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SHORT COMMUNICATION

Non-reversible airway obstruction in never smokers: Results from the Austrian BOLD study

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Summary
Background: The presence of non-reversible airway obstruction (AO) in never smokers has only received limited attention until now.
Methods: We analyzed data from the Austrian Burden of Obstructive Lung Disease (BOLD) study. We defined non-reversible AO as post-bronchodilator $FEV_1/FVC < 0.7$ which corresponds to COPD I and higher (COPD I+) according to current GOLD guidelines. Significant AO was defined as $FEV_1/FVC < 0.7$ and $FEV_1 < 80\%$ predicted (GOLD II and higher, GOLD II+). The prevalence and characteristics of non-reversible AO in never smokers were analyzed in relation to the severity of the disease.
Results: Never smokers comprised 47.3% of the study population. Non-reversible AO was seen in 18.2% of never smokers, and 5.5% of never smokers fulfilled criteria for significant non-reversible AO (GOLD stage II+). Therefore, the resulting population prevalence of significant non-reversible AO (GOLD stage II+) was 2.6%. Never smokers with non-reversible AO were predominantly female and slightly older. The airway obstruction was found to be less severe as compared with ever smokers. Despite this, 20% of never smokers with significant non-reversible AO (GOLD stage II+) reported respiratory symptoms and 50% reported impairment of quality of life. This burden of illness in never smokers was similar to that in smokers when severity of AO was taken into account.
Conclusion: Approximately every third subject with non-reversible AO has never smoked, yet still demonstrates a substantial burden of symptoms and impairment of quality of life. Never smokers should receive far greater attention when efforts are undertaken to prevent and treat chronic airway obstruction.

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Introduction

On a global scale, the majority of chronic non-reversible airway obstruction occurs in current or former smokers. However there is evidence that subjects who have never actively smoked themselves can also develop chronic airflow limitation and might thus comprise a substantial proportion of this disorder.[1]

Our understanding of genetic and environmental risk factors for the development of chronic, non-reversible airway obstruction is still incomplete and this is especially true for never smokers. Although this disorder appears to be fairly prevalent in never smokers, only a limited number of studies have described this population in greater detail.[1–3]

To estimate the burden of non-reversible airway obstruction in never smokers, we analyzed data from the population-based Austrian Burden of Obstructive Lung Disease (BOLD) study.[4] We reported the prevalence in never smokers and described the presence of symptoms and their impact on health-related quality of life.

Materials and Methods

Study population

The population consisted of participants of the Austrian Burden of Obstructive Lung Disease (BOLD) study.[4] In this study, a gender-stratified random sample of the inhabitants of Salzburg County aged 40 years and over was surveyed. The study was approved by the local Ethics Committee of Salzburg County, and all participants gave written informed consent.

Study measures

Spirometry was done according to American Thoracic Society (ATS) criteria[5] by trained and certified technicians using the NDD Easy One™ spirometer. Separate measurements were taken before and at least 15 min after two puffs of salbutamol (200 mcg). Only spirograms that met ATS acceptability and reproducibility criteria[5] were included. Of the 1349 participants with post-bronchodilator spirometry, 1258 (93%) met the quality control criteria and were included in this analysis.

Questionnaire data

The BOLD questionnaires, administered by trained and certified staff, included information on respiratory symptoms, risk factors for COPD, health status, co-morbidities, respiratory diagnoses, and limitation of activity. The BOLD Core questionnaire was developed from pre-existing validated questionnaires that had already been used in multi-national studies when possible.[6]

Definitions

In accordance to the GOLD guidelines, non-reversible airway obstruction was defined as a post-bronchodilator $FEV_1/FVC < 0.70$, which corresponds to GOLD stage I and higher. We also reported data for GOLD stage II or higher, which corresponds to $FEV_1/FVC < 0.70$ and a predicted $FEV_1 < 80\%$. COPD GOLD stage II or higher was defined as clinically significant disease. The NHANES III reference equations were used to calculate predicted values and lower limits of normal (LLNs).[7]

Doctor-diagnosed COPD was defined as a self-reported physician's diagnosis of chronic bronchitis, emphysema, or COPD.

Ever smoking (current or former smoking) was defined as smoking more than 20 packs of cigarettes in a lifetime or more than 1 cigarette/day for a year.

Exposure to passive smoke (y/n) was defined as an affirmative answer to the question asking whether anyone (other than the participant) had smoked a cigarette, pipe or cigar in the home during the past two weeks.

Exposure to agricultural dust (farming), flour, feed or grain milling, and cotton or jute processing was defined as occupational exposure to organic/biologic dust. Working with asbestos, coal mining, hard-rock mining, foundry or steel milling, and sandblasting was defined as occupational exposure to inorganic dust. Welding, fire-fighting, and chemical or plastic manufacturing was defined as occupational exposure to irritant gases, fumes or vapors. Biomass exposure included exposure to indoor open fire with coal, coke, wood, crop residue or dung.

Health status measures included four indicators of participants who: (1) responded *''excellent''* or *''very good''* when asked to rate their general health; (2) responded *''none of the time''* or *''a little of the time''* when asked how much of their time they experienced limitations in work or other activities *''as a result of your physical health,''*; (3) responded *''none of the time''* or *''a little of the time''* when asked how much of their time they accomplished less than they liked *''as a result of any emotional problems.''*; and (4) responded *''none of the time''* or *''a little of the time''* when asked how much of their time they felt downhearted or depressed *''as a result of your physical health''*.

Statistical analysis

In contrast to previously reported data,[4] no additional weighting class adjustments were made for sampling and differential response rates for different age categories. Statistical significance of differences was evaluated using the chi-squared test and the non-parametric Mann–Whitney *U*-Test. All statistical analyses were done with SAS 8.2 (SAS Institute Inc, Cary, NC, USA).

Results

Prevalence of non-reversible airways obstruction

In never smokers, the prevalence of non-reversible airway obstruction (GOLD stage I+) was 18.2%. Prevalence of COPD GOLD stage II+ was 5.5%. Altogether, never smokers comprised 27.7% of clinically significant disease (GOLD stage II+) (see Table 1). Similar GOLD stage II and higher COPD prevalences were seen when we used local prediction equations in place of the US NHANES III equations (data not shown). When the presence of non-reversible airway

Table 1 Demographic characteristics and prevalence of post-bronchodilator (PBD) airway obstruction in never smokers and ever smokers

	N	Age in years median (range)	Sex, female	PBD $FEV_1/FVC < 0.7$ (COPD GOLD I+)	PBD $FEV_1/FVC < 0.7$ & FEV_1 <80% pred. (COPD GOLD II+)
Never smoker	595 (47.3%)	58 (40–98)	320 (53.8%)*	108 (18.2%)$^+$	33 (5.5%)f
Ever smoker	663 (52.7%)	55 (40–89)	253 (38.2%)*	196 (29.6%)$^+$	86 (13.0%)f
Total	1258 (100%)	57 (40–98)	573 (45.6%)	304 (24.2%)	119 (9.5%)

*$p < 0.001$; +$p < 0.001$; f $p = 0.023$.

obstruction was based on a post-bronchodilator FEV_1/FVC ratio below the lower limit of normal (LLN), the prevalence of significant airway obstruction (FEV_1/FVC <LLN and FEV_1 <80% predicted) was 3.7%.

Risk factors for airway obstruction in never smokers

Never smokers with non-reversible airway obstruction (GOLD Stages I+) were significantly older (65.8 years vs 57.2 years, $p < 0.001$) than never smokers with normal lung function. Compared to smokers, never smokers with non-reversible airway obstruction were predominately female (e.g. 48.0% vs 38.2% for GOLD stage I, and 62.5% vs 32.9% for GOLD stage II). In our data, only occupational exposure to organic dust was found to be significant among the potential risk factors for non-reversible airway obstruction (see Table 2).

Co-morbidities, reported and undiagnosed airways diseases

Never smokers with airway obstruction reported significantly more co-morbid disease than never smokers with normal lung function (see Table 2).

In never smokers with significant non-reversible airway obstruction (FEV_1/FVC <0.7 and a predicted FEV_1 <80%, GOLD stage II+) only 21.2% reported a previous diagnosis of either asthma (12.1%) or COPD (9.1%). Therefore, 78.8% of never smokers with significant non-reversible airway obstruction were previously undiagnosed.

If all subjects who reported a prior doctor's diagnosis of ''asthma'' were excluded from the analyses, the prevalence of significant non-reversible airway obstruction in never smokers would decrease from 5.5% to 4.9%.

Respiratory symptoms and health-related quality of life

When never smokers and smokers demonstrated the same degree of airway obstruction, they were found to be similar in respect to the presence of respiratory symptoms (see Figure 1) and their health-related quality of life. Furthermore, presence of symptoms and impairment of quality of life increased in both groups parallel to the severity of disease.

Discussion

The results of our population-based study show that never smokers comprised 35% of all cases of non-reversible airway obstruction and 28% of significant airway obstruction (GOLD stage II+) in adults aged 40 years and over.

Risk factors for airway obstruction in never smokers

In our data, never smokers with non-reversible airway obstruction were predominately female. This was even more pronounced in significant disease (GOLD stage II+). This finding is consistent with the results of a population-based study in Spain, which showed that women 55 years and over constitute the majority of COPD cases among never smokers.[3] In developing countries, biomass fuels used

Table 2 Comparison of never smokers with and without non-reversible airway obstruction

	FEV_1/FVC <0.7 ($N = 108$)	FEV_1/FVC >0.7 ($N = 487$)	*P*-value
Characteristics			
Age, mean (SD)	65.8 (1.2)	57.2 (0.5)	<0.001
Sex, female	52.8%	54.0%	0.817
Education ≥12 years	22.2%	25.5%	0.511
Hospitalized for breathing problems <age of 10	2.8%	3.3%	0.786
Reported co-morbidities			
Asthma	13.9%	5.1%	<0.001
Heart disease	19.4%	10.3%	0.008
Hypertension	41.7%	31.0%	0.033
Diabetes	5.6%	6.0%	0.873
Stroke	5.6%	1.0%	0.002
Tuberculosis	2.8%	2.7%	0.950
Reported exposures			
Passive smoking at home	17.6%	15.0%	0.499
Indoor open fire with biomass for cooking	11.1%	13.1%	0.567
Indoor open fire with biomass for heating	12.0%	16.1%	0.299
Organic dust in the workplace	36.1%	25.5%	0.025
Inorganic dust in the workplace	3.7%	3.7%	0.997
Irritant gases/ fumes/vapors in the workplace	9.3%	9.7%	0.900

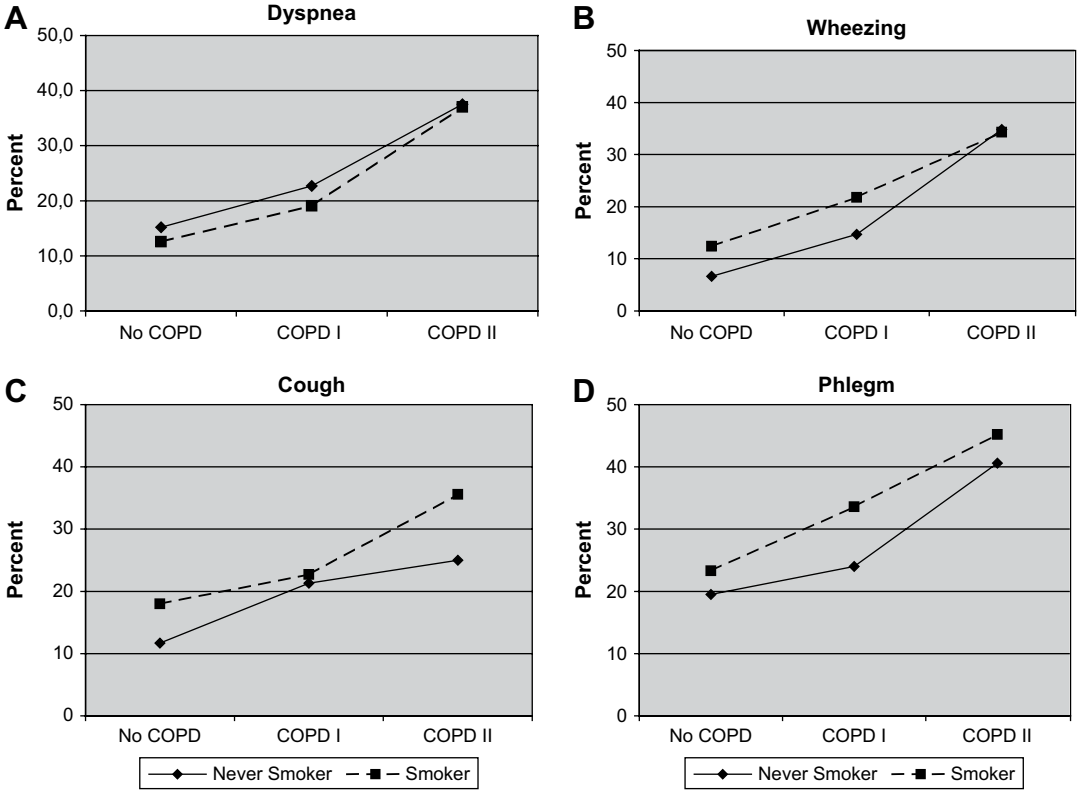

Figure 1 Presence of reported respiratory symptoms in never smokers and ever smokers according to severity of non-reversible airway obstruction. A: Dyspnea, B: wheezing, C: cough, and D: phlegm.

by women for cooking and heating have been shown to cause COPD in non-smoking women.[8–11] As some studies have suggested that women are more susceptible to the effects of tobacco smoke,[12,13] this could probably also apply for other exposures.

In our data, occupational exposure to organic dust was associated with a higher prevalence of non-reversible airway obstruction in never smokers. By definition, farming was categorized as occupational exposure to organic/biologic dusts. This particular exposure has previously been shown to be a risk factor for airway obstruction in the observed population.[14] This is consistent with results of a study in never smoking animal farmers in which an association between dust concentration and prevalence of COPD was shown.[15]

We did not found an association between passive smoking and non-reversible airway obstruction in never smokers. This could be due to the fact that the questionnaire only assessed current exposure to passive smoking (within the last 2 weeks) but included no information about a history of exposure to passive smoking.

Definition of airway obstruction, rate of underdiagnosis and potential misclassification

The definition of airway obstruction using the GOLD criteria may lead to some overdiagnosis of COPD in elderly never smokers.[16] Prevalence of airway obstruction is always a matter of definition. At present, the GOLD initiative continues to recommend the use of a fixed ratio, post-bronchodilator $FEV_1/FVC < 0.7$, to define airflow limitation,[17] whereas a joint ATS/ERS Task Force has proposed using the Lower Limit of Normal (LLN) as a cut-off value for the FEV_1/FVC ratio.[18] In our data, the prevalence of significant non-reversible airway obstruction in never smokers decreased by 33% when the LLN was used instead of the fixed ratio.

The present authors have decided to present the data on non-reversible airway obstruction in never smokers using the fixed ratio of post-bronchodilator $FEV_1/FVC < 0.7$, because currently recommended prediction equations for LLNs are based on pre-bronchodilator spirometry data.[7] Finally, a main problem with chronic airways disease might not be the most precise definition of airway obstruction but the fact that many affected people are undiagnosed and untreated.[19] In our data, the prevalence of doctor diagnosed COPD was far below the true burden in both smokers and never smokers. The proportion of previously undiagnosed obstructive airways disease was 78.8% in never smokers and 74% in smokers.

In our data, 14% of never smokers with non-reversible airway obstruction and 12% of never smokers with significant non-reversible airway obstruction reported a prior physician's diagnosis of asthma. As we determined post-bronchodilator airway obstruction, it seems reasonable that the majority of them suffer from COPD not asthma. However, when we excluded all subjects who reported a prior doctor's diagnosis of ''asthma'', the prevalence of significant non-reversible airway obstruction only decreased from 5.5% to 4.9%.

Respiratory symptoms, health-related quality of life and co-morbidities

The comparison of never smokers and smokers with non-reversible airway obstruction did not show a difference in terms of respiratory symptoms or health-related quality of life when the comparison was stratified by the severity of airway obstruction. Given this similar impact of airway obstruction on the subjective burden of disease, one could argue that a comparable lifetime burden of inhalational injury will lead to chronic inflammation and subsequent chronic airway disease irrespective of its origin.

Never smokers with non-reversible airway obstruction reported significantly higher amounts of co-morbidities (ischemic heart disease, hypertension) than never smokers with normal lung function. This again supports the argument that chronic airway obstruction in never smokers and ever smokers follows a similar course and involves co-morbid cardiovascular disease in either instance.

Limitations and conclusions

The site-specific sampling plan adopted for BOLD was not designed to provide sufficient power to clarify potential risk factors in detail. In particular, the assessment of passive smoking and occupational exposure by questionnaire was not sufficient to demonstrate a relationship with non-reversible airway obstruction in never smokers. The number of study participants in some occupations known to be risk factors for airways disease was far too low for a more detailed analysis.

However, never smokers who fulfill the criteria of COPD seem to have the same respiratory symptoms and breathing problems interfering with their daily life as smokers. The current GOLD guidelines recommend spirometry testing, when either risk factors or respiratory symptoms are present.[17] This might be a disadvantage for never smokers who don't have spirometry testing before the disease has become more severe and respiratory symptoms have developed. Due to the fact that more than 5% of adult never smokers suffer from significant non-reversible airway obstruction, spirometry testing should not be limited to smokers.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit for publication.

Conflict of interest statement

Bernd Lamprecht has no conflict of interest. Lea Schirnhofer has no conflict of interest. Bernhard Kaiser has no conflict of interest. Sonia Buist has received NIH funding $3M over last 5 years, has been a member of advisory boards of: Merck, GSK, Sepracor, Novartis, Schering Plough (all <$10,000 per year) and has been a speaker at a COPD meeting in Italy (2007) sponsored by Chiesi. Michael Studnicka has no conflict of interest.

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