COPD

Incidence, prognosis and comorbidity with special focus on heart disease

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

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Gothenburg, Sweden, 2017

Cover illustration by Berne Eriksson

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ISBN 978-91-629-0051-9 (print)
ISBN 978-91-629-0052-6 (pdf)
http://hdl.handle.net/2077/48664
Printed in Gothenburg, Sweden 2016
Ineko AB

To my patients

Abstract

The aim of the thesis was to contribute to the knowledge on chronic obstructive pulmonary disease (COPD) with respect to incidence, risk factors, prognosis and comorbidities. With the epidemiological approach, samples from the general population in Norrbotten and in Västra Götaland were analysed. The criterion used was the fixed ratio of the expiratory volume in the first second (FEV_1) through vital capacity (VC) of below 0.70. Incidence of COPD during 7 years was 11.0% and for more severe disease (GOLD II-IV) 4.9%. On the basis of incidence risk factors for COPD were found to be smoking and age. Prognosis of COPD was studied and we found that 46% were still alive after 20 years. Risk for death was associated with age, male sex, disease severity and comorbid heart failure and ischemic heart disease. COPD severity and low FEV_1 were signs for worse prognosis as well as symptoms of chronic bronchitis. The best prognosis was found among subjects with asthma like phenotype. Heart diseases and hypertension were prevalent in COPD, and COPD common among subjects reporting heart diseases. Present heart diseases was most pronounced in more severe grades of COPD and over 50% reported heart disease, hypertension or medication for these diseases in the most severe COPD. In a population with almost halved smoking frequency 15 years later COPD prevalence was lower, but the pattern of comorbidities in COPD remained similar. More severe COPD was found to be associated with low BMI and being underweight. Obesity was not more prevalent in COPD compared to the general population.

The studies give implications for the clinic. Spirometry should be used frequently, and repeatedly, in patients exposed to risk factors and with respiratory symptoms. In patients with COPD it is of great importance to consider concomitant diseases, particularly heart diseases. Equally important is to consider presence of airflow limitation among patients with heart diseases. This should have impact on treatment of both heart disease and COPD. Although prognosis is impaired among patients with COPD, reassurance can be communicated. Reversibility on spirometry should be evaluated in order to identify patients with asthma-COPD overlap since it may influence treatment. Both underweight and obesity in COPD should be identified and attempts to intervene should be considered. Identifying impaired lung function, especially in obesity, although not fulfilling COPD criterion is imperative.

Keywords

COPD, epidemiology, incidence, risk factors, comorbidity, heart diseases, BMI

Sammanfattning på svenska

Kroniskt obstruktiv lungsjukdom (KOL) är en vanlig sjukdom som ofta ger besvär med hosta, andfåddhet, nedsatt ork, trötthet och sänkt funktionsnivå. Sjukdomen kan leda till förtidig död. Diagnosen ställs med hjälp av spirometri, men spirometri används för lite inom sjukvården vilket innebär att många inte fått rätt diagnos.

Med spirometri kan man upptäcka luftvägsobstruktion genom att ensekundsvolymen, det man blåser ut under första sekunden, FEV_1, är mer sänkt än den volym man kan andas med, vitalkapaciteten, VC. Kvoten mellan FEV_1 och VC ska vara mindre än 0,70 för diagnosen KOL. De dominerande orsakerna till KOL är rökning och ålder, men det finns andra riskfaktorer. KOL kan finnas med andra sjukdomar hos en individ.

Syftet med den här avhandlingen är att bidra till kunskapen om KOL med avseende på hur många som insjuknar (incidens), riskafaktorer för KOL, prognos när man har KOL och sjukdomstillstånd som kan finnas samtidigt med KOL. Ansatsen är epidemiologisk och de studier som ingår i avhandligen baseras på urval ur den vuxna befolkningen i Norrbotten och i Västra Götaland.

I den första studien analyserades insjuknande i KOL under en period av 7 år. 11,0% insjuknade i KOL och 4,9% drabbades av svårare sjukdomsgrad, stadium 2-4 av KOL. Rökning och högre ålder var riskfaktorer för att insjukna i KOL. De som hade återkommande hosta med slem, ofta pipig andning och andfåddhet vid ansträngning mer än jämnåriga, hade hög risk att utveckla KOL.

Den andra studien fokuserade på prognos för de som har KOL. Studien visade att nästan hälften av de med KOL fortfarande levde efter 20 år. Risk för att dö var högre ålder, manligt kön, svårare grad av KOL, samtidig hjärtsvikt och ischemisk hjärtsjukdom. De som hade bäst prognos var de med tecken på samtidig astma.

I den tredje studien visas att hjärtsjukdomar och högt blodtryck är vanligt bland de som hade KOL, och sjukdomen KOL är vanlig bland de som har hjärtsjukdomar. Att ha hjärtsjukdom, hypertoni och medicinering för dessa var i studien vanligast vid svårare sjukdomsgrad av KOL. Över 50% av de med svårast KOL hade någon hjärtsjukdom, högt blodtryck eller medicinering för hjärtsjukdom

eller hypertoni. Vid restriktiv lungfunktionsnedsättning är både ensekundsvolymen, FEV_1, och vitalkapaciteten, VC, sänkt. Studien visade att även bland dessa individer är det mycket vanligt med hjärtsjukdom och högt blodtryck.

Det finns flera studier som visat att sjukdomem KOL ofta leder till undervikt. Men det är omtvistat om det finns ett samband mellan KOL och fetma. I den fjärde studien var syftet att analysera om det finns ett samband, med undervikt och med fetma. Studien kunde visa ett samband med undervikt och KOL, men bara i de svåraste stadierna av KOL. Studien baserades på ett urval ur den allmänna befolkningen och fetma hos de med KOL var lika vanligt som I befolkningen totalt.

Rökning har minskat i Sverige under senaste årtiondena. I den femte studien analyserades om de förändrade rökvanorna hade påverkat hur många som har KOL och om förekomsten av samtidig hjärtsjukdom och hypertoni bland de med KOL hade ändrats. Andelen som rökte var halverad jämfört med den tredje studien, som refererats ovan, 15 år tidigare. Andelen som hade sjukdomen KOL var också lägre. Men samtidig hjärtjukdom, hypertoni och medicinering hos de med KOL var rätt oförändrat jämfört 15 år tidigare.

Våra resultat visar att det är viktigt att göra om spirometriundersökningar för personer som utsatts för rökning eller andra riskfaktorer för KOL, och som har besvär från luftvägarna, även om den första spirometrin är normal. Prognosen om man har KOL är ganska god, men är viktigt att få rätt behandling och framför allt att sluta röka. Det är viktigt att tänka på att de som har KOL även kan ha hjärtsjukdom eller högt blodtryck och att utreda och behandla samtidig hjärtsjukdom. Det är också angeläget att komma ihåg att bland de som har hjärtsjukdom är risken att ha KOL hög. Det bör göras spirometri så att rådgivning och behandling kan sättas in. Undervikt vid KOL är vanligt. Även om fetma inte är vanligare hos de med KOL, än i befolkningen, finns fetma även bland de som har KOL och det utgör en risk för andra sjukdomar. Insatser kan behöva sätttas in för båda tillstånden.

List of papers

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

I. Lindberg A, **Eriksson B**, Larsson L-G, Rönmark E, Sandström T, Lundbäck B. **Seven-Year Cumulative Incidence of COPD in an Age-Stratified General Population Sample**. *CHEST* 2006: 129(4); 879-885.

II. Lundbäck B, **Eriksson B**, Lindberg A, Ekerljung L, Müllerova H, Larsson L-G, Rönmark E. **A 20-Year Follow-Up of a Population Study-Based COPD Cohort-Report from the Obstructive Lung Disease in Northern Sweden.** *COPD: Journal of Chronic Obstructive Pulmonary Disease* 2009, 6:263–271.

III. **Eriksson B**, Lindberg A, Müllerova H, Rönmark E, Lundbäck B. **Association of heart disease with COPD and restrictive lung function – Results from a population survey.** *Respiratory Medicine* 2013, 107(1):98-106.

IV. **Eriksson B**, Backman H, Bossios, A, Bjerg A, Hedman L, Lindberg A, Rönmark E, Lundbäck B. **Only severe COPD is associated with being underweight - results from a population survey**. *European Respiratory Journal Open Research* 2016; 2: 00051-2015. E-pub

V. **Eriksson B**, Backman H, Ekerljung L, Axelsson M, Lindberg A, Rönmark E, Lötvall J, Lundbäck B. **Impact of comorbidities on COPD in Sweden after decades of decreasing smoking burden.** *In manuscript.*

Content

Abbreviations

ATS	American Thoracic Society
BD	Bronchodilator
BTS	British Thoracic Society
COPD	Chronic Obstructive Pulmonary Disease
ECRHS	European Community Respiratory Health Survey
ERS	European Respiratory Society
FET	Forced Expiratory Time
FEV_1	Forced Expiratory Volume in the first second
FVC	Forced Vital Capacity
GLI	Global Lung Initiative
GOLD	Global Initiative for Obstructive Lung Disease
HR	Hazard Ratio
IUATLD	International Union Against Tuberculosis and Lung Diseases
LLN	Lower Limit of Normal
MVV	Maximal Voluntary Volume
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
PEF	Peak Expiratory Flow
SBU	Statens Beredning och Utvärdering av sjukvården
SLMF	Svensk Lungmedicinsk Förening
SMHI	The Swedish Meteorological and Hydrological Institute
SVC	Slow Vital Capacity
VC	Vital Capacity

Introduction

Author's perspective

This thesis is about Chronic Obstructive Pulmonary Disease (COPD). Although an academic text, the writing will uncover a physician's perspective. The academic approach is that of epidemiology where the group is analysed with respect to health, diseases, risk factors for diseases and prognosis. The focus of epidemiological research is the group, never the individual. As a physician my focus is the one patient in front of me. The uttermost aim of epidemiological research must be the wellbeing of patients. My research and clinical work are thus intertwined.

The goal of academic research is to find new valid knowledge. My perspective could be describes as follows: Research is like a gigantic crossword puzzle where single words are written in empty spaces, other words are changed. Or as a big canvas where the painting is an illustration, which helps understanding our world, and where I can contribute with some valuable insertions.

This thesis gives me the opportunity to summarize my research and to give a wider picture of my research and expose my clinical interest.

Aim

Chronic obstructive pulmonary disease (COPD) is a common disease often with symptoms, disabilities and untimely death. COPD has not been a clear entity and has developed from clinical observations of severe disease to be possible to identify by spirometry. Diagnosis is based on lung function testing (spirometry) where the ratio of the forced expiratory volume in the first second (FEV_1) and vital capacity (VC) should be less than 0.70, according to international guidelines. Underdiagnosis is a common problem in clinical practice most often due to limited utilization of lung function testing. The predominant causes for COPD are smoking and age; other risk factors are not satisfactorily identified. COPD often coexists with other diseases and with deviations from normal weight.

The overall aim of the present studies is to contribute to the knowledge of COPD with focus on incidence, risk factors, prognosis, and comorbidities. The particular aims are as follows:

1. To estimate the cumulative incidence of COPD and risk factors related to the development of COPD, including evaluation of the relationship between Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 0 (that is respiratory symptoms and normal lung function) and the development of COPD, in an age-stratified general population sample of middle-aged and elderly individuals.

2. To study 20-year outcomes, mainly mortality, in a COPD cohort derived from a population study.

3. To explore the association of COPD and restrictive lung function impairment, respectively, with heart diseases in the general population.

4. To determine the association between severity grades of airflow limitation in COPD, and both underweight and obesity when corrected for possible confounding factors.

5. The aim of the study was to investigate whether the pattern of comorbidities had changed in Sweden after decades of decrease in the prevalence of smoking.

Background

In the following I will give the background to my research, my perception of COPD, as the entity has emerged, and the rationale for my research. The delimitation of COPD has changed through history and, to a smaller degree, during the research period of the studies in this thesis.

How many will fall ill of COPD is of value to know for clinician and health care provider. Characteristics of individuals, before getting the disease, can be important clues to causes of COPD. Although a specific prognosis is not possible to establish for the individual patient, knowledge about disease progression is often requested and can provide us with a better understanding of the disease.

The possibility of other diseases present among individuals with COPD is of great importance in the clinic and the constituents of comorbid associations are not well identified. Nutritional status in COPD is important for our understanding of the disease and can be a reason to involve the dietician for the patient.

Smoking is an unhealthy habit. Various efforts have been made in society, and by health care workers, to minimize smoking. It is of importance to evaluate these efforts with respect to the prevalence of current smoking, of COPD, and of an influence on the presence of other diseases in COPD.

COPD - a pulmonary disease

Breathing, or ventilation, is essential for respiration, which is essential for life. We breathe no matter what. Breathing movements start episodically in utero, are continuous at birth and, except for the briefest of pauses, continue without respite (Feldman et al., 2003)[1].

Pulmonary diseases are numerous. Diseases of the ventilatory system are of obstructive or restrictive kind, or both. Obstructive impairment is

[1] In this thesis, if there is more than one author, the reference will be to the first name followed by et al. This is for increasing readability. In order to highlight articles where I have been involved my name is also included in the reference in the text.

mainly due to compromised airflow as in asthma and in COPD. The airflow limitation of asthma is reversible. In COPD the airflow obstruction is persistent and not fully reversible. The airflow limitation is due to narrowed airways and/or loss of elastic recoil of the lungs. Restrictive ventilatory limitation is due to delimited volumes and causes for restricted lung volumes are wide-ranging including pulmonary diseases, neuromuscular dysfunction, obesity and heart diseases, and other factors.

COPD characteristics

COPD is a common disease, affecting somewhere about 9 to 10% of adult population in the world (Halbert et al., 2006) with high costs for the individual and society (Jansson et al., 2002).

Major definitions of COPD are those of the American Thoracic Society (1995), the European Respiratory Society (Siafakas et al, 1995), the British Thoracic Society (BTS, 1997), and the adjoined ATS/ERS standard (Celli et al., 2004). The Global Initiative for Obstructive Lung Disease (GOLD) was published in 2001. The wording may be different but the content correspond. The definition of COPD according to GOLD (2017) is as follows:

> Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases (web-site).

Thus COPD is common, preventable, treatable, and characterised by persistent symptoms and airflow limitation. Airway and/or lung tissue abnormalities, as consequence of exposure, are the cause of the airflow limitation in COPD. A prerequisite for the diagnosis of COPD is a not fully reversible ratio of the forced expiratory volume in the first second (FEV_1) and the forced expiratory volume (FVC) of below 0.70 ($FEV_1/FVC<0.70$). The GOLD document has a strategic intention, and the criterion for COPD according to GOLD is adopted by several national societies and implemented in guidelines (NICE, 2010; Socialstyrelsen, 2015a). The GOLD versions have been thoroughly revised since 2001, mainly in 2006, 2011, and now 2017.

The present studies use foremost the criterion of the GOLD workgroup with respect to airflow limitation as the fixed ratio (paper I-IV) with other criteria in additional analyses (paper IV-V).

The disease of COPD

COPD is in the realm of diseases. What comprises a "disease" is, at first sight, easy: A disease is the opposite of health. That approach creates new questions such as on what health is. A pragmatic view is that disease is a condition that affects a person's wellbeing and prognosis.

What constitutes a disease has varied over time and in various cultures (Scully, 2004). Some conditions have developed into diseases while other conditions have disappeared from the realm of disease. Conditions previously considered as part of normal ageing are now seen as diseases. This change pertains to COPD as well. One of the earliest known descriptions from the realm of obstructive lung diseases is that of Badham (1808). The essay arose from clinical observations of patients with very severe and often deleterious disease and description contained dyspnoea, cough and observation of lungs that did not collapse at autopsy. This essay also contains detailed information on medical treatment. Laënnec (1834) named and described chronic bronchitis and emphysema, both from a clinical and from a pathoanatomical perspective. Chronic bronchitis with symptoms of cough and phlegm and emphysema were earlier often used as synonyms and later also as synonyms for COPD.

New diagnostic methods have broadened our view on disease. By means of biomarkers we can identify a disease early and often before clinical symptoms emerges and maybe never develops. The spirometer was invented by Hutchinson (1846), but his device measured only vital capacity with no flow measures. The French physician Tiffeneau (1947) was the first to describe time measured lung volumes. The spirometer that simultaneously can register volume and time is a necessity for the diagnosis of COPD.

New therapeutic options create new diseases. "Are new disease entities being created to match drug development? As the business literature shows, new clinical diagnoses are often welcomed primarily as opportunities for market growth" (Scully, 2004, p 651). Since COPD seems to affects more individuals than, for example diabetes, and is possible to treat, at least with respect to symptoms, the disease is of great

interest for the pharmaceutical industry. New drugs and devices have appeared with benefits for patients with COPD.

COPD in society

In December 1952 a severe air-pollution in London resulted in more than 4,000 deaths and several ten thousand respiratory illnesses. Although not initially appreciated by health officials, it is an important starting point for research on air pollution and acute and chronic pulmonary diseases (Bell et al., 2001; Davis, 2002; Fry et al., 1961). The interest is seen in Sweden by publications from SBU (2000), two National guidelines (Socialstyrelsen, 2004; 2015a), and The Medical Products Agency (Läkemedelsverket, 2015). Health professionals and scientists have been engaged in the workgroups but the mission is from the authorities.

COPD and research

The first publication with "Chronic obstructive pulmonary disease" is from 1960 (Karon et al., 1960). The report from the Mayo clinic certainly contains some subjects with COPD, as we define at now, and the study included lung function testing with maximal midexpiratory flow rate and maximal breathing capacity. There was an attempt to describe the risk factor for COPD and smoking was identified. The term COPD, though, was used somewhat arbitrary as "emphysema", "obstructive pulmonary disease" and "obstructive emphysema" were used as synonyms.

A sign of the rising interest in the chronic disease is a symposium, held by British researcher in 1958 (Fletcher et al., 1959), which recognized the common, and often disabling, disease and acknowledged the confusion and misunderstanding in the research field. The definitions delimited emphysema from chronic non-specific lung disease: chronic bronchitis, intermittent airflow obstruction and persistent obstruction of bronchial airflow. The latter can be seen as an origin to COPD. Lung function test was recommended including FEV_1 and FVC and calculating the ratio between these.

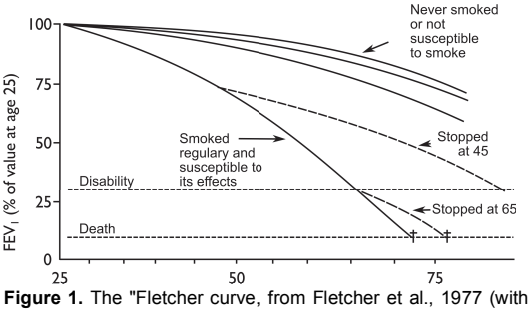


Figure 1. The "Fletcher curve, from Fletcher et al., 1977 (with permission).

The tests should be done before and after inhalation of a bronchodilator aerosol. No guidance was formulated for how to interpret the ratio.

An important and influential work is the study of Fletcher et al. (1976) and the accompanying article in the British Medical Journal in 1977 (Fletcher et al., 1977). The decline in FEV_1, as a marker for the natural history of chronic bronchitis, was in focus. The research identified smoking as the cause for lowered lung function and suggested that neither exacerbations nor chronic bronchitis contributed. A subgroup was identified as having obstruction defined as FEV_1/SVC (slow vital capacity) below 0.66⅔, comprising about 15% of the study population. The study of Fletcher *et al* has been important and influential in the work towards what is now considered COPD. The work, and especially the presentation of the curve of FEV_1 decline, is often presented as the "natural history of COPD". More correctly it would be "the accelerated decline of FEV_1 among smokers".

Much research, including epidemiological studies, has been performed since then with the aims of identifying risk factors for the disease. The terms "chronic bronchitis" and "emphysema" were used with different content in clinical and research articles and often interchangeable (Fletcher et al., 1984).

Despite the dedicated work on chronic pulmonary disease the uncertainty around the definition is mirrored in the following citation from a textbook on COPD 1995 (Snider, 1995):

> That the initial chapter of this book is on the definition of chronic obstructive lung disease (COPD) reflects not only the confusion that exists in the field of the obstructive airflow diseases, but also the confusion in nosology and definitions that has historically pervaded all of medicine (p. 1).

The GOLD document from 2001 acknowledges the problems of the definition of COPD, and the different usage in clinical and research contexts (GOLD, 2001). By the publication, and wide acknowledgment of the standard, focus came to be on lung function measured by spirometry. In several aspects this can be seen as a progression for research and for the clinic. COPD diagnosis became clearer for the clinician, and in research the standardization of diagnosis made research results more comparable.

The way we now define COPD can be regarded as a new entity with respect to previous understanding of, and focus on, chronic bronchitis and emphysema. Symptoms of bronchitis, that is recurrent cough and phlegm, are rather common in the general population and airflow obstruction is not always present. And not all with airflow obstruction report symptoms of bronchitis. Similarly emphysema is not always accompanied by airflow obstruction and not present in all subjects with COPD (GOLD, 2017).

The disease can be said to have gone from severe symptoms, often with a deleterious outcome, to a disease that can be identified by a biomarker, spirometry. This provides possibility to diagnose the disease early, identify risk factors, give advice regarding life style, and to treat non-pharmacologically and with medication. This change of focus toward a standardization of diagnosis in epidemiology has raised new questions and given new challenges for research, whereof some are addressed in this thesis.

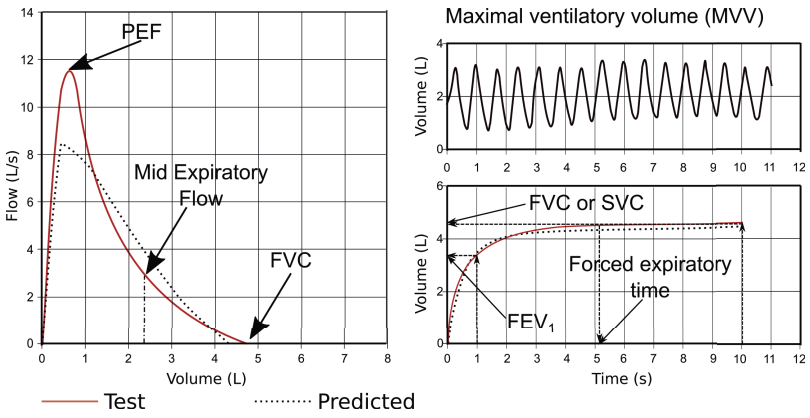


Figure 2. Example of normal spirometry, with explanations.

Airflow limitation in COPD

A key issue is the airflow limitation, or chronic obstruction, of COPD. Various variables have been used to identify airflow obstruction such as FEV_1 of reference value (Huhti et al., 1988), forced expiratory time (American Thoracic Society, 1995), maximal ventilator volume (Karon et

al., 1960), and other variables. A pathological ratio of FEV_1 versus VC[1] is a prerequisite since mid 1990 (BTS, 1997), but the cut-off level, and whether use slow vital capacity (SVC) or forced vital capacity (FVC), for a pathological ratio has been varying. Table 1 shows some major definitions of chronic obstruction.

Table 1. Some definitions of airflow limitation in COPD.

Fletcher 1976	$FEV_1/SVC < 0.66⅔$	
ATS 1986	$FEV_1/VC < 0.75$	(American Thoracic Society, 1986)
ERS 1995	FEV_1/VC <88% of reference values in men FEV_1/VC <89% of reference values in women (Siafakas, 1995)	
BTS 1997	$FEV_1/VC < 0.70$ and FEV_1 <80% of reference value	
ATS 1995	Disease description but no new definitions since 1986	
GOLD 2001	$FEV_1/FVC < 0.70$ after bronchodilation	
SLMF 2002	Max FEV_1/Max(SVC and FVC) before and after bronchodilation <0.70; age>65: <0.65	
NICE 2004	FEV1/VC <0.70 and FEV_1 <80% of reference value	
ATS/ERS 2004	$FEV_1/VC \leq 0.70$	(Celli, 2004)
ERS 2005	$FEV_1/SVC < LLN^{5th}$	(Pellegrino, 2005)
ERS 2011	$FEV_1/FVC < LLN^{5th}$	(Bakke et al., 2011

The two conflicting views on what constitutes an airflow limitation in COPD are the fixed ratio, i.e. a $FEV_1/FVC<0.70$ (GOLD, 2017), and the lower limit of normal (LLN^{5th}) criterion (Pellegrino et al., 2005), which implies a ratio of FEV_1/FVC below the fifth percentile of reference value. The first published studies with a fixed ratio of $FEV_1/FVC<0.70$ are from two Nordic countries (Bakke et al., 1991; Lange et al., 1989). Attempts to validate the two criteria have been performed (van Dijk et al., 2015; Vollmer et al., 2009).

Since 2011 version of GOLD, and in the most recent updated version of 2017, it is acknowledged that the fixed ratio of 0.70 may carry a risk of overdiagnosis of the elderly. In research, for example in epidemiology,

[1] VC often denotes slow vital capacity (SVC), but sometimes the highest value of SVC and FVC.

this would add “noise” to the material by including older subjects without other signs or symptoms and without known exposure in old age (Quanjer et al., 2010). In the clinical setting the risk of overdiagnosis is limited. A larger problem is the underutilization of spirometry (Lindberg et al., 2006; Quach et al., 2015), and there are no guidelines advocating screening by spirometry among healthy or un-exposed.

In the latest GOLD version, and since 2011, the LLN criterion is discussed, that the LLN criterion is dependent on the choice of valid reference equations, and that validating studies for the use of LLN are lacking (GOLD, 2011). In the same document the use of VC, i.e. the slow vital capacity, is an alternative and the same criterion of FEV_1/VC <0.70 is recommended.

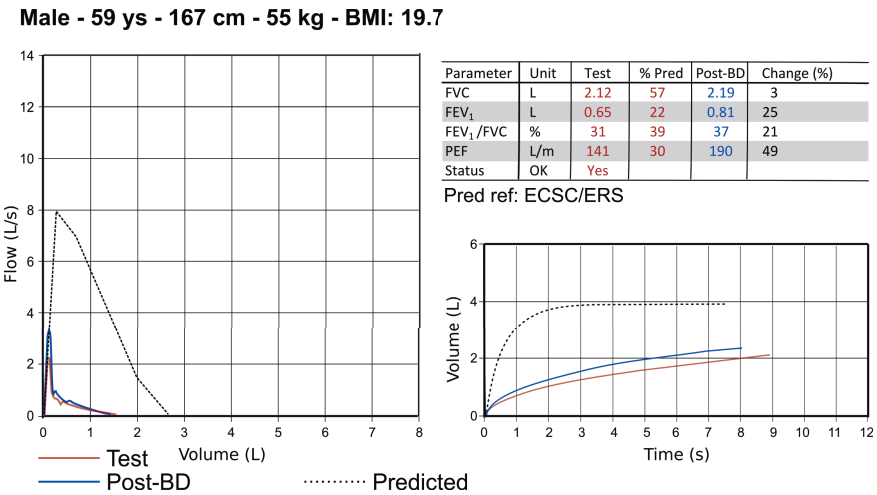
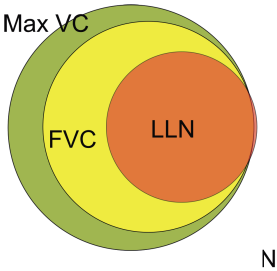


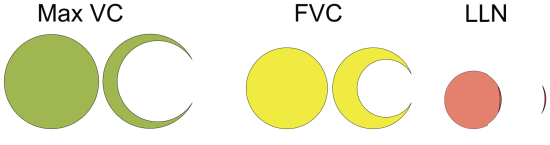
Figure 3. Spirometry with irreversible airflow limitation consistent with COPD.

In order to address an over-diagnosis among elderly the Swedish Pulmonary Society previously recommended a fixed ratio of FEV_1 to VC of below 0.65 for older patients and below 0.70 for other. The ratio should be calculated with the highest value of FEV_1, SVC and FVC before and after bronchodilation (Svensk Lungmedicinsk Förening, 2002). This recommendation remained up to 2015. In the studies on incidence, on prognosis and on comorbidities (paper I-III) we used the criterion of SLMF without the 65-years rule, i.e. a fixed ratio of 0.70 for all.

What is in focus in the attempt to identify airflow limitation for the diagnosis of COPD is a decision limit. The recommendations are established by consensus procedures and based on more deductive methods. There is still a need to evaluate the decision limits in research, and this ought to include prognosis, other health aspects, and effects of interventions and treatment.

The identification of COPD by airflow limitation is affected by the choice of slow and forced vital capacity, pre- and post-bronchodilator variables, fixed ratio or the lower limit of normal (LLN), and, for the latter, choice of reference values. An illustration of the consequences is shown in figure 4. The consequences of using three different criteria for airflow limitation in COPD is shown in the figure 4 (adapted from Eriksson et al., 2015). As is shown the more inclusive criterion, Max VC, does not only include mild COPD, nor mainly subjects without symptoms.





	Max VC		FVC		LLN	
N=	681	162	519	244	279	6
Age, ys	66.2	66.4	66.2	69.1	62.8	32.3
Men (%)	55	57	54	59	49	33
Ever smoke (%)	78	71	80	73	85	20
COPD prevalence(%)	17.2		13.1		7.0	
COPD 1 (%)	47	69	40	58	25	67
COPD 2 (%)	45	30	50	41	57	33
COPD 3 (%)	6	1	8	1	14	0
COPD 4 (%)	2	1	2	0	4	0
mMRC>1 (%)	29	24	31	25	36	33
CB (%)	42	34	44	35	53	17
Wheeze (%)	22	15	24	16	32	33
Dyspnoe, CB, wheeze (%)	58	46	62	52	70	67

Figure 4. Consequences of using three different criteria for airflow limitation in COPD. Max VC=highest value of FEV_1 /highest value of SVC/FVC, before and after BD; FVC=FEV_1/FVC after BD; LLN= FEV_1/FVC after BD < LLN5th defined by the GLI reference value.

COPD disease severity

The most commonly used variable for assessing disease severity of COPD is the level of FEV_1 of reference value. This was proposed by the GOLD document since 2001, by then into 3 stages. The staging was recommended for educational reasons for the purpose of simplicity and had not been clinically validated by then (GOLD, 2001), but subsequent studies show its validity for prognosis and other health aspects (Soriano et al., 2015). The GOLD document of 2001 included stage 0 or subjects at risk[1] of COPD. At risk denoted persons with symptoms, such as cough and dyspnoea, but with a normal FEV_1/VC ratio. Stage 0 was abandoned in the 2006 document, but all revisions recognize that symptoms of cough and sputum production may precede airflow limitation (GOLD, 2006). From 2011 stage was changed to grade (GOLD, 2011). In the 2011 document of GOLD a classification into ABCD groups was presented, based on history of exacerbations, grade of airflow limitation and symptom scoring. The purpose was for guiding of treatment. FEV_1 is used for grading of disease severity but is not a variable in the guide to treatment (GOLD, 2017).

Guidelines, and research, suggest that GOLD grades II-IV is a marker for more severe disease compared to grade I (BTS, 1997; Antonelli-Incalzi et al., 2003, Tsoumakidou et al., 2004). This cut-off limit for more severe disease has been used in two of the present studies (paper I and V). We have used the LLN criterion as an alternative (paper IV and V), and in paper V we used FEV_1<LLN for identifying more severe diseases as it is more consistent with the LLN model.

Reference values of lung function testing

Reference values of dynamic spirometric values are used for diagnosis of COPD with the LLN criterion, and for grading of disease severity according to the GOLD workgroup and ERS Task force. Reference values are not used for the fixed ratio criterion for diagnosis. In the Swedish context there has been two somewhat older reference equations: Hedenström et al. (1985, 1986), and Berglund et al. (1963). In addition the Coal and Steel equations (Quanjer et al., 1993) has been used in the clinic. Primarily in treatment studies other reference values, for example

[1] ”At risk” in this context represents subjects with a normal FEV_1/FVC ratio but with symptoms of airway disease. In epidemiology “at risk” denotes the “undiseased”, with respect to the disease in focus, in the study sample.

NHANES (Hankinson et al., 1999), have been used. Moreover there are several national and local reference values. The equations differ due to statistical methods and selection of reference population.

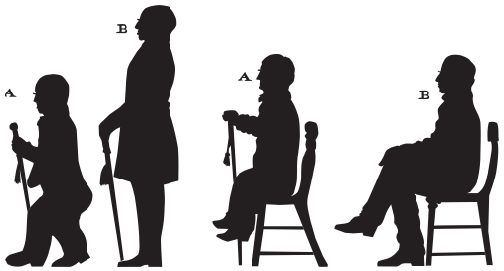


Figure 5. From Hutchinson (1846).

An attempt to create reference values as a standard globally is the work of the Global Lung Function Initiative (Quanjer et al., 2012) with equations that take ethnicity into account. There is some support for his view, based on observations. This also creates some problems. Ethnicity, or racial aspects, explains only a minor part of the difference in reference values (Harik-Khan et al., 2001). US-born Asians have higher lung function compared immigrant Asians (Fulambarker et al., 2010). Two Norwegian reference values from nearby areas differ (Langhammer et al., 2001). Socioeconomic class (Prescott et al., 1999), sitting height (Fulambarker et al., 2001) and other variables affect lung function. In a world with increasing migration and cross-cultural marriages, ethnicity becomes the more difficult to delimit.

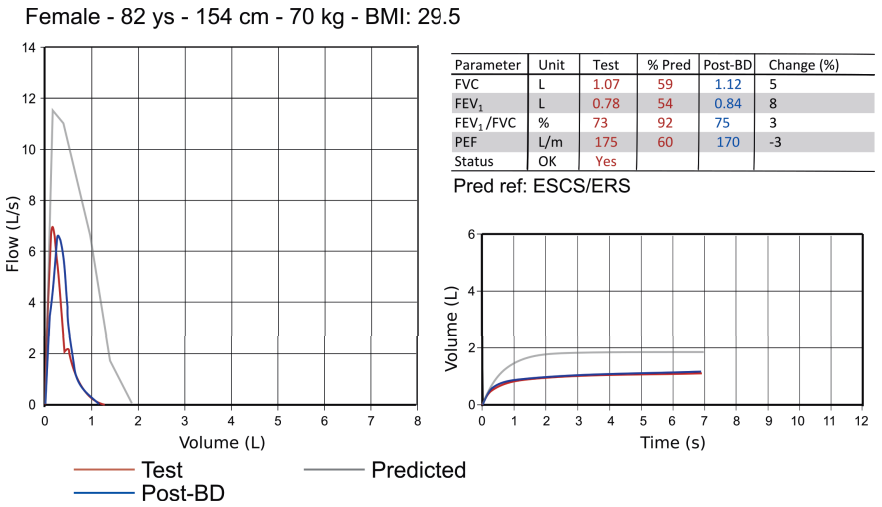
The OLIN group has calculated reference values based on healthy, non-smokers in Norrbotten (Backman et al., 2015a). In an evaluation of the GLI reference values on a healthy non-smoking cohort in Norrbotten, the GLI reference material seemed to represent lower lung function than corresponding subjects in Norrbotten. This was most pronounced for FVC and among women (Backman et al., 2015b).

In the studies of this thesis we have used the fixed ratio criterion (paper I to V), which is insensitive to reference values for diagnosis. For grading we have used Berglund's reference values (paper I-III), GLI equations (paper IV) and the OLIN reference values (paper V). In paper V we used both the fixed ratio criterion and the LLN criterion with the OLIN reference values.

Restrictive spirometry

As the diagnosis of COPD is based on a spirometry with a ratio of FEV_1 to FVC below 0.70, the non-COPD group will contain subjects with low

VC and also low FEV_1, that is with a normal ratio but with spirometric signs of lung disease or other condition or disease affecting lung function. Although restrictive pulmonary disease requires investigation of static lung volumes, in order to identify low TLC, a restrictive spirometric pattern on dynamic spirometry can indicate symptoms and disease. A restrictive spirometric pattern has been defined as FVC below 80% of reference value (Aaron et al., 1999; Mannino et al., 2008). The OLIN studies have also used FVC under LLN for a restrictive pattern (Backman, Eriksson et al., 2016a). A restrictive spirometric pattern has been shown to have a strong association with hypertension, diabetes and cardiovascular disease (Mannino et al., 2003, 2012).



Parameter	Unit	Test	% Pred	Post-BD	Change (%)
FVC	L	1.07	59	1.12	5
FEV_1	L	0.78	54	0.84	8
FEV_1/FVC	%	73	92	75	3
PEF	L/m	175	60	170	-3
Status	OK	Yes			

Figure 6. Spirometry with a restrictive pattern.

Subjects with a restrictive spirometry can have been included in the cases with obstructive lung disease in previous studies when criteria leaned on FEV_1 only, SVC only, Forced Expiratory Time (FET), or Maximal voluntary Volume (MVV). In later studies relying on a pathological ratio this group can have been included in the reference group (non-COPD).

In the present studies (paper III and IV) we used a definition of restrictive spirometry as the FVC below 80% of reference value after excluding subjects with a FEV_1/VC ratio below the decision limit.

Symptoms of COPD

As in most diseases, COPD is accompanied by symptoms. In COPD symptoms are described as dyspnoea, wheeze, cough, and phlegm. There is a great variation in the expression of these symptoms, and among individuals not having COPD report of respiratory symptoms is common. Especially dyspnoea is common in the general population, and found in several other diseases such as heart failure, asthma, obesity, and other. Subjects identified as having COPD, even COPD in more sever grades, do not always report or acknowledge these symptoms (Calverley et al, 2006 p. 7). Particularly subjects with mild COPD often do not report chronic symptoms (Kotaniemi et al., 2005). Thus it is not good enough to ask: "How does it feel, how does it feel". More careful inquiries are needed in order to identify symptoms of COPD. Several guides are possible to use. In the OLIN studies and in the WSAS study questions on chronic bronchitis, elaborate questions on wheeze, and on dyspnoea according to the Medical Research Council (MRC) recommendations are included.

COPD should be considered in a person with symptoms of breathing, and a history of exposure to known risk factors (GOLD, 2016). That methodology is good enough for the clinic, and screening patients without symptoms is not recommended in most guidelines (U.S. Preventive Services Task Force, 2008; GOLD, 2017). Limiting examinations to patients in the clinic with symptoms of breathing will not identify all with COPD and might thus miss some who will gain use of intervention. In research the aims can be to identify risk factors, provide knowledge on prognosis and to find avoidable exposure. Thus restricting research to individuals with symptoms might overlook much of important information.

Exposure

Diseases may be caused by a single factor such as a pathogenic microorganism, or a genetic aberration, but more often the cause is multifactorial and due to an interaction between the individual and the surroundings. Often identified causes do not lead to disease and thus the causes can be seen as risk factors for the disease (GOLD, 2017). This view implies that the disease is not a random phenomenon.

Risk factors, or exposures, are sometimes divided into external, internal, and other risk factors. External are current and previous smoking, second hand smoke, exposure to biomass fuel, socioeconomic status, occupation, environmental pollution, and diet. Internal risk factors include genetic factors, gender, and chronic mucus production. Other risk factors include airway hyper-responsiveness, asthma, perinatal events and respiratory illness during childhood, and recurrent bronchopulmonary infections (Vestbo et al., 2016). The only genetic predisposition clearly identified as a risk factor for COPD is antitrypsin deficiency (Brode et al., 2012). There are reasons to conclude that there is an interaction between host predispositions and environmental factors. Up to 50% of smokers develop COPD (Lundbäck et al., 2003), which means that about 50% of smokers may not develop COPD. A family history of obstructive airway disease is identified in some studies as associated with COPD (Kotaniemi et al., 2005; Lundbäck et al., 2003). Family history may reflect a genetic predisposition but can also represent a broad spectrum of external and other risk factors such as socioeconomic factors.

Suggested risk factors for COPD include:

- Smoking, current or previous
- Passive smoking
- Occupational exposure, foremost gas, dust and fumes
- Biomass fuel exposure
- Air pollution
- Socio-economic status
- Age
- Respiratory symptoms
- Tuberculosis
- Family history of airway disease

Several risk factors, or associations, are identified for COPD development. None, or several together, do not count for all risks, which leaves a statistical randomness. One important aim for research is to minimize randomness since this might represent unknown causes. Limiting research to known risk factors prevents finding other potential exposures.

Smoking

The research field is unanimous in pointing to smoke as the predominant risk factor for COPD, and that relates both to active smoking and former smoking with the highest the risk in current smoking. Cigarette smoking, as a cause for chronic bronchitis was suggested already in 1955 (Oswald et al., 1955; Fry et al., 1961). The study of Fletcher, et al (1976) clearly demonstrated the effect of smoking and progressive loss of FEV_1. Later studies have convincingly established evidence for a forceful impact of smoking on the development of COPD (Lundbäck et al., 2003; Stang et al., 2000). Passive smoking[1] has been seen as a risk factor for COPD (Hagstad et al., 2014). The causal inference of smoking for COPD is the strongest finding in cross-sectional studies. Incidence studies, based on previous definitions of COPD (Heederik et al., 1990; Huhti, 1980; Krzyzanowski et al., 1986) and a few new studies based on the fixed ratio criterion (Lindberg et al., 2006; Vestbo et al, 2002) gives support to the inference of smoking as a cause for COPD. Other risk factors found in incident studies have been male sex, exposure to gas, dust and fumes, and respiratory symptoms. With respect to these factors the results are conflicting. More recent studies (van Durme et al., 2009; Terzikan et al., 2016) are clear in identifying smoking, and level of smoke exposure, as a clear risk factor for COPD. A marked decrease of smoking during more than three decades has resulted in a diminished prevalence of COPD, especially more severe disease (Backman, Eriksson et al., 2016b).

Inflammation in COPD

Inflammatory components have been identified in earlier studies and guidelines have suggested that COPD is associated with an inflammatory response to noxious gases and particles. Much research has been done on smokers, and on clinically identified COPD. The inflammation in COPD is not fully understood, and the most recent GOLD revision downplays the inflammatory aspect (GOLD, 2017).

An autoimmune aspect of COPD has been suggested (Kheradmand et al., 2012). Some patients continue the loss of FEV_1 years after quitting smoking. On the other hand epidemiological studies show that the group that quit smoking restores some of the obstruction (Kohansal et al. 2009;

[1] Alternative terms are environmental tobacco smoke, or involuntary smoke exposure.

Pezzuto et al., 2013). Systemic inflammation in COPD is suggested as the connection in the systemic effects of COPD (Vanfleteren, et al. 2013).

The research field is challenging since COPD is a diverse disease with various causes and different phenotypes. It is reasonable to assume that these phenotypes represent different inflammatory responses.

Treatment

COPD is a treatable and preventable disease. Prevention is obvious as eliminating exposure can limit the progress. The effect of quitting smoking was illustrated by Fletcher et al. (1976) and validated in later studies (Anthonisen et al., 1994). Important aspects of treatment include multidisciplinary rehabilitation and long-term oxygen therapy in respiratory failure (Medical Research Council, 1981; Nocturnal Oxygen Therapy Group, 1980; The Long-Term Oxygen Treatment Trial Research Group, 2016). Medical treatment can limit airways symptoms and reduce exacerbation frequency. No randomized placebo-controlled studies have shown improved prognosis with medical treatment of COPD. First line therapy is suggested to be long acting muscarin antagonists (LAMA) or long acting beta stimulator (LABA). In more severe grades inhaled corticosteroids or dual bronchodilators are suggested as prevention for exacerbations (Socialstyrelsen, 2015).

Asthma and COPD - ACO

There is a rising interest of the coexistence of asthma and COPD (GOLD, 2016), and the prevalence seems to be higher than by predictions from prevalence of each condition with a statistical overlap (Alshabanat et al., 2015). The research field is unsettled whether it is a syndrome (ACOS), on its own, or two diseases coexisting (ACO). It seems that patients with ACO have more severe symptoms (Lee et al., 2016), Most treatment studies of either asthma or COPD do not include aspects of the other disease and research is needed for this group (Postma et al., 2015).

Treatment of asthma aims at adequate controller therapy including inhaled corticosteroids but not long-acting bronchodilators as monotherapy while patients with COPD should receive bronchodilators but not inhaled corticosteroids as monotherapy (GOLD 2016; Socialstyrelsen, 2015).

Both for the clinical setting and the research field measurement of reversibility could be of value in this context. This view is not fully supported by the GOLD statement (GOLD, 2017) and the guidelines of the Swedish Health Society (Socialstyrelsen, 2015b).

Conclusion

COPD has advanced into a disease with a more strict definition although there are still some uncertainties. Several areas have not been fully described or elucidated. Some of the research questions are addressed in the following.

Material and Methods

The present thesis is part of the Obstructive Lung disease Studies In Norrbotten (The OLIN studies) and part of the West Sweden Asthma Study (WSAS). Both studies have the epidemiological approach and the study base is the general population from which the study samples are recruited.

Study areas

Two geographical areas are utilized in the present study; Norrbotten, the northern most county in Sweden through the OLIN studies, and Västra Götaland, the southwest area of Sweden, through the WSAS study.

The County of Norrbotten has 14 municipalities. Norrbotten covers about 24% of the area of Sweden but represents only about 2.5% of the Swedish population (Länsstyrelsen i Norrbotten, 2016). Västra Götaland on the other hand has 48 municipalities and covers about 6% of the area of Sweden but represents 17% of the Swedish inhabitants (Statistics Sweden, 2016).

Figure 7. Study area of the OLIN studies (Norrbotten) and of the WSAS study (Västra Götaland).

Table 2. Descriptive statistics of Norrbotten, Västra Götaland, and Sweden 2015 (Länsstyrelsen i Norrbotten, 2016; SMHI, 2016; Statistics Sweden, 2016).

	Norrbotten	Västra Götaland	Sweden
Area	97 256	23 797	407 339
Population	249 733	1 648 682	9 851 017
Population increase (2000-2015)	-6 505 (-2.5)	137 392 (9.1)	968 225 (10.9)
Foreign background %	10.3	16.8	17.0
Mean age	43.7	41.0	41.2
Life expectancy at birth	81.9	82.0	81.9
Mean income (SKr)	276 022	277 405	282 860
Mean lowest/highest temperature (°C)	-12.2 /+15.4[1]	-0.9 /+16.3[2]	

[1.] Luleå. [2.] Göteborg

Study design

The OLIN studies

The OLIN studies were initiated in 1985 (The OLIN studies, 2016), with a postal questionnaire to 6,610 (Lundbäck et al., 1991) individuals living in Norrbotten. The OLIN studies have continued with follow-ups with questionnaires, interviews, and clinical examinations of both school-children and adults. New cohorts have been recruited.

With an epidemiological approach the overall aim of the OLIN studies is to prevent obstructive lung diseases (Lundbäck, 1993). The research includes epidemiological studies on asthma, type-1 allergies, chronic bronchitis, chronic obstructive pulmonary disease, sleep apnoea, and health economics. The methods used are cross-sectional, longitudinal, case-reference, and clinical studies. In total, more than 50,000 individuals aged from 7 to have participated. Today the oldest are 97 years.

The OLIN studies have also cooperated in several research projects, for example in the FinEsS (Finland, Estonia and Sweden) studies, in USA, New Zeeland, Vietnam, Italy, and Norway.

The WSAS study

The West Sweden Asthma Study was initiated with a postal questionnaire sent 2008 to 30,000 randomly selected individuals, 16 to 75 years of age, in Västra Götaland. Over 18,000 responded. Extensive clinical examinations have been preformed on a randomly selected sample of 2,000 subjects answering the postal questionnaire and in addition all individuals

reporting asthma. In total about 3,600 subjects have been invited to clinical examination and interviews. The West Sweden Asthma Study has several purposes (WSAS, 2016). The focus is on asthma and a primary aim is to investigate the course of prevalence of asthma, respiratory symptoms and allergic rhinitis. The study also aims at finding clinically relevant main phenotypes of asthma. A third phase is planned consisting of laboratory studies of inflammation in asthma and proteomics. The primary aims are focused on asthma, but COPD is included, based on spirometric tests, questionnaires.

OLIN cohorts

The sampling technique of the first two cohorts of the OLIN studies was by selecting certain age groups in 8 of the municipalities in Norrbotten. Thus in 1985 all inhabitants in the ages 35-36, 50-51 and 65-66 were recruited. A second sample was selected from the same area in 1992 in the ages 20-21, 35-36, 50-51, and 65-66. A third cohort was randomly selected also in 1992 from the same area in ages 20-69 years. Postal surveys were sent to all these individuals.

Figure 8. Municipalities of Norrbotten.

These three cohorts are subsequently used for random selection and stratified sampling based on respiratory symptoms and examined by means of questionnaires, lung function tests and anthropometric measures, while subsamples have undergone further investigations.

The clinically examined subjects from these three cohorts were examined in 2002 to 2004, and the pooled material was used for studies on association of COPD and BMI (paper IV).

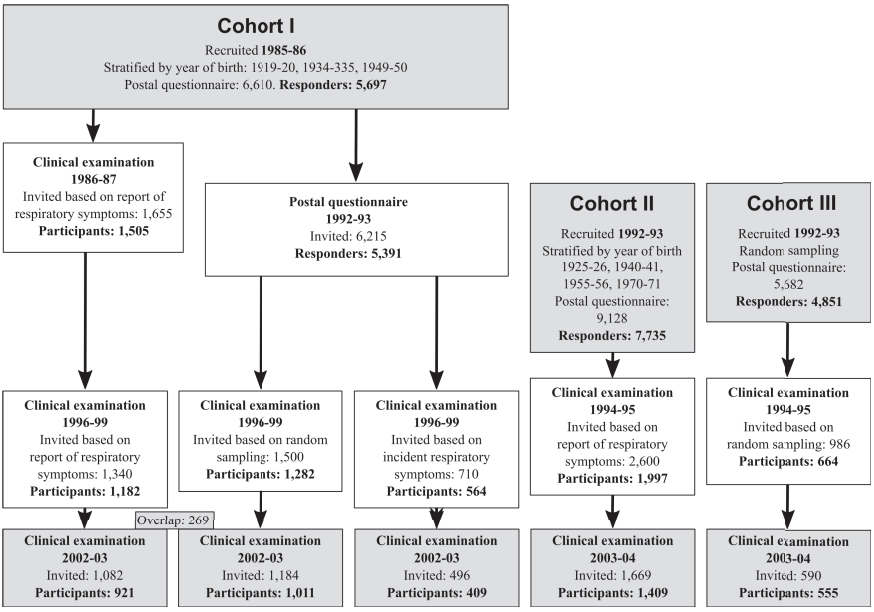


Figure 9. The OLIN cohorts of paper I to IV.

In 1996 a postal questionnaire was sent to a random sample of ages 20-74 years from the whole county. Ten years later a new investigation of the cohort was performed similarly. The same year, 2006, another sample in the ages 20-69 years, was selected and examined by means of postal questionnaires. After stratification by sex and age a random sample of 1016 subjects was invited to structured interviews, clinical examinations, and spirometry, which started in 2009.

The OLIN studies contain now 7 adult cohorts and five of these were used in the present studies (table 3) (paper I-IV) and also the WSAS cohort (paper V). Furthermore two cohorts of schoolchildren, aged 7-8 years at entry, are involved in longitudinal studies; however these are not used in this thesis.

Response rate

Table 3 shows response rates of the samples used in the present studies. Response rates to postal surveys, and participation rates in clinical examinations, were initially high. A slightly weakening trend may be seen in the OLIN studies but is obvious in the larger city area of Västra

Götaland (WSAS). The response rates in the present studies can be judged as high.

Table 3. Response rates in the cohorts. The studies included in this thesis are marked by grey. Cohorts recruited at age 7-8 years are not included.

Cohort	Method	Year	Invited	Response rate	Paper
OLIN I	Postal survey, age-stratified	1985-86	6,610	86.2%	
OLIN I(a)	Clinical examination, symptomatics	1986-87	1,655	90.9%	II
OLIN I	Postal survey, follow-up	1992-93	6,215	86.7%	
OLIN II	Postal survey, age-stratified	1992-93	9,128	84.7%	
OLIN III	Postal survey, random sample	1992-93	5,682	85.4%	
OLIN II	Clinical examination, symptomatics	1994-95	2,600	76.8%	
OLIN III	Clinical examination, random	1994-95	986	67.3%	III
OLIN I	Postal survey	1996	5,933	87.5%	
OLIN I(a)	Clinical examination, symptomatics	1996-99	1,340	88.2%	II
OLIN I(b)	Clinical examination, random	1996-99	1,500	85.5%	I
OLIN I(c)	Clinical examination, incident sympt.	1996-99	710	79.4%	
OLIN IV	Postal survey, random	1996	8,704	85.2%	
OLIN V	Clinical examination, case-control	1995-00	309*2	*	
OLIN I(a)	Clinical examination, symptomatics	2002-03	1,082	85.1%	I, II, IV
OLIN I(b)	Clinical examination, random	2002-03	1,148	85.4%	I, II, IV
OLIN I(c)	Clinical examination, symptomatics	2002-03	496	82.5%	II, IV
OLIN II	Clin. examination, sympt. follow-up	2003-04	1,669	84.4%	IV
OLIN III	Clini. examination, random follow-up	2003-04	590	94.1%	IV
OLIN IV	Postal survey, random follow-up	2006	7,004	84.1%	
OLIN V	Postal survey	2006	7,997	77.1%	
OLIN IV+VI	Postal survey, random	2008-10	15,001	80.0%	
OLIN VI	Postal survey, random sample	2006	7,997		
OLIN IV+VI	Clinical examination, random	2008-10	1,016	71.5%	V
WSAS	Postal survey, random	2008	30,000	60.3%	
WSAS	Clinical examination, random	2009-12	2,000	57.7%	V
OLIN IV	Postal survey, follow-up	2016	6,083	~80%	
OLIN VI	Postal survey, follow-up	2016	5,281	~76%	
OLIN VII	Postal survey, random sample	2016	12,000**	58,3%	

*Case-control study, all participated. ** 245 deceased or not possible to trace.

The participation rate of the clinical examination of cohort OLIN III in 1994-95 was somewhat lower and the difference can be attributed to examination circumstances: the subjects were asked to come to the central hospital in Norrbotten while all other examinations were performed at the local care centres in Norrbotten.

Questionnaires

The OLIN short version postal questionnaire and the longer interview questionnaires were originally developed in 1984-1985 mainly from a revised version of the 1960 British Medical Research Council respiratory questionnaire (Medical Research Council, 1965). The questionnaires were also influenced by the US National Heart, Lung and Blood Institute and the Tucson Studies questionnaires (Lebowitz et al., 1976). In 1992 and 1996 some questions about chest tightness and wheezing were added from the IUATLD questionnaire and the Swedish version of the ECRHS questionnaire (Burney et al., 1987; Björnsson et al., 1994). A question on dyspnea from the 1986 revised MRC questionnaire (Cotes, 1987) was also added in the 1990s.

The OLIN questionnaire has been used in studies in Nordic and Baltic countries (Pallasaho et al., 1999; Meren et al., 2001) and in Vietnam (Lam et al., 2011). Studies have been performed using the questionnaire in Sweden, Finland and Estonia under the FinEsS label (Pallasaho et al., 1999; Meren et al., 2001; Lindström et al., 2001; Backman et al., 2014). The questionnaires include mainly questions about asthma, rhinitis, chronic obstructive pulmonary disease, chronic bronchitis, emphysema, use of asthma medication, dyspnea, respiratory symptoms, and nasal symptoms. Possible determinants of disease, such as family history of atopic and obstructive respiratory diseases, smoking status and occupation are also included.

The questionnaires relating to this thesis have been used in all surveys of the OLIN cohorts among adults. The questionnaires have been described in detail previously (Lundbäck et al., 1991; Pallasaho et al., 1999; Rönmark EP, 2015). The short version of the questionnaire has also been validated against the GA(2)LEN questionnaire (Ekerljung et al., 2013). The core questions of the OLIN and WSAS questionnaires were close to identical. The short questionnaires have always been self-administrated by the subjects under study, while physicians, specially trained nurses and research assistants have performed the interviews. Data mainly collected by the interview version have been used in the papers of is thesis. The 2009 version is included in Appendices 1 and 2.

Clinical examinations

At the visit clinical examination included measures of height, weight, and spirometry. Some studies of the OLIN project clinical examinations included skin-prick test, methacholine provocation, blood-samples, ECG, handgrip, six minutes walk test, oxymetry and, if indicated, arterial blood-gas sampling; these examinations were not included in the present thesis.

Anthropometric values

The date of birth was collected from the Swedish national registry. In the examinations in 1994-1995 of OLIN III, and in all examinations since 2002, height was measured without shoes with 0.5 cm precision and weight with 0.5 kg precision with empty pockets and without jacket and shoes. At earlier examinations the participants were asked about height and weight. Self-reports of height and weight tend to underestimate weight and overestimate height (Gorber et al., 2007). Studies based on self-reports of height and weight may underestimate BMI. This does not affect identification of COPD, based on airflow limitation with the fixed ratio criterion. Since reference values include height it can influence the determination of the severity grade of the subject.

Lung function testing

Spirometry

Lung function testing was performed on all subjects capable of blowing. Only expiratory capacities were performed. Dynamic spirometry included slow vital capacity (SVC), forced vital capacity (FVC) and the volume exhaled during the first second of a forced manoeuvre (FEV_1). The procedures followed the ATS/ERS standards, except for the repeatability criterion. In all OLIN the repeatability criterion for FEV_1, SVC and FVC was ≤5% instead of ≤150ml deviation from the second highest value, or <100 ml difference if the spirometric values were <2 litres. In the WSAS study the goal has in addition a difference of <150 ml for the two highest values FEV_1, SVC and FVC, except for values <2 litres, where the OLIN criterion was applied. Spirometry was considered as adequate when it successfully followed the recommendations. When the repeatability criterion was not fulfilled, trained professionals assessed the flow-volume curves, either at the time of examination or during the subsequent data management process. Reversibility testing was

performed 15 minutes after distribution of 0.4 mg salbutamol powder via discus in subjects with FEV_1 <90% of reference values or a ratio of $FEV_1/VC<0.7$ in 1994, and in all subjects in the 2009-2012 surveys. In the WSAS study bronchodilation was performed with a combination of 0.4 mg salbutamol and 80 µg ipratropium bromide aerosols via spacer in all subjects. Trained personnel performed spirometries, which is of great importance since lung function testing depends on the individual's cooperation

Spirometers

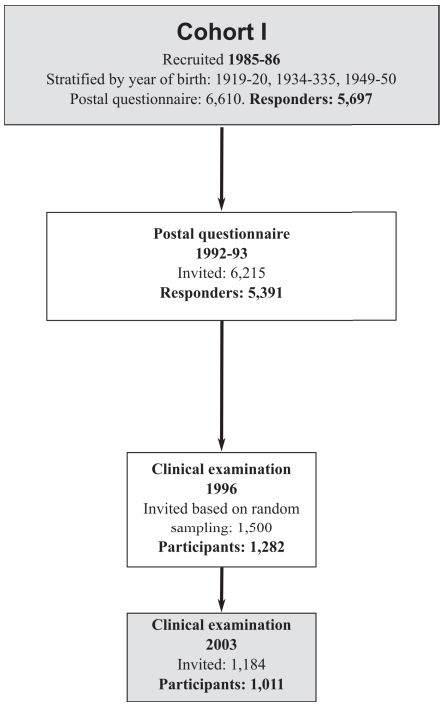
In all OLIN studies, a dry volume spirometer, the Dutch Mijnhardt Vicatest 5, was used until 2008 (paper I-IV). The Vicatest has been evaluated and regarded accurate (Weaver et al., 1981). From 2008 Jaegers pneumotachometer has been used in the OLIN studies and in the WSAS study. This is a flow-sensing device, which calculates flow and volumes based on pressure measurement over a membrane (Jaeger, JLAB version 5.21 software, CareFusion, Würzburg, Germany). The spirometer complies with the ATS standards (Jaeger, 2016). At examinations daily calibrations were performed.

Results

Incidence of COPD and risk factors based on incidence

Incidence

Our study on incidence of COPD with the fixed ratio criterion and incidence of COPD GOLD grade 2-4 (paper I) was based on 1,237 subjects in 1996 of whom 1,009 also participated 7 years later. We could include 963 subjects based on adequate spirometries in both 1996 and 2003. Point prevalence of COPD with the fixed ratio was 14.1%, who thus were excluded from the population at risk for developing COPD during the follow-up period. The point prevalence of COPD grade 2 to 4 (further named "GOLD II-IV") was 4.7% thus leaving a population at risk for GOLD II-IV of 918 subjects. Subjects attending the first visit but not the second had significantly lower lung function even when prevalent cases of COPD in 1996 were excluded. Thus the incidence could be underestimated to some degree as low lung function, measured as FEV_1 has been seen as a risk for further decrease.



Figur 10. Flow chart of the cohort of paper I.

Cumulative incidence of COPD during seven years was 11.0% for COPD according to the fixed ratio and 4.9% for COPD grade 2-4. Calculated incidence rate of COPD was 16 cases/1,000/person/year and 7 cases/1,000/year for GOLD II-IV. The cumulative incidence of COPD GOLD II-IV over the sever year-period was about six times greater among smokers (10.8%) than to non- smokers (1.6%).

Risk factors for COPD

Although more women than men developed COPD and COPD GOLD II-IV, this was not significant, and in the adjusted analyses ORs were 0.66 and 0.64 respectively. Thus we could not establish a difference in risk due to sex. Higher age at entry was significant for COPD grade 1 to 4 and smoking even for GOLD II-IV. All reported respiratory symptoms such as cough, sputum, chronic productive cough, recurrent wheeze and dyspnoea preceded COPD GOLD II, and this was true for incident COPD grade 1-4 except for cough. Airways symptoms were frequently reported in the study sample but about twice as common among incident cases of COPD, compared to non-COPD. Cough was found to be the weakest symptom indicating future COPD.

Prognosis

Based on reports of respiratory symptoms in the postal questionnaire in 1985-86 and a random selection of individuals with no reports of respiratory symptoms, a sample of 1,655 individuals was invited for clinical examinations in 1986, 1,505 participated. This sample was re-examined in 1996-97, in 2002-2003, and followed up to 2006. Based on spirometry performed in 1986, 266 individuals were identified as having chronic obstruction with a pathological ratio of FEV_1/VC <0.70. Information on mortality was collected until 2006. These subjects constitute the study sample for the study on prognosis of COPD (paper II).

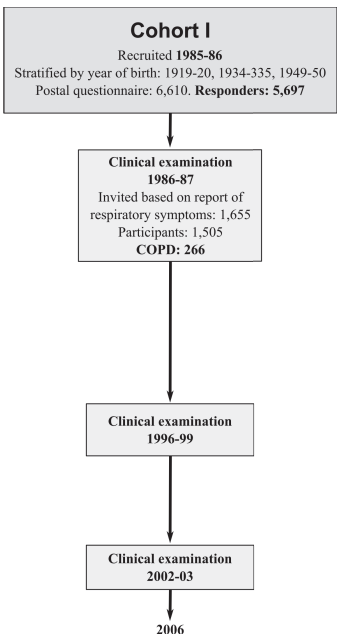


Figure 11. Flow chart of the cohort of paper II.

The overall prognosis for survival during 20 years in the study sample was 46%. This shows a better prognosis of COPD than most studies based on patients from hospitals or health care. Even inthe oldest age-group reaching 86-87 years, by the end of the 20 years of follow up, 25% were alive.

Risk factors for death

A somewhat higher proportion of women were alive at study end and men had significant higher risk for death in the regression model (H.R. 1.51; 95% CI 1.02-2-23). Smoking habits were analysed. Although non-smokers had the highest proportion of survivors, initial smoking habits were not risk factors for death in the regression model. There might be several reasons for this finding: quitters in 1986 might represent subjects with more advanced COPD or other cardiovascular disease leading to stop smoking; since the analyses did not include data on smoking habits after 1986, a large proportion of current smokers in 1986 might have become quitters.

Higher grades of COPD according to GOLD were clearly associated with an elevated risk of dying, as was level of lung function estimated as FEV_1 of reference values. In bi-variate analysis, manual workers in industry had a higher risk for death compared to other socioeconomic class. This can reflect several risk factors such as smoking, low education, economic burden, and life-style. In the adjusted analysis the association with socioeconomic class disappeared. Subjects reporting chronic bronchitis at study entry, that is productive cough during at least three months during the last two years, had worse prognosis than subjects not reporting chronic bronchitis.

Report of heart disease in 1986, i.e. myocardial infarction, heart failure, and any heart disease, was associated with higher risk of death but when adjusting for other factors only myocardial infarction remained significant. Respiratory symptoms such as productive cough and dyspnoea, but not wheeze, were associated with worse prognosis.

Markers for better prognosis

Subjects with either report of asthma, with a positive reversibility test (increase >15% in FEV_1 from baseline), or with hyper-reactivity to methacholine, were included in the study sample based on a pathological FEV_1/VC ratio below 0.70. These subjects had the best prognosis. This was also found in subjects with atopy, defined as rhinitis.

COPD and heart diseases

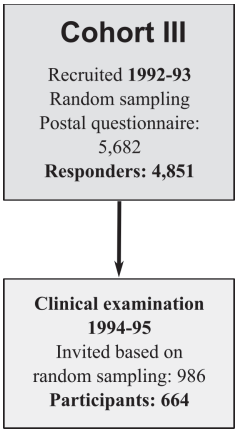


Figure 12. Flow chart of the cohort of paper III.

In 1994-95 a random sample, from the general population of Norrbotten, was selected for a study on COPD, restrictive spirometry and heart disease (paper III). The aim was to explore the association of heart diseases and hypertension with COPD and with restrictive lung function impairment. Consequently the study could analyse subjects with low lung function, both as COPD and as restriction, with normal lung function as control group with respect to associations with ischemic heart disease and hypertension.

We found high prevalence of ischemic heart disease, hypertension or medication for heart disease and hypertension in COPD grade 2 to 4, compared to normal lung function. Almost 60% of the subjects with COPD grade 3 and 4 had any of these cardio-vascular diseases The prevalence of these diseases in restrictive spirometry was similar as in COPD grade 3 and 4, also almost 60%. The prevalence of COPD and of restrictive lung function among subjects reporting heart diseases, hypertension and mediation was also significantly higher than among those not having these cardio-vascular diseases. Among subjects reporting heart failure and arrhythmia we did not find an association with COPD.

In the adjusted analyses risk factor patterns, or associations, were quite different for COPD, restrictive lung function, and ischemic heart disease. The single shared significant association was age. Smoking and family history of obstructive lung disease were associated with COPD. Although smoking is an established risk factor for coronary heart disease we could not significantly ascertain this association.

Intriguing associations remained between COPD and ischemic heart disease, and vice versa, in the adjusted analyses. These significant associations could be interpreted as causal inference although alternative explanations, such as common pathways and common exposures not included in our study, are more plausible.

In the period 2009 to 2014 (paper V) two studies based on the general population were performed, one in Västra Götaland and the other in Norrbotten. We used the pooled sample from these two cohorts, and the study sample represents random samples in the same age span of the two areas. As a comparison we used a previous study (paper III).

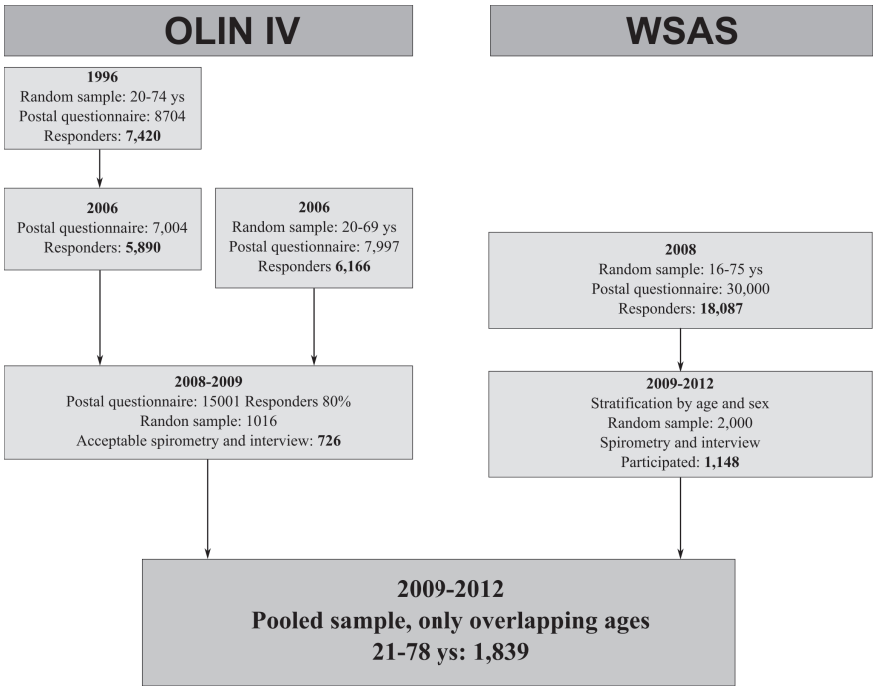


Figure 13. Flow chart of the cohort of paper V.

Compared to the study in 1994 (paper III), prevalence of current smoking was lower in Norrbotten, 26.5% versus 15.1 %, and even lower in Västra Götaland, 11.4%. The mean age span in the latter study included some younger and older subjects compared to the study in 1994. The prevalence of COPD was lower in 2009 to 2014 and especially more severe disease was less prevalent. The pattern of association of COPD and comorbid heart diseases and hypertension was similar with some exceptions. In the study of 1994 (paper III) ischemic heart disease, i.e. angina pectoris, myocardial infarction and coronary intervention, was significantly associated with COPD, an association that remained after

adjusting for confounders. This association was found in the study of 2009 to 2014 but was not significant in the adjusted model. In the earlier study we found no association between COPD and heart failure or intermittent claudication. The opposite was found in the latter study and heart failure remained after adjusting for confounders.

COPD and BMI

In the study (paper IV) our hypothesis was that both underweight and obesity were associated with COPD. Since our study sample was from the general population, the null-hypothesis would be that distribution of BMI among subjects with COPD is similar to subjects with normal lung function.

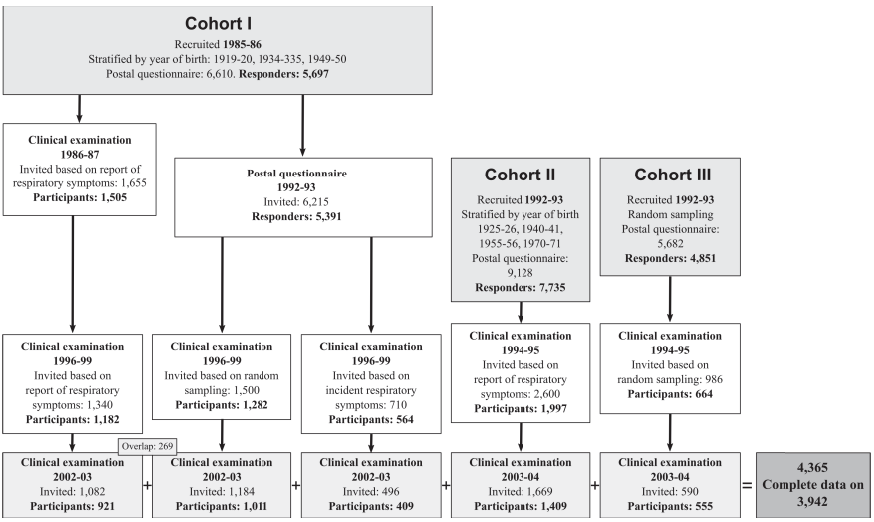


Figure 14. Flow chart of the cohorts used in paper V.

The study sample consisted of pooled data from several cohorts examined in 2002-2004 with a study sample of 3,942 subjects from the general population. Subjects with a restrictive spirometry were not included in the analyses. We used the BMI cut-off of 20 for denoting underweight for two reasons: that is the most common in the western world, and we had few subjects in the study sample with BMI<18.5.

Factors associated with high BMI, were male sex, former smokers, wheeze and dyspnoea, rural living, most heart diseases except for arrhythmia, diabetes, hypertension, and all socioeconomic groups compared to professionals and executives. Subjects reporting asthma had higher BMI while the COPD group had lower BMI, compared to subjects without asthma and COPD, respectively.

FEV_1, in percent of reference value, was not associated with BMI in subjects with normal lung function and among subjects with COPD grade 1 and 2. In the more severe grades we found a correlation between BMI and FEV_1: the more airflow limitation, the lower BMI. There were also associations of the ratio FEV_1/VC versus BMI grades in the COPD group where the correlation showed a higher ratio with higher BMI grades. Compared to subjects with normal spirometry we found significantly higher prevalence of underweight in severe COPD, i.e. GOLD grades 3 and 4. Regarding the other BMI grades in COPD there was no significant difference in prevalence versus the normal population except that COPD grade 2 had lower prevalence of pre-obesity and obesity. The association remained significant in the adjusted analysis.

As in previous studies our study supports the association of underweight and COPD. We found no support from our data of an association between COPD and obesity. The prevalence of obesity inclined from COPD grade 1 to grade 3 and 4 where it was similar to prevalence in normal lung function. There are no known physiological reasons for an association between COPD and obesity other than that subjects with COPD can be less active and immobilised, thus gaining weight. Obesity does not affect lung tissues since fat does not deposit in the lungs.

The distribution of BMI grades reflects the distribution in the normal population except that underweight is overrepresented in COPD severity grade 3 and 4. There is a strong case that underweight is caused by the disease. A reversed causation is not plausible in other aspects than that muscle weakness can produce low forced expiratory capacities. Since the study used forced capacities both for FEV_1 and VC, such a bias would be minimised.

Discussion

Discussion on methodology

Bias

The possibility or presence of bias should be considered and taken into account in all studies. Although it is stated: "Bias in studies should not happen" (Dawson et al., 2001, p. 306), this is seldom the case and not always desirable to avoid (Rothman et al., 2013). Bias is contextual and dependent on the research question. Bias can skew the data in several ways such as in selection, procedures, and measurements.

In the present studies, based on samples randomly selected (paper III and IV) or stratified based on birth year (paper I and II), or a combination (paper IV), control groups are included. Since it was likely that the cases, for example subjects with COPD, differed from the subjects in the control group, in other ways than just the disease, adjusted analyses, by means of binary multivariate logistic regression and Poisson regression methods, were performed. This approach has the dual intent to adjust for confounders and to identify associations that can represent risk factors.

Selection bias

When the purpose is to define prevalence, changes in prevalence or incidence in the population the study sample should be representative of the study base. In some studies (paper II and IV) selection of subjects is in part based on report of symptoms. This can represent bias if conclusions are on prevalence of disease or symptoms. As our intention was to study associations this selection method is of less importance. The strength of association can be overestimated but the association is still valid.

Non-responders and non-attendance can skew data somewhat. An intrinsic part of the problem with non-responders is the fact that analyses of non-response is limited, otherwise they would not be non-responders. High response rate limits the bias of non-responders and a high response rate will increase the power of the statistical analyses.

There is a growing concern for decreasing response rates in epidemiological studies. Non-responders reduce the effective sample size and this can introduce bias. Average response rates to mail surveys published in medical journals have previously been about 62% (Asch et al., 1997), and are probably lower at present.

The response rate in the present studies can be considered as high (table 3). A previous study of non-responders to the postal questionnaire of Cohort I (Rönmark et al., 1999), with 85% response rate, found that young men, current smokers, and manual workers were over-represented among non-responders. Respiratory symptoms and asthma were more prevalent in the non-response group. A study from Norway, with a response rate of 89%, found only minor differences between responders and non-responders. A calculated higher response rate did not alter the incidence rates of the five respiratory symptoms and asthma or their associations to sex, age, and smoking habits (Eagan et al., 2002). In a study on the WSAS material (Rönmark et al., 2009) non-responders and late responders, were analysed. The initial response rate was initially 33% rising to 62% when late responders were included. Analyses of late responders and non-responders revealed that increased participation rate did not alter the risk estimates. In this perspective response rates in the present studies can be assessed as adequate for the results.

Measurement bias

Measurement bias arises when measures do not reflect the outcome due to inappropriate methods. Measurements included in the present studies were lung function, anthropometric values, report of smoking habits, diseases, medication, educational level, and occupation etc.

Values of length and height were collected by direct measurement since 2002 and in the OLIN III cohort in 1994-1995. The studies on COPD comorbidities (paper III), on COPD and BMI (paper IV), and on COPD comorbidities in 2009-2014 (paper V), recorded height and weight by direct measure. In the study on incidence (paper I) the values were based on self-report. Height was recorded on the base of self-report, which can affect FEV_1 of reference value since there may be an overestimation of height also in our study. This can skew the data some and attribute higher COPD grades to subjects, than would be the case when using direct measures. BMI was not included in the analyses in the study on incidence. In the study on prognosis in COPD (paper II) anthropometric values were based on self-report. This can have an effect on BMI levels,

and on severity grades of COPD, as in the study on incidence. BMI levels may have been underestimated and COPD severity grades somewhat overestimated. The fixed ratio criterion was applied in all studies, and direct measures of height in analyses with the LLN criterion, the identification of airflow limitation, consistent with COPD, were used. Method of collecting data on length did not infer bias in this respect.

Measurements of lung function were performed by spirometers calibrated daily. A small random variation is acknowledged. In our studies we used strict criteria for labelling subjects as COPD, restrictive spirometric pattern and normal. It should be approved that the randomness in the measures has some impact for subjects just around the cut-off limit. There is also a day-to-day interindividual variation of expiratory volumes. This pertains to all epidemiological studies based on spirometry. The anthropometric measures are preformed similarly in all subjects. A measurement randomness, or imprecision, affects all measures, and should not affect our results in high degree.

We have used the spirometric values for calculating the ratio of FEV_1 and VC and, by this mean, identifying subjects with an airflow limitation consistent with COPD. In the first four studies (paper I-IV) we have used the fixed ratio with the highest values of FEV_1 and SVC/FVC before and after bronchodilation. This gives the highest prevalence of COPD (Gove et al., 1987), due to high sensitivity of airflow obstruction (Chhabra, 1998). The prevalent cases are used for identifying risk factors, prognosis, and comorbidities. The fixed ratio could identify older persons without disease, i.e. subjects without symptoms, limited exposure and a not compromised prognosis. This could give some "noise" to the "signal" (Silver, 2012) missing a significant association or lower the strength of association. We therefore, as tests of sensitivity, applied the LLN criterion (paper III and V), and the more strict criteria of the GOLD document, and of the ERS standard, that is, only post bronchodilator values as comparison (paper V). The patterns of associations remain similar but the strength of association varies somewhat.

In paper III we excluded subjects with a restrictive spirometric pattern from the group with a normal FEV_1/VC ratio, but included this group in the analyses. Subjects with low FVC but a normal ratio of FEV_1/FVC do have low FEV_1. In previous studies, based on one lung function variable, this group can have been included in the cases. In later studies, based on the FEV_1/VC ratio, this group can have been included in the normal

group. Those with both low FEV_1 and low VC share several characteristics with the COPD group but are divergent in other respects.

Our methods adhere to guidelines. There is no scientific evidence that would guide in the choice of the fixed ratio or the lower limit of normal criterion. The measurement methods we have used gives answers accordingly. Based on sensitivity analyses we conclude that our methods are apposite and our results sound.

Recall bias

Information on smoking, airway symptoms, diagnosis of pulmonary and other diseases and medication was based on self-reports from subjects in the interview situation. Physicians' diagnoses were not validated by patients' charts, and smoking habits were not validated by for example blood testing of cotinine. With respect to reports on other diseases and medication we do not have reason to suspect a systematic bias between subjects with airflow limitation, smoking habits and normal lung function. Smoking habits have been seen to be underreported in other studies (Todd, 1978). This may be the case in our studies, which could lead to an underestimation of association between smoking and COPD, and smoking and heart disease. On the other hand, in our longitudinal studies reports of smoking habits are rather stable between follow-up investigations. Smokers might underestimate symptoms of airways. The mMRC scale, although coarse, can be regarded as a valid instrument levelling out differences between smokers and non-smokers in recall bias.

In the present studies recall bias may underestimate smoking habits, which thus could yield somewhat lower strength of association, but we have no reason to suspect a systematic error making the findings invalid.

Observational bias

There are three aspects of observational bias: 1. Different persons preformed the interviews and the spirometries. 2. Selection of variables are decided on the basis of known and suspected associations and risk factors. 3. In a more philosophical aspect, every attempt to measure influences the measured object. This latter bias can be seen as present in all studies.

There is always some randomness in observations performed by the same observer and between observers that certainly is present in our studies. That this observational bias would infer a systematic error in the analyses of incidence, risk factors and comorbidities is unlikely since it can be assumed that observational bias is randomly distributed in the material.

All studies are, or should be, based on a hypothesis. Forming a hypothesis builds on what is already known with research questions not answered. The most important research mission is to further push the boundaries of what we know. Selection of variables and building hypotheses is based on the pre-understanding of the researcher and this will change over time and should progress. Our studies has taken stand on what is presumed to be known but attempts to address areas where research results are conflicting or where research questions still are unanswered.

Reliability and validity

Reliability and validity are often seen separate but are certainly interconnected. Reliability concerns the quality of measure and every aspect of validity is dependent on the reliability of the study. In the present studies there are several measures that could be discussed with respect to reliability. The lung function testings are probably among the best in the world performed by well-trained and experienced staff. There are day-to-day variations of FEV_1 and VC among normal subjects, and among COPD subjects but probably less in more severe grades (Albert et al., 2012). A systematic error in the spirometries is unlikely. Anthropometric measures are obtained similarly through out the studies and for all subjects and weight is based on measure and not self-report.

The quality of the self-reports of diseases is dependent on several crucial steps: physicians diagnosis and how correct that is, clear information to the patient, the patient's perception and remembrance, and the report in the interview situation. There is both underdiagnosis and misdiagnosis of COPD (Arne et al., 2010; Walters et al., 2011). In our study, airflow limitation consistent with COPD is obtained by spirometry, thus avoiding difficulties with self-reports. More acute diseases, such as myocardial infarction, and chronic diseases with long-term treatment, such as hypertension and diabetes, are more accurately reported (Okura et al., 2004). As discussed in paper V heart failure reports may be more correctly reported in recent years. There are readily accessible diagnostic tests, such as brain natriuretic peptides, and increased utilisation of

echocardiography. A shift has occurred from diuretics and digoxin to more active treatment with beta-blockers, ACE-inhibitors, and aldosterone antagonists. Various pacemaker devices,, such as implantable cardioverter defibrillator and cardiac resynchronization therapy (CRT), have come into use. It is plausible that information to patients have improved. The report of medication is based on meticulous inquiring, where subjects were asked to bring a list of their medication. Including data on medication thus gives a further strength to the report of diseases.

Smoking habits are often underreported. In later studies the simple question on smoking has been amended with a careful assessment of smoking habits during life-time (paper V). This can be assumed to limit underreport of smoking habits. Data on diseases reflects the subjects' perception of what disease they have.

Thus there are imprecisions in the measures which may underestimate strength of associations but we have no reason to believe that this have affected the presence of associations in our studies.

Validity

Some of our studies are based on randomly selected subjects (paper I, II, III and V) while one study also contains some subjects initially selected on the basis of symptoms. The first three studies can be judged as reflecting the population of Norrbotten. In paper V we included a cohort from the southwest of Sweden together with a cohort from Norrbotten.

Internal validity is dependent on minimizing systematic errors but should be judged with focus on the hypothesis. In research, internal validity is the extent to which a causal conclusion based on a study is warranted, which is determined by the degree to which a study minimizes systematic error (or bias). It contrasts with external validity, the degree to which it is warranted to generalize results to other contexts. Internal validity here reflects the accuracy of results for the study individuals, or dependability of associations found within the study. The results suggest that the previous studies of the OLIN cohort are valid for the rest of Sweden, and probably for COPD worldwide. Both internal and external validity are high in our studies.

Discussion on main results

Our studies are based on cohorts derived from the general population, and COPD is defined by lung function testing, thus giving the possibility to investigate risk factors, prognosis, and comorbid conditions without the bias of underdiagnosis of airflow limitation in COPD.

There are two important aspects affecting research outcome in epidemiological studies on COPD. As is seen in several studies before there is a great deal of underdiagnosis, and even misdiagnosis of COPD most often due to a low utilisation of lung function testing (Lindberg et al., 2006; Lindström et al., 2001; Mannino et al., 2000). Even some epidemiological studies, especially earlier studies, on COPD did not include spirometry as a criterion (Chen et al., 2000; Ställberg et al., 2013). Many studies on prevalence, risk factors, comorbidities and prognosis are based on patients in primary or secondary care settings (Steuten, 2006). These studies are valuable and valid in these particular contexts.

Incidence and risk factors for COPD

We conclude that the 7-year cumulative incidence, with the fixed ratio criterion of GOLD, and with a more restricted criterion of grade 2 and higher, is 11.0% and 4.9%. Incidence rates were correspondingly 16 and 7 cases/1,000/year. Incidence is of some interest by itself by giving an indication of how many new cases that could be in need of intervention in the health care system.

Two older studies on incidence (Huhti et al., 1980; Krzyzanowski et al., 1986) were not based on present criteria. Only few studies had been published with comparable criteria as of our study. Although based on a somewhat younger cohort, a report from the Copenhagen City Heart Study yielded an incidence rate of COPD of 19 and 9 cases/1,000/year based on 5 and 15 years cumulative incidence. In a symptomatic cohort of the OLIN studies (Lindberg et al, 2005) the incidence rate of COPD can be calculated to 14 cases/1,000/year, based on a 10-year follow-up. A report from Bergen (Johannessen et al., 2005), with a follow up time of 9 years, reported an incidence rate of 7 cases/1,000year, in a younger cohort than ours. In 2006 a 25-year follow-up study, also from Copenhagen (Løkke et al., 2006), reported incidence of COPD that can be estimated to 17 cases/1,000/years. A few years thereafter, the incidence of COPD in young and middle-aged cohort within the ECRHS,

with a median follow up of 8.9 years, was estimated to 2.8/1000 persons per year (de Marco et al., 2007). It is obvious that level of incidence is dependent on the study base, the study sample, and level of exposure, foremost the prevalence of current smoking in the population.

Incidence studies can avoid the risk of reverse causation, i.e., identifying a consequence of the disease as a risk factor. We found smoking carrying the highest risk for COPD, and ex-smoking also for GOLD II, that is more severe disease. Higher age was a risk factor for COPD, but the highest age was not a risk factor for GOLD II. We could not establish that any of the sexes had significantly higher risk for COPD. Smoking and age as risk factor for future COPD were identified in all studies referred to above. Sex as a risk factor was only found in the Danish study (Vestbo et al., 2002).

We found respiratory symptoms associated with future COPD. This was the finding in the incidence studies analysing respiratory symptoms (Johannessen et al., 2005; de Marco et al, 2007) except in the Danish study (Vestbo et al., 2002). We have interpreted our finding as an early sign of future COPD due to a common exposure leading to both respiratory symptoms and COPD. There may be a host factor not yet identified.

Age as a risk factor for COPD is more complex. There is strong support that COPD develops after years of unhealthy exposure. COPD is uncommon in age before middle-age. The assumption is that COPD is caused by exposure, where several have been identified, although not all. Age and exposure time co-vary. Thus, adjusting for age or operating with criteria that minimise the effect of age might yield an overadjusted analysis.

In incidence studies the study population consists of nondiseased with respect to the disease, the population "at-risk"[1] of developing disease. The distinguishing of these subjects is dependent on the criteria for identifying subjects with the disease, since these are excluded from the study group. If the time span is prolonged between the investigations there is a possibility that subjects developing the disease and rapidly

[1] "At risk" in this context represents the whole "un-diseased" (with respect to the disease in focus) population, in contrast to GOLD stage 0 where "at risk" denotes subjects without COPD but with symptoms of airway disease.

decline do not attend at the follow up. This can be seen as a minor problem with respect to COPD as it develops slowly in most cases. There is some support that individuals with low lung function from birth, due to various premature factors, can have a pathological FEV_1/VC ratio (Alonso-Gonzalez, et al., 2013). These subjects can be exposed to factors leading to COPD but are not included in the population at risk in incidence studies being, by definition, not part of the population at risk.

With the incidence study more solid conclusions can be drawn with respect to risk factors for COPD. Current smoking is a clear risk factor in our study, while ex-smoking is prominent in cross-sectional studies, especially in more severe COPD, where subjects have stopped smoking due to the disease. Smoking is thus the far most prominent risk factor for COPD.

Our study confirms smoking and age as important risk factors. It can be noted that former smoking had an O.R. of 1.71 and non-significant for the fixed ratio, but highly significant with an O.R. of 5 for COPD grade 2-4. This finding could reflect that some subjects continue to lose lung function despite quitting smoking (Fletcher 1976). Age, as a risk factor, can represent several aspects: since COPD is considered as caused by exposure during an extended time, age can thus indicate various exposures; decline in lung function is seen as part of normal ageing and since the decline in FEV_1 and VC are of similar magnitude, the ratio FEV_1/VC diminishes accordingly.

There is a clear linkage between incidence and prevalence. Prevalence could be described as the sum of inflow (incidence) and out-flow (either remission or death). In our cross-sectional studies (paper III, IV and V), the same associations were found, i.e. age and smoking. Both prevalence and disease severity were lower in the cohort with low prevalence of smoking (paper V) compared to the cohort with higher smoking prevalence (paper III).

In our study we used two criteria for COPD: a fixed ratio of the GOLD criterion and more severe disease with FEV_1 of less than 80% of reference values, which is equivalent to older BTS guidelines. Smoking remained as a risk factor preceding COPD with both criteria. Smoking precedes COPD and a reverse causation is therefore excluded, and certainly not plausible.

In the incidence study socioeconomic group was not significantly associated with incident COPD. In our cross-sectional studies socioeconomic status is associated with COPD but the strength of association did not stand in the adjusted analyses (paper III and IV). Socioeconomic group is a broad and indistinct variable for exposure, which can represent level of income, educational level, exposure at work and at home, food intake, physical activity and other. The most obvious association is with smoking habits. It might be that the difference of important exposure factors do not differ that much in the general population in Sweden of our studies.

Prognosis and COPD

In our study on prognosis of COPD subjects with COPD, defined by an airflow limitation with the fixed ratio criterion, were followed for 20 years or to death. Prognosis of chronic diseases, such as COPD, is dependent on included cases and disease severity at inclusion. Our study included all COPD severity grades, whereof 36% in grade I, i.e. mild disease, and sometimes seen as of minor clinical relevance. The risk of death in this group was as high as 20% in the group aged 50-51 at entry.

An important finding is that asthma phenotype of COPD, viz. subjects with some reversibility or concomitant asthma, but with persistent airflow limitation, revealed good prognosis and that subjects with chronic bronchitis phenotype had worse. Considering reversibility in spirometry might be of importance, contrary to the recommendations of several guidelines.

We did not collect cause of death, which can be seen as a limitation. However, the Swedish death certificates are of somewhat limited value since only about 10% are based on autopsies and for lung diseases as low as around 5% (Socialstyrelsen, 2013). The quality of death certificates could be as low as 50% with incorrect causes of death (Johansson et al., 2000).

Prognosis of a disease is of major interest although the prognosis for the individual patient often is hard to determine. COPD is, in our study, associated with a better prognosis than could be expected. Quitting smoking is the preeminent way to minimise the progression. Although not significant in our study, the efforts to prevent smoking and to support quitting are supported.

COPD and heart disease

Our studies verify and illustrate the presence of heart diseases, hypertension and medication for these diseases in accordance with most other studies. Especially ischemic heart disease (paper III) and heart failure (paper V) were significantly associated with COPD.

Smoking rates has been used to estimate the prevalence of COPD in the general population (Stang et al., 2000). With fifteen years apart prevalence of smoking was halved in our study areas and we found a lower prevalence of COPD but not of heart disease and hypertension comorbidities. COPD is a disease where smoking has high impact while risk factor pattern for heart diseases is more multifaceted. Although smoking is an established risk factor for coronary heart disease (Jousilahti et al., 1999; Khot et al., 2003), we could not significantly ascertain this association; risk factors for ischemic heart disease are multifactorial and complex with risk factors not included in our studies.

It is shown that COPD is associated with several comorbidities such as depression, anxiety disorders, osteoporosis, diabetes, hypertension, cardiovascular diseases, and TIA/stroke (Curkendall et al., 2005, Mannino et al., 2008). Many previous studies have been performed with older criteria, than current, or based on clinical diagnosis, or lack comparisons with subjects without COPD.

The overall finding of the two studies (paper III and IV) strengthens the conclusion that the co-existence of COPD and heart diseases and hypertension is present and important to recognize (Figure XX.).

COPD and heart disease share common risk factors such as smoking, work exposure and life style aspects. Smoking is solidly associated with development of COPD and a risk factor for ischemic heart disease although heart disease risk factor pattern is more complex.

Current smoking has diminished in Sweden since middle of the 1980th (Folkhälsomyndigheten, 2016). In the present study (paper V) the aim was to analyse prevalence of COPD and associations with, or risk factors for, COPD in two distinct geographical areas of Sweden. We used a pooled sample from the OLIN studies in Norrbotten with a sample from the WSAS study in Västra Götaland. The sample represents random

samples in the same age span of the two areas. As a comparison we used a previous study (paper III).

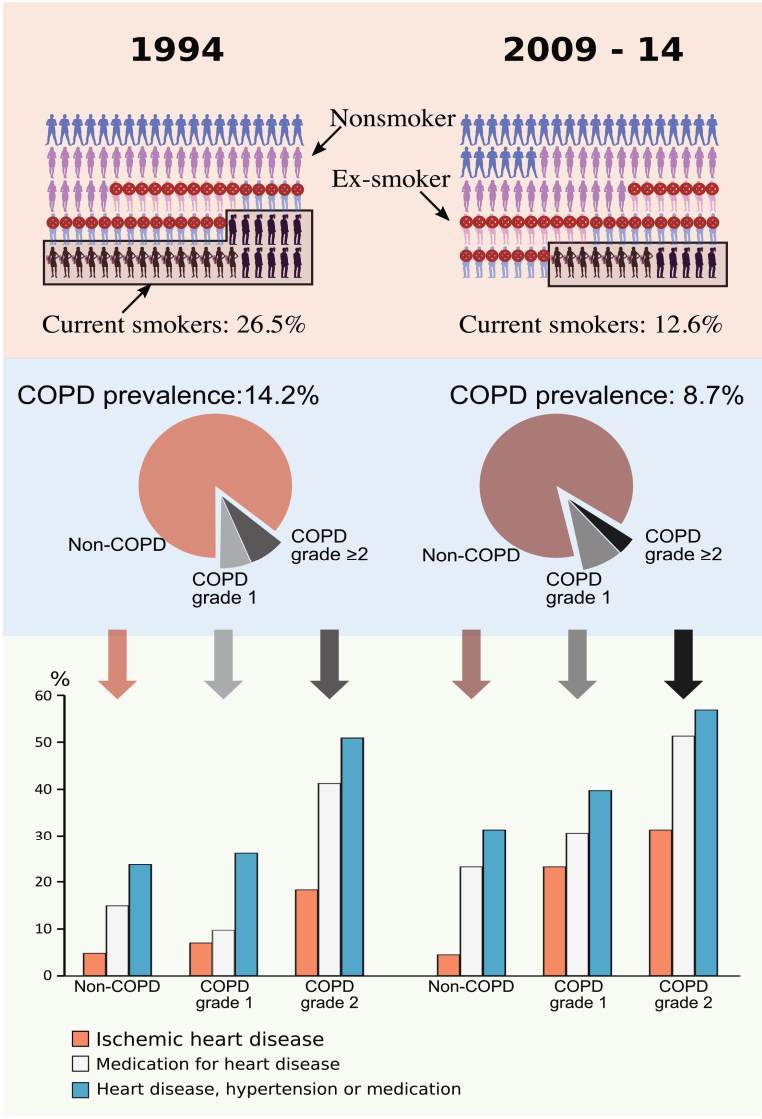


Figure 15. Comparison of prevaelnce of smoking, COPD and comorbidities in COPD in 1994 and 2009-2014, adapted from paper III and V.

When comparing prevalence of smoking and of COPD in 1994 (paper III) and 2009-2012 (paper V) there seems to be correlation. Low prevalence of current smoking is associated with a lower prevalence of COPD (Backman, Eriksson et al., 2016b). The association between COPD and heart diseases was not altered by lower smoking habits.

Socioeconomic status is in our study based on report of work based on SEI codes (Statistics Sweden, 1982) and our division in 5 groups can represent several exposures such as work exposure, income, living area, education and life-style. Socioeconomic classes revealed clear associations with ischemic heart disease but not for COPD nor for restrictive lung function.

Comorbidity can be due to common risk factors and common biological pathways but there are possibilities that one disease induces another. Few diseases come alone and many have multiple illnesses. Most ailments come with age and share common risk factors. Awareness of comorbidity, and even multimorbidity, probability and likelihood of such conditions is of great importance for the clinicians with respect to further investigation and treatment.

COPD and BMI

Underweight, i.e. low BMI, in COPD has been verified earlier and is most probable a consequence of COPD. We found underweight only in COPD grade ≥3. High prevalence of obesity in COPD has been seen in some studies. Adipose tissue plays an active role in immunological organs that secrete protein mediators, adipokines (Exley et al., 2014). The two best characterized adipokines are leptin and adiponectin and they play a role in impaired lung function including asthma (Newson et al., 2013). Leptin is correlated with increased BMI and induced inflammation, while adiponectin is decreased in obese patients, but can be elevated in COPD (Chan et al., 2010), and has an anti-inflammatory role. The balance between those two adipokines can modulate the systemic inflammation. Thus, obesity or underweight could indirectly modulate the COPD-induced systemic inflammation and the corresponding comorbidities, affecting the prognosis and the overall mortality.

Our studies did not reveal a higher prevalence of obesity compared to subjects with normal lung function, neither could we show an association with diabetes. Obesity and diabetes correspond. The findings in other studies might reflect the situation in that particular context, i.e. society.

Underweight and weight loss is associated with COPD and worse prognosis (Hallin et al., 2007; Lainscak et al., 2011) but the reverse seems to be the case with coronary artery disease (Flegal et al., 2007). Smoking is associated with low BMI, whereas ex-smoking with high BMI. Smoking and nicotine could reduce weight by different mechanism as appetite decrease and inducing energy expenditure (Chiolero et al., 2008). Smoking cessation has been associated with weight gain (Bush et al., 2016). In a recent study it was found that quitters gained 2.6 kg more over 5 years compared to continuing smokers (Tian et al., 2015). Thus the pattern of association is complex.

In a very recent study (The Global BMI Mortality Collaboration, 2016), based on more than 10.5 million participants, concludes that underweight, pre-obesity and obesity are all associated with a higher risk for death than normal BMI. This association was also present in respiratory disorders, but the best prognosis regarding respiratory diseases was found around 25, i.e. both under and slightly over 25. BMI in the range of pre-obesity had just slightly higher risk.

The association of underweight and COPD can be due to several aspects; COPD and underweight share the common risk factor of smoking, COPD in advanced grades can lead to underweight and the causes of this are discussed – malnutrition due to increased dyspnoea with ventricular filling, high energy expenditure and presence of cachectic mediators. Muscle weakness can generate a lower expiratory flow as measured with FEV_1 but with preserved vital capacity.

There are conflicting results and views of COPD and obesity. Some studies indicate high prevalence of obesity among subjects with COPD (Steuten et al, 2006, Eisner et al., 2007), and a review article also concludes that there might be a high prevalence of obesity in COPD (Franssen et al., 2008). The relationship between COPD and obesity is uncertain. COPD could lead to obesity due to limited physical activity with preserved energy intake. COPD and obesity can have the same life style factors. Adipose tissue assembles in the abdomen, the buttocks and in the extremities but not in the lungs. Adiposity would does not lead to narrowed airways.

Prevalence is dependent on incidence, remission and life expectancy. Incidence of COPD among subjects with obesity might be lower due to

our definition of COPD. Vital capacity is lower in obese subjects and that interfere with the FEV_1/VC ratio. Remission might occur due to the same fact, in case vital capacity lowers. It has been suggested that overweight and obesity can lead to underdiagnosis of COPD (Sahebjami et al., 1996, Çolak et al., 2015) since FVC is more affected than FEV_1 in subjects with high BMI. Life expectancy is shorter in subjects with obesity compared to subjects with normal weight and even underweight, except for cachexia. Thus there are many aspects to take into account in studies of lung function impairment and obesity, and lots of known unknowns, and unknown unknowns.

There are varying criteria for COPD and reference values differ. We have used the fixed criterion in most studies. The value of this decision limit is debated. For sensitivity testing we applied the LLN-criterion based on our own reference values and on the GLI reference values, and we also applied two other reference values on the study sample (paper IV). Since we excluded subjects from the analyses who had a restrictive pattern on spirometry based on FVC< 80% of various reference values, this influenced the size of the group with normal spirometry and the COPD group as well. With some variation the sensitivity analyses yielded similar associations of BMI grades and COPD.

Ethical considerations

Performing epidemiological studies raises some ethical issues. All the studies of the OLIN project and the WSAS study are, of course, confirmed by ethical committees. From within the OLIN studies 50.000 subjects were engaged in the present research project, and all participated voluntarily without recoupment. The same was the case in the WSAS study. The following ethical aspects can be identified:

Benefits compared to the cost for the research projects

All OLIN co-workers have performed large amount of dedicated work, some travelling and spending nights away from home. The OLIN and WSAS studies have resulted in several doctoral thesis and PhD degrees with individually achieved research competence. Furthermore a large amount of research articles, conference papers and more popular science articles. It can also be regarded as an obligation to use as much data as possible for analyses and publication since so many voluntarily have contributed with time, measures of lung function and other, answering questions.

Benefits and costs for the study subjects

The contribution of every subject has been seen as important and has been done without economic substitution. The present author, as several other participants in the studies, has had the opportunity to share our findings in several patients' organisations without grants.

Findings suggesting pathology or disease

The studies include lung function testing, measuring blood pressure, oxygen saturation and ECG. Pathological findings have been assessed by any of our physicians in the studyteam, and the individual has been referred to health care for consulting, when judged as needed. The author was engaged in the OLIN studies that way. An individual with a clearly pathological spirometry as of COPD was referred to my clinic, included in a COPD rehabilitation program, and was prescribed appropriate medication.

Findings of risk factors and unhealthy habits

The foremost unhealthy habit is current smoking. We have included questions on smoking habits in our studies. When a subject reported current smoking we included measurement of dependency and the individual has, with respect and integrity, been advised to quit smoking. Information on smoking cessation programs was been given and where to find these. No further advice were given with respect to healthy and unhealthy habits..

Gender aspects

The studies include subjects of both sexes and all are subject of the same investigations. Selection of subjects were preformed without respect to sex.

Conclusions

Incidence of COPD was found to be 11.0% during 7 years according to the fixed ratio criterion. For moderate to very severe COPD it was 4.9%. Risk factors for subsequent COPD were age and smoking habits. Report of respiratory symptoms at study entry was associated with succeeding COPD and could be regarded as early signs of the disease. We did not find gender or family history of obstructive lung disease to be risk factors for later COPD.

After 20 years follow up of subjects with COPD, identified by the fixed ratio criterion, 54% had died but prognosis was found to be better than formerly reported. Among subjects with very severe disease at entry the 20-year survival was as high as 19%. Death was related to age, male sex, disease severity, concomitant ischemic heart disease and heart failure at entry. Low lung function, measured as FEV_1 of reference value, was associated with death and survivors kept their lung function stable. Subjects reporting rhinitis, asthma, or showed bronchial variability, had the best prognosis while subjects reporting chronic bronchitis had worse prognosis.

We found a high prevalence of heart disease and hypertension among subjects with COPD, most pronounced in more severe disease. Also among subjects with report of heart diseases we found a high prevalence of COPD.

In the study on comorbidity in COPD with lower prevalence of current smoking, performed about 15 years later than the abover referred study, we found lower prevalence of COPD but the pattern of association of heart diseases and hypertension with COPD was similar.

We found BMI to be lower in subjects with COPD, than among subjects wit normal spirometry. Underweight, defined as BMI<20, was found only in severe disease. Contrary to previous suggestions we could not establish that obesity is associated with COPD.

Future perspectives

Epidemiological studies on COPD have several unanswered issues..

Major risk factors for COPD have been identified. In a context with low smoking prevalence, COPD might still be prevalent. Risk factors, other than current, past or passive smoking, are still to be identified. No single risk factor or all together can count as a full explanation. There is still a randomness to be investigated further.

Another issue to be addressed is the finding of low lung function but with a normal ratio of FEV_1/VC. The value of dynamic spirometry in identifying a restrictive pattern is still to be explored by science. Research results in this area can be of great importance in the clinic.

At the present there are somewhat divergent views on the decision limit for the airflow limitation of COPD. There is no scientific evidence supporting the two major conflicting views: the fixed ratio and LLN. There is a need of longitudinal studies, foremost with respect to prognosis and treatment outcome.

Acknowledgement

Many perform the work leading to this thesis. Skills and commitment is accompanied by deep devotion in the field work has led to many nights outside home for the purpose of acquiring data to the studies. The workers of the OLIN studies and the WSAS study are therefore especially to be recognized.

I say many thanks to my supervisors. Bo Lundbäck initiated the OLIN studies and was instrumental in the start of the WSAS study. Bo has shared his long experience and advised me thoroughly. Thanks for many long, good working hours and research guidance embedded in a comfortable atmosphere. Eva Rönmark, Anne Lindberg, and Apostolos Bossios have all contributed to my development as a researcher.

Thanks to my co-authors for fruitful cooperation. Besides my supervisors I say thanks to Helena Backman for guiding deeper into the riddles of statistics.

During my research period I have had explicit support from my clinical directors: Kenneth Lång, Dan Fors, Bengt Sallerfors, and Inga-Lill Baudlot. By recognizing the importance and value of physicians doing research they have all encouraged me to pursue the research task. Arne Zingmark encouraged and supported me in my first attempt to perform a clinical study. Thanks to Jonas Hansson for comments from another discipline, and to Philomina Igoe for help with the English language.

Thanks to Dr. Jan Singer for interesting discussions on tricky spirometric readings, and Professor Kjell Larsson for not giving up on my research endeavour.

Also thanks to our host family at Barba Petra Dvori in Sumartin, Croatia. Many of the papers and the text of this thesis have been written during undisturbed weeks of calm, rest, and a fantastic nature with lost of energy from the blue sea.

Foremost thanks to my family. My daughter Maria, and my sons Marcus and Jonthe. You have endured my hours in research, encouraged me and never asked me to give up. Especially thanks to Anki, my partner. With deep dialogs on research, on the goal, limitation, possibilities, and validity of research findings, and about science and truth, You have always been reassuring.

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Appendices

Appendix 1

The Swedish version of the OLIN questionnaire for structured interviews from 2009

Appendix 2

The English version of the OLIN questionnaire for structured interviews from 2009

Appendix 1

Vuxna intervjuformulär OLIN (2009)

Undersökningsdatum: år_____mån_____dag_____

Intervjuare _____

Personuppgifter

1. Namn _____

Adress _____

Telefonnummer hem _____

arbetet _____

2. Pnr _____

3. Etnisk tillhörighet

Kaukasier	( )
Afrikan	( )
Asiat/oriental	( )
Annan	( )

4. Kön

Man	( )
Kvinna	( )

5. Tätortsgradient ___

Undertecknad medger att blodprov tas och sparas för analys av allergi-antikroppar och andra allergi eller astma/KOL relaterade analyser inklusive genetiska markörer. Prover registreras vid Bio-banken, NLL.

……
Signatur

Appendix 1

Hosta och expektorat

6. Har Du haft långvarig hosta under det senaste året (12 månaderna)? Nej ( )
Ja ( )

7. Brukar Du hosta eller harkla Dig på morgonen? Nej ( )
Ja ( )

8. Brukar Du hosta eller harkla Dig under andra tider på dygnet? Nej ( )
Ja ( )

9. Brukar Du hosta eller harkla upp slem från bröstet, eller känner Du att det sitter slem i bröstet som Du har svårt att hosta eller harkla upp? Nej ( )
Ja ( )

10. Hostar eller harklar Du upp slem (eller har slem som det är svårt att få upp trots hosta) de flesta dagar i perioder om minst 3 månader per år? Nej ( )
Ja ( )

Om ja,

11. Sedan hur många år? Antal år ____

Pip i bröstet eller väsande andning

12. Brukar Du ha pip eller väser det i bröstet då Du andas? Nej ( )
Ja ( )

13. Har Du någonsin, nu eller tidigare, vid något tillfälle haft pip eller väsningar i bröstet då Du andas? Nej ( )
Ja ( )

14. Har Du haft pip eller har det väst i bröstet vid ***något tillfälle*** under de senaste 12 månaderna? Nej ( )
Ja ( )

Om Ja på 14, besvara 15-17

15. Har Du varit ***det minsta*** andfådd när Du haft pip eller väsningar i bröstet? Nej ( )
Ja ( )

16. Har Du haft detta pip eller väsande i bröstet ***utan*** att samtidigt vara förkyld? Nej ( )
Ja ( )

17. Har Du pip i bröstet eller väsande andning de flesta dagarna i veckan? Nej ( )
Ja, periodvis ( )
Ja ( )

Appendix 1

Andnöd

18. Är Du rörelsehindrad (av andra skäl än ev. hjärt- eller lungbesvär)?
Nej/ej rel ( )
Ja ( )

Om Ja,

19. Av vilka skäl?
Cerebrovaskulär sjukdom ( )
Muskelsjukdom ( )
Rörelseinskränkning i extrem. ( )
Övrigt:_____ ( )
Rullstolsburen ( )

20. Har Du någonsin besvär med din andning?
Nej ( )
Ja ( )

Om Ja,

21. Har Du dessa besvär
För jämnan så att andningen aldrig är riktigt bra ( )
Återkommande men avlösta av besvärsfria perioder ( )
Endast vid enstaka tillfällen ( )

22. Anfåddhet vid ansträngning - MRC dyspne skala

Vilket påstående stämmer bäst överens med dig? *ringa in ett alternativ*

Jag blir bara andfådd när jag anstränger mig rejält, inte när jag tar en snabb promenad eller går i uppförsbacke	0
Jag blir andfådd när jag tar en snabb promenad eller går i uppförsbacke	1
Jag blir andfådd när jag går på slät mark i samma takt som andra personer i min egen ålder. (och/eller:) Jag blir andfådd vid gång på slät mark så jag måste stanna upp trots att jag går i min egen takt.	2
Jag måste stanna på grund av andfåddhet efter cirka 100 m gång på slät mark	3
Jag blir andfådd när jag tvättar mig eller klär på mig	4
Frågan ej tillämplig pga nedsatt rörelseförmåga av annan anledning	99

Appendix 1

23. Har Du någon gång haft hastigt påkommande andnöd eller andfåddhet? Nej ( ) Ja ( )

Om Ja på 23, besvara 24

24. Har Du någon gång under de senaste 12 månaderna haft hastigt påkommande andnöd eller andfåddhet? Nej ( ) Ja ( )

25. Har Du någonsin haft hastigt påkommande andnöd med pip eller väsningar i bröstet? Nej ( ) Ja ( )

Om Ja på 25, besvara fråga 26-27

26. Har Du haft hastigt påkommande andnöd med pip eller väsningar i bröstet under de senaste 12 månaderna? Nej ( ) Ja ( )

27. Har Du någonsin haft anfall av andnöd med pip eller väsningar i bröstet eller astmasymtom på Din arbetsplats? Nej ( ) Ja ( )

Astma, kronisk bronkit, emfysem och KOL

28. Har Du eller har Du haft astma? Nej ( ) Ja ( ) Vet ej ( )

29. Har Du av läkare fått diagnosen astma? Nej ( ) Ja ( ) Vet ej ( )

30. Hade Du pip eller väsningar i bröstet i tidig barndom eller astma under barndomen? Nej ( ) Ja ( ) Vet ej ( )

Om Ja på någon av frågorna 28-30,

31. Hur gammal var Du när Du första gången hade pip i bröstet eller hade besvär av andnöd eller märkte av astma? ……år

Om Du inte minns tydligt, var det:

a) Före skolåldern ( )
b) Under skolåldern men före 20 års åldern ( )
c) Mellan 20 och 30 årsåldern ( )
d) Mellan 30 och 40 årsåldern ( )
e) Mellan 40 och 50 årsåldern ( )
f) Efter 50 årsåldern ( )
g) Minns inte alls ( )

31x. Hur gammal var du när du senast hade astmabesvär? ……ålder

32. Har du använt astmamediciner regelbundet eller vid behov under de senaste 12 månaderna? Nej ( ) Ja ( )

Om NEJ, besvara fråga 33.

33. Har Du tidigare använt astmamedicin? Nej ( ) Ja ( )

Appendix 1

34. Har Du av läkare fått diagnosen kronisk luftrörskatarr eller kronisk bronkit?
Nej ( )
Ja ( )
Vet ej ( )

35. Har Du av läkare fått diagnosen KOL?
Nej ( )
Ja ( )
Vet ej ( )

36. Har Du av läkare fått diagnosen emfysem?
Nej ( )
Ja ( )
Vet ej ( )

37. Har du använt mediciner regelbundet eller vid behov mot kronisk luftrörskatarr, KOL eller emfysem under de senaste 12 månaderna?
Nej ( )
Ja ( )

Om NEJ, besvara fråga 38

38. Har Du tidigare använt medicin mot kronisk luftrörskatarr, KOL eller emfysem
Nej ( )
Ja ( )

39. Reagerar Du på någon av följande exponeringar?

	Inga besvär	Ögon-besvär	Näs-besvär	Klåda i mun och svalg	Andnings-besvär	Kliande utslag / eksem	Diarré eller ont i magen
Pollenexponering (gräs, björk, gråbo, mm)							
Pälsdjursexponering (katt, hund, häst, kanin, marsvin, mm)							
Födoämnen (fisk, skaldjur)							
Födoämnen (nötter, kärnförande frukter)							
Mjölk (Laktosintolerens)							
Mjöl (Glutenintolerens)							
……..							
……..							

Appendix 1

40. Har Du, eller har Du haft, någon annan lung/luftvägssjukdom än astma, kronisk luftrörskatarr, KOL eller emfysem? Nej ( ) Ja ( )

Om JA,

41. Vilken/vilka?_____
_____
_____

42. Har du haft Tbc Nej ( ) Ja, lungtbc ( ) Ja, annan tbc ( )

Sjukvårdsbehov pga lung- eller luftvägsbesvär eller annan sjukdom

43. Har du någonsin sökt läkare eller sjukvård pga andfåddhet, andnöd eller pip i bröstet, hosta, slemhosta eller andra luftvägsbesvär inklusive förkylning? Nej ( ) Ja ( )

Om Ja,

44. Har du under senaste 12 månaderna sökt för detta beskrivet ovan? Nej ( ) Ja ( )

45. Har Du någon gång behövt uppsöka akutmottagning pga andningsbesvär? Nej ( ) Ja ( )

Om Ja,

46. Har du sökt akut under de senaste 12 månaderna? Nej ( ) Ja ( )

47. Har Du någon gång varit inlagd på sjukhus för andningsbesvär? Nej ( ) Ja ( )

Om Ja,

48. Har du varit inlagd under de senaste 12 månaderna? Nej ( ) Ja ( )

Appendix 1

Frågor om allergiska näs-ögonbesvär

49. Har Du eller har Du haft allergiska näsbesvär eller hösnuva? Nej ( )
Ja ( )

Om JA på 49 besvara 50,

50. Hur gammal var Du när Du första gången hade hösnuva eller allergiska näsbesvär? …… år

51. Har Du någon gång haft besvär med nysningar, rinnande näsa eller nästäppa utan att Du varit förkyld? Nej ( )
Ja ( )

Om JA på 51,,besvara fråga 52-53

52. Har Du haft besvär med nysningar, rinnande näsa eller nästäppa utan att Du varit förkyld under senaste 12 månaderna? Nej ( )
Ja ( )

53. Har dessa näsproblem uppträtt samtidigt med kliande eller rinnande ögon? Nej ( )
Ja ( )

Om JA på fråga 52

54. Vilka faktorer kan utlösa dessa näsproblem?

	JA	NEJ
a) Pollen från träd som björk, rönn, al m.m.	( )	( )
b) Pollen från gräs	( )	( )
c) Pälsdjur som katt, hund, häst, kanin etc	( )	( )
d) Mögel	( )	( )
e) Parfymer, lukter eller rök	( )	( )
f) Temperaturförändringar	( )	( )
g) Trycksvärta	( )	( )

55. Har Du använt mediciner mot hösnuva/allergiska näsproblem eller nästäppa av icke-allergisk natur någon gång under de senaste 5 åren? Nej ( )
Ja ( )

56. Har Du använt mediciner mot hösnuva/allergiska näsproblem eller nästäppa av icke-allergisk natur någon gång under de senaste 12 mån? Nej ( )
Ja ( )

Om JA på fråga 56, besvara nedan om mediciner

57**.** Antihistaminer i tablettform? Nej ( )
(Aerius, Cetirizin, Clarityn, Kestine, Mizollen, Periactin, Polaramin prolongatum, Semprex, Tavegyl, Teldanex, Telfast, Zyrlex, Versal) Ja ( )

58. Nasala steroider? Nej ( )
(Becotide nasal, Flutide nasal, Nasacort, Nasonex, Rhinocort) Ja ( )

59. Övrigt för näsa eller ögon? (Inkl Antasten privin, Atrovent nasal, Emadine, Lastin, Livostin, Lomudal, Pollyferm, Rinil, Tilavist, Zaditen, Zincfrin) Nej ( )
Ja ( )

60. Kortisonspruta (Depo-Medrol el dyl) Nej ( )
Ja ( )

Appendix 1

Övriga sjukdomar

61. Har du eller har du haft hjärtproblem eller hjärtsjukdom?

Nej	( )
Kärlkramp	( )
Hjärtinfarkt	( )
Hjärtsvikt	( )
Rytmrubbning	( )
Annan hjärtsjukdom	( )
Kranskärlsopererad/ (Kärlkrampsopererad)	( )

62. Använder Du hjärt-, kärlmediciner ? Inklusive proppförebyggande

Nej	( )
En medicin	( )
Två mediciner	( )
Tre mediciner	( )
Fyra mediciner eller fler	( )

63. Har du eller har du haft högt blodtryck?

Nej	( )
Ja	( )

64. Använder du mediciner mot högt blodtryck?

Nej	( )
Ja	( )

65. Har du eller har du haft fönstertittarsjukan (klaudikatio, kärlkramp i benen)?

Nej	( )
Ja	( )

66. Har du eller har du haft blodpropp eller blödning i hjärnan (TIA, stroke)?

Nej	( )
Ja	( )

67. Har du eller har du haft förhöjda blodfetter?

Nej	( )
Ja	( )

68. Tar Du medicin mot förhöjda blodfetter?

Nej	( )
Ja	( )

69. Har du eller har du haft diabetes?

Nej	( )
Ja	( )

70. Har du eller har du haft reumatisk sjukdom?

Nej	( )
Ja	( )

71. Använder Du hormontabletter eller p-piller? (endast kvinnor)

Nej	( )
Ja	( )

72. Har du eller har du haft halsbränna eller sura uppstötningar (Reflux)?

Nej	( )
Ja	( )

Om *JA på fråga 72*

72 b) Inträffar detta efter måltider?

Nej	( )
Ja	( )

Appendix 1

73. Har du eller har du haft några andra sjukdomar än vad som nämnts ovan?
…….. ……
…… …….

Uppväxttid

74. Rökte någon av dina föräldrar eller andra anhöriga i Din hemmiljö under Din uppväxttid innan Du började i skolan?

Nej	( )
Mor	( )
Far	( )
Annan	( )

75. Rökte Din mor då hon var gravid och väntade Dig?

Nej	( )
Ja	( )
Vet ej	( )

76. Hade ni pälsdjur eller burfåglar i hemmiljön eller i den nära omgivningen under Din uppväxttid innan Du började i skolan?

Nej	( )
Ja	( )

Om Ja, vilka?

	Nej	Ja
Katt	( )	( )
Hund	( )	( )
Marsvin/smågnagare	( )	( )
Häst	( )	( )
Kor	( )	( )
Renar	( )	( )
Burfåglar	( )	( )

77. Finns pälsdjur, eller fåglar i hemmiljön nu?

	Nej	Ja
Katt	( )	( )
Hund	( )	( )
Marsvin/smågnagare	( )	( )
Häst	( )	( )
Kor	( )	( )
Renar	( )	( )
Burfåglar	( )	( )

78. Hade Du någon allvarlig luftrörs- eller lunginfektion före skolåldern, t. ex. kikhosta eller krupp?

Nej	( )
Ja	( )
Vet ej	( )

79. Brukade Du dela sovrum med andra barn före skolåldern?

Nej	( )
Ja	( )
Vet ej	( )

80. Hur många syskon har Du eller har Du haft? Antal _____

Appendix 1

81. Hur många äldre syskon har Du eller har Du haft? Antal _____

82. Vistades Du över ett år på daghem, lekskola eller barnhem tillsammans med andra barn före skolåldern?
Nej ( )
Ja ( )
Vet ej ( )

83. Hur bodde Du mestadels före skolstart?
Villa/radhus ( )
Lägenhet ( )

84. Var bodde Du mestadels före skolstart?
Landsbygd ( )
Förort ( )
Stad/tätort ( )

85. Bodde Du mestadels i Sverige före skolstart
Nej ( )
Ja ( )

Om Nej,

86. Vilket land bodde Du mestadels i? ……...

87. Vilken var Din födelsevikt?
< 2500g ( )
2500-3000g ( )
3000-4000g ( )
>4000g ( )
Vet ( )
ej

88. Vad är Ditt nuvarande eller senaste yrke?
SEI ……
Antal år ……

……

89. Har Du arbetat mer än 5 år i något annat yrke?
Nej ( )
Ja ( )

Om JA på fråga 89:

90. Vilket yrke/yrken?
SEI ……
Antal år ……

……

……
SEI ……
Antal år ……

Appendix 1

Rökning och nikotinanvändning

91.	Är Du…..	Icke rökare Före detta rökare Rökare	( ) ( ) ( )
92.	Har du någonsin rökt minst ett år? (minst en cigarett/dag - minst en cigarr/vecka eller minst 30 gram tobak/månad - under minst ett års tid)	Nej Ja	( ) ( )

Om Ja,

93. Hur gammal var Du när Du började röka? Ålder_____

Fråga 94-95 besvaras av icke-rökare och före detta rökare

94.	Händer det att du röker ibland? (mindre än varje vecka)	Nej Ja	( ) ( )
95.	*Om Ja,* Hur många cigaretter i genomsnitt per månad?	Antal _____	

Fråga 96 besvaras av före detta rökare

96. Hur gammal var Du när Du slutade röka? Ålder ___

Frågorna 97-99 besvaras av rökare

97.	Om Du röker cigaretter, hur många röker Du i genomsnitt per dag? Antal_____	Röker ej cigaretter 1 –4 5 – 14 15 – 24 25 eller fler	( ) ( ) ( ) ( ) ( )
98.	Om Du röker cigarrer/cigariller, hur många röker Du i genomsnitt per dag?	Röker ej cigarr 0 – 1 2 - 4 5 - >	( ) ( ) ( ) ( )
99.	Om du är piprökare, hur mycket förbrukar Du i genomsnitt per vecka?	Röker ej pipa <50g >50g - <100g >100g	( ) ( ) ( ) ( )

Appendix 1

Frågorna 100-102 besvaras av rökare och ex-rökare

100. Hur mycket har Du rökt?

Ålder	”rökår”	Cigaretter/dag	Cigarrer/dag	Piptobak g/vecka	
0-20					
21-40					
41-60					
60+					

101. Hur många år har Du rökt? Antal_____

102. Uppskattade antal pack-year? Antal_____

Frågorna 103-105 besvaras av icke-rökare

103. Är Du eller har Du varit utsatt för rökning i din hemmiljö?
Nej ( )
Ja, tidigare ej nu ( )
Ja, nu ( )

104. Är Du eller har Du varit utsatt för rökning på arbetsplatsen?
Nej ( )
Ja, tidigare ej nu ( )
Ja, nu ( )

105. Hur mycket passiv tobaksrök har Du utsatts för under Ditt liv?

	I hemmet			**Arbete/skola/fritid**		
Ålder	”rökår”	timmar/dygn		”rökår”	timmar/dygn	
0-7						
8-15						
16-25						
26-40						
41-60						
61 -						

Saturationsmätning

106. Saturation i vila _____%

Appendix 2

OLIN structured interview questions for adults (2009)

Date of examination: year month day_____

Interviewer _____

Personal data

1. Name _____

Address _____

Telephone number home _____

work _____

2. Civic registration number _____

3. Ethnicity

Caucasian	( )
African	( )
Asian/oriental	( )
Other	( )

4. Sex

Male	( )
Female	( )

5. Gradient of population density ___

The undersigned allows blood samples to be taken and saved for analysis of allergy-antibodies and other analyses related to allergy or asthma/COPD including genetic markers. Samples are registered at the Bio-bank, Norrbotten County Council (NLL).

……
Signature

Appendix 2

Cough and phlegm

6. Have you had longstanding cough during the last year (12 months)? No ( )
Yes ( )

7. Do you usually cough or clear your throat in the morning? No ( )
Yes ( )

8. Do you usually cough or clear your throat other times of the day? No ( )
Yes ( )

9. Do you usually cough or bring up phlegm from your chest, or do you feel that there is phlegm in your chest which is difficult to bring up by coughing or clearing your throat? No ( )
Yes ( )

10. Do you cough or bring up phlegm (or have phlegm difficult to bring up in spite of coughing) most days during periods of at least three months a year? No ( )
Yes ( )

If Yes,

11. Since how many years? Number of years ____

Wheezing in the chest or whistling breathing

12. Do you usually have wheezing or whistling in your chest when breathing? No ( )
Yes ( )

13. Have you ever, now or previously, at any occasion had wheezing or whistling in your chest when breathing? No ( )
Yes ( )

14. Have you at any time during the last 12 months had wheezing or whistling in your chest? No ( )
Yes ( )

If yes on 14, please answer 15 - 17

15. Have you been at all breathless when the wheezing or whistling was present? No ( )
Yes ( )

16. Have you at any time had this wheezing or whistling when you did not have a cold? No ( )
Yes ( )

17. Do you have wheezing or whistling in your chest most days of the week? No ( )
Yes, periodically ( )
Yes ( )

Appendix 2

Shortness of breath

18. Are you disabled (by other reasons than any heart- or lung problems)?

No/not relevant ( )
Yes ( )

If Yes,

19. For what reasons?

Cerebrovascular disease ( )
Muscle disease (myopathy) ( )
Mobility restriction in extremities ( )
Other:_____ ( )
Wheelchair-bound ( )

20. Do you ever have trouble with your breathing?

No ( )
Yes ( )

If Yes,

21. Do you have this trouble

Continuously, so that your breathing is never quite right ( )
Repeatedly, but it always gets completely better ( )
Only rarely ( )

22. Shortness of breath at effort – MRC dyspnoea scale

Which statement suites you best? *encircle one alternative*

I only get troubled by shortness of breath at strenuous exercise, not when hurrying on level ground or walking up a slight hill	0
I get short of breath when hurrying on level ground or walking up a slight hill	1
I get short of breath when walking on level ground at the same pace as other people of my own age. (and/or:) I get short of breath when walking on level ground so that I have to stop in spite of walking at my own pace	2
I have to stop because of shortness of breath after some 100 m walk on level ground	3
I get short of breath when washing myself or getting dressed	4
The question not applicable because of disability for other reason	99

Appendix 2

23. Have you ever had an attack of shortness of breath or breathlessness? No ( )
Yes ( )

If Yes on 23, go to 24

24. Have you at any time during the last 12 months had an attack of shortness of breath or breathlessness? No ( )
Yes ( )

25. Have you ever had an attack of shortness of breath with wheezing or whistling in your chest? No ( )
Yes ( )

If Yes on 25, go to 26-27

26. Have you had an attack of shortness of breath with wheezing or whistling in your chest during the last 12 months? No ( )
Yes ( )

27. Have you ever had an attack of shortness of breath with wheezing or whistling in your chest or symptoms of asthma at your place of work? No ( )
Yes ( )

Asthma, chronic bronchitis, emphysema and COPD

28. Do you have or have you ever had asthma? No ( )
Yes ( )
Don't know ( )

29. Have you been diagnosed as having asthma by a doctor? No ( )
Yes ( )
Don't know ( )

30. Did you have wheezing or whistling in your chest in early childhood or asthma during childhood? No ( )
Yes ( )
Don't know ( )

If Yes on any of the questions28 – 30,

31. How old were you when you for the first time had wheezing in your chest or had problems with shortness of breath or noticed asthma? ……years

If you don´t remember clearly, was it:

a) Before school age ( )
b) During school age but before 20 years of age ( )
c) Between 20 and 30 years of age ( )
d) Between 30 and 40 years of age ( )
e) Between 40 and 50 years of age ( )
f) After 50 years of age ( )
g) Don´t remember at all ( )

31x. How old were you when you last had asthma problems ……age

32. Have you used medication for asthma regularly or as needed during the last 12 months? No ( )
Yes ( )

If NO, go to question 33.

33. Have you previously used asthma medication? No ( )
Yes ( )

Appendix 2

34. Have you been diagnosed as having chronic bronchitis by a doctor? No ( )
Yes ( )
Don't know ( )

35. Have you been diagnosed as having COPD by a doctor? No ( )
Yes ( )
Don't know ( )

36. Have you been diagnosed as having emphysema by a doctor? No ( )
Yes ( )
Don't know ( )

37. Have you used medication regularly or as needed for chronic bronchitis, COPD or emphysema during the last 12 months? No ( )
Yes ( )
If NO, please answer question 38

38. Have you previously used medication for chronic bronchitis, COPD or emphysema No ( )
Yes ( )

39. Do you react on any of the following exposures?

	No problems	Eye problems	Nose problems	Itching of mouth and throat	Breathing problems	Itching eruptions/eczema	Diarrhea or abdominal pains
Exposure to pollen (grass, birch, mugwort, others)							
Exposure to furred animals (cat, dog, horse, rabbit, guinea pig, others)							
Food (fish, shellfish)							
Food (nuts, stone fruits)							
Milk (Lactose intolerance)							
Flour (Gluten intolerance)							
……..							
……..							

Appendix 2

40. Have you or have you had any other lung/respiratory disease beside asthma, chronic bronchitis, COPD or emphysema? No ( ) Yes ( )

If YES,

41. Which? _____
_____
_____

42. Have you had tuberculosis (TBC) No ( ) Yes, pulmonary tuberculosis ( ) Yes, other tuberculosis ( )

Need of medical attendance because of lung- or respiratory problems or other disease

43. Have you ever consulted a physician or other medical care because of shortness of breath, breathlessness or wheezing in your chest, cough with or without phlegm or other airway problems including common cold? No ( ) Yes ( )

If Yes,

44. Have you during the last 12 months sought for that described above No ( ) Yes ( )

45. Have you ever had to visit an emergency unit because of problems with your breathing? No ( ) Yes ( )

If Yes,

46. Have you sought emergency help within the last 12 months? No ( ) Yes ( )

47. Have you ever been hospitalized because of problems with your breathing? No ( ) Yes ( )

If Yes,

48. Have you been hospitalized during the last 12 months? No ( ) Yes ( )

Appendix 2

Questions about allergic nose-eyes problems

49. Do you have or have you had any allergic nose problems or hay fever? No ( )
Yes ( )

If YES on 49, answer 50,

50. How old were you when you for the first time had hay fever or allergic nose problems?…… years

51. Have you ever had problems with sneezing, runny nose or blocking of your nose without having a cold? No ( )
Yes ( )

If YES on 51, answer questions 52 - 53

52. Have you during the last 12 months had problems with sneezing, runny nose or blocking of your nose without having a cold? No ( )
Yes ( )

53. Have these nose problems occurred along with itching or watery eyes? No ( )
Yes ( )

If YES, please answer question 52

54. What factors can trigger these nose problems?

	YES	NO
a) Pollen from trees like birch, mountain ash, alder etc	( )	( )
b) Pollen from grass	( )	( )
c) Furred animals like cat, dog, horse, rabbit etc.	( )	( )
d) Moulds	( )	( )
e) Perfumes, smells or smoke	( )	( )
f) Changes in temperature	( )	( )
g) Printing ink	( )	( )

55. Have you used medication for hay fever/allergic nose problems or blocking of your nose of non- allergic nature at any time during the last 5 years? No ( )
Yes ( )

56. Have you used medication for hay fever/allergic nose problems or blocking of your nose of non- allergic nature at any time during the last 12 months? No ( )
Yes ( )

If YES on question 56, please answer below about medication

57**.** Antihistamines as pills (peroral antihistamines)? (Aerius, Cetirizin, Clarityn, Kestine, Mizollen, Periactin, Polaramin prolongatum, Semprex, Tavegyl, Teldanex, Telfast, Zyrlex, Versal) No ( )
Yes ( )

58. Nasal steroids? (Becotide nasal, Flutide nasal, Nasacort, Nasonex, Rhinocort) Nej ( )
Ja ( )

59. Other for nose or eyes? (Incl. Antasten privin, Atrovent nasal, Emadine, Lastin, Livostin, Lomudal, Pollyferm, Rinil, Tilavist, Zaditen, Zincfrin) Nej ( )
Ja ( )

60. Corticosteroid injection (Depo-Medrol etc.) No ( )
Yes ( )

Appendix 2

Other diseases

61. Do you have or have you had heart problems or heart disease?

- No ( )
- Angina ( )
- Heart attack (cardiac infarct.) ( )
- Heart failure (insufficiency) ( )
- Arrythmia (dysrhythmia) ( )
- Other heart disease ( )
- Coronary artery surgery/(angina surgery) ( )

62. Do you use medication for heart-, vascular problems? Including for the prevention of thrombosis?

- No ( )
- One medication ( )
- Two medications ( )
- Three medications ( )
- Four medications or more ( )

63. Do you have or have you had high blood pressure (hypertension)?

- No ( )
- Yes ( )

64. Do you use medications for high blood pressure (hypertension)?

- No ( )
- Yes ( )

65. Do you have or have you had claudication (vascular spasm in the legs)?

- No ( )
- Yes ( )

66. Do you have or have you had thrombosis or haemorrhage in the brain (TIA, stroke)?

- No ( )
- Yes ( )

67. Do you have or have you had elevated blood lipids?

- No ( )
- Yes ( )

68. Are you taking medications for elevated blood lipids?

- No ( )
- Yes ( )

69. Do you have or have you had diabetes?

- No ( )
- Yes ( )

70. Do you have or have you had rheumatic disease?

- No ( )
- Yes ( )

71. Do you use hormone pills or contraceptive pills (only women)

- No ( )
- Yes ( )

72. Do you have or have you had heartburn or acid reflux?

- No ( )
- Yes ( )

If YES on question 72

72 b) Does this happen after meals?

- No ( )
- Yes ( )

Appendix 2

73. Do you have or have you had any other diseases than what is mentioned above?

…….. …….

…… …….

Childhood and adolescence

74. Did any of your parents or other relatives in your home environment smoke during your childhood before you started school?

No ( )
Mother ( )
Father ( )
Other ( )

75. Did your mother smoke while being pregnant and expecting you?

No ( )
Yes ( )
Don't know ( )

76. Did you have furred animals or cage birds in your home environment or in your close surroundings during your childhood before you started school?

No ( )
Yes ( )

If Yes, which ones?

	No	Yes
Cat	( )	( )
Dog	( )	( )
Guinea pig/small rodent	( )	( )
Horse	( )	( )
Cows	( )	( )
Reindeer	( )	( )
Cage birds	( )	( )

77. Are there furred animals or birds in the home environment now?

	No	Yes
Cat	( )	( )
Dog	( )	( )
Guinea pig/small rodent	( )	( )
Horse	( )	( )
Cows	( )	( )
Reindeer	( )	( )
Cage birds	( )	( )

78. Did you have any severe bronchial- or pulmonary infections before school age, for instance whooping-cough or croup?

No ( )
Yes ( )
Don't know ( )

79. Did you regularly share bedroom with other children before school age?

No ( )
Yes ( )
Don't know ( )

80. How many siblings do you have or have you had? Number _____

Appendix 2

81. How many older siblings do you have or have you had? Number _____

82. Did you stay more than a year in kindergarten, pre-school or orphanage together with other children before school age?
No ( )
Yes ( )
Don't know ( )

83. Before school age, how did you mostly live?
House ( )
Apartment ( )

84. Before school age, where did you mostly live?
Countryside ( )
Suburb ( )
Town/city ( )

85. Before school age, did you mostly live in Sweden?
No ( )
Yes ( )

If No,

86. In what country did you mostly live? ……...

87. What was your birth weight?
< 2500g ( )
2500-3000g ( )
3000-4000g ( )
>4000g ( )
Don't know ( )

88. What is your current or most recent occupation? SEI ……
Number of years ……
……

89. Have you had any other occupation for more than 5 years?
No ( )
Yes ( )

If YES on question 89:

90. What occupation/occupations? SEI ……
Number of years ……
……

…… SEI ……
Number of years ……

Appendix 2

Smoking and nicotine use

91.	Are you a…..	Non- smoker Ex-smoker Smoker	( ) ( ) ( )
92.	Have you ever smoked for at least a year? (at least one cigarette/day-at least one cigar/week or at least 30 grams of tobacco/month - during at least one years' time)	No Yes	( ) ( )

If Yes,

93.	How old were you when you started to smoke?	Age_____	

Question 94-94 are answered by non-smokers and ex-smokers

94.	Do you smoke occasionally? (less than every week)	No Yes	( ) ( )
95.	*If Yes,* How many cigarettes on average per month?	Number _____	

Question 96 is answered by ex-smokers

96.	How old were you when you stopped smoking?	Age	___

Questions 97-99 are answered by smokers

97.	If you smoke cigarettes, how many do you smoke per day on average? Number_____	Don´t smoke cig. 1 –4 5 – 14 15 – 24 25 or more	( ) ( ) ( ) ( ) ( )
98.	If you smoke cigars/cigarillos, how many do you on average smoke per day?	Don´t smoke cigars 0 – 1 2 - 4 5 - >	( ) ( ) ( ) ( )
99.	If you are a pipe smoker, how much do you on average consume per week?	Don´t smoke pipe <50g >50g - <100g >100g	( ) ( ) ( ) ( )

Appendix 2

Questions 100-102 are answered by smokers and ex-smokers

100. How much have you smoked?

Age	”pack-years”	Cigarettes/day	Cigars/day	Pipe tobacco g/week	
0-20					
21-40					
41-60					
60+					

101. How many years have you smoked? Number_____

102. Estimated number of pack-years? Number_____

Questions 103-105 are answered by non-smokers

103. Are you or have you been exposed to smoking in your home environment?

No ( )
Yes, earlier, not now ( )
Yes, now ( )

104. Are you or have you been exposed to smoking in your working environment?

No ( )
Yes, earlier, not now ( )
Yes, now ( )

105. How much passive tobacco smoke have you been exposed to during your life?

	At home			**Work/school/spare time**		
Age	”pack-years”	hours/day		”packyears”	hours/day	
0-7						
8-15						
16-25						
26-40						
41-60						
61 -						

Saturation

106. Saturation at rest _____%