

ORIGINAL RESEARCH

Co-morbidity in Mild-to-Moderate COPD: Comparison to Normal and Restrictive Lung Function

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Background: A relationship between local and systemic inflammation and different co-morbidities, such as cardiovascular, has been discussed in relation to disease process and prognosis in COPD. **Aim:** To evaluate if conditions as cardiovascular diseases, diabetes, chronic rhinitis and gastroesophageal reflux are overrepresented in COPD. **Methods:** All subjects with COPD according to GOLD, $FEV_1/FVC < 0.70$, were identified ($n = 993$) from the clinical follow-up in 2002–04 of the OLIN (Obstructive Lung Disease in Northern Sweden) studies' cohorts together with 993 gender- and age-matched reference subjects without COPD (non-COPD, further divided into normal and restrictive lung function). Interview data on co-morbidity and symptoms were used. **Results:** Cardiovascular co-morbidity, taken together heart disease, hypertension, stroke and intermittent claudication, was the most common and higher in COPD compared to in normal lung function (Nlf) 50.1% vs 41.0% ($p < 0.001$). The prevalence of chronic rhinitis and gastroesophageal reflux (GERD) was higher in COPD compared to in Nlf (43.1% vs 32.3%, $p < 0.001$ and 16.7% vs 12.0%, $p = 0.011$). In restrictive lung function the prevalence of chronic rhinitis, cardiovascular disease, hyperlipemia and diabetes was higher compared to in Nlf (41.0% vs 32.3%, $p = 0.017$, 59.0% vs 41.0%, $p < 0.001$, 29.2% vs 12.9%, $p = 0.033$, 20.9% vs 8.6%, $p < 0.001$). In COPD and heart disease, 62.5% had chronic rhinitis and/or GERD, while in Nlf the corresponding proportion was 42.5%. **Conclusion:** Co-morbid conditions such as cardiovascular disease, chronic rhinitis and gastroesophageal reflux were common in COPD. The overlap between heart disease, chronic rhinitis and GERD was large in COPD. Restrictive lung function did also identify a population with increased disease burden.

Keywords: COPD, Co-morbidity, Cardiovascular disease, Chronic rhinitis, Gastroesophageal reflux, Restrictive lung function.

INTRODUCTION

Chronic Obstructive Pulmonary Disease, COPD, is expected to be the fourth greatest burden of disease by year 2030 (1), and COPD will result in a high cost to society (2). The prevalence among adults is reported in the range of 6–10% (3) with a strong correlation to tobacco smoking and increasing age; close to every other elderly smoker fulfils the spirometric criteria for COPD (4). Besides disease severity based on level of lung function impairment, co-morbidity also affects the prognosis and health status of patients with COPD; however, population-based studies addressing these topics are scarce.

In a recently published review, the prevalence of co-morbid conditions in COPD was for heart disease in the range of 13–65%, hypertension 18–52%, diabetes 5–16% and gastrointestinal disturbances 15–62% (5). The ranges of prevalence data are wide and reflect the selection of the study populations differentiating from general population samples. Large population studies in the United States found that male gender, age and BMI were associated with a higher risk for diabetes, hypertension and cardiovascular disease, and COPD and restricted lung function to be risk factors for these diseases (6).

The underdiagnosis of COPD (7, 8) contributes to an underestimation of the impact of COPD on mortality. Co-morbidity, and especially cardiovascular co-morbidity, is associated with an increased mortality (9). On the other hand, reduced FEV_1 is a marker of cardiovascular death (9) and reports on increased mortality in subjects with chronic bronchitis have been published (10, 11). Further, a relationship between local and systemic inflammation and different co-morbidities including cardiovascular disease, chronic rhinitis and chronic bronchitis has been discussed in relation to the disease progress of COPD (9, 12). Population-based surveys evaluating concomitant diseases in COPD can

Funding: Main funding from the Swedish Heart-Lung Foundation, the Northern Sweden Regional Health Authorities and Umeå University (Visare Norr and ALF). The Swedish Research Council supports the management of the OLIN studies large data bases. Additional support has been given by the county council in the county of Norrbotten.

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increase the understanding of interactions between different conditions of importance for the prognosis.

The aim of this study was to evaluate the impact of chronic rhinitis, cardiovascular diseases, diabetes and gastroesophageal reflux in subjects with COPD compared to subjects without obstructive lung function impairment divided into normal and restrictive lung function. A further aim was to evaluate the co-existence of and relation between co-morbid diseases as heart disease, chronic rhinitis and gastroesophageal reflux in subjects with COPD.

METHODS

Study population

Within the Obstructive Lung disease in Northern Sweden (OLIN) studies four adult cohorts, randomly selected from the general population, were re-examined with spirometry and structured interview in 2002–2004. All subjects with COPD according to the Global Initiative for Obstructive Lung Disease (GOLD) spirometric criteria (13), $FEV_1/FVC < 0.70$, were identified, $n = 993$, together with an age- and gender matched reference population without obstructive lung function impairment, $n = 993$ (14). This study cohort, $n = 1986$, has been invited to yearly examinations since 2005. Baseline data collected at the cohort recruitment in 2002–2004 have been used in the analyses.

Baseline measurements

Structured interview. A previously validated questionnaire was used at the structured interview (4, 7, 15). The questionnaire included questions on smoking habits, respiratory symptoms and diseases, medication, co-morbid conditions, among all cardiovascular diseases, diabetes, gastroesophageal reflux disease (GERD) and chronic rhinitis.

Spirometry

The lung function testing was performed according to the ATS guidelines (16), using a dry volume spirometer, the Mi-jnhardt Vicatest (5). The best value of forced vital capacity (FVC) and slow vital capacity (SVC) was used to define the vital capacity (VC). When the ratio of FEV_1/VC was $< 70\%$ or if FEV_1 was $< 90\%$ of predicted value a reversibility test was performed. The Swedish normal values for FEV_1 and VC by Berglund et al. were used (17).

Classification by spirometry

Spirometric classification of COPD according to GOLD, $FEV_1/VC < 0.7$, was used (13). The classification of severity of COPD includes for stages based on $FEV_1\%$ predicted.

Stage I $FEV_1 \geq 80\%$ predicted

Stage II $FEV_1 \geq 50$ and $< 80\%$ predicted

Stage III $FEV_1 \geq 30$ and $< 50\%$ predicted

Stage IV $FEV_1 < 30\%$ predicted

In the analyses disease severity in COPD was divided into stage I and stage $\geq II$. The non-COPD population was characterized by $FEV_1/VC > 0.7$. The non-COPD popula-

tion was further divided into normal lung function, $FEV_1/VC > 0.7$ and $VC > 80\%$ predicted, and restrictive lung function, $FEV_1/VC > 0.7$ and $VC < 80\%$ predicted.

Definitions

The variable “cardiovascular disease” (CVD) included heart disease, hypertension, stroke and intermittent claudication (in figures and tables labelled claudication). The variable ‘heart disease’ included self-reported angina pectoris, previous coronary artery bypass surgery, previous percutaneous coronary intervention, myocardial infarction or heart failure. GERD was defined as reported treatment for gastroesophageal reflux, hyperlipemia as reported treatment for hyperlipemia, and chronic rhinitis as reported “usually having nasal blocking or a chronically runny nose.” Bronchitis was defined as positive answer to the question “Have you had productive cough on most days during at least three months during the last year?” Smoking habits were classified into non-smokers, ex-smokers (stopped at least one year before the baseline visit), and current smokers.

Statistical analysis

Statistical calculations were made using the Statistical Package for the Social Sciences (SPSS) software version PASW 18.0. Independent sample *t*-test was used for comparison of means. The chi-squared test was used for bi-variate comparisons and to test for trends. When multiple comparisons were performed, data on presence of significance after Bonferroni correction are presented. A *p*-value of < 0.05 was regarded as significant. COPD stage I, COPD stage $\geq II$ and restrictive lung function were analysed as risk factors for diabetes, chronic rhinitis, GERD, heart disease, hypertension, intermittent claudication, stroke, and cardiovascular disease, in a multivariate model adjusting for the co-variables gender, BMI, age and smoking habits.

RESULTS

Basic characteristics

Basic characteristics of the study population are shown in Table 1. The distribution of COPD by disease severity according to GOLD was stage I 56.0%, stage II 37.6% and stage III–IV 6.4%. In subjects without obstructive lung function impairment, non-COPD, 78.1% had normal and 21.9% had restrictive lung function. BMI was significantly lower in subjects with COPD compared to non-COPD. Those with restrictive lung function had significantly higher mean age and BMI compared to both those with normal lung function and COPD. Smoking habits were highly significantly different between the groups.

Non-COPD and COPD by disease severity

All respiratory symptoms as well as bronchitis were significantly more common in subjects with COPD compared to non-COPD, and increase by disease severity (Table 2). Cardiovascular disease was significantly more common in COPD, but among the single disease entities only intermittent claudication reached statistical significance. In COPD

Table 1. Study population, basic characteristics by lung function (lf), gender, age, BMI and smoking habits

	Non-COPD	COPD	p ¹	Normal lf	Restrictive lf	p ²	p ³	p ⁴
N (%)	993	993		776 (78.1)	217 (21.9)			
GOLD I, n (%)		556 (56.0)						
GOLD II		373 (37.6)						
GOLD III-IV		64 (6.4)						
Gender, n (%)								
Men	540 (54.3)	544 (54.8)		383 (49.4)	157 (72.4)			
Women	453 (45.6)	449 (45.2)	0.857	393 (50.6)	60 (27.6)	<0.001		
Age, mean	64.3	64.8	0.332	62.8	69.7	<0.001	<0.001 ⁵	<0.001 ⁵
BMI, mean	26.58	26.06	0.003	26.48	26.95	0.113	0.027	0.004 ⁵
Smoking habits, n (%)								
Non-smoker	474 (47.7)	239 (24.2)		373 (48.1)	101 (46.5)			
Ex-smoker	394 (39.7)	419 (42.4)		293 (37.8)	101 (46.5)			
Current smoker	125 (12.6)	331 (33.5)	<0.001	110 (14.2)	15 (6.9)	0.005		

¹p-value comparing non-COPD and COPD.²p-value comparing normal and restrictive lung function in non-COPD.³p-value comparing normal lung function and COPD.⁴p-value comparing restrictive lung function and COPD.⁵After Bonferroni correction (p³, p⁴).

stage $\geq$ II heart disease was significantly more common compared to non-COPD.

Within COPD those with bronchitis had significantly higher prevalence of intermittent claudication, 9.2% vs 5.3% ($p = 0.024$), chronic rhinitis 51.7% vs 36.0% ($p < 0.001$), and GERD 20.5% vs 13.2% ($p = 0.004$) compared to those with COPD without bronchitis.

When comparing subjects with COPD to those with normal lung function and to those with non-COPD including the restrictive group, the findings were similar except when comparing COPD to normal lung function, also heart disease and hypertension were significantly more common (Table 2). Chronic rhinitis, intermittent claudication and the cardiovas-

cular diseases taken together (CVD) were significantly more common in COPD stage I as well as in stage II when compared to subjects with normal lung function. Heart disease, hypertension and GERD were significantly more common in COPD stage II but not in stage I when compared to subjects with normal lung function (Figure 1).

The overlap between heart disease, GERD and chronic rhinitis in subjects with COPD is illustrated by a proportional Venn diagram (Figure 2a). In subjects with COPD and concomitant heart disease 62.5% had chronic rhinitis and/or GERD, or 11.5% of all subjects with COPD. In subjects with COPD, bronchitis and concomitant heart disease 73.8% had chronic rhinitis and/or GERD, or 14.6% of all subjects with

Table 2. Respiratory symptoms and co-morbidity in normal compared to restrictive lung function, in non-COPD compared to COPD, and by disease severity divided into GOLD stage I and $\geq$ stage II, and in COPD compared to normal and also restrictive lung function

	Normal	Restrictive	p ¹	Non-COPD	COPD	p ²	COPD Stage I	p ³	COPD Stage $\geq$ II	p ³	p ⁴	p ⁵
Long-standing cough	20.1	24.9	0.130	21.2	32.4	<0.001	26.5	0.017 ²	39.9	<0.001 ⁶	<0.001 ⁷	0.039 ⁷
Need to clear the throat	49.5	57.6	0.034	51.3	69.9	<0.001	66.3	<0.001 ²	74.6	<0.001 ⁶	<0.001 ⁷	<0.001 ⁷
Bronchitis	21.3	34.9	<0.001	23.9	43.8	<0.001	39.1	<0.001 ²	49.6	<0.001 ⁶	<0.001 ⁷	0.005 ⁷
Recurrent wheeze	16.5	26.9	0.001	18.8	49.7	<0.001	38.5	<0.001 ²	64.0	<0.001 ⁶	<0.001 ⁷	<0.001 ⁷
Chronic rhinitis	32.3	41.0	0.017	34.2	43.1	<0.001	41.0	0.008 ²	45.8	<0.001 ⁶	<0.001 ⁷	0.573
Heart disease	13.7	24.4	<0.001	16.0	18.5	0.138	15.6	0.851	22.2	0.005 ⁶	0.006 ⁷	0.047
Stroke	6.4	9.5	0.159	7.1	7.7	0.624	7.8	0.647	7.7	0.729	0.333	0.425
Hypertension	33.9	46.1	0.001	36.6	39.6	0.171	37.9	0.596	41.6	0.070	0.015 ⁷	0.077
Claudication*	2.0	8.3	<0.001	3.4	7.0	0.001	5.6	0.052	8.7	<0.001 ⁶	<0.001 ⁷	0.521
CVD**	41.0	59.0	<0.001	44.9	50.1	0.022	47.7	0.298	53.1	0.004 ⁶	<0.001 ⁷	0.017 ⁷
Hyperlipemia	12.9	19.2	0.033	14.3	14.8	0.786	15.0	0.746	14.6	0.914	0.301	0.132
Diabetes	8.6	20.9	<0.001	11.3	10.0	0.392	9.0	0.174	11.4	0.964	0.335	<0.001 ⁷
GERD***	12.0	16.0	0.165	12.9	16.7	0.027	15.1	0.262	18.8	0.007 ⁶	0.011 ⁷	0.819

¹p-value when comparing normal lung function and restrictive lung function.²p-value when comparing non-COPD to COPD.³p-value when comparing COPD stage I and stage $\geq$ II to non-COPD.⁴p-value when comparing COPD and normal lung function.⁵p-value when comparing COPD and restrictive lung function.^{6,7}significant also after Bonferroni correction when comparing COPD stage I and stage $\geq$ II to non-COPD and COPD to normal and restrictive lung function, respectively.

*Intermittent claudication.

**Cardiovascular disease.

***Gastroesophageal reflux.

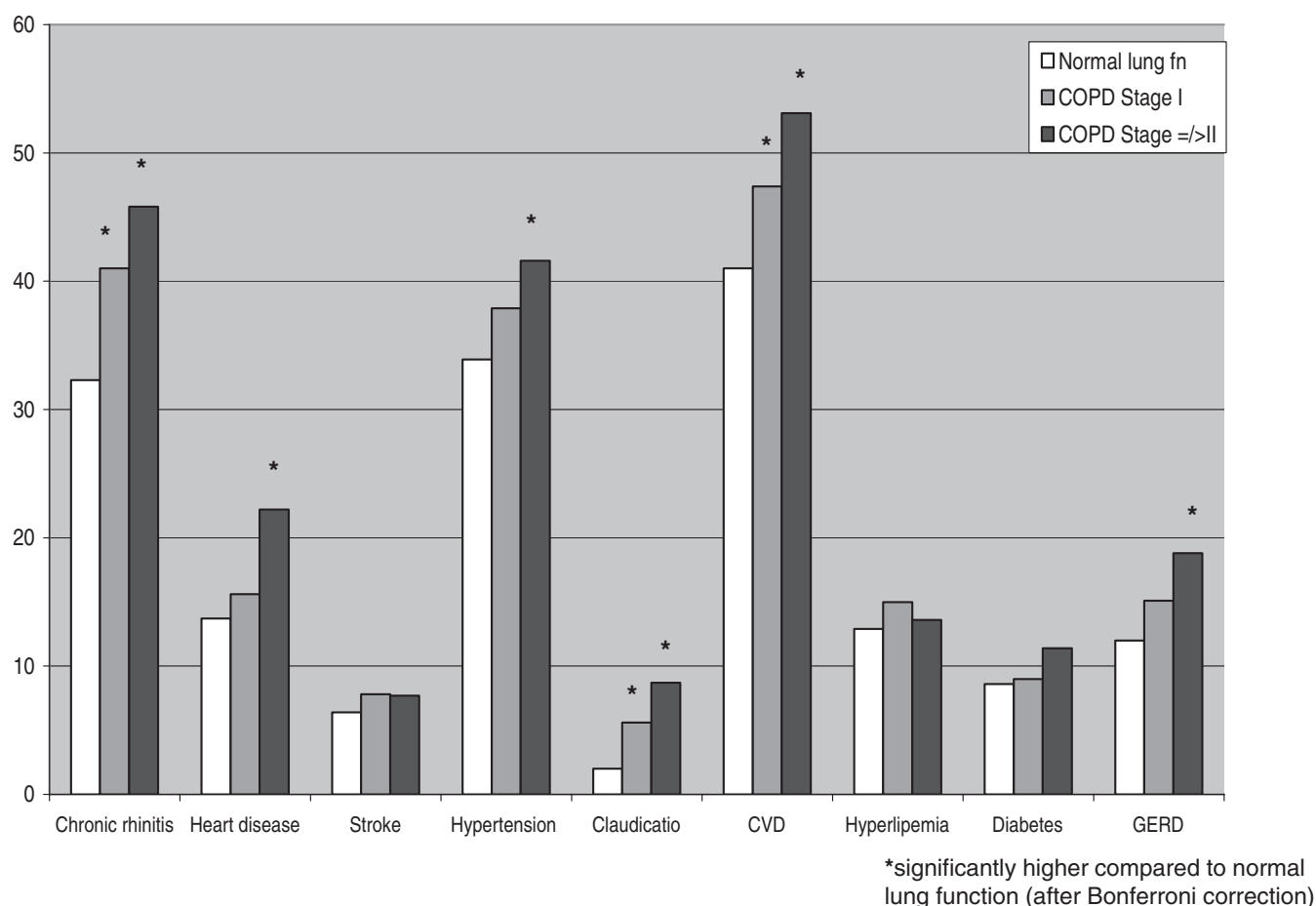


Figure 1. Symptoms and diseases in subjects with normal lung function (Nlf) and in subjects with COPD, by disease severity (divided into stage I and stage $\geq$ II), in percent.

COPD and bronchitis. In subjects with normal lung function and heart disease 42.5% had chronic rhinitis and/or GERD, or 5.7% of all subjects with normal lung function (Figure 2b).

Non-COPD; normal lung function and restrictive

All respiratory symptoms but long-standing cough was significantly more common in the restricted group compared to subjects with normal lung function. The prevalence of diabetes, hyperlipemia, and each disease entity of cardiovascular disease was higher in the restricted group, and significantly so for all but stroke (Table 2).

Gender aspects

Non-COPD and COPD were matched by gender according to study design. In the restricted group the proportion of men was significantly higher. Both men and women with COPD reported significantly more respiratory symptoms and chronic rhinitis compared to those in non-COPD. Among men, comparing subjects with COPD and non-COPD, significant differences were found for chronic rhinitis (41.2% vs 34.8%, $p = 0.030$), heart disease (23.2% vs 18.3%, $p = 0.050$) and intermittent claudication (7.0% vs 2.9%, $p = 0.004$). Correspondingly among women only chronic rhinitis (45.4% vs 33.6%, $p < 0.001$) was more common in subjects

with COPD. Comparison by gender within non-COPD and COPD, respectively, are shown in Table 3. Men had, compared to women, a significantly higher prevalence of stroke and hyperlipemia in non-COPD, and heart disease in both COPD and in non-COPD, while women had a significantly higher prevalence of hypertension in COPD.

Multivariate analyses

COPD stage I, COPD stage $\geq$ II and restrictive lung functions were analysed as risk factors of each included co-morbid condition in a multivariate model adjusting for gender, age, BMI and smoking habits (Table 4). COPD stage I yielded a significantly increased risk for intermittent claudication and chronic rhinitis, and close to for hypertension. COPD stage $\geq$ II yielded a significantly increased risk for heart disease, intermittent claudication, hypertension, cardiovascular disease, and chronic rhinitis and close to significant for GERD. If COPD was divided into the stages I, II and III-IV, stage III-IV significantly increased the risk for GERD (OR 2.48, 95% CI 1.34–4.56).

Neither COPD nor restrictive lung function increased the risk for hyperlipemia (data not shown). Restrictive lung function yielded an increased risk for intermittent claudication, cardiovascular disease, diabetes and chronic rhinitis.

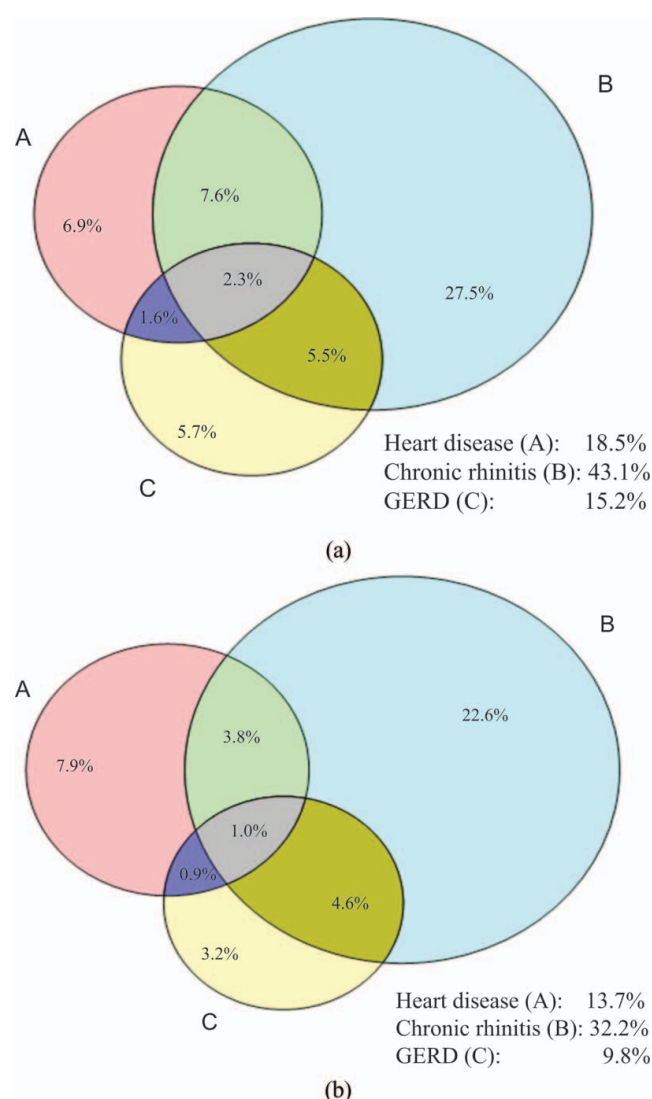


Figure 2. (a). Prevalence of and overlap between heart disease, chronic rhinitis and gastroesophageal reflux (GERD) in subjects with COPD (presented as percentage of all subjects with COPD, $n = 993$). (b). Prevalence of and overlap between heart disease, chronic rhinitis and gastroesophageal reflux (GERD) in subjects with normal lung function (presented as percentage of all subjects with normal lungfunction, $n = 776$).

Regarding gender, there was an increased risk for heart disease, stroke, hyperlipemia and diabetes in men while the risk for hypertension was increased in women (Table 4).

DISCUSSION

Our study verifies that co-morbid diseases are common in subjects with COPD and several co-morbid conditions occur already in COPD GOLD stage I. Further, also subjects with restrictive lung function have several co-morbid diseases. Our main finding was that not only bronchitis, but also chronic rhinitis and GERD, were common in subjects with COPD. These 3 separate conditions are associated to an increased risk of exacerbations in COPD (12, 18, 19). In subjects with both COPD and heart disease a majority had chronic rhinitis and/or GERD. Among subjects with COPD and bronchitis and concomitant heart disease the proportion with chronic rhinitis and/or GERD was even higher.

Cardiovascular diseases are common in COPD and contributes to the increased mortality in COPD (5, 6). In our study, cardiovascular diseases were by far the most common co-morbid conditions in subjects with COPD, corresponding to the top level of other reports (5). Taken together, cardiovascular diseases were significantly more common already in COPD stage I compared to subjects with normal lung function, and COPD stage $\geq$ II increased the risk for cardiovascular diseases by 50%. Intermittent claudication was the disease entity among cardiovascular diseases with the highest risk related to COPD; COPD stage I more than doubled and COPD stage $\geq$ II more than tripled this risk. No other disease entity among the cardiovascular diseases reached statistical significance in COPD stage I. When comparing gender, heart disease was more common in men in both COPD and non-COPD, and besides heart disease, men had an increased risk for hyperlipemia and stroke, in line with the large U.S. study where male sex was associated to cardiovascular disease (6).

In our study the prevalence of subjects treated for GERD, indicating a more severe condition than merely symptomatic GERD, was 16.7% in COPD and 18.8% in COPD stage $\geq$ II, both significantly higher compared to non-COPD. The prevalence of symptomatic GERD was 19% in 100

Table 3. Comparing respiratory symptoms and co-morbidity by gender in non-COPD and in COPD, respectively

	Non-COPD		p^1	COPD		p^1
	Men	Women		Men	Women	
Chronic rhinitis	34.8	33.6	0.691	41.2	45.4	0.178
Heart disease	18.3	13.2	0.029	23.2	12.9	<0.001
Stroke	9.2	4.6	0.010	8.5	6.7	0.304
Hypertension	34.6	38.9	0.161	36.4	43.4	0.024
Claudication*	2.9	4.0	0.377	7.0	7.0	0.993
CVD**	45.0	44.8	0.953	49.8	50.3	0.871
Hyperlipemia	17.9	10.1	0.002	16.7	12.5	0.070
Diabetes	13.2	9.1	0.064	12.3	7.2	0.011
GERD***	12.7	13.1	0.882	14.9	18.8	0.113

¹Comparing men and women.

²Heart disease or hypertension or stroke or claudication.

*Intermittent claudication.

**Cardiovascular disease.

***Gastroesophageal reflux.

Table 4. COPD stage I, COPD stage $\geq$ II and restricted lung function analysed as risk factors for heart disease, hypertension, intermittent claudication (claudication), stroke, cardiovascular disease (CVD), diabetes, GERD and chronic rhinitis in a multivariate model adjusting for the co-variables gender, BMI, smoking habits and age presented as odds ratio, OR (95% confidence interval, CI)

Lung function	Heart disease ¹	Hypertension ²	*Claudication ⁰	Stroke ¹	**CVD ⁰	Diabetes ¹	***GERD ⁰	Chronic rhinitis ⁰
Normal	1	1	1	1	1	1	1	1
COPD stage I	0.89 (0.64–1.25)	1.26 (0.99–1.61)	2.21 (1.11–4.40)	0.91 (0.56–1.48)	1.25 (0.98–1.59)	1.03 (0.67–1.58)	1.19 (0.83–1.69)	1.37 (1.09–1.74)
COPD stage $\geq$ II	1.52 (1.08–2.14)	1.41 (1.08–1.61)	3.51 (1.77–6.97)	1.05 (0.63–1.77)	1.56 (1.19–2.03)	1.32 (0.85–2.05)	1.43 (0.99–2.06)	1.73 (1.34–2.23)
Restricted	1.08 (0.72–1.62)	1.36 (0.98–1.89)	2.86 (1.29–6.31)	0.87 (0.47–1.63)	1.42 (1.02–1.97)	1.84 (1.14–2.97)	1.35 (0.83–2.20)	1.38 (1.00–1.90)

¹Increased risk in men.

²Increased risk in women.

⁰No significant gender difference.

*Intermittent claudication.

**Cardiovascular disease.

***Gastroesophageal reflux.

cases of mild-to-severe COPD from an outpatient clinic, and the prevalence increased by disease severity (20). For comparison, the prevalence of symptomatic GERD was 37% in mainly severe and very severe COPD patients on routine checkup at pulmonary clinic, and the presence of GERD increased the frequency of exacerbation (19). In our study COPD stage $\geq$ II increased the risk for GERD by 1.43, and the results indicate that GERD can be related to COPD not only in selected clinic-populations but also in general population samples. Whether GERD is related to exacerbations also in mild-to-moderate COPD has to be further explored.

COPD is associated to chronic nasal symptoms, increased nasal inflammation and to lower airway inflammation according to a recent review (12). However, the individual studies were small and did not include all severity stages of COPD. In our study the prevalence of chronic rhinitis was significantly higher in COPD compared to non-COPD. COPD, both stage I and stage $\geq$ 2 increased the risk for chronic rhinitis, independently of gender, age, BMI and smoking habits.

Not only in cardiovascular diseases (9, 21), but also in GERD (22) and nasal symptoms (12), local and systemic inflammation have been discussed in relation to airway disease. The overlap between heart diseases, chronic rhinitis and GERD in subjects with COPD is large, as illustrated by the Venn diagram, and has not been described previously in population studies. In subjects with COPD and bronchitis and concomitant heart disease almost three quarters had chronic rhinitis and/or GERD. It can be questioned whether the overlap between bronchitis, chronic rhinitis, GERD and heart disease contributes to and interact in a viscous circle aggravating the inflammatory cascade, predispose to exacerbations and also to disease progress and systemic effects in COPD. The positive effect of smoking cessation on the disease process in COPD is well known. However, the disease process continues long after smoking cessation and if the treatment of potentially modifiable conditions, as chronic rhinitis and GERD, can affect the outcome of COPD is not known.

Restrictive lung function impairment was associated to male sex, high age and high BMI. Subjects with restrictive lung function had more respiratory symptoms, heart diseases, intermittent claudication, hypertension, hyperlipemia and diabetes compared to those with normal lung function. Restrictive lung function increased the risk for intermittent claudication almost threefold and almost doubled the risk for diabetes. Those with restrictive lung function was the only group with a significantly increased prevalence of diabetes, 20.9% compared to 8.6% in subjects with normal lung function and 10.0% in subjects with COPD. It is known that restrictive spirometry is associated with increased cardiovascular mortality, and increased prevalence of diabetes and hypertension (6, 23).

The ability for a dynamic spirometry to identify restrictive lung function impairment has yet to be considered. The reasons for a restrictive pattern on dynamic spirometry are highly heterogeneous and reflect different underlying disorders such as idiopathic pulmonary fibrosis, thoracic deformities, obesity, pleural effusion, cardiac insufficiency and neuromuscular diseases. There is, however, a longitudinal

follow-up of subjects with restrictive spirometric pattern, identified by dynamic spirometry, where 38% developed obstructive lung function (23).

The remaining subjects had either inconsistent or recurrent restrictive spirometry, and they had an increased risk for mortality in diabetes, heart disease and stroke. Thus restrictive pattern on dynamic spirometry identifies a population with a high risk of serious co-morbidities, findings supported also by our results.

The strength of our study is the large number of subjects with COPD identified by standardized spirometry, comparable to that of the NHANES I (24). The distribution of disease severity is similar to what is known for the general population (4), including a majority within GOLD stages I and II. The gender- and age-matched population of similar size without having obstructive lung function impairment gives an excellent opportunity to evaluate the impact of co-morbidity in COPD and to what extent COPD is a risk factor for having cardiovascular and other diseases. The large number of subjects with COPD guarantees a large statistical power contributing to new data, for example the shown connection between intermittent claudication and COPD, and also to describe the close connections between different co-morbid conditions.

Further, a validated structured interview questionnaire was used to collect demographics and clinical information, and according to literature, there is a good agreement between the disease self-reports and objectively assessed occurrence of diseases such as hypertension, myocardial infarction and stroke (25,26); however, less good agreement with heart failure (27).

In conclusion, the burden of a wide range of symptoms and diseases with a known association to local and systemic inflammation was higher in subjects with predominantly mild-to-moderate COPD, compared to subjects with normal lung function. Besides COPD, also restrictive lung function identified a population with increased disease burden. Cardiovascular co-morbidity, recognized to affect the prognosis, was the most common in COPD. However, the influence of concurrent conditions considered less harmful, such as GERD and chronic rhinitis, on the disease progress and prognosis in COPD need to be evaluated.

ACKNOWLEDGMENT

The authors also thank the research assistants, Ann-Christine Jonsson, Sigrid Sundberg and Linnea Hedman for collecting the data. Ola Bernhoff is acknowledged for work with creating the data base of the study and Viktor Johansson for computerising the data. Further, the late associate professor, Staffan Andersson, and Håkan Forsberg are acknowledged for their contributions.

ETHICS APPROVAL

The study was approved by the Regional Ethics Committee at University Hospital of Northern Sweden and Umeå University.

DECLARATION OF INTEREST

The authors declare that they have no competing interests. The authors alone are responsible for the content and writing of the paper. Anne Lindberg designed study, analysed data, wrote the paper; Lars-Gunnar Larsson, wrote the paper; Eva Rönmark, designed study, wrote the paper; and, Bo Lundbäck, designed study, wrote the paper.

REFERENCES

- Mathers CD, Loncar D. Updated projections of global mortality and burden of disease, 2002–2030: data sources, methods and results. <http://www.who.int/healthinfo/statistics/bodprojections/paper.pdf>.
- Jansson SA, Lindberg A, Ericsson A, Borg S, et al. Cost differences for COPD with and without physician-diagnosis. *COPD* 2005; 2(4):427–434.
- Halbert RJ, Isonaka S, George D, et al. Interpreting COPD prevalence estimates. What is the true burden of disease? *Chest* 2003; 123:1684–1692.
- Lundbäck B, Lindberg A, Lindstrom M, et al. Not 15 but 50% of smokers develop COPD?—Report from the Obstructive Lung Disease in Northern Sweden Studies. *Respir Med* 2003; 97(2):115–122.
- Chatila WM, Thomashow BM, Minai OA, et al. Comorbidities in chronic obstructive pulmonary disease. *Proc Am Thorac Soc* 2008; 5:549–555.
- Mannino DM, Thom D, Swensen A. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. *Eur Respir J* 2008; 32:962–969.
- Lindberg A, Bjerg A, Rönmark 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(2):264–272.
- Siafakas NM, Vermeire P, Pride NB, et al. ERS Consensus Statement. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Respir J* 1995; 8:1398–1420.
- Sin DD, Anthonisen NR, Soriano JB, et al. Mortality in COPD: role of comorbidities. *Eur Respir J* 2006; 28:1245–1257.
- Annesi I, Kauffmann F. Is respiratory mucus hypersecretion really an innocent disorder? A 22-year mortality survey of 1,061 working men. *Am Rev Respir Dis* 1986; 134(4):688–693.
- Lundbäck B, Eriksson B, Lindberg A, et al. A 20-year follow-up of a population study-based COPD cohort-report from the obstructive lung disease in Northern Sweden studies. *COPD* 2009; 6(4):263–271.
- Hurst JR. Upper airway. 3: Sinonasal involvement in chronic obstructive pulmonary disease. *Thorax* 2010; 65:85–90.
- www.goldcopd.com.
- Lindberg A, Lundbäck B. The OLIN COPD study. Design, the first year participation and mortality. *Clin Respir J* 2008; 2:64–71.
- Lindberg A, Larsson LG, Rönmark E, et al. Decline in FEV1 in relation to incident chronic obstructive pulmonary disease in a cohort with respiratory symptoms. *COPD* 2007 Mar; 4(1):5–13.
- American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995; 152(3):1107–1136.
- Berglund E, Birath G, Bjure J, et al. Spirometric studies in normal subjects, Forced expirograms in subjects between 7 and 70 years of age. *Acta Med Scand* 1963; 173:185–192.
- Hurst JR, Vestbo J, Anzueto A, et al. Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) Investigators. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med* 2010; 363(12):1128–1138.
- Mokhlesi B, Morris AL, Huang CF, et al. Increased prevalence of gastroesophageal reflux symptoms in patients with COPD. *Chest* 2001 Apr; 119(4):1043–1048.
- Rascon Aguilar, Pamer M, Wludyka P, et al. Role of gastroesophageal reflux symptoms in exacerbations of COPD. *Chest* 2006; 130:1096–1101.
- Gan WQ, Man SF. Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and meta-analysis. *Thorax* 2004; 59:574–580.
- Brownlee IA, Aseeri A, Ward C, et al. From gastric aspiration to airway inflammation Monaldi Arch Chest Dis 2010 Jun; 73(2):54–63.
- Guerra S, Sherrill D L, Venker C, et al. Morbidity and mortality associated with the restrictive spirometric pattern; a longitudinal study. *Thorax* 2010; 65:499–504.
- Mannino DM, Buist A S, Petty TL, et al. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax* 2003; 58:388–393.
- Lampe F, Walker M, Lennon L, et al. Validity of a self-reported history of doctor-diagnosed angina. *J Clin Epidemiol* 1999; 52:73–81.
- Olofsson M, Edebro D, Boman K. Are elderly patients with suspected HF misdiagnosed? A Primary Health Care Center Study. *Cardiology* 2006; 107:226–232.
- Okura Y, Urban L, Mahoney W, 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.