COPD among never-smokers Prevalence, risk factors and comorbidities

The Obstructive Lung Disease in Northern Sweden (OLIN) Studies Thesis XIII

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Each thing I do, I rush through so I can do something else

In such a way do the days pass

Stephen Dobyns, Pursuit

Hurry up please, it's time

T.S. Eliot, the Waste Land

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ABSTRACT

The overall aim of this thesis was to investigate prevalence, risk factors and comorbidity of COPD among never-smokers. COPD was in this thesis defined as a syndrome also including prior asthma diagnosis with chronic airway obstruction. In papers I-III population-based cohorts of the Obstructive Lung Disease in Northern Sweden (OLIN) studies were used. In paper IV data from the OLIN studies was pooled with data from the West Sweden Asthma study.

Prevalence of COPD among never-smokers was 3.0-7.7% depending on spirometric definition, and similar in 1994-1996 vs. 2009-2012. Corresponding prevalence of GOLD ≥2 was 1.3-3.5%. Symptoms were highly prevalent in subjects with GOLD ≥2, regardless of smoking status. No significant regional differences in prevalence between OLIN and WSAS were seen. Risk factors for COPD among never-smokers included age, physician-diagnosed asthma and occupational exposure to gas, dust or fumes. Passive smoking in multiple settings was independently associated with an incrementally increased risk of COPD. Comorbidities, in particular cardiac and cardiovascular conditions, were highly prevalent among subjects with GOLD ≥2 regardless of smoking status.

In conclusion, COPD is a common condition among never-smokers, and associated with previous asthma and exposures including passive smoking and occupational gas, dust or fumes. Never-smoking subjects with COPD had significantly more respiratory symptoms and comorbidities than never-smokers without COPD. Comorbidities are highly prevalent in COPD regardless of smoking history.

Keywords: COPD, never-smokers, epidemiology, population-based, passive smoking, comorbidities, risk factor, prevalence

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SAMMANFATTNING PÅ SVENSKA

Kronisk obstruktiv lungsjukdom, KOL, är en av våra stora folksjukdomar. Förekomsten har beräknats till >10 % bland den allmänna befolkningen över 40 år. Vanliga symptom vid KOL innefattar slemhosta, pip i bröstet samt andnöd. KOL är en vanlig orsak till förtida död och innebär stora kostnader för samhället i stort. Den vanligaste riskfaktorn för KOL är tobaksrökning. Dock har tidigare populationsbaserade studier påvisat att KOL även förekommer hos individer som själva aldrig rökt. Syftet med denna avhandling var att kartlägga förekomsten av KOL bland aldrig-rökare samt identifiera riskfaktorer och förekomst av samsjuklighet i denna grupp.

Med KOL avses i denna avhandling ett syndrom som också innefattar tidigare astma som utvecklat kronisk obstruktivitet. Avhandlingen baseras främst på material insamlat i Norrbotten, där slumpvis utvalda individer undersökts med lungfunktionstester samt enkätdata. I den fjärde delstudien ingick även material från Västra Götaland. I den första delstudien sågs att 6.9% av aldrig-rökarna hade KOL. Bland alla individer med KOL hade var femte aldrig själv rökt. Riskfaktorer för KOL bland aldrig-rökare var hög ålder samt en tidigare astmadiagnos. I den andra delstudien undersöktes betydelsen av passiv rökning. Passiv rökning i flera miljöer, exempelvis hemma och i arbetet, befanns vara den efter ålder starkaste riskfaktorn för KOL bland aldrig-rökare.

Den tredje delstudien undersökte förekomsten av andra sjukdomar bland aldrig-rökare med KOL. Aldrig-rökande individer med minst medelsvår KOL hade andra sjukdomar i motsvarande utsträckning som rökande individer med samma svårighetsgrad av KOL. Särskilt tydligt var detta för hjärt- och kärlsjukdomar. I den fjärde delstudien sammanfogades databaser från Norrbotten och Västra Götaland, där slumpvis utvalda deltagare undersökts med motsvarande metoder inkluderande intervjuer och lungfunktionsundersökningar. Förekomsten av KOL var 7.7% bland aldrig-rökare, och 2.0% hade minst medelsvår KOL. Bland aldrig-rökarna var exponering för gaser, damm eller rök på arbetsplatsen en oberoende riskfaktor för KOL.

Sammantaget visar avhandlingen att KOL förekommer bland 6.9-7.7% av aldrig-rökare. Passiv rökning och yrkesexponering för gaser, damm eller rök är viktiga riskfaktorer i denna grupp, vilket belyser vikten av att minska sådan ofrivillig exponering. Sjukvården bör vara uppmärksam på att samtidig hjärt-kärlsjukdom är vanligt vid KOL även bland aldrig-rökare.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Hagstad S**, Ekerljung L, Lindberg A, Backman H, Rönmark E, Lundbäck B. COPD among non-smokers – Report from the Obstructive Lung Disease in Northern Sweden (OLIN) studies. *Respiratory Medicine* 2012;106;980-988.

II. **Hagstad S**, Bjerg A, Ekerljung L, Backman H, Lindberg A, Rönmark E, Lundbäck B. Passive smoking exposure is associated with increased risk of COPD in never smokers. *Ches*t 2014;145(6);1298-1304.

III. **Hagstad S**, Backman H, Ekerljung L, Bossios A, Hedman L, Lindberg A, Rönmark E, Lundbäck B, Bjerg A. Comorbidities are common also in never-smokers with COPD. *Submitted*.

IV. **Hagstad S**, Backman H, Bjerg A, Ekerljung L, Xiong Y, Hedman L, Lindberg A, Torén K, Lötvall J, Rönmark E, Lundbäck B. Prevalence and risk factors of COPD among never-smokers in two areas of Sweden – occupational exposure to gas, dust or fumes is an important risk factor. *In manuscript*.

For the papers that had been published at the time of the printing of this thesis, permission was obtained from the publisher.

CONTENT

ABBREVIATIONS

ACOS	Asthma-COPD overlap syndrome
ATS	American Thoracic Society
BD	Bronchodilator
BTS	British Thoracic Society
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
ERS	European Respiratory Society
ETS	Environmental Tobacco Smoke
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GLI	Global Lung Initiative
LLN	Lower Limit of Normal
OLIN	Obstructive Lung Disease in Northern Sweden studies
OR	Odds Ratio
SVC	Slow Vital Capacity
US	United States
VC	Vital Capacity
WHO	World Health Organization

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common condition, estimated to affect 10% of all subjects aged >40 years.[1] It is currently estimated to be the third cause of death globally[2] and is associated with reduction in quality of life for those affected[3] as well as substantial costs to society.[4] COPD as a disease entity was characterized relatively recently and although these last years have brought an increased awareness both among medical professionals and the general public regarding COPD, under-diagnosis remains a common problem,[5] in part due to limited use of lung function testing in clinical practice.[6]

The main established risk factor for COPD is active smoking, which accounts for the majority of known cases both in the developed and developing countries.[7] As the link between smoking and COPD is so strong, it has often been viewed as a smoker's disease. However, large-scale epidemiological surveys have identified substantial proportions of subjects with COPD who have never smoked themselves[8-11] although these relatively new findings have not yet been fully disseminated outside the research community. As smoking prevalence is currently decreasing in the developed world,[12] it can be expected that other risk factors than active smoking may in the future play a more apparent role as causal factors for COPD. Thus, to increase knowledge both among the medical community and general public on the possibility of COPD also occurring in never-smokers, further large scale studies are warranted. Indeed, not belonging to an obvious high-risk group could in itself increase the risk of under-diagnosis.

For subjects with established COPD, the presence of comorbidities represents a main contributor to the overall burden of disease. In fact, among subjects with moderate COPD, the main causes of death are cardiovascular conditions and cancer, rather than obstructive respiratory disease.[13] Comorbidities in COPD also represent a substantial additive cost for society.[14] The impact of comorbidities among never-smokers with COPD has however not been investigated.

To date, the only clearly established methods of reducing mortality in COPD are smoking cessation[15] and use of supplementary oxygen in the presence of respiratory failure.[16,17] Currently, medications commonly used in COPD are primarily aimed toward symptom relief and reduction of exacerbations. Subjects without a smoking history are generally not included in clinical

trials of pharmaceutical compounds for COPD.[18-20] Recommendations regarding therapy in this group are thus not evidence-based.

Papers I-III in this thesis are based on data from the Obstructive Lung Disease in Northern Sweden (OLIN) Studies, which after its inception in 1985 has grown to become the largest ongoing epidemiological study of respiratory diseases in Sweden. In addition, paper IV is based on pooled data from the OLIN studies and the West Sweden Asthma Studies (WSAS). The aim of this thesis was to study prevalence, risk factors and comorbidities of COPD among never-smokers.

2 BACKGROUND

2.1 Definition, pathophysiology and natural history of COPD

COPD has been defined as a common, preventable and treatable disease, characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response to noxious particles or gases.[21] Current guidelines proscribe that the diagnosis of COPD should be considered in any subject presenting with dyspnea, chronic cough and/or sputum production together with a history of exposure to risk factors for COPD.[21] The presence of airflow limitation is established using spirometry, which remains the most widely available and reproducible test for lung function.[22] The exact definition of airflow has been under considerable debate, which will be discussed further in this thesis.

Inhalation of noxious agents, such as tobacco smoke, causes inflammation in the airways also among "healthy" subjects.[23] This process seems to be altered and amplified among subjects with COPD.[24] While the underlying mechanisms are not well understood, a plethora of genetic polymorphisms, gene-environment interactions, immunoregulatory and host-pathogen interactions are implicated.[25] Common pathophysiological features of COPD include inflammation of peripheral airways, destruction of lung parenchyma and alveoli causing emphysema, and increased number of mucus-producing cells such as epithelial goblet cells or mucus glands.[26-28] These pathological changes underlie the main symptoms of COPD, namely chronic cough, sputum production, wheezing and dyspnea. In later stages of COPD, pulmonary hypertension can develop as a response to hypoxia-induced vaso-constriction and ensuing structural changes of the vascular bed.[29] Pulmonary hypertension may in turn lead to right-side cardiac failure, which is associated with a high rate of morbidity and mortality.[30]

In addition to these chronic and progressive phenomena, acute aggravations, or exacerbations, are another common feature of COPD. Characterized by worsening of respiratory symptoms, this is purely a clinical diagnosis.[21] Although mostly triggered by microbiological agents, the causal factor cannot always be determined.[31] Not only associated with a substantial morbidity and mortality in the acute phase,[32] exacerbations are also

associated with an accelerated rate of decline in lung function,[33] reduced quality of life[34] and increased long-term mortality.[35]

Particularly, in mild cases of COPD, a history of relevant exposures must actively be sought after, and, where relevant, discontinued. In many cases this is tantamount to smoke cessation counseling. Often, mild cases of COPD warrant no medical treatment.

The current available pharmacologic treatment of stable COPD includes inhaled corticosteroids, short-acting and long-acting beta2-agonists, short-acting and long-acting muscarinic antagonists and PDE4-inhibitors. Treatment options are guided by disease severity stages.[21,36] Noteworthy, monotherapy with inhaled corticosteroids, in the absence of beta-2-agonists or muscarinic antagonists, is not recommended in current guidelines.[21] If the subject is hypoxic at rest, long-term oxygen therapy may be indicated. In addition, non-pharmacological interventions such as pulmonary rehabilitation and in particular smoking cessation remain fundamental in the overall treatment of COPD. Treatment of exacerbations commonly includes use of corticosteroids, antibiotics and in severe cases oxygen and/or mechanical ventilation to combat acute respiratory failure. Of all available treatment options in stable COPD, only long-term oxygen and smoking cessation have been found to significantly affect mortality,[15-17] implicating that prevention and early recognition is highly important.

COPD is generally viewed as a progressive disease,[37] yet the rate of decline varies considerably between individuals. While some subjects rapidly progress towards respiratory failure and premature death, others may express a more stable decline in lung function.[38] As symptoms, prognosis and quality of life in COPD are related to disease severity,[39-41] factors affecting excessive rate of decline in lung function have been explored. In 1976 Fletcher and Peto published a landmark study in which the lung function of 792 men was studied longitudinally. They demonstrated that subjects who smoked expressed an accelerated rate of decline in lung function. Subjects who had stopped smoking could benefit from a reduced rate of decline in lung function.[42]

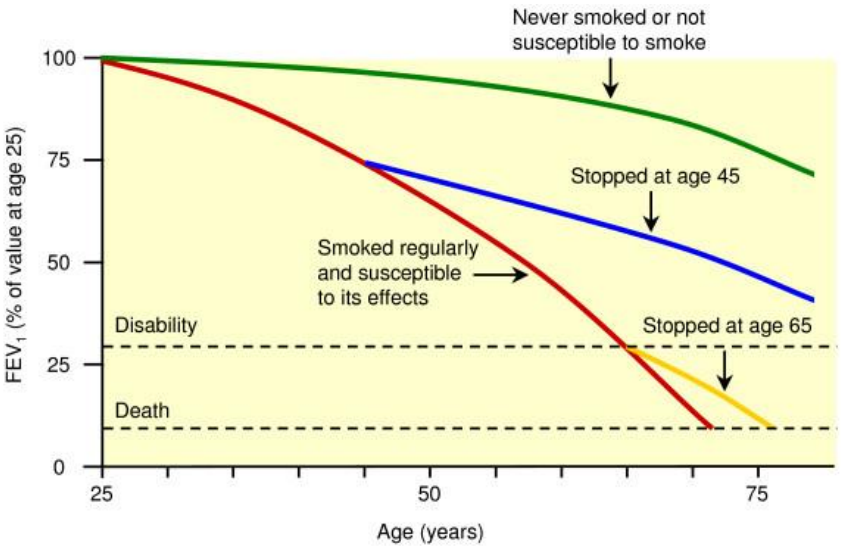

Figure 1. Originally adapted from Fletcher et al.[42] Reproduced from Kotz et al with permission from the publisher.[43]

Traditionally, the "normal", or anticipated, decline in lung function has been estimated to reduction of FEV1 of about 20 mL/year from ages 20-25 years until middle age, after which this reduction rate is slightly increased.[44] Being a smoker would then add to this reduction another 10-30 mL/year.[45,46] While data is consistent that smoking status, as expressed in pack-years consumed, is related to excessive decline in lung function on a population level,[42,44,47] there is still confusion as to why certain individuals experience a more rapid decline than others. Respiratory symptoms are associated, and may be independent predictors for excessive rate of decline.[48-50] Generally, subjects with mild COPD experience predominately bronchitic symptoms (e.g. sputum production, cough), whereas dyspnea tends to emerge when subjects already have more advanced stages of the disease.[51] In population-based studies, asymptomatic subjects with advanced COPD are rare.[51,52]

2.2 Early recognitions of COPD

While the concept of COPD was formally defined towards the end of the 20th century, descriptions correlating to this disease entity have been reported since the 17th century. The Swiss physician Bonet published case reports referring to "voluminous lungs" in 1679, and the Italian anatomist Morgagni, otherwise famous for his descriptions of gynecological anatomy, reported 19 cases of "turgid", or bloated, lungs in 1769.[53] The British physician Charles

Badham was the first person to refer to "catarrh", or chronic inflammation of the mucous membrane, and in 1808 he identified bronchiolitis and chronic bronchitis as disabling health conditions.[54] The French physician Laënnec, incidentally the inventor of the stethoscope, published the classical description of emphysema in 1827 in which he described lungs that did not collapse when opening the chest during post-mortem examinations and noted that the lungs were full of air and the airways occluded by mucus.[55] Interestingly, Laënnec believed emphysema to be caused by environmental factors.

Whereas obstructive diseases of the airways originally was diagnosed solely based on medical history or patho-anatomical examination, the first step towards a physiological approach to diagnostics was taken by John Hutchinson who constructed the first working spirometer in 1846.[56] The first spirometer based on a closed circuit system was constructed by Jules Tissot in 1904.[57] In 1947, Tiffeneau and Pinelli proposed measurement of "pulmonary capacity usable on exercise", which evolved into the Forced Expiratory Volume in one second, FEV1.[58] The Tiffeneau-Pinelli index, consisting of the ratio between the FEV1 and vital capacity, still finds application today.[59]

Interest in obstructive airway diseases became decidedly more pronounced after a severe air pollution event, named "The great Smog of '52", occurred in London in December of 1952. While previously estimated to have caused more than 4000 premature deaths in one single week, in particular among the very young, very old and subjects with pre-existing respiratory disease, later research have implicated that the true number of deaths may have been as high as 12000.[60] While there had been previous reports of adverse health effects in conjunction with environmental air pollution, the sheer scope of this disaster prompted an increased awareness and research activity into the field of respiratory epidemiology. One problem was the lack of accepted definitions where, for example, in the United States, the clinical term emphysema was used for the condition labeled chronic bronchitis in the United Kingdom. An early attempt to address the perceived need for standardization came during the CIBA guest symposium in 1959, where formal definitions of chronic bronchitis, emphysema and asthma were proposed.[61]

2.3 Standardization of the term COPD

The term COPD, or chronic obstructive pulmonary disease, was first used by William Briscoe in 1965, and already in 1962-64 Mitchell and Philly used the correlating term broncho-obstructive pulmonary disease.[62,63] However, in subsequent years a plethora of terms describing this disease entity were coined: *COAD*, chronic obstructive airways disease; *COLD*, chronic obstructive lung disease; *CORD*, chronic obstructive respiratory disease; *CAO*, chronic airflow obstruction and *CAL*, chronic airflow limitation. Following the 1980's COPD became the term of choice of respiratory physicians and researchers and is now the established term in the medical community and general population.

Correspondingly with the confusion in terminology, there has over the years been much debate regarding the spirometric definition of COPD. Various organizations have presented individual guidelines, in which COPD is defined in a variety of ways. The historical perspective will be addressed also in the discussion of methodology.

In the 1990s, the US National Heart, Lung and Blood institute together with World Health Organization founded an international study group, entitled Global initiative of Chronic Obstructive Lung Disease (GOLD), in response to a perceived need for standardization and also to promote awareness of COPD. The first consensus document published in 2001 advocated the fixed ratio of post-bronchodilator FEV1/FVC <0.70 as the means for establishing the spirometric diagnosis of COPD, and FEV1 as a marker for disease severity grading.[64] The ATS/ERS position paper published in 2004 used the same spirometric definitions of COPD.[65] Both GOLD and the ERS/ATS advocated disease stratification using FEV1 in percent of predicted value.

However, arguments were raised that use of the fixed ratio would lead to over-estimation of COPD, especially among the 'healthy' elderly.[66] Thus, the ERS/ATS issued a new statement proposing the concept of lower limit of normal (LLN) as an alternate method of diagnosing airway obstruction. Being statistically derived, age and sex-specific, the cut-off value was set at the 5th percentile of the normal distribution of the FEV1/VC ratio.[67] Proponents of the fixed ratio have in their turn argued that the fixed ratio is intuitive, easy to understand and not dependent on other reference values.[68] Also, by using the LLN one runs the risk of misdiagnosis in severe cases due to wide confidence intervals. For example, in a subject with measured FEV1 of 0.6L, and a FVC of 0.9L, this subject could be classified as having no broncho-obstruction despite critically reduced lung function. Importantly, the

fixed ratio definition forms the basis of diagnosis used in most clinical trials to date for the main therapeutic agents now in use for COPD.[18,19,69,70]

ATS/ERS criteria	
Mild	FEV1/VC <5th percentile of predicted and FEV1 ≥70% predicted
Moderate	FEV1/VC <5th percentile of predicted and FEV1 60-69% predicted
Moderately severe	FEV1/VC <5th percentile of predicted and FEV1 50-59% predicted
Severe	FEV1/VC <5th percentile of predicted and FEV1 35-49% predicted
Very Severe	FEV1/VC <5th percentile of predicted and FEV1 % <35%predicted
GOLD criteria	
Mild	FEV1/FVC <0.70 and FEV1 >80 % predicted
Moderate	FEV1/FVC <0.70 and 50%≤FEV1<80% predicted
Severe	FEV1/FVC <0.70 and 30%≤FEV1<50% predicted
Very Severe	FEV1/FVC <0.70 and FEV1 <30 % predicted
FEV1: forced expiratory volume in 1 second. VC: vital capacity. FVC: forced vital capacity.	

Table 1. Spirometric definition of COPD and disease severity stratification according to the GOLD and ERS/ATS guidelines.[71] Adapted and reproduced with permission of the European Respiratory Society©

One recent systematic review comparing the fixed ratio with the LLN as a means of diagnosing COPD spirometrically in large population-based studies implied that use of LLN tended to better reflect decline of FEV1 and presence of respiratory symptoms, but that the fixed ratio could be a better predictor of comorbidities.[72] The debate is ongoing[68,73] and while both definitions are currently used, in clinical practice, the fixed ratio of FEV1/FVC <0.70 continues to be the most widely used definition. In large population-derived studies, the choice of spirometric definition considerably affects the prevalence estimates,[74,75] illustrating the importance of standardization.

The GOLD guidelines have since been continuously updated, with the latest guidelines being published in 2013.[21] This version states that spirometry is now regarded as a prerequisite for the diagnosis of COPD, and emphasizes the importance of post-bronchodilator spirometry in order to reduce misclassification. In addition to spirometric grading of severity, a model incorporating symptom burden and exacerbation frequency was introduced (grades A-D), as a means for aiding clinicians in choice of therapy for the individual patient. It is expected that new guidelines will be forthcoming in the near future, reflecting the ongoing evolution in our knowledge on COPD.

In addition to the debate regarding the spirometric definition of COPD, another potential source of bias concerns the use of normal values of spirometry. It has long been acknowledged that spirometric normal values vary by population and ethnic group, in part due to anatomic differences in chest dimensions and ratio of trunk length relative to standing height.[76] Thus, many countries and research groups have constructed their own reference values often based on a small number of healthy, young and middle-aged adults.[77,78] This approach however has limitations, pertaining to low statistical power and large variation in reference values e.g. in the elderly.[79]

A recent attempt to harmonize spirometric reference values was through the Global Lung Initiative (GLI), in which following recruitment and examination of subjects of various ages from various centers, equations for predicted spirometric reference values of ages 3-95 were published.[80] To what extent these reference values truly are applicable to all populations remain unclear, however the GLI equations are recommended to be used widely and have also been endorsed by the European Respiratory Society (ERS) and the American Thoracic Society (ATS). ERS, and the GLI consortium itself, recommends that the GLI equations be validated in population-based surveys, and be further developed by adding new adequately collected data.[81] Although the GLI reference equations are

endorsed by many respiratory societies, the consensus may still be that, when available, applicable local population-specific reference values are preferred.[67,82] The choice of reference equation is a potential source of bias and adds to the overall confusion regarding the optimal choice of diagnostic criteria in COPD.

2.4 Phenotypes and systemic involvement in COPD

The classical phenotypes, or clinical presentations, in COPD include the division in emphysema and chronic bronchitis. During the 1960s, in particular researchers from the United Kingdom advocated the theory that the main established entities of obstructive airway disease (asthma, chronic bronchitis and emphysema) were patho-physiologically separate diseases. This theory became known as '*the British Hypothesis'*. The main reason for the progressive reduction in lung function among subjects with chronic bronchitis was ascribed to recurrent infections.[83] In contrast, researchers in the Netherlands argued that asthma was closely related to chronic bronchitis and emphysema, and that all three diseases were in fact sub-groups, or phenotypes, of a single disease entity, called Chronic Non-Specific Lung Disease (CNSLD).[84,85] According to this theory, dubbed "*the Dutch hypothesis*", special host characteristics, such as atopy and bronchial hyperreactivity would determine the subject's susceptibility to different exposures (e.g. tobacco smoke). However, the term CNSLD did not become an established term in clinical praxis.

Currently, COPD is increasingly being recognized as a highly heterogeneous disease entity. In particular, the systemic nature of COPD is becoming increasingly apparent.[86] Subjects with COPD tend to express increased markers of systemic inflammation,[87] indicative of systemic involvement. While often not immediately apparent, the systemic nature of COPD becomes more pronounced with concurrent disease progression.[88,89] Importantly, subjects with COPD often have co-existing diseases, or comorbidities, such as cardiovascular disease and lung cancer.[90,91] The presence of comorbidities have an impact on the overall prognosis,[13] rate of hospitalization[92] and quality of life in subjects with COPD.[93] This has been attributed to shared exposures of the different diseases, in particular cigarette smoking, but also to shared pathophysiological pathways reflecting the systemic nature of COPD.[87]

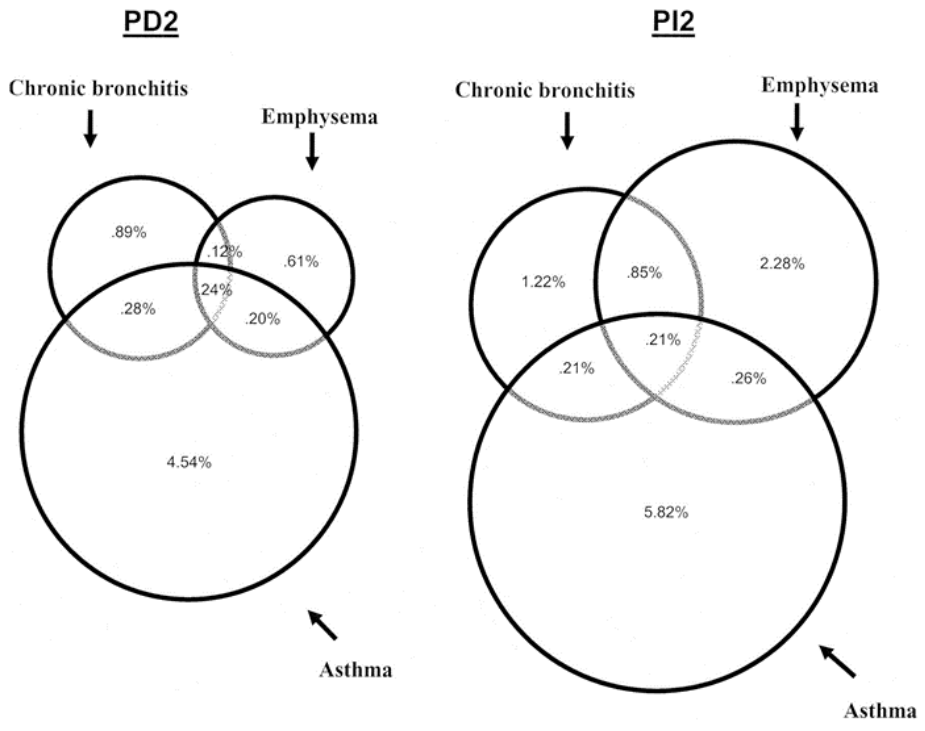

Figure 2. Proportional Venn diagram of Obstructive Lung Diseases from two population-based study populations of Italy. [94]PD2= Po Delta sample, PI2= Pisa sample. Reprinted with permission from the American College of Chest Physicians©.

The differential diagnosis between COPD and asthma remains not fully defined. As shown in figure 2, obstructive lung diseases can overlap considerably. While known from previous studies that subjects with bronchial hyperreactivity express increased rate of lung function decline,[95] and that long-standing asthma is a risk factor for airway obstruction tantamount to COPD,[96] to what extent these conditions co-exist remains not fully established. Now entitled the Asthma-COPD Overlap Syndrome (ACOS), a heterogeneous phenotype within the syndrome of COPD,[97] is increasingly becoming an area of interest, as studies have suggested subjects with assumed ACOS to be more prone to have exacerbations[98] more reduced lung function[98] and further impaired quality of life.[99] On the other hand, in a 20 year follow-up study on subjects who at baseline fulfilled spirometric criteria of COPD, subjects with chronic bronchitis had a significant higher mortality as compared to subjects who had baseline met the criteria for ACOS.[40]

2.5 Prevalence of COPD

Prevalence of COPD in different geographic settings has proven difficult to estimate, owing both to differences in study populations but also variations in diagnostic criteria. Bearing this in mind, one meta-analysis approximated the prevalence rate of COPD to 9-10% among subjects aged >40 years.[1] Here various definitions of COPD were included and noteworthy, pooled prevalence of COPD was considerably higher in studies using spirometric criteria as opposed to patient-reported COPD (9.2% versus 4.9%, respectively). These results are in line with previous population-based studies, where prevalence of COPD has consistently been in excess of 10% in the general population.[71]

The Burden of obstructive lung disease (BOLD) study examined 9425 subjects from 12 different centers in various countries across the globe.[100] Using post-bronchodilator spirometry in a standardized manner and defining COPD according to the GOLD criteria, prevalence rate of COPD ranged from 11.4% in Guangzhou, China to 23.8% in Cape Town, South Africa. By severity grade, overall prevalence of GOLD ≥2 was 10.1%, highest in Cape Town (19.1%) and lowest in Hannover, Germany (5.9%). Using the same definition of COPD and including 5571 subjects, the PLATINO study from Latin America found prevalence to range from 7.8% in Mexico City to 19.7% in Montevideo, Uruguay.[8] The heterogeneous findings in prevalence observed in these multi-center studies illustrate the difference by geographic setting, although a standardized approach was used. While potential confounders such as regional differences in cigarette consumption, levels of air pollution, socio-economic factors and other comorbidities such as tuberculosis have been advanced as potential explanations for these observations, the reason has not been fully determined. The latest US National Health and Nutrition Examination Survey (NHANES) dating from 2007-10 using pre- and post-bronchodilator (BD) spirometry examined 5477 and 564 subjects, respectively.[101] Comparing the pre- versus post-BD values, as well as LLN and the fixed ratio as diagnostic criteria for COPD, estimated prevalence among US adults aged 40-79 ranged from 10.2% to 20.9%. Although limited by low numbers of subjects completing post-BD spirometry, this highlights the importance of consistency in choice of diagnostic criteria.

Some of the larger population-based studies on COPD prevalence have been performed in northern Europe.[11,102,103] Scandinavian countries have the advantage of large public registries which aid in collection of data. From the Copenhagen City Heart Study, prevalence of COPD in a study population of

5299 aged ≥35 years was estimated at 17.4%.[104] Noteworthy, in this study only pre-BD spirometry was available. From the Hordaland County Cohort Study based in Bergen, Norway 1664 subjects were examined using post-BD spirometry. Here, prevalence of COPD according to the GOLD criteria was 13.7%.[105] From the Swedish OLIN Studies, using the same diagnostic criteria as in Bergen, in a randomly selected population-based sample of 1237 subjects, prevalence of COPD was estimated at 14.3%.[52] Another study using a different study population but the same diagnostic criteria from within the OLIN studies yielded a similar prevalence of 14.1%, which supports the accuracy of the previously obtained prevalence estimate.[11]

2.6 Risk factors for COPD

The current opinion is that susceptibility to COPD is as a complex interaction between genetic predisposition and environmental factors.[106] This said, the singularly most important and established risk factor for COPD is active smoking.[21] The risk of COPD increases with cumulative life-time consumption[107] and there is no threshold below which tobacco could be safely consumed.[107] Up to 50% of active smokers develop COPD if they smoke long enough.[52,108,109]

In one meta-analysis, the proportion of COPD in the population attributable to smoking varied considerably, between 9.7-97.9%.[110] The proportion of COPD in the general population caused by smoking is dependent on smoking prevalence and the age distribution of the study sample. As a result of industrialization, during the latter half of the 19th century tobacco products went from luxuries to mass-market consumables in the Western world. By the time of the first US surgeon general's report on the health effects of tobacco smoking in 1964, 42% of adult Americans were smokers.[111] Although, fortunately, smoking prevalence appears to be decreasing in developed countries,[71] still approximately one billion people worldwide are smokers.[112] In particular, smoking is becoming more common among women.[113] This is in contrast to earlier times, when smoking was predominately a male pastime, which could also be an explanation as to why COPD was previously considered to mostly affect men.[114] However, women seem to be more susceptible to the detrimental effects of tobacco,[47,115,116] possibly attributed to smaller lung volumes or sex-specific differences in inflammatory response.[117,118]

Exposure to passive smoke, or environmental tobacco smoke (ETS) has in previous studies been associated with respiratory symptoms[119,120] and asthma,[121,122] although the impact of ETS as a risk factor for COPD has at

times been disputed.[123,124] Noteworthy, previous studies have included active smokers in the study population,[125] as well as defining COPD without the use of spirometry.[126] Although it stands to reason that passive smoke is inherently not healthy, it has been comparatively little studied among adult never-smokers as a risk for COPD defined using objective measures of lung function, especially post-BD spirometry.[127,128] Considering that many countries still lack effective legislation as pertaining to tobacco control, research into the health effects of passive smoking remains warranted.

Occupational exposure to noxious substances, such as vapors, gas, dust and fumes has been implicated as a cause of COPD in approximately 15% of cases[129,130] Several occupational categories, such as mining workers, farmers and construction workers, have been associated with an increased risk of COPD.[131-134] The true burden of occupational exposure on COPD risk is however difficult to ascertain, largely owing to few standardized studies and variance in the definition of COPD used.

Globally, 3 billion individuals are estimated to use biomass fuel for heating or cooking purposes in the home.[135] Several studies have confirmed exposure to biomass fuel as a risk factor for COPD.[136] A recent study from Mexico compared never-smoking women exposed to biomass smoke with ex-smokers.[137] Although post-BD spirometry was equal in both groups, subjects exposed to biomass fuel reported more symptoms and lower saturation at 6 minute walk test as compared to smokers. As the use of biomass fuel is highly concentrated to developing countries, where often the extent of medical care is limited when compared to developed countries, the true impact can be bigger than previously assumed. However, also in developed countries indoor air pollution constitutes a risk factor for COPD.[138]

Although outdoor air pollution as a risk factor for COPD remains disputed,[139,140] several studies have implicated outdoor air pollution as a cause for respiratory symptoms and disease.[141,142] One Scottish study found respiratory symptoms to be less common among subjects living in a rural setting, although prevalence of COPD did not differ by area of domicile,[143] and urban dwelling has also been associated with increased bronchial hyperresponsiveness.[144] The importance of outdoor air pollution on lung function was highlighted in a recent publication from California from the Children's Health Study, where improvement in air quality over time was associated with higher lung function in children.[145]

Socio-economic status has previously been shown to be an independent risk factor associated with COPD.[146] Poor socio-economic status in this context

presumably represents other factors influencing respiratory health including poor nutrition, poor housing, higher exposure to passive smoking and other indoor air pollutants, in addition to poorer working conditions. The lifetime effect of socioeconomic status on lung function has been estimated at 300 mL FEV1 in males and 200 mL FEV1 in females.[147]

COPD is predominately found among older subjects, and age has been identified as an independent risk factor for COPD.[148] In humans, lung function reaches maximum development somewhere between 18 and 25 years of age, after which it slowly decreases. Factors affecting both early lung development, leading to a lower maximal lung function than would otherwise be the case, as well as influencing an accelerated rate of decline would then be important factors in the development of COPD. Low birth weight and respiratory infections during childhood[149-151] have in some studies been implicated as factors negatively affecting lung function development, yet consensus has not fully been reached.[152,153]

Chronic, long-standing asthma has in several studies been recognized as a risk factor for COPD.[148] In one study, asthma was an even stronger risk factor for COPD than tobacco smoke.[96] Another study found subjects with asthma to present with a lower lung function and subsequent greater rate of decline in FEV1 than subjects without asthma.[154] Subtypes of severe asthma have also been found to express a predominately neutrophil airway inflammation and reduced responsiveness to corticosteroids, features which are otherwise associated with COPD.[155] Other studies have shown some asthmatic subjects to develop radiological features commonly associated with COPD, such as emphysema, also among never-smokers.[156-159]

Pulmonary tuberculosis can result in scarring of the airways and an immune response to mycobacteria resulting in airway inflammation.[160] Globally, 2 billion people are estimated to be infected with mycobacterium tuberculosis, incurring 9 million new cases and 1.5 million fatalities in 2013 alone.[161] Prevalence of COPD after infection with tuberculosis has in different studies ranged between 28-68 %.[162,163] One South African study[164] showed tuberculosis to be more strongly related to chronic bronchitis than tobacco smoke (OR 4.9, 95% CI 3.7-11.9), and this observation has also been substantiated in the PLATINO study.[8]

The influence of genetic factors in the development of COPD remains not fully established. Among genetic disorders, the strongest causal relationship with COPD has been demonstrated in α-1-antitrypsin deficiency,[165] which has been approximated to account for 1-2% of subjects with emphysema.[166]

Family history of COPD has been linked with increased risk.[52,108] Currently, there are a number of candidate genes implicated in an increased risk for COPD,[110] but no clear causal relationship has been demonstrated.

2.7 COPD in never-smokers

There is an ongoing debate as to the veracity and appropriateness of labeling subjects expressing irreversible obstruction on spirometry, yet lacking a history of established exposure (such as tobacco smoke) as having COPD. As, for example, the GOLD guidelines mandate a history of relevant exposure to be present in addition to irreversible obstruction for a diagnosis of COPD to be made, the absence of exposure in a subject with a spirometric finding otherwise indicative of COPD could render some diagnostic confusion. This duly noted, as COPD is increasingly becoming recognized as a syndrome of systemic nature, rather than singular disease entity, the author of this thesis argues that it is not incorrect to label this condition as COPD, all the while acknowledging the ongoing and progressive discussion pertaining to taxonomy and nomenclature.

The strong link between smoking and COPD has caused many to view COPD exclusively as a smoker's disease, a view that still predominates in clinical practice. From large-scale population based surveys it has however become apparent that subjects with no smoking history also express spirometric evidence of COPD.[8,167,168] It should be noted that spirometry only establishes the presence or absence of irreversible airflow limitation tantamount to COPD, while not adding information regarding further pathophysiology, e.g. the type of inflammation, or exposures. There is at present no recognized epidemiological method of differentiating between the spirometrically defined COPD versus the clinical entity of COPD. In this thesis, COPD is consistently defined spirometrically in accordance with current guidelines and in corresponding manner to other large-scale epidemiological studies, regardless of reported exposure.

Although spirometry forms the basis of diagnosis in COPD, the limited use of spirometry in clinical setting contributes to the underdiagnosis of COPD. Presently, the GOLD guidelines dictate that diagnosis of COPD should be considered in subjects with respiratory symptoms and a history of exposure to risk factors for the disease. In the ATS/ERS guidelines, COPD should be considered in those with either respiratory symptoms OR history of exposure to risk factors. Thus, depending on the guidelines, presence of symptoms could by themselves be deemed indicative whether a diagnosis of COPD should be considered.

As previously noted, there is a great variance in report of prevalence of COPD, and the same holds true for COPD among never-smokers. From the BOLD study, overall prevalence of COPD among never-smokers using the GOLD criteria was 12.2%, and GOLD grade ≥2 5.6%.[169] Corresponding numbers from the PLATINO study found that 10.5% of never-smokers had COPD, and 3.5% GOLD ≥2.[170] A recent study from China identified COPD in 4.0% of female and 5.1% male never-smokers.[171] Importantly, in several studies never-smokers consistently constitute a considerable proportion of all subjects with COPD, ranging from 20-30%.[172]

To what extent COPD among never-smokers presents with a different clinical profile than that of smokers with COPD has yet to be determined. From population-based surveys we know that very severe degree of airflow limitation is less commonly found in never-smokers with COPD as compared to smokers with COPD.[170] Never-smokers with COPD however commonly report respiratory symptoms. In the BOLD study, any respiratory symptom was reported by 72.5% of the never-smoking subjects with GOLD ≥2, as opposed to 44.5% among those with no COPD.[169] A study from New Zealand comparing the clinical profiles of never-smokers versus smokers with COPD noted that the burden of symptom was high, regardless of smoking status.[173]

An interesting aspect is whether never-smokers with COPD present a different type of inflammatory response than smokers with COPD. This could in turn have implications for therapeutic options, as inflammation in COPD compared to asthma has proven less responsive to corticosteroids.[174] One study of subjects with COPD with no or limited smoking history found two different subsets, where 9 subjects had predominately eosinophilic sputum, and the remaining 13 predominately neutrophilic sputum.[175] Although commonly associated with asthma, presence of sputum eosinophilia has been reported in 20-40% of COPD cases.[176] Interestingly, a previous study found use of inhaled corticosteroids in COPD subjects with sputum eosinophilia to be associated with a small, yet significant, improvement in lung function.[177] Currently, new treatments for COPD targeting IL-5, and thus eosinophilic inflammation, are being investigated in clinical trials, although the add-on efficacy in relation to established treatment remains to be decided.[178]

Asthma has in several studies been associated with increased risk for COPD among never-smokers.[169,170,179] In one, albeit small, study from New Zeeland, virtually all never-smokers with COPD had a prior physician-diagnosis of asthma,[173] As previously mentioned, the Asthma-COPD overlap syndrome[97] has received an increasing amount of attention in recent years and may well

prove to become an established clinical entity in the near future. Presently however, much work is needed in regards to clinical profiling and possible therapeutic options.

Comorbidities are a main cause for increased morbidity and mortality among subjects with COPD. To what extent this holds true also for never-smokers with COPD is not fully established. In the BOLD study, heart disease and hypertension was more prevalent among subjects with GOLD $\geq$2 as compared to subjects with no COPD, yet comorbidities were not independently associated with increased degree of airflow limitation.[169] In one study from Copenhagen, cardiovascular comorbidities were not associated with COPD in never-smokers. However, only pre-bronchodilator spirometry was used and COPD was not classified by disease severity in the analyses.[180] Considering the impact of comorbidities among subjects with COPD in general, it would seem intuitive to also screen for comorbidities among never-smokers with COPD, yet no clear consensus exists at present.

2.8 Obstructive Lung Disease in Northern Sweden (OLIN) Studies

The Obstructive Lung Disease in Northern Sweden studies was founded in 1985 with the expressed purpose of studying the epidemiology of respiratory diseases in children and adults. Since its inception, more than 50000 subjects aged 7-96 years have participated at some stage. The methods employed include longitudinal cohort studies, case-control studies, cross-sectional studies and qualitative studies. Prevalence, incidence, risk factors and remission of obstructive airway diseases and allergic diseases have been studied both among adults and children. This thesis is the 13th originating from the OLIN Studies. In addition, data from the OLIN Studies have been used in approximately 10 doctoral theses and 200 original and review articles. A number of PhD-projects from the OLIN Studies are currently ongoing. This present thesis uses data from the OLIN studies in all papers.

2.9 West Sweden Asthma Study

The West Sweden Asthma Study (WSAS) was launched as a translational and multidisciplinary projected aimed to study various aspects of obstructive airways diseases and allergic diseases. Based in Gothenburg, Sweden, it has resulted in several publications and doctoral dissertations originating from the epidemiological as well as laboratory setting. This present thesis includes pooled data from WSAS in paper IV.

3 AIMS

The overall aim of this thesis was to study the prevalence, risk factors and comorbidities of COPD among never-smokers.

3.1 Specific aims

- To estimate the prevalence of COPD among never-smokers in Sweden (Paper I, IV)
- To determine main risk factors for COPD among never-smokers (Paper I, IV)
- To determine the burden of symptoms among never-smokers with COPD in Sweden (Paper I, IV)
- To determine the impact of passive smoking as an independent risk factor for COPD among never-smokers (Paper II)
- To investigate the comorbidity profile among never-smokers with COPD (Paper III)
- To investigate whether there is a regional difference in prevalence of COPD among never-smokers in Sweden (Paper IV)

4 METHODS

The studies in this thesis (papers I-III) are based on data from the Obstructive Lung disease in Northern Sweden (OLIN) studies. Paper IV is based on data both from the OLIN Studies and the West Sweden Asthma Study.

4.1 Study area

The county of Norrbotten is the northernmost and largest county of Sweden. While covering roughly one fourth of the national area of Sweden, it is home to only 250 000 inhabitants,[181] which corresponds to 2.6% of the national population. The most densely populated areas are concentrated to the coastline, where approximately 200 000 people live. Here lie the main cities of Boden, home to the main garrison of the Swedish army and where formerly the main hospital of the county was located, of Luleå, the county capital and home to the regional university and of Piteå. Above the Arctic Circle, to the far north, population is mainly concentrated in the cities of Gällivare and Kiruna, both mining towns and the principal source of iron ore in Sweden. The climate is predominately dry and cold, and exhibits considerable regional differences. Kiruna, being the northernmost city in Sweden, experiences midnight sun in the summer and prolonged periods of darkness in which the sun never rises above the horizon during the winter. The main hospital of Norrbotten is located in between Luleå and Boden, with subsidiary hospitals in Kiruna, Gällivare, Kalix and Piteå.

Västra Götaland is the second most populous county in Sweden, home to 1 630 000 inhabitants.[181] The main city is Gothenburg with about 600 000 inhabitants, while about 1 million live within the metropolitan area. Outside of Gothenburg, the county is comprised of large agricultural areas and forests. The climate in the western part of Västra Götaland is oceanic with cool summers and mild winters.

4.2 Study design and population

While the overall aim and design of the cohorts have been described elsewhere[182-184] the study population relating to the papers included in this thesis is described in turn below.

4.2.1 Paper I

The first cohort of the OLIN studies was originally invited in 1985/86, and consisted of 6610 subjects born 1919-20, 1934-35 and 1949-50 living in eight geographically representative areas of Norrbotten, Sweden. The response rate to the original questionnaire was 86% (5697 individuals).[185] In 1992, a repeat questionnaire was dispatched and of the 6215 subjects still comprising cohort 1, 5391 responded (87%).[186] The third survey took place in 1996. The cohort now comprised 5933 subjects, of which 5892 could be traced, and 5189 (88%) responded. Of these responders, 1500 were randomly selected for a follow-up study in which 1282 subjects participated in clinical examinations including a structured interview. In total 1237 performed lung function tests with an acceptable technique.[52]

In 1992 the third cohort of the OLIN studies was recruited when a postal questionnaire was sent to all subjects aged 20-69 years born on the 15th living in the whole county of Norrbotten. In total 5681 were invited, and 4851 (85%) responded.[187] A random sample of these responders was in 1994/95 invited for clinical examinations. Of the 970 invited, 664 (68%) participated and 660 performed lung function tests with an acceptable technique.[11] Identical methods and techniques were used in the two studies described above, and data was pooled. In total, study population of paper I comprised of 1897 subjects.

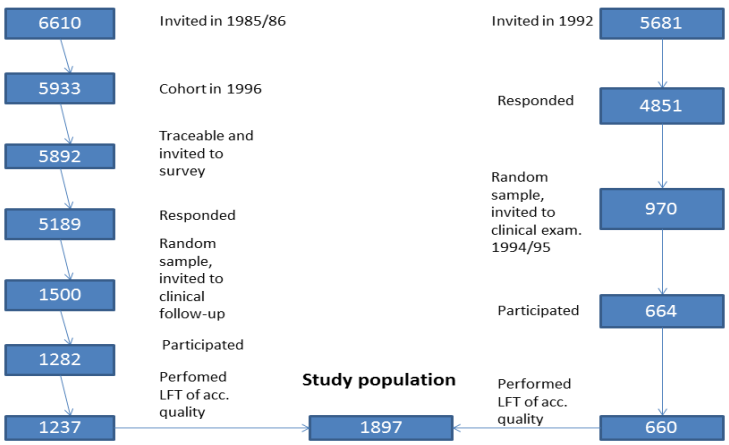

Figure 3. Study population used in paper I.

4.2.2 Paper II

The study population of paper II consisted of pooled data from three cohorts of the OLIN study.

Among the 5697 responders to the first questionnaire dispatched in 1985/86, 1655 subjects were invited to clinical examinations in 1986. These were subjects who had in the questionnaire reported presence of respiratory symptoms or asthma (n=1340) as well as randomly selected subjects with no report of respiratory symptoms or disease (n=315). In total 1505 subjects (91%) participated in 1986. In 1996 this sub-cohort consisted of 1340 individuals who were subsequently invited to clinical exams, in which 1182 (88%) participated.[48] In addition, among the 5933 subjects previously described who participated in the postal questionnaire of 1996, 710 subjects who had reported respiratory symptoms were additionally invited to clinical examinations and 564 (79%) of these participated. As 334 subjects belonged to both the random and stratified study subsets described here, in total 2694 subjects belonging to the first cohort participated in the clinical examinations of 1996. The inclusion of 664 subjects from the third cohort remained unchanged between paper I and II.

The second cohort of the OLIN studies was also recruited in 1992, when a postal questionnaire was dispatched to all individuals aged 20/21, 35/36, 50/51 and 65/66 years of age living in Norrbotten, and 7735 (85%) responded. A follow-up was performed in 1993/94 among subjects who had reported respiratory symptoms, in which 1997 subjects participated.[51]

In total from the three cohorts 5355 subjects were examined in 1994-96. Of these 2182 were never-smokers and the 2118 never-smoking subjects who performed lung function tests with acceptable quality thus comprised the study population of paper II.

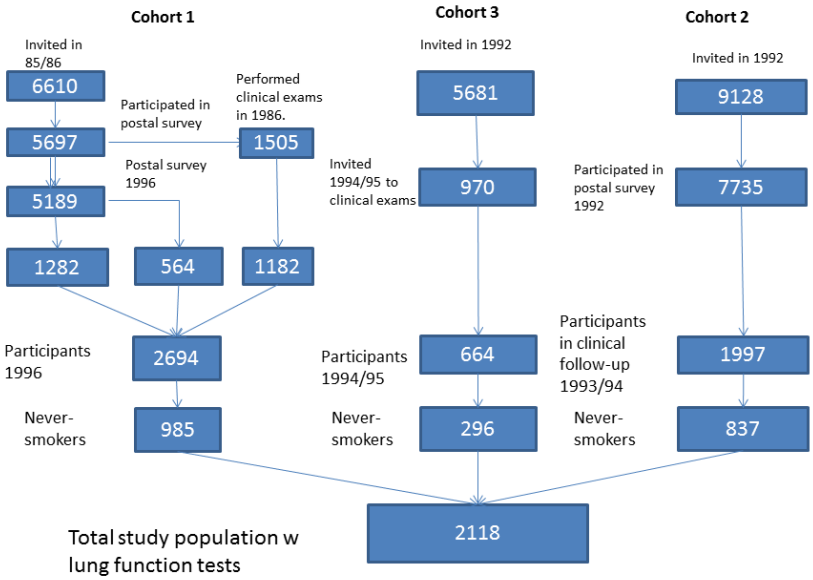

Figure 4. Study population used in paper II.

4.2.3 Paper III

All 5355 participants in the clinical examinations of 1994-96 were invited for re-examination in 2002-04. In total 4024 participated and the 3963 subjects who performed lung function tests with acceptable quality comprised the study population of paper III.

4.2.4 Paper IV

The study population of paper IV consisted of pooled data from both the OLIN study and WSAS. The individual parts are described in turn below.

OLIN

In 1996, cohort 4 of the OLIN studies was recruited by inviting 8704 randomly selected subjects living in Norrbotten, Sweden aged 20-74 to partake in a postal questionnaire.[188] Of these, 7399 subjects (85%) responded. In 2006 a follow-up questionnaire was distributed to the responders of the original questionnaire. In total 7004 subjects were invited and 5890 subjects (84%) responded.[189] Cohort 8 of the OLIN studies was recruited in 2006 with

the expressed purpose to compare prevalence rates cohort 4.[189] In all, 7997 randomly selected subjects aged 20-69 years old living in Norrbotten were invited to partake in a postal questionnaire identical to that used for cohort 4. 6165 subjects belonging to cohort 8 responded, response rate 77%. A clinical follow-up was performed in 2008-10 on randomly selected subjects from both cohort 4 and cohort 8. 1016 subjects were stratified by gender and age-groups (21-30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years and 71-86 years), matching the age and gender proportions of Norrbotten county.[190] Of these 737 subjects partook in interviews and 726 performed lung function testing.

WSAS

In 2008 a postal questionnaire was distributed to 30000 randomly selected subjects, stratified by age and gender to match the population in Västra Götaland, Sweden. Invited individuals were aged 16-75 years and 15000 were living in the metropolitan area of Gothenburg. 782 subjects could either not be traced, were deceased or otherwise unable to participate. In total 18087 subjects (62% of traceable subjects) responded.[191] The questionnaire used in the study consisted in part of the OLIN-questionnaire and the Swedish part of the GA^{2}LEN-questionnaire. Of the responders, 2000 subjects were randomly invited for clinical examination which took place 2009-2012.[192] In total, 1172 subjects (59% of invited) aged 18-78 years participated, and 1158 completed lung function tests.

Data from both studies were pooled, yielding a total of 1909 subjects. To achieve a matching age distribution, only subjects aged 21-78 (the overlapping age span of both cohorts) were included in the final study population, which consisted of 1861 subjects. Of these, 1839 performed spirometry with acceptable quality.

4.3 Structured questionnaires

The postal and interview questionnaires were originally developed mainly from the respiratory questionnaires of the British Medical Research Council,[193] and the questionnaires used in the US Tucson studies[194] and the International Union Against Tuberculosis and Lung Diseases (IUATLD) questionnaire.[195] The questionnaires relating to the papers in this thesis have been used in all surveys of the OLIN cohorts among adults, yet over time additional questions have been successively added. Examples include questions of presence of any wheeze in the last month; or any wheeze in the absence of colds, which were added in 1992 and based on the Swedish part of

the European Community Respiratory Health Survey (ECRHS) questionnaire.[196] The questionnaires have been described in detail previously.[185,197] The English translations of the questionnaires pertaining to the OLIN part of paper IV are presented in the appendix. The core questions of the OLIN and WSAS questionnaires were virtually identical. Specially trained nurses and research assistants performed the interviews.

4.4 Lung function testing

The lung function tests pertaining to paper I-III were performed using a dry spirometer (Mijnhardt Vicatest 5, The Netherlands). In paper IV lung function tests were performed using Masterscope Jaeger in both the OLIN and WSAS cohorts. Spirometers were calibrated in a standardized manner at the start of every working day and tests were performed following the ATS guidelines, except that nose clips were not used and the examination was performed with the subjects standing up. Vital capacity (VC) was defined as the best value of either forced vital capacity (FVC) or slow vital capacity (SVC). In paper I and II, Swedish reference values that had been found to conform well to the symptom-free population of the OLIN studies born before the mid of the 20th century were used.[77] In paper I, when calculating LLN for the sensitivity analyses the equation by Viljanen et al[198] was used, as at that time GLI equations were not published. In paper III, Global Lung Function Initiative reference values were used.[80] In paper IV, original reference values constructed and validated out of the OLIN study population were used.[199] In papers I-III, 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. In paper IV in OLIN, a reversibility test was performed using 0.4 mg salbutamol via spacer in all subjects. In WSAS, bronchodilation test was performed using a combination of 0.4 mg salbutamol and 80 mcg ipratropium bromide via spacer in all subjects.

4.5 Spirometric definition of COPD

COPD was consistently defined according to the GOLD criteria using the fixed ratio definition of FEV1/(F)VC <0.70.[21] In addition, we used the Lower limit of normal (LLN) as an alternative method of defining airway obstruction in papers I, III, and IV.

Disease severity was graded according to the GOLD criteria:[21]

GOLD 1 FEV1/VC <0.70 and FEV1 ≥80 % of predicted value

GOLD 2 FEV1/VC <0.70 and FEV1 50-79 % of predicted value

GOLD 3 FEV1/VC <0.70 and FEV1 30-49 % of predicted value

GOLD 4 FEV1/VC <0.70 and FEV1 <30 % of predicted value

4.6 Definitions

Commonly used terms in this thesis include the following:

Smoking history was defined as follows: non-smoker (smoked <1 cigarette/day <1year); ex-smoker (stopped smoking more than 12 months prior to the interview); current smoker (currently smoking every week or had stopped smoking within 12 months prior to the interview). The categories ex-smoker and current smoker were categorized as ever-smokers. The term never-smokers (paper II, III, IV) was utilized synonymous with the term non-smokers, used in paper I.

Exposure to environmental tobacco smoke (ETS) (paper II) was defined by affirmative answers to questions relating exposure to ETS in the following settings: are you currently exposed to ETS in your home environment (ETS current at home); were you previously exposed to ETS in your home environment (ETS previously at home); are you exposed to ETS at your current work in public settings (ETS at current work); were you exposed to ETS at your previous main work (ETS at previous work). An affirmative answer to either ETS current at home or ETS previous at home was defined as ETS ever at home. An affirmative answer to both ETS at current work and ETS at previous work was defined as ETS at both previous and current work. In paper IV the questions on ETS exposure were the following: (Home) are you, or have you previously been, exposed to passive smoke in your home? Answers: yes, now; yes, previously but not now; no. (Work) Are you, or have you previously been, exposed to passive smoke at your work? Answers: Yes, now; yes, previously but not now; no.

Exposure to gas, dust or fumes (paper IV): have you been heavily exposed to dust, gas or fumes at work?

Physician-diagnosis of asthma: have you been diagnosed with asthma by a physician? Physician-diagnosis of asthma was defined as report of asthma in paper II.

Socio-economic classification was based on reported occupation according to definitions by Statistics Sweden. The following main groups were used: 1 professional and executive, 2 assistant non-manual employee, 3 manual worker in industry, 4 manual worker in service, 5 self-employed, 6 housewife and 7 occupation unknown. In paper IV socio-economic classification was based on educational history, where subjects who reported only high school education or less were contrasted with subjects reporting at least some college/university education.

Area of domicile (paper I) was defined as follows: living in urban areas (>10000 inhabitants), small towns (2000-9999 inhabitants) or rural areas (<2000 inhabitants).

Family history of obstructive airway disease (paper I, II) was considered positive if a subject reported a first-degree relative with asthma, chronic bronchitis, emphysema or COPD.

The following definitions pertaining to comorbidities were used:

Any cardiac disease (paper I and paper III): answering yes to the question "do you have/have you previously had" any of the following: angina pectoris; acute myocardial infarction; heart failure; arrhythmia; other cardiac disease. In paper IV Ischemic heart disease was defined as yes to any of the following: angina pectoris, previous myocardial infarction, previous percutaneous transluminal coronary angioplasty or coronary-artery bypass surgery.

Any cardiovascular disease (paper III): Reporting either any cardiac disease, or answering yes to the question "Do you have/have you previously had" any of the following: hypertension; claudicatio intermittens; cerebral blood clot/cerebral bleeding.

Any comorbidity (paper III): Reporting either any cardiovascular disease, or answering yes to the question "Do you have/have you had" any of the following: Diabetes, rheumatic disease or "have you had tuberculosis?" or "do you have or have you had problems with worry, anxiety or depression?"

The following questions pertaining to symptoms were used:

Sputum production: “Do you usually have phlegm when coughing?” or “Do you have phlegm that is difficult to bring up”

Chronic productive cough: “Do you usually have phlegm when coughing, or have phlegm that is difficult to bring up, most days in periods of at least three months, during at least two successive years?”

Any wheeze: “Have you at any time during the last 12 months had wheezing or whistling in your chest when breathing?”

Recurrent wheeze: “Do you usually have wheezing, whistling or a ‘noisy sound’ in your chest when breathing?”

Long-standing cough: Paper I: yes to any of the following: “Have you experienced long-standing cough these last years”, “Do you usually cough in the morning?”, “Do you usually cough during other times during the day?”, “Do you cough throughout the year?”, “Do you cough during a specific season?” Paper III and paper IV: yes to “Have you had persistent cough these last years”.

Dyspnea: yes to either of the following: “Do you get short of breath when walking on level ground with people of the same age as you?”, “Do you have to stop to catch your breath when walking on level ground in your own pace?”, “Do you get short of breath when dressing/undressing?”

4.7 Statistical analyses

All statistical analysis performed in this thesis were conducted using the Statistical Package for Social Science (SPSS) software version 18-21 (IBM, New York, USA). Fisher’s exact test was used for bivariate comparisons of categorical variables. Mantel-Haenszel test for trend was used for comparison of categorical variables applied in a 2 x k contingency table. Student’s t-test was used for normally distributed continuous data and Mann-Whitney U test for non-parametric continuous data. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were calculated using multivariate regression analysis. In all papers a p-value of <0.05 was considered statistically significant.

5 RESULTS

5.1 Prevalence and risk factors for COPD among never-smokers

The study population consisted of 2470 subjects drawn from the general population and examined in 1994-96, and of these 770 subjects were never-smokers. Defining COPD as FEV1/VC <0.70, 6.9% (n=53) had COPD, and 3.5% (n=27) had GOLD grade ≥2. Among all subjects, and using the same definition of COPD, prevalence was 14% and of GOLD ≥2 7.3%, correspondingly. The proportion of never-smokers among subjects with COPD was 20.0%. Viewed by sex, the proportion of never-smokers among men with COPD was 14.1%, while the corresponding proportion among women was 26.8%. Subjects with GOLD ≥2 reported more respiratory symptoms than subjects with no airflow limitation, irrespective of smoking status. Sputum production was reported by 55.6% of never-smoking subjects with GOLD ≥2, compared to 19.4% of those with no COPD (p <0.001). Corresponding figures for any wheeze was 59.3% versus 25.7% (p<0.001) and dyspnea 33.3% versus 10.5% (p=0.002).

There were no statistically significant differences in report of symptoms between never-smokers and ever-smokers with GOLD ≥2. A previous physician diagnosis of asthma was reported by 40.7% of never-smokers with GOLD ≥2, compared to 9.6% of never-smokers with no COPD (p<0.001). Among ever-smokers corresponding figures were 29.7% and 9.6%, respectively (p<0.001). Adjusted risk factors for COPD among never-smokers using multiple logistic regression analysis model were age above 66 years (OR 5.56, 95% CI 2.53-12.2), and a physician-diagnosed asthma (OR 2.96, 1.44-6.08).

Using the LLN as a criterion for irreversible airway obstruction, prevalence of COPD was 6.8% (52/770). Age above 66 years and physician-diagnosed asthma remained independent risk factors for COPD among never-smokers, albeit with lower odds ratios; 2.20 (1.11-4.40) and 2.43 (1.18-5.00), respectively.

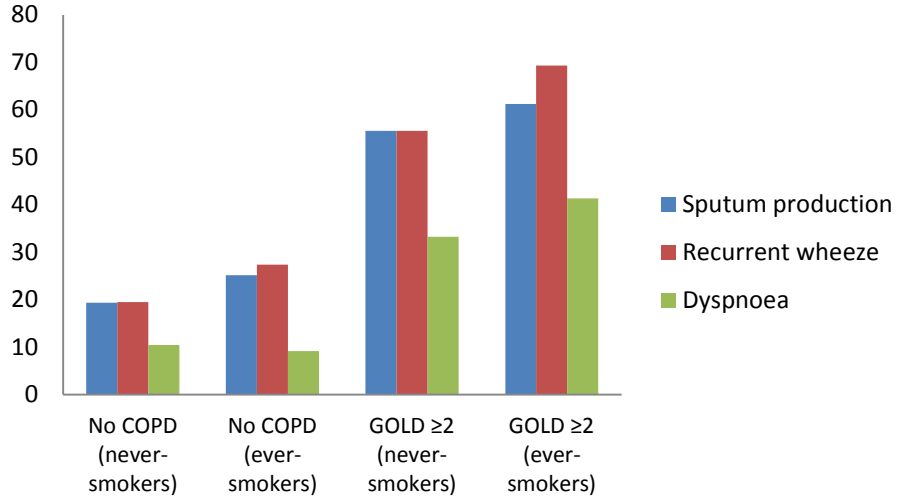

Figure 5. Prevalence (%) of symptoms by smoking status and severity of airflow limitation

5.2 Passive smoking as a risk factor for COPD among never-smokers

Data from three OLIN-cohorts sampled in 1994-94 were pooled, yielding 5355 subjects. Of these only the never-smokers were selected and formed the study population of paper II. COPD was defined as FEV1/VC <0.70. Among the 2118 never-smoking subjects the impact of passive smoking, or environmental tobacco smoke (ETS) on COPD was analyzed. In this never-smoking population, 6.6% (n= 140) had COPD, 3.4% (n=71) had GOLD ≥2. ETS in any setting was reported by 69.0%. Among subjects who reported no exposure to ETS at all, prevalence of COPD was 4.2%. Exposure to ETS in multiple settings yielded an increased prevalence of COPD: ETS ever at home 8.0%; ETS at previous work 8.3%; ETS ever at home and at both previous and current work 14.7%; ETS current at home and at both previous and current work 18.8% (figure 6 below).

Performing the analyses in only subjects aged ≤65 years yielded similar results, with increasing degree of exposure rendering a higher prevalence of COPD. Among subjects aged ≤65 who reported ETS exposure both current at home and at both previous and current place of work, prevalence of COPD was 18.8%, as compared to 3.0% of subjects reporting no ETS exposure, p-value=0.015. Multiple logistic regression analysis adjusting for age, sex, report of asthma, family history of obstructive airway diseases and

socioeconomic status yielded a statistically significant association between COPD and reported exposure to ETS ever at home and at both current and previous work, adjusted OR 3.80 (1.29-11.2).

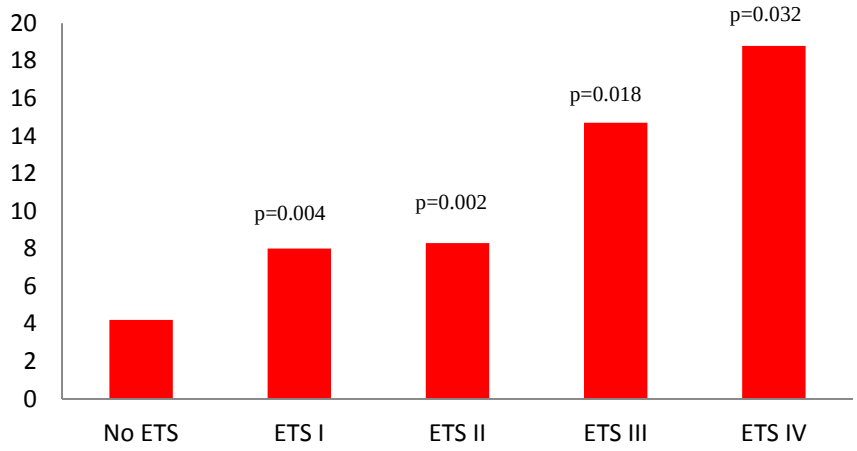

Figure 6. Prevalence (%) of COPD according to GOLD by ETS exposure among neversmoking subjects. ETS exposure was characterized as no ETS exposure; ETS I (ever at home); ETS II (at previous workplace); ETS III (ever at home and at both previous and current workplace); ETS IV (current at home and at both previous and current workplace). P-value versus no ETS exposure.

5.3 Comorbidities among never-smokers with COPD

The study population of paper III consisted of 3963 subjects with valid lung function data, all previously examined in 1994-96 as part of the OLIN studies. Among the 1609 never-smokers, overall prevalence of COPD defined as FEV1/VC <0.70 was 9.3%, and 4.4% had GOLD ≥2. The corresponding prevalence among all subjects irrespective of smoking status was 17.2% for any COPD, and 9.1% for GOLD ≥2. Prevalence of the composite comorbidity variables any comorbidity, any cardiovascular disease and any cardiac disease was significantly related to severity of airflow limitation among never-smokers. Almost all cardiovascular comorbidities, but not diabetes, rheumatic disease and depression were significantly associated with obstructive lung function impairment. These associations were generally irrespective of smoking status. In addition, respiratory symptoms were significantly related to airflow limitation severity regardless of smoking history.

Stratified by smoking status, logistic regression analysis in which age, sex and socio-economic status were adjusted for, GOLD ≥2 among never-smokers was associated to any comorbidity, OR 2.19 (1.17-4.13) and any cardiovascular disease, OR 1.87 (1.09-3.21). Corresponding figures for ever-smokers was 1.33 (0.99-1.79) for any comorbidity and 1.32 (1.01-1.73) for any cardiovascular disease.

	Never-smokers				Ever-smokers			
	No COPD	GOLD I	GOLD ≥2	p-value	No COPD	GOLD I	GOLD ≥2	p-value
Any comorbidity	59.1	70.9	81.7	<0.001	62.9	64.7	75.3	<0.001
Any cardiovascular disease	43.9	58.2	69.0	<0.001	46.1	51.7	61.5	<0.001
Any cardiac disease	20.2	20.3	32.4	0.028	22.4	25.2	33.8	<0.001
Long-standing cough	26.0	21.5	43.7	0.012	25.8	26.1	39.2	<0.001
Dyspnoea	15.1	13.9	45.1	<0.001	13.9	16.0	39.9	<0.001
Chronic Bronchitis	23.1	24.1	40.8	0.002	28.6	44.5	54.2	<0.001
Recurrent Wheeze	28.6	24.1	53.5	<0.001	33.4	40.3	64.2	<0.001

Table 2. Prevalence (%) of comorbidities and respiratory symptoms among never- and ever-smokers, respectively by COPD severity according to GOLD

5.4 Prevalence and risk factors of COPD among never-smokers in two areas of Sweden

Using pooled data from Norrbotten and West Sweden, the study population consisted of 1839 subjects, of these 967 (52.6%) were never-smokers. Prevalence of COPD defined as FEV1/VC <0.70 was 7.7% (n=74) and GOLD ≥2 was present in 2.0% of never-smokers (n=19). By geographic location, a similar proportion of COPD in both Norrbotten and Västra Götaland was observed (7.9% versus 7.5%, p=0.90). Defining COPD as FEV1/FVC <0.70 and LLN yielded a prevalence of 4.9% and 3.0%, respectively and of GOLD ≥2 of 1.4% and 1.3%, respectively.

A previous physician diagnosis of any airway disease (asthma or COPD) was present among eight out of 19 never-smoking subjects with GOLD ≥2, which was in line with ever-smoking subjects of the same disease severity (51%).

GDF exposure at work was reported by 494 subjects, of these 232 (47.0%) were never-smokers. Only four subjects reported both current exposure to ETS at home and at work, one of which was a never-smoker.

Risk factors for COPD among never-smokers in this material were age >60 years, OR 8.40 (3.70-19.1) and occupational exposure to gas, dust and fumes, OR 1.85 (1.03-3.33). Physician-diagnosis of asthma was significantly associated with GOLD ≥2, OR 3.88 (1.37-11.0). Sex, family history of obstructive airway disease, area of domicile, exposure to passive smoke at work and educational level did not reach statistical significance. The risk factor pattern remained essentially unchanged also when defining COPD by using FEV1/FVC <0.70 or FEV1/FVC <LLN.

6 DISCUSSION OF METHODOLOGY

Methodological aspects of the thesis will be discussed in light of key concepts used in epidemiological research. Here follows a discussion on specific elements pertaining to disease definitions.

6.1 Epidemiological concepts

6.1.1 Validity

Validity, or *accuracy*, refers to the extent to which a study or an experiment is unaffected by systematical errors; i.e., that it accurately measures what was intended. Two subtypes of validity are usually identified: *internal* and *external* validity, respectively. Internal validity here reflects the accuracy of results for the study individuals, or dependability of associations found within the study. External validity reflects to what degree results from one study can be applied to other settings or populations. Systematical errors are not influenced by study size, as opposed to reliability which is addressed further below.

The main factors affecting internal validity are selection bias, information bias and confounding.

6.1.2 Selection bias

After having formulated a hypothesis and identified potential study subjects, selection bias may result in a study sample that deviates from the intended population under study. Plainly, the sample may not be representative if certain subjects refrain from, or conversely, are more prone to accept an invitation to participate in a systematic manner. To minimize selection bias, all subjects must be recruited in a uniform, pre-determined way and participation should ideally be high, since the degree of selection bias is related to the response rate. In this thesis participation was high in the studies based on OLIN data. It was somewhat lower in the WSAS sample, why a study of non-responders was conducted to assess and control for selection bias. The differences between responders and non-responders were found to be small in terms of symptomatology and burden of disease.[200] Non-responders tended to be younger and more often smokers. Hence, it is less likely that selection bias had a major impact of prevalence found in the included papers.

6.1.3 Information bias

Arising from errors in measurement, examples of information bias include reporting bias and recall bias. The main outcomes used in all papers I-IV were based on objective measurements of lung function, meaning that mainly the independent variables could have been subject to information bias. Reporting bias can be understood as e.g. systematical under- or over-reporting of symptoms/diseases by study participants. To reduce reporting bias the questionnaires used in this thesis have previously been validated on several occasions.[182,183,201,202] Recall bias is a time-dependent systematical error. Examples include subjects who forget to report past-time symptoms, or subjects with disease who overestimate the impact of a previous exposure to a supposedly noxious substance. Cross-sectional studies are inherently susceptible to recall bias. The risk can be reduced, e.g. by asking for exposures or symptoms that occurred in the preceding year as was done for respiratory symptoms in papers I, III and IV, or as in paper II by using broad exposure categories pertaining to passive smoke exposure. Some questionnaire items have been verified as being highly robust, such as the question on exposure of gas, dust or fumes used in paper IV.[203]

6.1.4 Confounding

A confounding factor is a variable that is independently associated with both the dependent and independent variable, e.g. the exposure and the outcome. The confounder may lead to either over- or underestimation of the true association. To reduce the effect of confounding, it is important to investigate and take into account as many confounders as possible. Owing to the large scale of the studies presented in this thesis, an extensive amount of information based on questionnaire and spirometric data was present. This in turn enabled us to use two common methods to counteract confounding, namely stratified and adjusted analyses. We note that on multiple occasions and in different study populations the same factors were identified as being statistically significantly associated with the outcomes. In addition, a number of potential confounders were tested by inclusion in multivariate models without affecting the main risk associations, as described in sensitivity analyses. This leads us to believe that the main confounders have been accounted for. That said, it cannot be ruled out that potential, yet unknown confounders not controlled for may have caused bias.

6.1.5 External validity

Essential for the generalizability of a study, or external validity, is sound internal validity. Indicative of lacking external validity is if the study population is not representative. In the studies of COPD prevalence, i.e. papers I and IV, the study populations were drawn from the general population, vouching for high external validity. In papers II and III, which aimed at studying specific risk associations, the study population in part consisted of subjects who had in previous postal questionnaires reported presence of respiratory symptoms. In paper II, the found independent association between passive smoke and COPD is not dependent on history of respiratory symptoms. Similarly in paper III, the association between reduced lung function and comorbidities is unlikely to be dependent on the proportion of subjects with respiratory symptom. Furthermore, it was robust to adjustment for other known risk factors. It was clearly stated in papers II and III that the data cannot be used to estimate prevalence of disease, and that this was not the aim of those studies. In addition, our main findings are in line with those of several previous studies, further supporting a high external validity.[127,169,170]

6.1.6 Reliability

Reliability, or *precision*, refers to the extent to which repeated measurements yield identical results given all other factors being constant, i.e. the impact and degree of non-systematical errors. The reliability increases with the size of the study population. In all papers included in this thesis, large study populations were used. In addition to the previously discussed questionnaire items, the spirometry protocols adhered to international recommendations and measurements were conducted by small groups of specifically trained and experienced staff, which further increased precision.

6.1.7 Study design

Various types of epidemiological studies exist, such as cross-sectional, retrospective and longitudinal studies. Cross-sectional studies are used to measure prevalence, defined as the proportion of individuals affected with a specific condition in a study population. In contrast, the new or incident cases arising in a study population are identified using a longitudinal study. The papers presented in this thesis aimed to investigate prevalence and risk factors for COPD among never-smokers. An inherent limitation to the cross-sectional design is that inferences on causality are deemed less reliable as compared to the longitudinal design, due to temporal uncertainties regarding cause and consequence. COPD develops gradually with age, often as a result

of decades of noxious exposure. The associations found in paper II are fully in line with previous studies showing detrimental effects of passive smoke exposure,[127,128] which also holds true for the findings on occupational exposure.[204] Regarding the associations of COPD with comorbidities the cause-consequence relationships have not been firmly established, in part due to the fact that the majority of studies have included subjects with a smoking history, which by itself is a shared risk factor for e.g. cardiovascular disease and COPD. We thus believe that our using the cross-sectional methodology is generally appropriate.

6.2 Definitions of disease

In epidemiological materials, there exist various ways of defining COPD. One method applied is subjects reporting either a physician-diagnosis or symptoms indicative of disease.[125] Most recent studies tend to use spirometry as a backbone for diagnosing COPD in a uniform manner, in accordance with current guidelines. However, depending on the study, establishing airway limitation consistent with COPD has been defined differently. First, use of pre- or post-bronchodilator spirometry will influence the prevalence rates. It is well established that use of only pre-bronchodilator spirometry has been found to over-estimate COPD, with e.g. data from the PLATINO study suggesting that use of pre-bronchodilator spirometry only can over-estimate prevalence of COPD by approximately 35%.[205] Second, as mentioned in the background section of this thesis, choice of cut-off value determining airflow limitation corresponding to COPD has been under much debate. Studies have implied a risk of over-estimating COPD in older adults using the fixed ratio of FEV1/FVC <0.70 as advocated by GOLD. This is more pronounced if only pre-bronchodilator spirometric values are available.[102] Noteworthy, in several of the major clinical trials, from which we derive our recommendations for medical therapy in COPD, the fixed ratio of FEV1/FVC <0.70 was used.[18,19,69] This notwithstanding, it is frequently argued that use of the Lower Limit of Normal (LLN) constitutes a more physiological manner in which to establish airflow limitation and reduces overestimation of COPD. It should be noted however that the LLN, like the fixed ratio of FEV1/FVC, ultimately also represents an arbitrary definition of COPD. In paper III of this thesis, COPD prevalence among never-smokers ranged from 9.3%, when defined as FEV1/(F)VC <0.70 to 2.5% using the LLN 5th percentile. Importantly, 42 never-smoking subjects who were classified as GOLD ≥2 using the fixed ratio of FEV1/(F)VC <0.70, were deemed as normal using the LLN, equating 59.1% of all never-smoking subjects with GOLD ≥2 using the fixed ratio definition. In addition, 73.8% of

these subjects reported chronic or recurrent respiratory symptoms, and comorbidities were also common in this group. This we believe implies that using LLN only as a means of defining irreversible airway obstruction tantamount to COPD has limitations in our material.

The varying results of studies of prevalence of COPD have also a history background. Thus a brief summary of the development of the definition of COPD can be useful.

6.3 Evolution of the definition of COPD

As previously described in this thesis the use and development of the term COPD have progressed for more than 50 years, and still researchers disagree about how COPD should be defined. The history has been reviewed by several papers and recently briefly in the chapter about COPD in the ERS Monograph *Respiratory Epidemiology*.[71] A large number of more or less synonymous terms were used for more than 30 years. This mishmash lasted until the mid-1990's, when efforts of creating a more homogenous definition of COPD were summarized in several important international and national documents. The guidelines for diagnosing and managing COPD with the greatest impact were probably those presented in 1995-1997 by the ATS,[206] ERS[114] and BTS.[207] Importantly, all three documents defined COPD as irreversible lung function impairment, and highlighted the importance of prevention. Both ATS and BTS advocated the fixed ratio of FEV1/(F)VC for defining COPD. ATS used a ratio of <0.75 and BTS <0.70. ATS used FVC as the denominator, while BTS and ERS mentioned both FVC and VC (i.e. SVC or the highest of SVC and FVC, as was done in this thesis). BTS also required a reduction in FEV1 <80% of predicted for COPD diagnosis. In contrast to ATS and BTS, ERS acknowledged that this ratio decreases by increasing age, and COPD was defined in men as FEV1/FVC <88% of the expected age-dependent ratio of FEV1/FVC, while the corresponding ratio in women should be <89% of predicted. These different diagnostic criteria resulted in highly varying estimates of prevalence in the same populations.[9,11] Further, the impact of other factors than spirometry, such as symptoms and exposures or risk factors, on the diagnosis varied considerably between these now 20 year old guidelines.

Partly as a reaction to these guidelines, another view on COPD was brought forward in 2000-2001 by the Global Initiative of Chronic Obstructive Lung Disease (GOLD) consortium, which defined COPD as a not fully reversible airway obstruction and also suggested a new and more detailed severity grading.[64] Similar to BTS, also GOLD defined COPD using the same fixed

ratio, however, a limitation in FEV1 per se was not required. Further, the use of post-bronchodilator values was introduced. The GOLD definition rapidly became the Golden Standard both in clinical practice, epidemiology and clinical trials. After a few years the successor of the BTS document, the British National Institute of Clinical Excellence (NICE)[208] adopted several of the disease criteria suggested by the GOLD. However, the use of the fixed ratio became questioned, and the ATS and ERS statements[65] suggested also the use of lower limit of normal (LLN) of the ratio of FEV1/FVC for defining COPD closely in line with the ERS guidelines from 1995, while the severity grading of GOLD was adopted with few exceptions. Please, see table 1 in the background section on page 8.

In Sweden during the 1990:s the BTS definition of COPD was recommended, and VC has been used as the denominator of the ratio between forced expiratory volume and vital capacity for decades, which results in about 10-20% higher prevalence compared to when FVC is used.[74] The over-diagnosis among elderly by using the fixed ratio was partly addressed by the additional requirement of FEV1 being <80% of predicted. The first publications on COPD from the OLIN Studies used that definition parallel with the GOLD definition.[11,41,48,51,52] The GOLD definition became the gold standard also in Sweden after the year 2000, and was subsequently introduced in several Swedish national and local guidelines, while VC remained as the denominator. Although GOLD recommends FVC to be used as the denominator, it also accepts the use of VC.[209] After some years attempts were made to correct for over-diagnosis among elderly, introducing the "65-65"-rule, which means that among subjects aged >65 years the ratio of FEV1/VC should be <0.65 instead of <0.70 to designate significant airflow obstruction tantamount to COPD. This rule has not been used in international OLIN publications, as it pertains solely to Sweden. In this thesis, the Swedish definition of COPD was used with complementary addition of the LLN 5th percentile of the ratio of FEV1/FVC in papers I, III and IV and in paper IV also the fixed ratio definition with FVC as the denominator.

The very definition of normal lung function is dependent on the study population and reference equations used, both of which are in constant state of change. We know that results of studies of prevalence of COPD are influenced by the definition of COPD, use of pre- or post-bronchodilator values, the representativeness of the reference equations for spirometry, the age composition of the studied samples and the exposures, in Europe particularly the smoking habits. What was deemed as "normal" and physiological 50 years hence, may not be representative today. In paper I and paper II, spirometric normal values from Berglund et al were used.[77] In paper

III, values from GLI were used.[80] In papers IV OLIN reference values were used.[199] This reflects the reality of ongoing research, in the sense that new knowledge is implemented ad hoc upon being made available.

The debate continues about how to define both irreversible airway obstruction and the disease, or syndrome, COPD. The GOLD consortium has argued for the use of the fixed ratio of FEV1/FVC <0.70, while an increasing number of researchers argue for a strict physiological definition of airway obstruction using the lower limit of normal (LLN) defined as the lowest 5th percentile. Both approaches have their pros and cons. Regarding the use of the fixed quota, concerns about overdiagnosis as described above have been raised.[66,210,211] However, one important strength of the fixed quota is its simplicity, which makes it suitable for everyday clinical use also in primary care where presumably the majority of subjects with COPD are diagnosed and managed. Considering the ever-increasing body of knowledge clinicians are expected to ingest and apply, guidelines should be as self-explanatory and clear as possible. This is further underlined by the fact that underdiagnosis of COPD remains a large problem also in high-income countries with developed healthcare systems, as exemplified in the papers in this thesis.

From a pathophysiological perspective however, clarity alone is hardly a reason for using a certain definition. Arguments against the fixed ratio tend to use examples like e.g. elderly, asymptomatic never-smokers with a ratio of FEV1/FVC of 0.69, and ask rhetorically: "Do these have COPD?" Meanwhile, if the same subjects present with repeated measures of a resting blood pressure of 141/91, they would be diagnosed with hypertension.[212] We acknowledge that COPD and hypertension are two different disease entities and that the future risks associated with marginally decreased lung function in e.g. otherwise healthy elderly subjects is to date largely unknown. The rapidly expanding research about other features of COPD than spirometric impairment, such as immunological mechanisms, local and systemic inflammation and also comorbidities, will likely lead to a more comprehensive understanding of the disease in the future.

6.4 Asthma with chronic airflow limitation versus COPD

Equal to COPD, asthma is also a heterogeneous disease. Asthma is usually characterized by chronic airway inflammation and defined by history of recurring respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable

expiratory airflow limitation.[213] Asthma is common, with prevalence ranging from 1-18% depending on its definition, the methods of asthma diagnosis and geographic location.[213] In previous OLIN materials, defining asthma by questionnaire reports using the question "Have you been diagnosed by a physician as having asthma?", the prevalence of asthma among adults in Norrbotten has increased from 5% in 1985[185] to almost 12% in 2006,[189] while recent results from the Swedish part of the GA^{2}LEN ended in between these two estimates.[214] Clinical examinations tend to result in slightly higher estimates, as suggested by clinical data from West Sweden.[215,216]

It is increasingly recognized that asthma and COPD have several overlapping features, and that the differential diagnosis can be difficult.[97] In addition, persistent and in particular severe asthma leads to an accelerated loss of lung function (FEV1, FEV1/FVC) compared to non-asthmatic subjects, and this is further pronounced in asthmatic subjects who smoke.[217,218] Subgroups of subjects with asthma may thus be at increased risk of developing irreversible airflow obstruction.[219] A proposed description from GINA-GOLD states that the Asthma-COPD overlap syndrome (ACOS) is defined by the features it shares with both asthma and COPD. Noteworthy, in the current version of the guidelines, one feature that favors COPD is record of persistent airflow limitation, here defined as post-bronchodilator FEV1/FVC <0.70. The definition of ACOS is however not fully established, but that this may represent a subgroup worthy of special attention is implied from studies showing subjects with ACOS to have increased rates of exacerbations as compared to subjects with COPD alone.[220] In the papers included in this thesis, we used spirometry to define chronic airflow obstruction. In several previous studies the diagnosis of obstructive airway diseases has been in part registry-based,[221,222] which in turn can lead to misclassification.[223] We conclude that however difficult, one of the main issues in the coming years for the research community should be to address the taxonomy of obstructive airway diseases. Here epidemiological research can play a valuable part.

7 DISCUSSION OF MAIN RESULTS

7.1 Prevalence of COPD among never-smokers

Paramount to understanding the scope of a disease is investigations of how common it is, i.e. its prevalence. COPD is often viewed as a smokers' disease, and this is where the vast majority of studies have been directed. In paper I we examined the prevalence of COPD among never-smokers, using a large, population-based sample. We found the prevalence to be 6.9%, which is well in line with other large-scale studies.[168-170,179] Prevalence of GOLD ≥2 was 3.5%. It is also of interest to compare our results with other studies from comparable areas. From the Norwegian Hordaland County Cohort Study, prevalence of GOLD-defined COPD among never-smokers was in one study found to be 7%.[105] From the Copenhagen City Heart Study, prevalence of COPD among never-smokers was 7.9% according to the GOLD criteria, and prevalence of GOLD ≥2 was 4.6%.[104] Noteworthy, only pre-bronchodilator spirometry was available from the Danish study, but subjects with self-reported asthma were excluded.

Acknowledging the continual changes in society in regards to overall health and environmental factors that has, and still is, taking place, in Paper IV we aimed to estimate the prevalence in never-smokers in a contemporary sample. Here, we note that although the overall prevalence of COPD defined as FEV1/VC <0.70 was in line with the data from 1994-1995 presented in paper I, the prevalence of GOLD ≥2 was 2.0%. Whether this truly represents a shift towards milder disease among never-smokers with spirometrically defined COPD remains unresolved, and will require further and larger studies to be addressed.

Defining COPD using the FEV1/FVC <0.70 and LLN respectively in paper IV, yielded a prevalence of COPD of 4.9% and 3.0%, respectively. Using the above definitions, GOLD ≥2 was present in 1.4% and 1.3%, respectively. This again demonstrates the high variability of prevalence by choice of definition, as has previously been discussed in this thesis and which has been corroborated in previous studies. One study originating from the United States drawing subjects from the general population, in which the GOLD and ATS/ERS criteria were compared, found prevalence of GOLD ≥2 among never-smokers to be 3.9%, although prevalence of moderate or more severe obstruction using the ATS/ERS criteria in the same group was 1.1%.[224] One

implication of the importance of spirometric definition also among never-smokers can however be inferred from the findings of paper III, as a substantial proportion of subjects with GOLD ≥2 were classified as normal using the LLN. Interestingly, a previous study on the so-called discordant cases, i.e. subjects classified as normal using the LLN but having COPD according to the fixed ratio, found that comorbid disease in this group was highly prevalent and could thus represent a specific risk group.[225]

7.2 Symptomatology among never-smokers with COPD

While subjects with COPD can remain asymptomatic in the earlier stages of disease,[37] among those with pronounced airflow limitation few subjects are free from symptoms.[51] One aim of this thesis was to investigate the burden of symptoms among never-smokers with COPD. In previous guidelines, subjects with a normal spirometry, yet presenting with respiratory symptoms were classified as "at risk".[64,65] This category, in the initial GOLD document defined as "GOLD 0", were subsequently dropped in the newer guidelines, due to a perceived lack of evidence whether subjects in GOLD 0 actually were at an elevated risk of progressing to GOLD 1.[226] Longitudinal studies have however shown subjects with respiratory symptoms to express an elevated risk for disease progression, which suggests the importance of respiratory symptoms as markers of COPD.[48,227,228]

As shown in paper I symptoms were highly reported by subjects with GOLD ≥2, also among never-smokers. In paper III we once again noted that respiratory symptoms were highly related to the severity of airflow limitation and that the level among never-smokers was on par with that in ever-smokers. Taken together, these findings confirm that COPD in never-smokers is associated with a significant symptom burden. In addition, the similarity in symptom burden between smokers and never-smokers with comparable levels of airflow obstruction underlines that COPD should not be neglected in subjects who have never smoked. In paper IV, which was based on a more recent sample, never-smoking subjects with GOLD ≥2 were considerably fewer as compared to previous papers. This can probably account for the finding that although the overall trend was that symptoms where more commonly reported among never-smoking subjects with GOLD ≥2 as compared to subjects with no airway obstruction, statistically significant differences were evident only for any wheeze and sputum production.

7.3 Risk factors for COPD among never-smokers

The aim of paper II was to establish whether exposure to passive smoking was a risk factor for COPD among never-smokers. It stands to reason that exposure to passive smoke is not beneficial, as it has been associated with increased risk for heart disease,[229] lung cancer [230] and asthma.[121] The importance of passive smoking as a contributing factor for disease in general is additionally highlighted from one large study implicating passive smoke as a cause of 1% of overall global mortality.[231] Although excess risk of COPD in association with passive smoking exposure have been described,[232] earlier studies tended to define obstructive lung disease without the use of spirometry,[233] or used pre-BD spirometry only to define COPD.[127,128] While experimental studies have shown subjects exposed to passive smoke to express an inflammatory response similar to that of smokers,[234,235] the long-term effects of passive smoke can for ethical reasons only be examined in an epidemiological setting.

In the data sampled from the study participants we had access to post-bronchodilator spirometry, and also related questions pertaining to exposure to passive smoke in work and at home. The data was also sampled in the mid 1990's, at a time when passive smoke was still prevalent at e.g. workplaces in Sweden. Owing to progressive legislation and attitude changes in society, workplace exposure to passive smoking is now becoming less common in several countries, with consequent positive effects for respiratory health.[236-238] Smoking-related regulation remains however limited in many other parts of the world.[239] From paper II, we noted that the association between passive smoking and COPD among never-smokers was statistically significant only when passive smoking was reported in multiple settings. The risk was highest in subjects who reported both past and present passive smoke exposure both at work and at home. This is indeed logical considering that COPD as a disease entity develops gradually over time and at least in the case of smokers, in response to repeated and prolonged exposure.[240] Results from the Chinese Guangzhou Biobank Cohort Study of passive smoke exposure in never-smokers also implied that it was the overall duration of smoke exposure as measured in hours of exposure/week, rather than the intensity of passive smoke that was harmful in relation to COPD development.[127] Although, as stated in paper II, we did not have exact time measurements, the surrogate variables serves as an indicator of prolonged exposure (exposed at current work, currently at home) all through the day, presumably for years at an end. Hopefully legislation aimed towards reduction of involuntary

exposure to passive smoke will progress to the point that this will become a non-issue in the coming years.

In paper IV we identified occupational exposure to gas, dust or fumes (GDF) as a major risk factor for COPD among never-smokers. Previously, occupational-related exposures have been implicated as a source of 15% of COPD cases.[129] In addition, a Swedish study using registry-based data found increased mortality from COPD associated with GDF also among never-smokers.[241] The item on GDF was not included in the questionnaires used in the previous papers of this thesis, and to what extent exposure to GDF could explain COPD among never-smokers in the study population of papers I-III is thus not certain. The finding that exposure to GDF was highly related to COPD among never-smokers, regardless of spirometric definition, adds strength to the public health argument of stringent and enforced regulations aimed at respiratory health in the workplace.

GDF exposure has previously been associated with various conditions such as asthma, eczema and allergic sensitization,[214,242,243] and also increases the risk of work change due to respiratory conditions.[244] Thus, what among younger subjects can result in respiratory symptoms and asthma, could equate a COPD diagnosis among elderly subjects. Analogous to exposure to passive smoke, occupational exposure takes place without the individual's consent. We believe our findings add strength to the public health argument of stringent and enforced regulations concerning inhalant exposures in the workplace.

We note that in all our studies, age was independently associated with COPD which is hardly surprising. Defining age as the progressive decline of homeostasis that occurs after the reproductive phase in life is complete,[245] COPD can be viewed in part as the result of a lifetime's worth of accumulated exposures to noxious substances, as well as general degenerative changes in the airways and parenchyma, although the molecular processes involved are complex and not fully elucidated.[245] It has previously been established that the vital capacity diminishes with age, although the total lung capacity remains essentially the same.[246] In addition, respiratory muscles also weaken with age.[247] Altogether, there is an inherent age-dependent component in the natural history of respiratory indices which predisposes elderly subjects for decreased FEV1/(F)VC ratio. This of course is mitigated by using the LLN definition of COPD which takes age into account; however this has some implications related to respiratory symptoms as previously mentioned, and also for comorbidities as is described below. Which definition of chronic irreversible airflow obstruction is the best predictor of

future symptoms, adverse events and reduced quality of life will require longitudinal materials to further disentangle, and is thus beyond the scope of this thesis.

7.4 Prevalence and impact of comorbidities among never-smokers with COPD

Among subjects with mild-to-moderate COPD, the main cause of death is not primarily respiratory, but cardiovascular conditions and malignant diseases.[13,15] Comorbidities in COPD are by themselves associated with increased overall mortality, reduced quality of life and increased societal costs.[248-251] As discussed in more detail previously in this thesis, COPD is increasingly being recognized as a syndrome with systemic implications,[252] and that subjects with COPD often suffer from various other diseases has also been a subject of increasing interest in recent years.[90,253]

In paper III, we aimed to examine whether this was the case also among never-smoking subjects. We found airflow limitation severity to be highly related to reported comorbidities, in particular cardiovascular conditions. Viewed by smoking status, the composite variables of any comorbidity, any cardiovascular disease and any cardiac disease were highly related to the severity of airflow limitation, regardless of smoking status. Viewed as individual disease categories, although an overall trend towards higher prevalence among subjects with more pronounced airflow limitation was seen, this was not in all instances statistically significant. We believe this to be in part a power issue, as the number of never-smoking subjects with GOLD $\geq$2 was limited and the prevalence of comorbidities in these was similar to that seen in smokers with GOLD $\geq$2.

These findings have clear clinical implications. Physicians should be aware that not only do smokers constitute a high-risk group for cardiovascular conditions, but that so do subjects with irreversible airflow obstruction regardless of their smoking history. We are of the opinion that an investigation of e.g. respiratory symptoms which by necessity includes spirometry should also include cardiovascular screening. Many cardiovascular conditions, such as hypertension, are initially asymptomatic upon presentation which may in turn lead to a prolonged delay to proper diagnosis and treatment.[254] Moreover, the potential role of spirometry in cardiovascular work-up should be evaluated, considering not only the findings in paper III and similar studies but also the general associations between decreased FEV1 and all-cause mortality.[255] It is our hope that these

findings can contribute to an overall improvement in public health, perhaps through more standardized protocols, in particular when dealing with individuals that do not belong to what is traditionally recognized as high-risk groups.

8 CONCLUSIONS

This thesis focused on never-smokers with COPD and aimed to characterize the prevalence, symptomatology, risk factors and comorbidities in this group. COPD was highly prevalent among never-smokers in Sweden. Never-smokers with COPD, in particular subjects with GOLD ≥2, report more respiratory symptoms and have more co-morbidities than never-smokers without COPD. Passive smoking in multiple settings was not only associated with COPD among never-smokers, it was the second strongest risk factor for COPD among never-smokers after belonging to the oldest age group. Notably, only approximately half of never-smokers with GOLD ≥2 had any previous diagnosis of either asthma or chronic bronchitis/emphysema. Use of spirometry is mandated for diagnosis of obstructive pulmonary disease and should be used more frequently in order to arrive at a proper diagnosis and guidance of management.

- Prevalence of COPD, defined as FEV1/VC<0.70 was about 7% among never-smokers and considerably lower when defined using LLN.
- One in five subjects with COPD were never-smokers
- Risk factors for COPD among never-smokers included age >60 years, physician-diagnosed asthma and occupational exposure to gas, dust or fumes, and for GOLD ≥2 also a family history of obstructive airways disease
- The burden of symptoms among never-smokers with COPD was high, among subjects with GOLD ≥2 on par to that of ever-smokers with GOLD ≥2
- Passive smoking was a risk factor for COPD among never-smokers
- Comorbid conditions proved common among never-smoking subjects with COPD
- No significant difference in prevalence of COPD among never-smokers between Norrbotten and West Sweden was noted

9 FUTURE PERSPECTIVES

Our knowledge of COPD among never-smokers is mainly derived from large, epidemiological surveys which have provided information on general characteristics such as age distribution of those affected, risk factor pattern and symptomatology. Still, we lack evidenced-based therapeutic strategies for this group. Should never-smoking patients with COPD be treated in the same way as patients with a history of smoking? As previous large randomized clinical trials in COPD have included only subjects with a smoking history, we do not know for sure at this moment. Considering the significant prevalence of COPD in this group noted not only in the papers included in this thesis, but also in other large population-based studies, this obviously constitutes a problem.

Future in-depth mechanistic studies of obstructive lung diseases hold fascinating opportunities for novel therapeutic strategies. In recent years, the pharmacopeia of COPD has received much attention. Considering the vast numbers of afflicted individuals, and the not always impressive efficacy of available treatment, this is hardly surprising. Again, to what extent new therapeutics can be applied to never-smokers with COPD remains to be seen.

Prior to inclusion of subjects in clinical trials, we first have to identify them. Here epidemiological surveys can play a valuable part, not only in better characterization but also to bring the matter to further attention. In particular, longitudinal surveys will most certainly aid our understanding of long-term outcomes in this group. Bearing in mind the problem of under-diagnosis smokers with COPD have faced due to both patient- and doctors-delay, this can surely be expected to affect more strongly those not belonging to an obvious high-risk group. Importantly, for clinical research to have meaning the results must disseminate to the clinical setting where subjects at risk and those already afflicted with disease present to the individual physician. Further studies and debate can thus not only advance science, but aid clinicians to offer the best available care to their patients.

Finally, prevention of disease remains preferable to treatment. Sadly, the burden of respiratory disease related to involuntary exposures remains high. Thus, measures aimed at reduction of noxious air pollutants should continue unabated. Hopefully, this will lead to future follow-up studies being able to present data on global improvements of respiratory and overall health.

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APPENDIX

Appendix I – English translation of the OLIN postal questionnaire

Appendix II – English translation of the OLIN interview questionnaire