Respiratory Medicine (2012) 106, 980–988

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

COPD among non-smokers — Report from the Obstructive Lung Disease in Northern Sweden (OLIN) studies

Stig Hagstad [a,b,*], Linda Ekerljung [a], Anne Lindberg [b,c], Helena Backman [b], Eva Rönmark [b,c], Bo Lundbäck [a,b]

[a] Krefting Research Centre, Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Box 424, SE-405 30, Gothenburg, Sweden
[b] Obstructive Lung Disease In Northern Sweden (OLIN) studies, Department of Medicine, Sunderby Central Hospital of Norrbotten, SE-971 89, Luleå, Sweden
[c] Department of Public Health and Clinical Medicine, University of Umeå, SE-901 85, Umeå, Sweden

Received 22 September 2011; accepted 16 March 2012
Available online 11 April 2012

KEYWORDS
COPD;
Non-smokers;
Risk factors;
Population study;
Epidemiology

Summary
Background: In westernized countries smoking and increasing age are the most important risk factors for COPD. Prevalence and risk factors of COPD among non-smokers are not well studied.
Aim: To study the prevalence and risk factors of COPD among non-smokers and to determine the proportion of non-smokers among subjects with COPD.
Methods: A random sample of 2470 subjects drawn from a population-based postal survey of 10,040 (85–88% participation) adults (aged 20–77) in Norrbotten, Sweden, were invited to structured interviews and lung function tests, and 1897 participated. COPD was classified using the fixed ratio (GOLD) definition and for comparison the lower limit of normal (LLN).
Results: The prevalence of airway obstruction was 6.9% among non-smokers and strongly age related. The prevalence of GOLD stage ≥II among non-smokers was 3.5%. Both among subjects with airway obstruction and among subjects with GOLD stage ≥II, the proportions of non-smokers were 20%. Of men with airway obstruction, 14.1% were non-smokers versus 26.8% among women. Non-smokers with GOLD stage ≥II had significantly more symptoms and higher co-morbidity than non-smokers without airway obstruction. Sex, area of domicile and exposure to environmental tobacco smoke was not significantly associated to airway obstruction among non-smokers. Using LLN for defining airway obstruction yielded a similar prevalence.

* Corresponding author. Krefting Research Centre, Department of Internal Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Box 424, SE-405 30, Gothenburg, Sweden. Tel.: +46 31 786 6719, +46 73 812 1137; fax: +46 31 786 6730.
E-mail address: stig.hagstad@gu.se (S. Hagstad).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2012.03.010

Conclusion: The prevalence of airway obstruction among non-smokers was close to 7% and was associated with increasing age. One out of seven men with airway obstruction, defined using the fixed ratio, versus one out of four women had never smoked.

Introduction

COPD is a major global health issue and is expected to be the third most common cause of death worldwide by 2030.[1] In westernized countries including Sweden, smoking and increasing age are the most important risk factors for COPD.[2–5] In contrast, COPD is not uncommon among non-smokers in developing countries where open fire stoves are used for heating of houses and cooking.[6] Until recently COPD was regarded as an entirely environmental disease with different air polluting sources being the most important causal factor. Historically, COPD has been regarded as either a predominantly emphysematous or predominantly bronchitic.[7] A more recent view is that both components exist in varying degree in most subjects with COPD, and today COPD is regarded as a syndrome with several clinically different phenotypes.[8]

In clinically based settings it is not always obvious that COPD also develops among never- smokers.[9,10] In contrast, epidemiological studies have identified a relatively large proportion of subjects with COPD who never have been smokers.[2,11,12] It is not known whether COPD in non-smokers constitute a specific phenotype, or if several clinically important phenotypes of COPD may occur also among non-smokers. Prevalence, clinical presentation including severity of disease, and particularly risk factors of COPD among never smokers are still not well studied.

Within the research program The Obstructive Lung Disease in Northern Sweden (OLIN) Studies the epidemiology of obstructive airway diseases has been studied since 1985.[2,13–15] Results indicate COPD to be common in women who never have been smokers.[2,16] The aim of this study is to investigate the prevalence and risk factors of COPD and the clinical presentation of COPD among lifelong non-smokers. A further aim is to compare COPD among non-smokers with COPD among ever-smokers with regard to differences in risk factors and clinical presentation.

Materials and methods

Study population

The study population consisted of two randomly selected samples of the responders to two postal questionnaire surveys of the OLIN Studies.

The first cohort was invited in 1985/86, and consisted of 6610 subjects born in 1919–1920, 1934–1935 and 1949–1950 living in eight representative areas of the Norrbotten County in Sweden.[13] In 1996, this cohort comprised 5933 subjects of whom 5892 could be traced. These 5892 subjects were invited to a third survey where 5189 subjects responded. Of these responders, 1500 subjects were randomly selected for a follow-up study. Out of the 1500, 1282 participated in clinical examinations including a structured interview, and 1237 performed lung function tests with acceptable technique.[2] In 1992 the third cohort of the OLIN Studies was recruited from the same area as the 1985/86 year cohort. Of 5681 invited subjects aged 20–69 years, 4851 (85%) responded. A random sample of the responders, 970 subjects, was invited to clinical examinations in 1994/95, and 664 (68%) participated in a structured interview, and 660 subjects performed acceptable lung function tests.[5] Identical methods and techniques were used in the 1994/95 and the 1996 studies, and the data from the two studies have been pooled.

The study was approved by the ethical committee at the University Hospital of Northern Sweden in Umeå.

Methods

Structured interview

The questionnaire consisted of questions about respiratory symptoms, use of medications, smoking habits, socio-economic status, history of exposure to environmental tobacco smoke and family history of obstructive airway diseases.[13] The original questionnaire was developed in 1985 for the first OLIN survey mainly from the respiratory questionnaires of the British Medical Research Council (MRC), the International Union Against Tuberculosis and Lung Diseases (IUATLD) and the questionnaires used at the US Tucson, Arizona studies, and has been used with minor modifications in all surveys of the OLIN cohorts among adults. Furthermore has it later been used in several other Swedish and Northern European studies.[17–20] The interviews and the lung function tests as well were performed by specially trained nurses.

Lung function tests

The lung function tests were performed using a dry spirometer (Mijnhardt Vicatest 5, The Netherlands). The tests were performed following the ATS guidelines. Swedish reference values that have been found to conform well to the symptom-free population of the OLIN-studies were used.[21] A reversibility test using 0.8 mg salbutamol (Ventoline Discus®) was performed in all subjects having either a ratio of FEV1/FVC or VC <0.7 or FEV1 $<90\%$ of the predicted value.

Definitions

COPD was classified using the fixed ratio definition and disease severity staging according to the Global Initiative of COPD (GOLD) guidelines.[22] In this study, clinically relevant COPD was defined as GOLD stage $\geq$II, as several medical conditions are associated with a FEV1/FVC <0.70 and

a normal FEV1.[23] Presence of a post-bronchodilator ratio of FEV1/FVC <0.70 was termed airway obstruction. For comparison, airway obstruction was defined also by using the lower limit of normal (LLN). For defining LLN, the equation by Viljanen et al., Finland,[24] in which the LLN has been estimated at 88% of predicted for both men and women. Our study population, as well as the study area, is climatologically similar to Finland.

Non-smokers were defined as those who had smoked on average <1 cigarette/day for <1 year or had never smoked. Ex-smokers were defined as subjects who had ceased smoking at least 12 months prior to the interview. Ever-smokers refer to either current or ex-smokers. Urban areas were defined as having >10,000 inhabitants, small towns 2000–9999 and rural areas as <2000 inhabitants. Socio-economic status was based on reported occupation according to definitions by Statistics Sweden. Subjects who reported previous or current history of angina pectoris, myocardial infarction or congestive heart failure were referred to as "any cardiac disease".

A subject who reported wheezing at any time 12 months prior to the study was defined as having "any wheeze". Dyspnoea was graded according to the modified Medical Research Council dyspnoea scale and significant dyspnoea was regarded as grade 2 or higher.[25] Any nasal symptom was considered positive if the subject reported a history of rhinitis, nasal congestion or nasal polyps. Family history of obstructive airway disease was considered positive in those subjects who reported a first-degree relative with asthma, chronic bronchitis, emphysema or COPD. Use of medication for obstructive airway disease was considered positive if the subject reported past or present use of any asthma- or other bronchodilating medication. History of environmental tobacco smoke during childhood was considered positive if at least one person in the household was a habitual indoor smoker during the subject's childhood. Other pulmonary disease was considered positive if the subject reported any pulmonary disease apart from obstructive airway disease (asthma, chronic bronchitis or emphysema).

Contact with health care was considered to have occurred if the subject reported having either sought medical attention for respiratory symptoms other than common cold, to have visited the emergency room for respiratory symptoms, or to have been admitted due to respiratory illnesses.

Analyses

Statistical analyses were performed using the statistical package for the social sciences (PASW) version 18. Fisher's exact test was used for bi-variate comparisons between groups and Mantel–Haenzsel was used for test for trend. Consistently, a *p*-value of <0.05 was considered significant.

Calculations of odds ratios (OR) and 95% confidence intervals (CI) were performed using multiple logistic regression analysis with dependent variables airway obstruction and GOLD stage ≥II in non-smokers. The independent variables included sex, age group, area of domicile, socio-economic group and exposure to environmental tobacco smoke (ETS) at home, family history of obstructive airway disease and previous physician diagnosis of asthma.

Table 1 Smoking habits by age and sex (%). Difference (*p*-value) by age and sex.

	≤50 years		51-65 years		≥66 years			All ages			
	M	F	M	F	M	F	*p*-Value[a]	M	F	Total	*p*-Value[b]
(*N*)	450	482	344	346	152	169		946	997	1943	
Non-smokers (%)	36.2	39.2	31.1	51.4	24.3	73.4	**<0.001**	32.5	49.2	41.1	**<0.001**
Ex-smokers (%)	36.2	26.3	44.5	22.5	66.4	18.3	**0.002**	44.1	23.7	33.6	**<0.001**
Current smokers (%)	27.6	34.4	24.4	26.0	9.2	8.3	**<0.001**	23.5	27.1	25.3	0.068

Bold text indicates statistical significance.
[a] Test for trend comparing smoking status by age group
[b] Comparing smoking status by sex

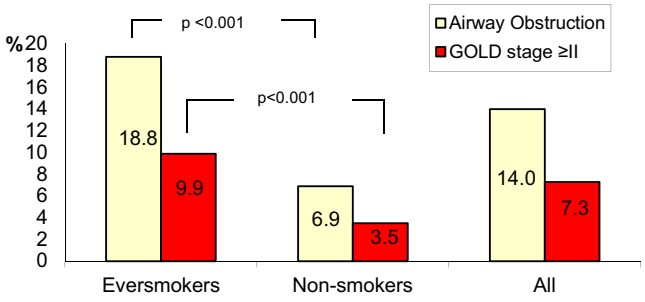

Fig. 1 Prevalence (%) of airway obstruction in ever- and never-smokers, respectively, by disease severity. Difference (*p*-value) between ever- and non-smokers.

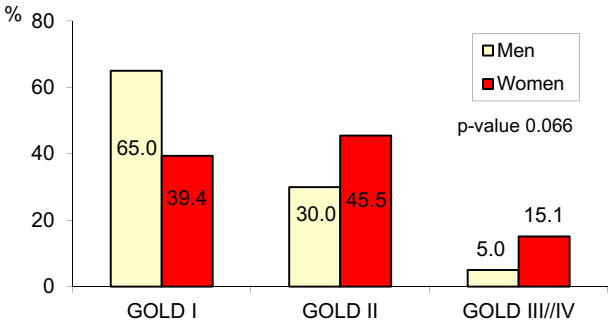

Fig. 2 Distribution (%) of COPD by GOLD severity stages among non-smoking men and women. Test for trend comparison between men and women.

Results

Participation by smoking habits and prevalence of airway obstruction

Seven hundred and ninety-eight non-smokers completed the interview and 770 (96.5%) the lung function tests. By comparison 653 ex-smokers and 492 current smokers completed the interview and 646 (98.9%) ex-smokers and 480 (97.6%) current smokers performed lung function tests. Among all participating subjects, 41.1% were non-smokers. Never-smoking was more common among women in all age groups, although this gender difference was decidedly less marked in the youngest age group. Ex-smokers were predominately male, while there was no gender difference among current smokers (Table 1).

Of non-smokers 6.9% (6.6% among men; 7.0% women; n.s.) had airflow obstruction according to the GOLD spirometric criteria compared to 15.2% among ex-smokers and 23.8% among current smokers ($p < 0.001$).

The prevalence of COPD GOLD stage ≥II was 3.5% among non-smokers versus 7.4% among ex-smokers and 13.1% among current smokers ($p < 0.001$). Overall, the prevalence of airflow obstruction was 14.0% and of GOLD stage ≥II 7.3% (Fig. 1). Of the 53 non-smokers with airflow obstruction, there were 26 subjects with GOLD stage I, 21 with GOLD stage II, 5 with GOLD stage III, and 1 subject with GOLD stage IV (Table 2).

Altogether, among all subjects fulfilling the GOLD spirometric criteria of airway obstruction, non-smokers accounted for 20.0%. Correspondingly, among subjects with GOLD stage ≥II non-smokers accounted for 19.6%. By gender, 14.1% of men with airflow obstruction were non-smokers versus 26.8% of women ($p = 0.013$) (Fig. 2). Among non-smokers a significant association ($p < 0.001$) between increasing age and prevalence of airflow obstruction was found (Table 2).

Relation to socio-economic status and environmental tobacco smoke

No significant difference between non-smokers without airflow obstruction and the subjects with GOLD stage ≥II was found in socio-economic status, area of domicile and exposure to ETS, apart from exposure to tobacco smoke at current workplace, which was less common among the subjects with GOLD stage ≥II than those without airflow obstruction. Regarding socio-economic status, there was a trend of a greater proportion of ever-smokers in manual workers in industry (Table 3).

Respiratory symptoms and co-morbidity in non-smokers with COPD

When comparing non-smokers with versus without airflow obstruction a trend was noted towards more symptoms and higher co-morbidity. However, this was not entirely of statistical significance. When comparing the non-smokers with GOLD stage I with those without airflow obstruction, no

Table 2 Prevalence (%) of airway obstruction among non-smokers by age group and disease severity (GOLD stage) in men and women. Difference (*p*-value) by age and sex.

	≤50 years		51-65 years		≥66 years		All ages			*p*-Value	
	M	W	M	W	M	W	M	W	Total (*n*)	By age[a]	By sex[b]
(*N*)	160	185	106	172	35	112	301	469	770		
GOLD I	2.5	1.1	5.7	2.3	8.6	6.3	2.8	2.8	26	**0.003**	0.309
GOLD II	1.3	2.2	0.9	2.3	8.6	6.3	2.0	3.2	21	**0.004**	0.372
GOLD III/IV	0	0.5	0	0.6	2.9	2.7	0.3	1.1	6	**0.010**	0.413
All COPD	3.8	3.8	6.6	5.2	20.0	15.2	6.6	7.0	53	**<0.001**	0.885

Bold text indicates statistical significance.
[a] Test for trend comparing disease severity by each GOLD stage respectively and age group.
[b] Comparing disease severity by each GOLD stage respectively and sex.

Table 3 Demographic and exposure characteristics (%): exposure to environmental tobacco smoke, socio-economic status and area of domicile by smoking habits and presence of GOLD stage ≥II. Difference (*p*-value) by having GOLD stage ≥II or not having airway obstruction (AO) in non-smokers and ever-smokers, respectively.

Variables	Categories	Non-smokers			Ever-smokers			
		Not AO	GOLD≥II	*p*-Value[a]	Not AO	GOLD≥II	*p*-Value[b]	*p*-Value[c]
	(*N*)	717	27		914	111		
Exposure to environmental tobacco smoke	At home	39.0	37.0	1.000	85.7	92.8	**0.039**	**<0.001**
	At current workplace	28.0	7.4	**0.015**	41.2	30.9	**0.039**	**0.014**
	At previous workplace	68.6	70.8	1.000	76.3	86.5	**0.018**	0.072
	At home during childhood	52.7	40.7	0.244	64.0	46.8	**0.001**	0.668
Socio-economic status	Manual workers in industry	17.5	13.0	0.648[d]	22.8	31.8	0.155[d]	0.566[d]
	Manual workers in service	29.7	34.8		26.7	28.0		
	Non-manual assistant employees	15.4	30.4		15.3	10.3		
	Civil servants and academics	28.3	13.0		27.4	16.8		
	Self-employed and others	9.1	8.7		7.7	13.1		
Area of domicile	Urban	60.6	42.3	0.266[d]	60.4	58.7	0.680[d]	0.319[d]
	Small town	22.6	42.3		25.5	25.7		
	Rural area	16.8	15.8		14.2	15.6		

Bold text indicates statistical significance.
[a] Not AO versus GOLD≥II in non-smokers.
[b] Not AO versus GOLD≥II in ever-smokers.
[c] GOLD≥II in non-smokers versus ever-smokers.
[d] Test for trend.

difference was found in symptoms or co-morbidity (data not shown). After stratifying by disease severity and comparing the non-smokers with GOLD stage ≥II and those without airflow obstruction, significantly more symptoms and a higher ratio of co-morbidity was found. In addition a prior diagnosis of asthma, but not of chronic bronchitis or emphysema, was significantly more common among subjects with GOLD stage ≥II in non-smokers (Table 4). Current or prior use of medication for obstructive airway disease was also markedly more common among the non-smokers with GOLD stage ≥II (59.3%) than those without airflow obstruction (16.6%).

Of non-smokers with GOLD stage ≥II, 40.7% had a prior diagnosis of asthma and 11.1% had a prior diagnosis of chronic bronchitis or emphysema. Among ever-smokers with the same disease severity 29.7% had a prior diagnosis of asthma and 27.9% a diagnosis of chronic bronchitis or emphysema. History of tuberculosis was significantly more common among the ever-smokers with GOLD stage ≥II compared to those without airway obstruction, but there was no significant difference in the never-smoking group. A family history of obstructive airway disease was significantly more prevalent among subjects with GOLD stage ≥II compared to subjects without airway obstruction (Table 4).

Risk factors for COPD among non-smokers

The most predominant risk factor for airway obstruction among non-smokers was increasing age. Further, a previous diagnosis of asthma was an independent risk factor for airway obstruction among non-smokers and among the subjects with GOLD stage ≥II. A family history of obstructive airway disease remained a significant risk factor for GOLD≥II also in the multivariate setting. Sex, area of domicile, socio-economic status and exposure for ETS at home failed to reach statistical significance (Table 5).

Airway obstruction defined by LLN

We found the prevalence of airway obstruction among non-smokers to be 52/770 (6.8%) by using the LLN as a criterion for obstruction. In comparison to the GOLD criteria, eight elderly subjects were not classified as having airway obstruction when using the LLN-criterion, while seven younger subjects became classified as having obstruction. The distribution by gender and severity was similar. When using multivariate logistic regression risk analysis, age >65 years versus age ≤50 years yielded an OR of 2.20 (95% CI 1.11—4.40) and physician-diagnosed asthma an OR of 2.43 (95% CI 1.18—5.00). Thus both age and asthma remained independent risk factors for airway obstruction in never-smokers, but the odds ratios was lower in comparison with obstruction defined by using the fixed ratio.

Discussion

In our study non-smokers accounted for 20% of all subjects with airway obstruction. This is in line with previous results from the US NHANES III study (25%), the Austrian part of the BOLD study (18%), and the ECRHS (17%),[11,26,27] although lower when compared to studies from developing countries and regions such as the Chinese CESCOPD study (39%) and the Columbian PREPOCOL study (38%) where use of biomass fuel and tuberculosis is considerably more common than in Europe and USA.[28,29]

Using both the fixed ratio of FEV_1/VC below 0.7 and the lower limit of normal (LLN) for defining airway obstruction yielded a similar prevalence, about 7%, of obstruction in never-smokers. As expected, somewhat fewer subjects among the elderly and slightly more among the younger

Table 4 Respiratory symptoms, co-morbidity, family history of obstructive airway disease, health care consumption and previous physician diagnosis of obstructive airway disease by smoking status and disease severity (%). Difference (*p*-value) by having or not having GOLD stage ≥II or not having airway obstruction (AO) in non-smokers and ever-smokers, respectively.

Symptom or condition	Non-smokers			Ever-smokers			
	Not AO	GOLD≥II	*p*-Value[a]	Not AO	GOLD≥II	*p*-Value[b]	*p*-Value[c]
(*N*)	717	27		914	111		
Sputum production	19.4	55.6	**<0.001**	25.2	61.3	**<0.001**	0.663
Long-standing cough	42.8	81.5	**<0.001**	47.4	80.2	**<0.001**	1.000
Chronic productive cough	5.6	11.1	0.201	10.3	19.8	**0.006**	0.407
Recurrent wheeze	19.5	55.6	**<0.001**	27.4	69.4	**<0.001**	0.180
Any wheeze	25.7	59.3	**<0.001**	37.6	73.0	**<0.001**	0.168
Dyspnoea	10.5	33.3	**0.002**	9.2	41.4	**<0.001**	0.515
History of rhinitis	21.3	25.9	0.632	16.5	15.3	0.892	0.255
Any nasal symptoms	39.2	59.3	**0.045**	40.5	40.5	1.000	0.088
History of cardiac disease	7.8	22.2	**0.019**	9.5	22.5	**<0.001**	1.000
Hypertension	24.8	25.9	0.825	19.4	35.1	**<0.001**	0.495
Respiratory disease during childhood	18.5	33.3	0.076	18.8	17.1	0.796	0.106
History of TBC	2.4	3.7	0.490	2.1	6.3	**0.017**	1.000
History of other pulmonary disease	24.7	51.9	**0.003**	27.7	51.4	**<0.001**	1.000
Previous physician diagnosis of asthma	9.6	40.7	**<0.001**	9.6	29.7	**<0.001**	0.357
Previous physician diagnosis of chronic bronchitis/emphysema	4.2	11.1	0.113	6.2	27.9	**<0.001**	0.083
Use of medication for obstructive airway disease	16.6	59.3	**<0.001**	15.1	43.6	**<0.001**	0.196
Family history of obstructive airway disease	14.9	32.0	**0.042**	25.0	30.6	0.223	1.000
Previous contact with health care due to respiratory symptoms	27.3	59.3	**0.001**	27.6	54.1	**<0.001**	0.671

Bold text indicates statistical significance.
[a] Not AO versus GOLD≥II in non-smokers.
[b] Not AO versus GOLD≥II in ever-smokers.
[c] GOLD≥II in non-smokers versus ever-smokers.

were classified as having airway obstruction when the LLN was used for defining obstruction. A previous study in ages 22–72 years, the former ERS-criteria[30] and the fixed ratio of 0.7 also resulted in a similar prevalence of airway obstruction, about 14%, among all studied and 6–7% among non-smokers.[5] The former ERS-criteria yielded a prevalence of 12.5% in an Italian study in similar ages.[31] Results from the BOLD studies in middle aged and elderly suggest lower prevalence estimates of airway obstruction when using the LLN compared with the fixed ratio.[32]

Our observation that increasing age is a risk factor for airway obstruction in non-smokers, as well as for COPD in general, is in accordance with previous findings,[19,33] yet the relationship with sex is not entirely clear. Some studies have found non-smokers with airway obstruction to be predominantly male,[28,34] while others have found female sex to be a risk factor.[35,36] In our study we found that although among all subjects with airway obstruction the proportion of non-smokers was higher in women, the prevalence of airway obstruction among non-smokers was similar in men and women and sex was not an independent risk factor for airway obstruction in non-smokers according to the multivariate analysis.

On a global scale, exposure to biomass fuel has been presented as a major risk factor for COPD.[9] It has been proposed that use of biomass fuel could be more prevalent than previously assumed also in developed countries.[37] However, we lacked data to analyze this. More research is needed to properly evaluate to what degree biomass fuel might attribute to COPD in high income countries.

In our material a prior history of tuberculosis as a risk factor of airway obstruction in non-smokers did not reach statistical significance, although such a trend could be noted. This can probably be attributed to the low numbers entailed. Numerous studies have shown a link between tuberculosis and airway obstruction,[34,38–41] which also may help to explain the higher prevalence of COPD among non-smokers in developing regions.

When comparing the clinical presentation between the non-smokers without airway obstruction and GOLD stage ≥II, the subjects with more severe obstruction had significantly more symptoms, whereas when comparing non-smokers without airway obstruction with the non-smokers with GOLD stage I, no difference was found in symptoms or co-morbidity. There has been a discussion on the validity of classifying subjects without known risk factors or symptoms as part of the COPD syndrome based on spirometries alone, especially in older subjects.[42,43] Others have proposed that the established fact of under-diagnosis is a greater threat than potential over-diagnosis,[44,45] and we are inclined to agree. It remains well known that COPD remains underdiagnosed, even in symptomatic subjects and also among those with a more severe disease.[16,46,47] Thus, subjects who are not obviously a part of a high risk group can be expected to be at even greater risk for underdiagnosis.

Table 5 Risk factors (Odds ratios and 95% confidence intervals, CI) among non-smokers for COPD according to GOLD and GOLD≥II by multiple logistic regression analysis.

Variables	Categories	Independent variables		Dependent variables	
		All COPD		COPD-GOLD≥II	
		OR	95% CI	OR	95% CI
Age	≤50 years	1		1	
	51–65 years	1.69	0.78–3.68	1.24	0.39–3.96
	≥66 years	**5.56**	**2.53–12.21**	**6.06**	**2.09–17.61**
Sex	Men	1		1	
	Women	0.82	0.41–1.65	1.27	0.47–3.62
Family history of obstructive airway disease	No	1		1	
	Yes	1.81	0.88–3.73	**2.90**	**1.12–7.53**
Environmental tobacco smoke	No	1		1	
	At home	1.02	0.55–1.89	0.49	0.20–1.23
Area of domicile	Rural	1		1	
	Urban	1.08	0.48–2.41	1.06	0.33–3.44
Physician-diagnosed asthma	No	1		1	
	Yes	**2.96**	**1.44–6.08**	**5.91**	**2.39–14.60**
Socio-economic group	Academics	1		1	
	Manual workers in industry	0.86	0.32–2.29	1.27	0.23–7.00
	Manual workers in service	0.67	0.27–1.69	1.60	0.37–6.96
	Assistant non-manual employees	1.28	0.52–3.16	3.47	0.81–14.80
	Self-employed	0.88	0.24–3.24	1.74	0.23–13.04
	Housewives and others	0.84	0.19–3.70	0.78	0.06–10.12
	Unknown	1.07	0.25–4.62	2.77	0.44–17.44

Bold text indicates statistical significance.

Among the non-smokers with GOLD stage ≥II, 26% had a history of rhinitis and 59% reported any nasal symptoms, while among ever-smokers with the same disease severity 15% had a history of rhinitis and 40% had any nasal symptoms. This could indicate a different phenotype for the non-smokers who develop chronic obstruction. One study of COPD in non-smokers with in depth examinations of sputum and radiological profiles found evidence of two subgroups divided by sputum profiles. One group showed significant sputum eosinophilia and the other group had a raised neutrophilic sputum count. In the former group, although a quarter of the subjects had positive allergen-specific IgE, there was no underlying evidence of pre-existing asthma. The latter group showed a high prevalence of organ-specific autoimmune disease. This would indicate that there could be various underlying causes of chronic obstruction in non-smokers.[48]

More than a half of the non-smokers (59%) with GOLD stage ≥II reported that they had previously been in contact with either their primary care physician or a hospital due to respiratory symptoms as opposed to 27% of those without airway obstruction. In addition, among non-smokers with GOLD stage ≥II 59% reported a history of use of medication for obstructive airway disease as opposed to one out of six subjects without airway obstruction. Among the ever-smokers, 44% with GOLD stage ≥II reported past or present use of any medication for obstructive airway disease. This might be due to the fact that when these surveys were conducted, there were fewer therapeutic alternatives for the treatment of COPD. Whatever the cause, the figures imply that the group as a whole does suffer more from their condition regardless of the underlying diagnosis.

Using multiple logistic regression analysis we found increasing age, a previous diagnosis of asthma and a family history of obstructive airway disease to be statistically significant risk factors for airway obstruction in non-smokers, but not exposure to environmental tobacco smoke. The relationship between environmental tobacco smoke and asthma,[49] as well as morbidity in general,[50] has been thoroughly investigated. However, this relationship has also been implicated in some studies of COPD.[51,52] When viewing some of the studies focused on COPD in non-smokers, the relationship between airway obstruction and environmental tobacco smoke is not established in some studies[11,26] while others have found environmental tobacco smoke to be a risk factor.[28] These conflicting results might be associated with the size of the study population. To ensure that the sample size is sufficient to infer valid statistical relationships, we will in upcoming studies increase the statistical power by pooling data from several cohorts in order to study the impact of potential risk factors for COPD in non-smokers, such as environmental tobacco smoke, living close to heavy trafficked roads and other possible risk factors for COPD.

As in all studies of COPD among non-smokers, some doubt remains whether all non-smokers with airway obstruction in our study should be diagnosed specifically with COPD, or if some or even several of them should be

labelled with another diagnosis. In our material half of the non-smokers fulfilling the spirometric criteria of GOLD had a diagnosis of obstructive airway disease. Of them the majority were classified as having or having had asthma. Thus some could have or have had an asthma that progressed into chronic obstruction as asthma has been identified as a risk factor of COPD.[53] However, that half of the non-smokers with GOLD stage ≥II had no diagnosis of any obstructive lung disease at all this implies that the total burden of disease fail to receive appropriate attention.

Strengths of this study include the total number of subjects involved, exact spirometry and accurate mapping of risk factors. Limitations of this study include the low numbers of non-smokers with COPD, especially those with more severe obstruction, as well as lack of data of exposure to biomass fuel and occupationally related noxious gases.

We conclude that a substantial proportion of the subjects fulfilling the criteria of COPD according to GOLD had never smoked, and half of the non-smokers with GOLD stage ≥II had no prior diagnosis of any obstructive lung disease. Airway obstruction in non-smokers was associated with increasing age, but no gender difference was found. The non-smokers with GOLD stage ≥II had significantly more symptoms than non-smokers without airway obstruction as well as significantly more co-morbid conditions. The origin of airway obstruction in non-smokers in western countries is still not well understood.

Conflict of interest

We declare no conflict of interest.

Acknowledgments

The Swedish Heart Lung Foundation and the Health Authorities of Norrbotten are acknowledged for financial support of the data collection and the staff of the OLIN Studies for collecting the data. The VBG Group Herman Krefting Foundation for Asthma and Allergy Research is gratefully acknowledged for funding of the first author for the time for the analyses and writing of the manuscript.

References

1. Murray C, Lopez A. Alternative projections of mortality and disability by cause 1990—2020: global burden of disease study. *Lancet* 1997;**349**:1498—504.
2. Lundbäck B, Lindberg A, Lindström M, Rönmark E, Jonsson AC, Jönsson E, et al. Not 15 but 50% of smokers develop COPD? — report from the obstructive lung disease in Northern Sweden Studies. *Respir Med* 2003;**97**:115—22.
3. Raherison C, Girodet P-O. Epidemiology of COPD. *Eur Respir Rev* 2009;**18**:213—21.
4. Viegi G, Pistelli F, Sherill DL, Maio S, Baldacci S, Carrozzi L. Definition, epidemiology and natural history of COPD. *Eur Respir J* 2007;**30**:993—1013.
5. Lindberg A, Jonsson AC, Rönmark E, Lundgren R, Larsson LG, Lundbäck B. Prevalence of chronic obstructive pulmonary disease according to BTS, ERS, GOLD and ATS criteria in relation to Doctor's diagnosis, symptoms, age, gender and smoking habits. *Respiration* 2005;**72**:471—9.
6. Hu G, Zhou Y, Tian J, Yao W, Li J, Li B, et al. Risk of COPD from exposure to biomass smoke: a metaanalysis. *Chest* 2010;**138**:20—31.
7. Fletcher C, Peto R, Tinker C, Speizer FE. *The natural history of chronic bronchitis and emphysema*. London: Oxford University Press; 1976.
8. Friedlander AL, Lynch D, Dyar LA, Bowler RP. Phenotypes of chronic obstructive pulmonary disease. *COPD* 2007;**4**:355—84.
9. Salvi SS, Barnes PJ. Chronic obstructive pulmonary disease in non-smokers. *Lancet* 2009;**374**:733—43.
10. Izquierdo JL, Martin A, de Lucas P, Rodriguez-Gonzales-Moro JM, Almonacid C, Paravisini A. Misdiagnosis of patients receiving inhalation therapies in primary care. *Int J Chron Obstruct Pulmon Dis* 2010;**5**:241—9.
11. Lamprecht B, Shirnhofer L, Kaiser B, Buist S, Studnicka M. Non-reversible airway obstruction in never smokers: results from the Austrian BOLD study. *Respir Med* 2008;**102**:1833—8.
12. Celli BR, Halbert RJ, Nordyke RJ, Schau B. Airway obstruction in never smokers: results from the third national health and nutrition examination survey. *Am J Med* 2005;**118**:1364—72.
13. Lundbäck B, Nyström L, Rosenhall L, Stjernberg N. Obstructive lung disease in northern Sweden: respiratory symptoms assessed in a postal survey. *Eur Resp J* 1991;**4**:257—66.
14. Lundbäck B, Eriksson B, Lindberg A, Ekerljung L, Muellerova H, Larsson LG, 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**:263—71.
15. Lindberg A, Eriksson B, Larsson LG, Rönmark E, Sandström T, Lundbäck B. Seven-year cumulative incidence of COPD in an age-stratified general population sample. *Chest* 2006;**129**:879—85.
16. Lindberg A, Bjerg A, Rönmark E, Larsson LG, Lundbäck B. Prevalence and underdiagnosis of COPD by disease severity and the attributable fraction of smoking. Report from the Obstructive Lung Disease in Northern Sweden studies. *Respir Med* 2006;**100**:264—72.
17. Montnemery P, Bengtsson P, Elliot A, Lindholm LH, Nyberg P, Löfdahl CG. Prevalence of obstructive lung diseases in relation to living environment and socio-economic group. *Respir Med* 2001;**95**:744—52.
18. Kotaniemi JT, Lundbäck B, Nieminen MM, Sovijärvi AR, Laitinen LA. Increase of asthma in adults in northern Finland? — a report from the FinEsS study. *Allergy* 2001;**56**:169—74.
19. Lindstrom M, Kotaniemi J, Jönsson E, Lundbäck B. Smoking, respiratory symptoms and diseases: a comparative study between Northern Sweden and Northern Finland: report from the FinEsS study. *Chest* 2001;**119**:852—61.
20. Meren M, Jannus-Pruljan L, Loit HM, Polluste J, Jönsson E, Kiviloog J, et al. Asthma, chronic bronchitis and respiratory symptoms among adults in Estonia according to a postal questionnaire. *Respir Med* 2001;**95**:954—64.
21. Berglund E, Birath G, Grimsby G, Kjelmer I, Sandqvist L, Södeholm B. Spirometric studies in normal subjects. forced expirograms in subjects between 7 and 70 years of age. *Acta Med Scand* 1963;**173**:185—92.
22. Rabe KF, Hurd S, Anzueto A, Barnes PJ, Buist SA, Calverley P, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;**176**:532—55.
23. Celli BR, Halbert RJ, Isonaka S, Schau B. Population impact of different definitions of airway obstruction. *Eur Resp J* 2003;**22**:268—73.
24. Viljanen AA, Haltunen PK, Kreus K-E, Viljanen BC. Spirometric studies in non-smoking, healthy adults. *Scand J Clin Lab Invest* 1982;**42**:5—20.
25. Mahler DA, Wells CK. Evaluation of clinical methods for rating dyspnea. *Chest* 1988;**93**:580—6.

26. Behrendt CE. Mild and moderate-to-severe COPD in nonsmokers: distinct demographic prophiles. *Chest* 2005;**128**: 1239—44.
27. Cerveri I, Accordini S, Verlato G, Corsico A, Zoia MC, Casali L, et al. European Community Respiratory Health Study (ECRHS) study group. Variations in the prevalence across countries of chronic bronchitis and smoking habits in young adults. *Eur Resp J* 2001;**18**:85—92.
28. Zhou Y, Wang C, Yao W, Chen P, Kang J, Huang S, et al. COPD in Chinese nonsmokers. *Eur Resp J* 2009;**33**:509—18.
29. Caballero A, Torres-Duque CA, Jaramillo C, Bolivar F, Sanabria F, Osorio P, et al. Prevalence of COPD in five Colombian cities situated at low, medium and high altitude (PREPOCOL study). *Chest* 2008;**133**:343—9.
30. Siafkas NM, Vermiere P, Pride NB, Paoletti P, Gibson J, Rees J, et al. Optimal assessment and management of chronic obstructive pulmonary disease (COPD). *Eur Resp J* 1995;**8**: 1396—420.
31. Viegi G, Pedreschi M, Pistelli F, Di Pede F, Baldacci L, Giunti C, et al. Prevalence of airways obstruction in a general population. *Chest* 2000;**117**:339S—45S.
32. Vollmer WM, Gíslason T, Burney P, Enright PL, Gulsvik A, Buist AS, et al. Comparison of spirometry criteria for the diagnosis of COPD: results from the BOLD study. *Eur Resp J* 2009;**34**:588—97.
33. Fukuchi Y, Nishimura M, Ichinose M, Adachi M, Nagai A, Kuriyama T, et al. COPD in Japan: the Nippon COPD epidemiology study. *Respirology* 2004;**9**:458—65.
34. Bridevaux P-O, Probst-Hensch NM, Schindler C, Curjuric I, Felber Dietrich D, Braendli O, et al. Prevalence of airflow obstruction in smokers and never-smokers in Switzerland. *Eur Respir J* 2010;**36**:1259—69.
35. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (The BOLD Study): a population-based prevalence study. *Lancet* 2007;**370**:741—50.
36. Miravittles M, Ferrer M, Pont A, Luis Viejo J, Fernando Masa J, Gabriel R, et al. Characteristics of a population of COPD patients identified from a population-based study. Focus on previous diagnosis and never smokers. *Respir Med* 2005;**99**:985—95.
37. Orozco-Levi M, Garcia-Aymerich J, Villar J, Ramirez-Sarmiento A, Anto JM, Gea J. Wood exposure and risk of chronic obstructive pulmonary disease. *Eur Respir J* 2006;**27**:542—6.
38. Brashier B, Gangavane S, Valsa S, Gaikwad SN, Ghorpade SV, Mandrekar S, et al. Almost half the patients treated for pulmonary tuberculosis (TB) show evidence of obstructive airway disease (OAD). European Respiratory Society Annual Congress, Stockholm, Sweden; Sept 15—19, 2007. Abstr E2585.
39. Wilcox PA, Ferguson AD. Chronic obstructive airway disease following treated pulmonary tuberculosis. *Respir Med* 1989;**83**: 195—8.
40. Ehrlich RI, White N, Norman R, Laubscher R, Steyn K, Lombard C, et al. Predictors of chronic bronchitis in South African adults. *Int J Tuberc Lung Dis* 2004;**8**:369—76.
41. Menezes AM, Hallal PC, Perez-Padilla R, Jardim JR, Muino A, Lopez MV, et al. Tuberculosis and airflow obstruction: evidence from the PLATINO study in Latin America. *Eur Respir J* 2007;**30**: 1180—5.
42. Chilvers ER, Lomas DA. Diagnosing COPD in non-smokers: splitting not lumping. *Thorax* 2010;**65**:465—6.
43. Hardie JA, Buist AS, Vollmer WM, Ellingsen I, Bakke PS, Morkve O. Risk of over-diagnosis of COPD in asymptomatic elderly never-smokers. *Eur Respir J* 2002;**20**:1117—22.
44. Mannino DM. Defining chronic obstructive pulmonary disease and the elephant in the room. *Eur Respir J* 2007;**30**:189—90.
45. Mannino DM, Buist AS, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function? *Thorax* 2007;**62**:237—41.
46. Bednarek M, Maciejewski J, Wozniak M, Kuca P, Zielinski J. Prevalence, severity and underdiagnosis of COPD in the primary care setting. *Thorax* 2008;**63**:402—7.
47. Yawn B, Mannino D, Littlejohn T, Ruoff G, Emmett A, Raphiou I, et al. Prevalence of COPD among symptomatic patients in a primary care setting. *Curr Med Res Opin* 2009; **25**:2671—7.
48. Birring SS, Brightling CE, Bradding P, Entwistle JJ, Vara DD, Grigg J, et al. Clinical, radiologic, and induced sputum features of chronic obstructive pulmonary disease in nonsmokers. *Am J Respir Crit Care Med* 2002;**166**:1078—83.
49. Janson C. The effect of passive smoking on respiratory health in children and adults. *Int J Tuberc Lung Dis* 2004;**8**:510—6.
50. Öberg M, Jaakola MS, Woodward A, Peruga A, Pruss-Ustun A. Worldwide burden of disease from exposure to second-hand smoke: a retrospective analysis of data from 192 countries. *Lancet* 2011;**377**:139—46.
51. Eisner MD, Balmes J, Katz PP, Trupin L, Yelin EH, Blanc PD. Lifetime environmental tobacco smoke exposure and the risk of chronic obstructive pulmonary disease. *Environ Health* 2005;**4**:7.
52. Yin P, Jiang CQ, Cheng KK, Lam TH, Lam KH, Miller MR, et al. Passive smoking exposure and the risk of COPD among adults in China: the Guangzhou Biobank Cohort Study. *Lancet* 2007;**370**: 751—7.
53. Silva GE, Sherill DL, Guerra S, Barbee RA. Asthma as a risk factor for COPD in a longitudinal study. *Chest* 2004;**126**:59—65.