1.98–2.39)
Liver diseases	45,202	2695 624	2.64 (2.54–2.74)	2.51 (2.42–2.61)	2.39 (2.27–2.52)	2.64 (2.50–2.79)
Malabsorptive disorders	10,777	2705 051	1.83 (1.67–2.01)	1.88 (1.72–2.06)	1.82 (1.59–2.10)	1.89 (1.68–2.13)
Psychiatric						
Bipolar disorder	11,383	2696 563	1.68 (1.53–1.84)	1.71 (1.55–1.88)	1.59 (1.36–1.86)	1.80 (1.60–2.03)
Depression	138 674	2672 963	2.61 (2.56–2.67)	2.58 (2.53–2.64)	2.54 (2.46–2.63)	2.61 (2.54–2.68)
Psychosis	20,868	2688 358	1.74 (1.63–1.86)	1.69 (1.59–1.81)	1.76 (1.59–1.96)	1.66 (1.53–1.80)
Neurological						
Dementia	259 137	2689 815	1.36 (1.34–1.38)	1.32 (1.30–1.35)	1.31 (1.28–1.34)	1.34 (1.31–1.37)
Epilepsy	57,109	2691 131	1.72 (1.66–1.79)	1.66 (1.59–1.72)	1.62 (1.54–1.71)	1.71 (1.61–1.81)
Parkinson's disease	45,796	2699 274	0.73 (0.69–0.77)	0.71 (0.67–0.76)	0.73 (0.67–0.78)	0.69 (0.62–0.76)
Respiratory						
Asthma	107 742	2673 236	6.58 (6.46–6.70)	6.62 (6.50–6.74)	6.77 (6.58–6.97)	6.48 (6.33–6.63)
Others						
Chronic kidney disease	150 665	2702 633	3.29 (3.23–3.34)	3.07 (3.02–3.12)	2.75 (2.69–2.81)	3.70 (3.60–3.80)
Psoriasis	61,655	2701 412	2.00 (1.93–2.08)	1.98 (1.91–2.05)	1.86 (1.76–1.97)	2.06 (1.96–2.17)
Rheumatic disease	125 965	2680 907	1.68 (1.63–1.72)	1.70 (1.65–1.74)	1.71 (1.64–1.78)	1.68 (1.62–1.73)
Cancers						
Bladder	39,262	2698 309	2.09 (2.01–2.18)	1.96 (1.88–2.04)	1.89 (1.80–1.98)	2.18 (2.01–2.36)
Brain[b]	5885	1793 722	1.34 (1.10–1.64)	1.36 (1.12–1.66)	1.00 (0.71–1.43)	1.63 (1.28–2.07)
Breast	74,489	1411 074	1.14 (1.09–1.19)	1.14 (1.09–1.19)		1.14 (1.09–1.19)

(*Continued*)

Table 3 (Continued).

	No of Outcome Events	No of Individuals[a]	Unadjusted	Adjusted		
					Males	Females
Outcome	**n**	**n**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
Cervical	3120	1438 287	1.87 (1.59–2.21)	1.84 (1.56–2.16)		1.84 (1.56–2.16)
Colorectal	91,027	2690 827	1.38 (1.33–1.42)	1.36 (1.31–1.40)	1.31 (1.26–1.37)	1.41 (1.34–1.47)
Endometrial	22,263	1432 571	0.65 (0.59–0.72)	0.66 (0.59–0.72)		0.66 (0.59–0.72)
Kidney	16,581	2703 280	1.65 (1.54–1.78)	1.62 (1.50–1.74)	1.50 (1.36–1.65)	1.81 (1.62–2.01)
Leukaemia	36,340	2701 753	1.38 (1.31–1.45)	1.34 (1.28–1.41)	1.34 (1.25–1.43)	1.34 (1.24–1.45)
Liver	7952	2706 685	2.36 (2.17–2.58)	2.23 (2.05–2.43)	2.17 (1.95–2.42)	2.34 (2.03–2.71)
Lung	57,585	2704 570	6.35 (6.21–6.50)	6.04 (5.90–6.18)	5.09 (4.93–5.26)	7.20 (6.96–7.44)
Lymphoma	23,396	2702 496	1.35 (1.26–1.44)	1.32 (1.24–1.41)	1.27 (1.16–1.39)	1.39 (1.26–1.53)
Melanoma[c]	20,341	2464 853	0.79 (0.72–0.87)	0.80 (0.72–0.88)	0.76 (0.66–0.87)	0.85 (0.73–0.98)
Oesophagus	6595	2706 577	2.88 (2.63–3.15)	2.67 (2.44–2.92)	2.66 (2.39–2.95)	2.74 (2.31–3.25)
Oral	13,874	2703 304	2.27 (2.12–2.44)	2.14 (1.99–2.29)	2.08 (1.91–2.27)	2.25 (2.01–2.53)
Ovarian	9024	1437 013	1.08 (0.95–1.22)	1.07 (0.94–1.22)		1.07 (0.94–1.22)
Pancreas	16,225	2706 586	1.90 (1.78–2.04)	1.88 (1.76–2.01)	1.80 (1.63–1.99)	1.96 (1.79–2.15)
Prostate	146 473	1245 767	0.94 (0.91–0.97)	0.94 (0.91–0.97)	0.94 (0.91–0.97)	
Stomach	14,116	2705 278	1.58 (1.46–1.70)	1.50 (1.39–1.62)	1.50 (1.37–1.65)	1.48 (1.30–1.69)
Cause of death						
Cancer	384 729	2706 814	3.34 (3.30–3.37)	3.22 (3.19–3.26)	2.97 (2.93–3.01)	3.51 (3.46–3.57)
Cardiovascular	761 203	2706 814	3.75 (3.72–3.77)	3.62 (3.59–3.64)	3.37 (3.34–3.40)	4.03 (3.99–4.07)
Respiratory	298 988	2706 814	12.49 (12.39–12.59)	11.98 (11.88–12.07)	9.93 (9.82–10.04)	15.04 (14.87–15.22)

Notes: Cox regressions with COPD diagnosis being modelled as a time-varying covariate. The adjusted HRs were obtained by controlling for sex, highest attained level of education and county of residence in 1997. [a]Number of individuals in analysis after exclusion due to diagnosis of outcome disease prior to 1997. [b]Truncated at 70 years. [c]Truncated at 80 years.

Abbreviations: HR, hazard ratio; CI, confidence interval.

our study, the median age at diagnosis was 76 years, so the first hospital diagnosis of COPD is suggested to be later for most patients. The accumulation of morbidity we found indicates that the disease accumulation started long before the COPD diagnosis is evident. The similarity between the results of the cohort study and the nested case-control suggests a greater susceptibility to morbidity both before and after diagnosis of COPD.

As is well known and detailed by a recent meta-analysis, patients with COPD had a higher risk of cardiovascular diseases.[17] In our study, we found higher risks of all cardiovascular diseases for COPD patients than non-COPD patients, both prior to and after the COPD diagnosis. The relative risks were most notably increased at younger ages, and sex-stratified analyses showed higher risks for women than men. The high frequency of cardiovascular diseases and the often-shared symptoms with COPD makes it a comorbidity to be expected in COPD patients. We found an increased risk of cardiovascular mortality in COPD patients, as well as for respiratory causes and cancer. Hospital admission for an acute exacerbation has been associated with increased mortality in cardiovascular events.[18]

Osteoporosis is a common comorbidity of COPD, sharing risk factors like age, smoking, and systemic inflammation.[19] We found an increased risk of osteoporosis both before and after a COPD diagnosis and especially

Table 4 Risk of Disease After COPD Diagnosis by Age

	Follow-Up Until 65 Years			Follow-Up Until 75 Years		
Outcome	**No of Outcome Events**	**No of Individuals[a]**	**Adjusted HR (95% CI)**	**No of Outcome Events**	**No of Individuals[a]**	**Adjusted HR (95% CI)**
Cardiovascular						
Atrial fibrillation	37,304	1407 563	3.25 (3.04–3.47)	185 378	2118 357	2.38 (2.33–2.43)
Cerebrovascular disease	39,834	1403 424	2.66 (2.48–2.85)	165 973	2110 948	1.93 (1.89–1.98)
Chronic heart failure	26,037	1412 485	9.14 (8.70–9.60)	134 318	2128 441	5.56 (5.46–5.66)
Ischemic heart disease	74,187	1371 326	3.34 (3.18–3.51)	243 322	2037 862	2.47 (2.42–2.52)
Peripheral arterial disease	17,767	1414 416	4.56 (4.23–4.93)	85,138	2140 266	3.56 (3.47–3.65)
Endocrine						
Diabetes	59,650	1415 814	2.40 (2.26–2.55)	197 673	2104 327	1.73 (1.68–1.77)
Osteoporosis	10,255	1420 283	7.36 (6.81–7.95)	51,158	2154 727	4.92 (4.78–5.06)
Gastrointestinal						
Crohn's disease	2871	1418 475	2.71 (2.08–3.53)	6722	2154 297	2.54 (2.26–2.86)
Ulcerative colitis	4932	1417 987	1.80 (1.41–2.30)	11,731	2153 356	2.11 (1.91–2.32)
Liver diseases	10,054	1415 112	3.71 (3.30–4.16)	28,372	2148 694	3.08 (2.92–3.24)
Malabsorptive disorders	2707	1420 257	2.36 (1.79–3.11)	7082	2156 524	2.13 (1.88–2.41)
Psychiatric						
Bipolar disorder	3395	1415 355	2.86 (2.27–3.60)	7792	2149 444	2.25 (2.00–2.53)
Depression	22,859	1407 247	4.04 (3.74–4.36)	66,480	2134 806	3.40 (3.29–3.51)
Psychosis	4747	1411 748	2.92 (2.41–3.54)	11,222	2144 039	2.25 (2.05–2.47)
Neurological						
Dementia	4456	1420 137	2.89 (2.42–3.45)	45,231	2153 371	1.88 (1.80–1.96)
Epilepsy	9574	1414 243	2.94 (2.57–3.37)	28,545	2146 434	2.21 (2.08–2.34)
Parkinson's disease	3225	1420 266	1.04 (0.72–1.50)	18,958	2154 605	0.80 (0.72–0.89)
Respiratory						
Asthma	18,176	1410 189	12.46 (11.78–13.18)	58,334	2135 786	7.46 (7.26–7.66)
Others						
Chronic kidney disease	7226	1419 641	5.57 (5.00–6.21)	44,038	2155 073	4.08 (3.95–4.22)
Psoriasis	16,265	1418 611	2.50 (2.24–2.79)	43,166	2153 725	2.11 (2.01–2.22)
Rheumatic disease	18,928	1411 635	2.11 (1.89–2.36)	61,170	2139 596	1.92 (1.84–2.00)
Cancers						
Bladder	4022	1419 187	2.77 (2.25–3.41)	17,902	2152 841	2.10 (1.96–2.25)
Brain	3354	1419 559	1.54 (1.12–2.12)	[b]	[b]	[b]
Breast	17,748	699 689	1.26 (1.09–1.46)	47,291	1089 057	1.17 (1.10–1.24)
Cervical	635	710 792	2.21 (1.25–3.92)	1670	1109 087	2.23 (1.76–2.83)

(*Continued*)

Table 4 (Continued).

	Follow-Up Until 65 Years			Follow-Up Until 75 Years		
Outcome	**No of Outcome Events**	**No of Individuals[a]**	**Adjusted HR (95% CI)**	**No of Outcome Events**	**No of Individuals[a]**	**Adjusted HR (95% CI)**
Colorectal	9572	1417 791	1.25 (1.03–1.52)	41,518	2149 123	1.42 (1.34–1.50)
Endometrial	4027	709 194	0.83 (0.57–1.19)	12,841	1105 030	0.64 (0.55–0.75)
Kidney	2559	1419 996	2.85 (2.20–3.69)	9589	2155 492	1.91 (1.72–2.11)
Leukaemia	4117	1419 620	1.89 (1.47–2.43)	17,085	2154 646	1.50 (1.38–1.64)
Liver	861	1421 007	3.68 (2.52–5.38)	3946	2157 745	2.82 (2.48–3.21)
Lung	8296	1420 284	10.00 (9.24–10.82)	33,072	2156 149	6.99 (6.77–7.22)
Lymphoma	3170	1419 474	1.48 (1.07–2.04)	11,691	2154 866	1.44 (1.29–1.60)
Melanoma	4285	1418 085	0.96 (0.67–1.37)	14,731	2152 773	0.77 (0.68–0.88)
Oesophagus	957	1420 975	5.60 (4.14–7.58)	3577	2157 669	3.51 (3.09–3.99)
Oral	2523	1419 931	2.51 (1.90–3.30)	7974	2155 490	2.54 (2.30–2.81)
Ovarian	2175	710 315	1.04 (0.66–1.63)	5722	1108 092	1.11 (0.93–1.33)
Pancreas	2098	1420 948	3.42 (2.65–4.42)	8806	2157 656	2.27 (2.06–2.51)
Prostate	19,752	707 532	1.11 (0.96–1.29)	85,744	1037 740	0.98 (0.94–1.03)
Stomach	1604	1420 701	3.23 (2.37–4.39)	6278	2156 979	1.84 (1.62–2.09)
Cause of death						
Cancer	31,411	1421 045	5.99 (5.70–6.31)	139 658	2157 831	4.61 (4.53–4.70)
Cardiovascular	29,152	1421 045	9.86 (9.44–10.29)	155 918	2157 831	6.48 (6.39–6.58)
Respiratory	10,932	1421 045	38.29 (36.63–40.03)	66,790	2157 831	23.06 (22.69–23.44)

Notes: Cox regressions with COPD diagnosis being modelled as a time-varying covariate. Adjusted HRs were obtained by controlling for sex, highest attained level of education and county of residence in 1997. Follow-up until 65 years and 75 years. [a]Number of individuals in analysis after exclusion due to diagnosis of outcome disease prior to 1997. [b]Brain cancer was not truncated at age 75 years due to violation of the proportional hazards assumption after age 70.
Abbreviations: HR, hazard ratio; CI, confidence interval.

for men. The age-defined analyses showed higher relative risk especially at younger ages and prior to the first COPD diagnosis. COPD has been reported to be the most frequent cause of secondary osteoporosis in men.[20] In clinical practice, COPD may be a pointer to look for osteoporosis, which may more often be overlooked in men.

The risk of psychiatric disorders was higher for individuals with COPD, both before and after the COPD diagnosis, but especially for subsequent depression. Individuals diagnosed with psychiatric disorders have been found to be more likely to smoke than those without such diagnoses,[21] thus potentially increasing the risk of COPD. Depression is a common comorbidity of COPD, associated with increased risk of exacerbations and mortality.[3] Still, depression is often unrecognised and untreated in COPD patients.[22] Our findings suggest that a more active approach towards diagnosis and treatment could be of value.

Smoking has been suggested having a protective effect for development of Parkinson's disease.[23] Also in our study, COPD patients had a lower risk of having Parkinson's disease both before and after the COPD diagnosis. Observational studies have reported an increased risk of cognitive decline and dementia in patients with COPD.[24] A recent Mendelian randomisation study did not find any evidence of a causal association between COPD and Alzheimer's disease, and suggested unmeasured confounding, or other types of dementia as an explanation.[25] We found a significantly increased risk of vascular dementia in COPD patients, while the risk of Alzheimer's was not significantly different from the non-COPD population. Prior to the COPD diagnosis, we found a lower risk of dementia in future COPD patients compared to

those who would not develop COPD. Thus, clinicians should be aware of subsequent vascular dementia, which is consistent with the generally elevated risk of cardiovascular comorbidities in COPD.

A Danish study reported increased incidences of both tobacco-related and other cancers in COPD patients compared with the general population.[26] We found increased risks for most cancers, both before and after the diagnosis of COPD, exceptions being melanoma and endometrial cancer. Previous observational studies have reported inverse associations for endometrial cancer and melanoma with cigarette smoking.[27,28]

Our findings of increased morbidity among COPD patients are consistent with recent studies from other European countries. In Denmark, a population-based study found the highest increased risks among those with COPD for mood disorders, osteoporosis, heart failure, smoking-related cancers, and peripheral arterial disease, compared with the general population.[29] In Germany, patients with COPD had higher relative risks for cardiovascular diseases, diabetes, chronic kidney disease, osteoporosis, and psychiatric diseases, among others.[30]

Early diagnosis of COPD has been advocated as a possible way to improve management of the disease.[31] Further research should quantify the value of clinicians being vigilant and considering early diagnosis of COPD in individuals with other chronic morbidity and identifying likely comorbid diseases at an early stage through monitoring, providing the opportunity to plan management strategies that consider COPD in the context of other conditions.

Strengths and Limitations

Strengths of our study are the uniquely large sample size and the use of longitudinal national registers with high coverage and prospectively recorded data.[6,9,10] The Patient Register has high validity for some diagnoses but less likely to identify some conditions commonly treated in primary care, such as hypertension.[6] The Swedish healthcare system provides tax-supported health care to all residents, why inability to pay healthcare fees should not be a source of bias in the study. The Cause of Death Register has high completeness data, but the quality of the diagnoses is dependent on the clinicians, and agreement between the register and systematically reviewed medical records has been found to vary between age groups and diagnosis.[10]

This study has some potential limitations that are typical for large register-based studies. We defined the date of diagnosis of COPD and other morbidity as the earliest date of a record in the Patient Register, thus the first admission or referral to hospital. The patient may have received the diagnosis in primary care prior to this. Hence, the index date of COPD is partly arbitrary but also reflecting the clinical reality: COPD patients often have had lower respiratory symptoms a long time before finally being diagnosed with COPD.[7] We identified COPD from age 50 years, as it is usually diagnosed later in life.[8] In our study, the median age of COPD diagnosis was 76 years. However, to have undiagnosed COPD cases among the controls or non-COPD reference group would attenuate rather than inflate the associations.

We have no information about whether the diagnosis of COPD was confirmed by spirometry, and this may have implications for diagnostic accuracy. Although the use of diagnostic spirometry for COPD has increased in recent years in Sweden, its use remains incomplete.[32] A previous validation study found that less than 10% of the COPD diagnoses in the Swedish Inpatient Register were misclassified or uncertain.[33] Yet, there may be an overdiagnosis of COPD in patients admitted to hospital.[34] However, this diagnostic heterogeneity of COPD in our study would again reflect the clinical reality.

This study was designed to examine COPD patients that are at some point treated in hospital. Therefore, patients that are managed strictly in primary care and who have never been referred to secondary care were not included in the study. A previous Swedish population-based study on inpatient care estimated that approximately 20–40% of patients with airflow limitation corresponding to COPD were never admitted to hospital.[35] The admission rate was highest for male smokers, and lowest for female never-smokers and ex-smokers. Thus, the COPD patients identified in this study may represent the individuals with more severe disease than average.

Another limitation was that we were not able to identify lifestyle risk factors such as smoking, although the focus of this study was to identify patterns of disease accumulation, not the associated risk factors. The increased surveillance of people having one or more chronic disease diagnoses would likely inflate the number of new diagnoses, possibly resulting in surveillance bias if one group is more or less likely to receive a disease diagnosis, investigated in this study, than the other. However, this would be true both of people with COPD and people with other chronic disorders. During the study period, several county councils used payment systems based on the number of diagnoses, which have been found to increase the number of secondary diagnoses in the records.[36] Since this may strengthen the possibility of surveillance bias, we

performed sensitivity analyses, including only those with a primary diagnosis of COPD. The results were consistent with the main analyses, and surveillance bias does not seem to be the main explanation of our results. The results of our study may have limited generalisability in countries with different healthcare systems or smoking habits.

Conclusion

Accumulation of chronic morbidity may precede a COPD diagnosis. Following the COPD diagnosis, a higher-than-average risk of multimorbidity should be anticipated and addressed in clinical practice. An increased burden of cardiovascular disease and cancer is to be expected, but subsequent depression, vascular dementia, and osteoporosis – particularly among men – should also be anticipated.

Data Sharing Statement

The data underlying this study cannot be shared publicly due to regulations under the relevant Swedish laws. Researchers who are interested in Swedish register data can refer to https://www.registerforskning.se/en/. Inquiries about the data used for this study can be addressed to the corresponding author.

Funding

The data used for the study was obtained with support from the Swedish Research Council for Health, Working Life and Welfare (number: 2019-01236).

Disclosure

BS has received honoraria for educational activities and lectures from AstraZeneca, Boehringer Ingelheim, Chiesi, Meda, Novartis and Teva, and has served on advisory boards arranged by AstraZeneca, Novartis, Meda, GlaxoSmithKline, Teva and Boehringer Ingelheim. HS has received honoraria for educational activities from Boehringer Ingelheim, Novartis, AstraZeneca, Chiesi, and TEVA, an unrestricted research grant from AstraZeneca, and has served on advisory boards arranged by AstraZeneca, Novartis, Chiesi, OrionPharma, and GlaxoSmithKline. The authors report no other conflicts of interest in this work.

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