Lung function and prevalence trends in asthma and COPD

THE OBSTRUCTIVE LUNG DISEASE
IN NORTHERN SWEDEN
THESIS XVI

By Helena Backman

Dedicated to my family

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Abstract

Background

Asthma and chronic obstructive pulmonary disease (COPD) are common obstructive airway diseases with a substantial burden in terms of morbidity, mortality and costs. Smoking is the single most important risk factor for COPD, and is associated with incident asthma. It is important to know if the prevalence of asthma and COPD is increasing or decreasing in the population in order to effectively allocate health care resources. The definitions of these diseases have varied over time which makes it difficult to measure changes in prevalence. The preferred method is to estimate the prevalence with the same procedures and definitions based on cross-sectional population samples with identical age distributions in the same geographical area at different time points. Measurements of lung function (spirometry) are required to diagnose COPD, and spirometry is used to evaluate disease severity and progress of both asthma and COPD, where observed values are compared to reference values. The most commonly used reference values in Sweden are published during the mid 1980s, and there are few evaluations of how appropriate they are today based on Swedish population samples. The aim of the thesis was to estimate trends in the prevalence of asthma and COPD in relation to smoking habits, and to evaluate and estimate reference values for spirometry.

Methods

The project was based on population-based samples of adults from the Obstructive Lung Disease in Northern Sweden (OLIN) studies. Postal questionnaires were sent to large cohorts, recruited in 1992 (n=4851, 20-69 years), 1996 (n=7420, 20-74 years) and 2006 (n=6165, 20-69 years), respectively. The questionnaire included questions on respiratory symptoms and diseases, their comorbidities and several possible risk factors including smoking habits. Structured interviews and spirometry were performed in random samples of the responders to the 1992 and 2006 surveys, of which n=660 (in 1994) and n=623 (in 2009) were within identical age-spans (23-72 years). The trend in asthma prevalence was estimated by comparing the postal questionnaire surveys in 1996 and 2006, and the trend in COPD prevalence was estimated by comparing the samples participating in dynamic spirometry in 1994 and 2009, respectively. The prevalence of COPD was estimated based on two different definitions of COPD. Commonly used reference values for spirometry were evaluated based on randomly sampled healthy non-smokers defined in clinical examinations of participants in the

2006 postal questionnaire (n=501). The main focus of the evaluation was the global lung function initiative (GLI) reference values published in 2012, for which Z-scores and percent of predicted values were analysed. New sex-specific reference values for spirometry were estimated by linear regression, with age and height as predictors. These new OLIN reference values were also evaluated on a sample of healthy non-smokers identified in the population-based West Sweden Asthma Study.

Results

Although the prevalence of smoking decreased from 27.4% to 19.1%, p<0.001, between 1996 and 2006, the prevalence of physician-diagnosed asthma increased from 9.4% to 11.6%, p<0.001. The prevalence of symptoms common in asthma such as recurrent wheeze did not change significantly between the surveys or tended to decrease, while bronchitis symptoms such as cough and sputum production decreased significantly. The evaluation of the GLI reference values showed that the predicted values were significantly lower compared to the observed values in Norrbotten, which makes the percent of predicted too high. This was especially true for FVC percent predicted with a mean of 106%. In general, the deviations were more pronounced among women. New OLIN reference values valid for the Norrbotten sample were modelled and showed a high external validity when applied on the sample from western Sweden. The prevalence of moderate to severe COPD decreased substantially over the 15-year period between 1994 and 2009, regardless of definition.

Conclusions

In parallel with substantially decreased smoking habits in the population between 1996 and 2006, the prevalence of several airway symptoms decreased while the prevalence of physician-diagnosed asthma increased. These results suggest increased diagnostic activity for asthma, but may also suggest that the asthma prevalence has continued to increase. In contrast to asthma, the prevalence of COPD tended to decrease and moderate to severe COPD decreased substantially. The continuous decrease in smoking in Sweden during several decades prior to the study period is most likely contributing to these results. The evaluation of reference values showed that the GLI reference values were lower than the observed spirometric values in the population, especially for women, why the new up-to date reference values may be of importance for disease evaluation in epidemiology and in the health care as well.

Sammanfattning på svenska

Bakgrund

Astma och kroniskt obstruktiv lungsjukdom (KOL) är vanliga luftvägssjukdomar som medför stor börda i form av sjuklighet, dödlighet och kostnader för både individ och samhälle. Vid sidan av hög ålder är rökning den enskilt största riskfaktorn för KOL och samband finns även mellan rökning och astma. Det är viktigt att veta om astma och KOL ökar eller minskar i förekomst i befolkningen för att möjliggöra effektiv fördelning av sjukvårdsresurser. Definitionerna av dessa sjukdomar har dock varierat över tid vilket försvårar jämförelser. Jämförelser över tid bör göras genom upprepade tvärsnittsstudier med samma metoder i slumpurval från befolkningen inom samma åldersspann och i samma geografiska område. Diagnostiken av KOL bygger på mätning av lungfunktion och vid bedömning av såväl sjukdomsutveckling som svårighetsgrad av både astma och KOL används lungfunktion, där observerade värden jämförs med referensvärden. De vanligast använda svenska referensvärdena för lungfunktion publicerades under mitten av 1980-talet men det finns få utvärderingar av hur dessa och nyare internationella referensvärden passar befolkningen idag. Målet med avhandlingen var att studera tidstrender i förekomst av astma och KOL i relation till förändrade rökvanor i befolkningen samt att utvärdera och framställa nya referensvärden för lungfunktion.

Metoder

Avhandlingen baserades på befolkningsurval av vuxna individer i Norrbotten inom ramen för Obstruktiv Lungsjukdom i Norrbotten (OLIN) studierna. Frågeformulär skickades med post till slumpurval år 1992 (4851 individer, 20-69 år), 1996 (7420 individer, 20-74 år) och 2006 (6165 individer, 20-69 år). Frågeformulären innehöll frågor om astma, KOL och luftvägssymptom samt om olika faktorer som kan ha samband med utveckling av sjukdomarna, inklusive rökvanor. Sedan inbjöds slumpurval av de som besvarade enkäterna år 1992 och 2006 till undersökningar som innefattade intervjuer och mätning av lungfunktion och totalt deltog 660 individer år 1994 och 623 individer år 2009 i åldersspannet 23-72 år. Förändring i förekomst av astma analyserades genom att jämföra svaren på enkätunderökningarna 1996 och 2006, och förändring i förekomst av KOL analyserades genom att jämföra resultaten från lungfunktions-undersökningarna år 1994 och 2009. Förändringen i förekomst av KOL analyserades genom att använda olika definitioner av sjukdomen och på så sätt studera hur resultatet förändrades beroende på definition. Olika

referensvärden för spirometri utvärderades på ett urval av 501 friska icke-rökande individer från urvalet från 2006 som sedan undersöktes kliniskt. Huvudfokus för utvärderingen var de internationella referensvärden från 2012 med namnet Global Lung function Initiative (GLI). Sedan framställdes nya referensvärden för spirometri separat för män och kvinnor, där ålder och längd predikterar hur stora lungfunktionsvärden en frisk individ från Norrbotten förväntas ha. Dessa nya referensvärden utvärderades sedan på ett urval av friska icke-rökande individer från befolkningsstudier i Västra Götaland.

Resultat

Trots att förekomsten av rökning minskade markant, från 27.4% till 19.1%, mellan 1996 och 2006 så ökade astma i förekomst från 9.4% till 11.6% under samma tidsperiod. Förekomsten av luftvägssymptom som exempelvis pip i bröstet eller hosta tenderade däremot att minska eller vara oförändrade i förekomst. KOL däremot minskade i förekomst, från 9.5-10.5% år 1994 till 6.3-8.5% år 2009, där prevalensen skiljer sig något beroende på definition av sjukdomen. Svårighetsgraden av KOL minskade markant. Utvärderingen av GLI referensvärden visade att de var lägre än de observerade värdena i Norrbotten vilket gör att resultat uttryckta som procent av förväntat värde blir överskattade. Detta var särskilt framträdande för forcerad vitalkapacitet. Det var även tydligt att kvinnornas observerade värden skilde sig mer från GLI referensvärden än männens. Nya referensvärden för Norrbotten framställdes och den externa validiteten var god när den utvärderades på ett urval från Västra Götaland.

Slutsatser

Parallellt med markant minskade rökvanor i befolkningen minskade förekomsten av ett flertal luftvägssymtom medan läkardiagnosticerad astma ökade i förekomst mellan 1996 och 2006. Detta tyder på en ökad diagnostik av astma men kan även tyda på en reell ökning av astma i befolkningen. I motsats till astma tenderade KOL att minska i förekomst mellan 1994 och 2009, oavsett definition, och även svårighetsgraden av KOL minskade. Detta är troligtvis ett resultat av minskade rökvanor i befolkningen under flera årtionden. Utvärderingen av GLI referensvärden visade att dessa var lägre än de observerade värdena i befolkningen, särskilt för kvinnor, varför de nya lokala referensvärdena kan vara av värde för utvärdering av obstruktiva lungsjukdomar inom både epidemiologin och sjukvården.

Abbreviations

ATS	American Thoracic Society
B.C.	Before Christ
BMI	Body Mass Index
BTS	British Thoracic Society
CI	Confidence Interval
CIBA	Chemische Industrie Basel
COPD	Chronic Obstructive Pulmonary Disease
ECRHS	European Community Respiratory Health Survey
ECSC	European Coal and Steel Community
EPI-SCAN	The Epidemiologic Study of COPD in Spain
ERS	European Rsespiratory Society
ETS	Environmental Tobacco Smoke
FEV1	Forced Expiratory Volume in 1 second
FinEsS	Finland, Estonia, Sweden
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GLI	Global Lung function Initiative
GOLD	Global Initiative for Obstructive Lung Disease
IBERPOC	Epidemiological study of chronic obstructive pulmonary disease in Spain
IBM	International Business Machines Corporation
IHD	Ischemic Heart Disease
IUATLD	International Union against Tuberculosis and Lung Diseases
JLAB	Jaeger LAB
LLN	Lower Limit of Normal
MRC	Medical Research Council
OAD	Obstructive Airway Diseases
OLIN	Obstructive Lung Disease in Northern Sweden
OR	Odds Ratio
PAR	Population Attributable Risk
PEF	Peak Expiratory Flow
RR	Relative Risk
SBC	Schwarz Bayesian Criterion
SD	Standard Deviation
SPSS	Statistical Package for Social Science
SVC	Slow Vital Capacity
US	United States (of America)
USA	United States of America
VC	Vital Capacity
WHO	World Health Organization

Original papers

I   Backman H, Hedman L, Jansson SA, Lindberg A, Lundbäck
         B, Rönmark E. Prevalence trends in respiratory symptoms
         and asthma in relation to smoking - two cross-sectional
         studies ten years apart among adults in northern Sweden.
         World Allergy Organ J. 2014 Jan 2;7(1):1.

II   Backman H, Eriksson B, Rönmark E, Hedman L, Stridsman
         C, Jansson SA, Lindberg A, Lundbäck B. Decreased
         prevalence of moderate to severe COPD over 15 years in
         northern Sweden (in manuscript)

III   Backman H, Lindberg A, Sovijärvi A, Larsson K, Lundbäck B,
         Rönmark E. Evaluation of the global lung function initiative
         2012 reference values for spirometry in a Swedish population
         sample. BMC Pulm Med. 2015 Mar 25;15:26.

IV   Backman H, Lindberg A, Oden A, Ekerljung L, Hedman L,
         Kainu A, Sovijärvi A, Lundbäck B, Rönmark E. Reference
         values for spirometry - report from the Obstructive Lung
         Disease in Northern Sweden studies. European Clinical
         Respiratory Journal 2015 Jul 20; 2: 26375

Introduction

The Obstructive Lung Disease in Northern Sweden (OLIN) studies are large population-based epidemiological studies initiated in 1985. For more than 30 years, the epidemiology of asthma and COPD in adults has been studied both cross-sectionally and longitudinally. Since 1996, also children and adolescents have been included in this large research program, in which more than 50,000 subjects have participated.

Prior to this thesis, 15 medical theses solely based on data from the OLIN studies have been published since 1993 and more than ten additional theses include data from the OLIN studies. Until today, the PhD-students originate from five different countries: Sweden, Finland, Estonia, Germany and the USA.

Since more than 20 years, the OLIN studies have collaborated with researchers from other countries, from the USA in the west to New Zeeland and Vietnam in the east. The PoRiverDelta studies in Pisa, Italy, and the OLIN studies started co-operations in the early 1990's. An extensive international multi-centre collaboration has been established within the FinEsS-studies (Finland, Estonia and Sweden), which is still ongoing with new large cohorts being recruited in 2016. Several OLIN-researchers currently have or have had leading positions in the European Respiratory Society (ERS), which has resulted in several publications including policy documents on respiratory research in epidemiology.

In Sweden, the OLIN studies is an integrated part of the department of Public Health and Clinical Medicine at Umeå university. Collaborations are also on-going with the departments of Clinical Science and Nursing at Umeå university, along with Karolinska Institutet, the University of Gothenburg and Luleå University of Technology where several PhD students base parts of their research on data from the OLIN studies. Specific research projects have also been performed together with researchers at the University of Uppsala and the University of Lund. Within the FinEsS-studies there has also been collaboration with the University of Örebro.

This is the Obstructive Lung Disease in Northern Sweden Thesis XVI.

Background

In summary:

Asthma and chronic obstructive pulmonary disease (COPD) are common diseases. Asthma occurs in all ages while COPD mainly occurs in middle aged and elderly. Asthma has been known since thousands of years and the knowledge of asthma has increased over the past four hundred years, although a precise definition was developed first in the middle of the past century. After the 1960s further refinements of the definition and diagnostic criteria have evolved. COPD originates from chronic bronchitis and emphysema. Both these two conditions were described about 200 years ago while the term COPD was first mentioned in 1960s, although not clearly defined until the 1990s. In contrast to asthma, the definitions and precise diagnostic criteria of COPD are still under debate. Lung function is an utmost important measure in the evaluation of many lung and airway diseases. The techniques of measuring lung function have been developed during less than 200 years, and defining normality is important when diagnosing airway diseases and the severity of disease. The aims of this thesis were to estimate recent trends in the prevalence of asthma, respiratory symptoms, COPD, their risk factors, and in the severity of airflow limitation. Further aims were to evaluate recently published reference values for lung function for world-wide use, and also to develop reference values suitable for the population in Norrbotten.

Asthma and COPD are obstructive airway diseases and comprise the largest disease group among chronic respiratory diseases. They contribute a major burden on the society in terms of disability, mortality and costs [1-6]. Regarding airway obstruction, asthma is characterised by variable airway obstruction, while COPD is characterised by chronic airway obstruction. Measurements of lung function are utilized to evaluate the severity of both asthma and COPD, where observed values are compared to reference values in order to identify abnormal lung function.

Asthma

Historical overview - asthma

Symptoms of asthma were known already in very early civilizations, in China already for about 4000 years ago and in Egypt and Babylon for more than 3000 years ago. In Greece, symptoms of asthma were described about 700 years B.C. in the Iliad by Homer (Homeros), and the first known written document describing asthma [7] was authored about 400 B.C. by Hippocrates and his school. During the 1st century, Aretaeus introduced the term asthma as a clinical entity rather than a symptom, but Claudius Galen (Galenos) who was mainly active as a physician in Rome during the 2nd century is known for being one of the first to provide more detailed descriptions of asthma and breathing problems [7]. Galen believed that asthma originated in the brain, from where phlegm was transported to the lungs and caused breathing problems [7-11].

After the collapse of the Roman Empire in the 5th century, the evolvement of medical science in Europe more or less stagnated for the forthcoming millennium. The eastern part of the empire survived as Byzantium, where the medicine continued to rely on the old Greek and Roman beliefs. Meanwhile, the understanding of diseases progressed in parts of Asia and the Arabic world. The Arabic physician Rhazes (Abu Bakr Muhammad ibn Zakariya al-Razi) who was active in Baghdad described asthma more in detail around year 900, when he basically described the unified airway theory (the simultaneous inflammation in the nose and the lower airways) more than 1000 years before the recent discovery in our time period of this connection. In Japan, India and particularly China textbooks about medicine were written based on a considerably better understanding of asthma than that of the ancient Roman and Greek physicians [11-13].

One of the first in Europe who clearly opposed the theories by Galen was the Flemish physician Johann Baptista van Helmont, who in the beginning of the 17th century suggested in his "Ortus medicinae" that asthma was the result of cramp in the air passages and further that the origin of asthma was not in the brain but in the lungs and airways [13]. Thomas Willis proposed asthma as a very severe disease, described different phenotypes of asthma and concluded that symptoms were caused by airway obstruction [14]. Other important contributions were published by John Floyer [15], who described asthma as intermittent and episodic and who proposed that asthma treatment should include both rescue and controller therapy.

During the 18th century, almost a century after the Arabic and Chinese physicians had described the inhalation of exposures as a causal factor of asthma attacks, this knowledge reached Europe. Scotson discovered that asthma was an exogenous disease, and a hundred years later Charles Blackley discovered and proved the association between pollen exposure and airway symptoms by means of a skin prick test, probably used for the first time ever. In 1906, Clemens von Pirquet introduced the term allergy for this reaction [16,17]. In the beginning of the 20th century, asthma became considered an allergic disease, and several reports of asthma were published. Asthma was increasingly common among children why pediatricians got involved in asthma epidemiology, although contemporary reports suggested the prevalence to be low, around or even less than 1%. One of the first reports about asthma prevalence was from the US [18], but most reports were based on hospital admissions, or on physician reports of asthma or asthma attacks [19-21]. The prevalence tended to exceed 1% from the 1950s and forward [22].

Definitions of asthma were imprecise until the late 1950s, when a general agreement was reached on how asthma and other airway diseases should be defined. In the field of respiratory diseases, the main interest among other than pediatricians was on bronchitis rather than on asthma. As a result of discussions on how bronchitis should be defined, also asthma became clearly defined in the late 1950s [23,24].

The definition of asthma

The diagnosis of asthma is arbitrary and the definition has varied over time, but recurrent episodes of respiratory symptoms such as wheeze or shortness of breath have been a prerequisite for the diagnosis of asthma in all guidelines since the mid 1900s. The first consensus of a definition of asthma was reached by mainly British researchers in 1959 at the CIBA Guest Symposium [23], a symposium organized in collaboration with and sponsored by the pharmaceutical company CIBA (today Novartis). Afterwards, both the World Health Organization (WHO) [25] and the American Thoracic Society (ATS) [26] agreed upon this definition with very few modifications during subsequent years. The ATS definition of asthma was the following:

"*Asthma is a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli and manifested by a widespread narrowing of the airways that changes in severity either spontaneously or as a result of therapy.* [26]"

Thereafter, the emphasis on objective tests for the diagnosis of asthma, such as reversibility, hyperreactivity, bronchial variability and more recently on asthma characterized by systemic inflammation has increased [27]. Further, the existence of respiratory symptoms became mandatory for both the definition and the diagnosis of asthma. In clinical practice the diagnosis of asthma is mostly based on the combination of respiratory symptoms and variable airway obstruction. Such a definition has been valid when compared with physiological tests [28], and is commonly used in asthma epidemiology (physician-diagnosed asthma). A typical such clinical definition still in use is the Swedish:

"*Astma är ett symtomgivande tillstånd kännetecknat av luftvägs-obstruktion som varierar i betydande grad under relativt kort tid. Variationen kan uppträda spontant eller till följd av behandling. [29]*"

Thus, the airflow limitation in asthma is often reversible, either spontaneously or by treatment [30,31]. Today, several international guidelines on asthma diagnosis and treatment exist, of which the Global Initiative for Asthma (GINA) is well-known and frequently utilized. In the 2015 update of the GINA guidelines [31], asthma was defined accordingly:

"*Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation*" [31].

In both clinical practice and epidemiology, asthma is commonly divided into broad subgroups such as e.g. allergic or non-allergic disease [32-35], but also increasingly recognized as a broad syndrome including many different clinical phenotypes and biological endotypes [36]. In epidemiology, as in clinical work, the definition of asthma often varies between areas and over time [37,38], a consequence of the lack of golden standard for the diagnosis. Structured questionnaires on symptoms common in asthma have been useful tools in large-scale epidemiological studies aiming to assess asthma prevalence in the population. Since there previously has existed an under-diagnosis of asthma [39], the sole use of questions on asthma or physician-diagnosed asthma has been insufficient to estimate the "true" prevalence in the population. Thus, questions on respiratory symptoms are also required to accurately mirror the prevalence, also because symptoms precede a diagnosis of an obstructive airway disease [40]. At the same time, symptoms common in asthma are not exclusive for the disease. In 1960, the British Medical Research Council (MRC) questionnaire was developed [41-44] and

subsequently revised [45]. Several other questionnaires were developed during the 1960s-1980s, such as the European Coal and Steel Community (ECSC) [46], the US National Heart, Lung and Blood Institute [47], the International Union against Tuberculosis and Lung Diseases (IUATLD) [48], the Tucson study [49] and the American Thoracic Society (ATS) [50]. In 1984-85 the Obstructive Lung Disease in Northern Sweden (OLIN) questionnaire [51] was developed. The European Community Respiratory Health survey (ECRHS) questionnaire was mainly based on the IUATLD questionnaire and was finalized in 1990 [52].

Trends in asthma prevalence

Prior to the Second World War, there are few publications on asthma prevalence, but results from the USA imply a prevalence of 1-2% during the first half of the 20th century [18,19]. Since the 1950s, there are numerous reports on increasing asthma prevalence worldwide [38,39,53-61]. Some recent studies imply that the asthma increase might have reached a plateau in some westernized countries [62-65], but there still seems to be an ongoing increase in countries with a rapid urbanization [66]. It has been argued that observed differences over time and between studies may be due to differences in definitions and methods [37,38,67]. Several studies point to the fact that a substantial increase in diagnostic activities and altered diagnostic practices along with increased awareness of both asthma and respiratory symptoms in the society may explain findings of diverging prevalence estimates [37,56,65,68]. It is obvious that subjects with milder disease more frequently get diagnosed today compared to half a century ago, why it can be difficult to evaluate the "true" magnitude of time-trends in prevalence [38,69]. Despite these facts, it is unlikely that the differences in methods explain the entire increase over time.
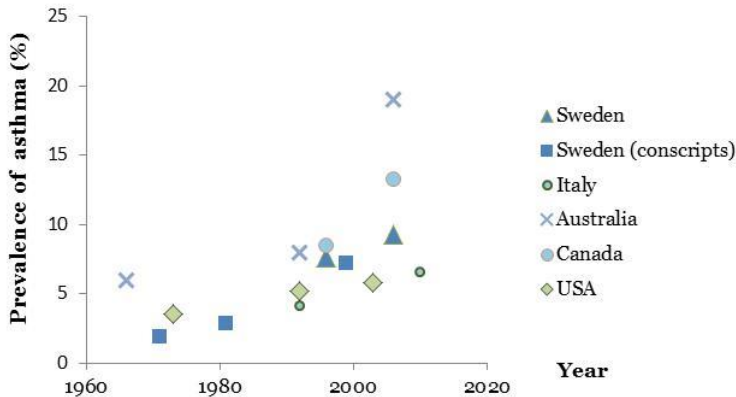
Figure A. Asthma prevalence trends among adults
Sweden: Ekerljung et al [62], Sweden (conscripts): Bråbäck et al and Åberg et al [70,71], Italy: de Marco et al [53], Australia: James et al [57], Canada: Gershon et al [58], and USA: McHugh et al [72].

Risk factors for asthma

In order to enable prevention of a disease, knowledge on modifiable risk factors is required. For asthma, most risk factor analyses are performed among children. Positive associations with male sex, urbanization, low birth weight, atopic sensitization, high body mass index (BMI), sedentary behavior, paracetamol intake, maternal and paternal smoking and outdoor air pollution have been found, while negative associations have been found for diets including vegetables and fruit, day care attendance and growing up on a farm [32,73,74].

However, asthma also develops in adulthood [34,68,75-77], why risk factor analyses among adults are of importance. Among adults, asthma is positively associated with female sex [34,68,75-78], younger adult ages [34,78], high BMI [34,77], occupational exposures [79] and low socio-economic status [78]. A family history of asthma is a prominent risk factor throughout life [34,80,81]. In children and up to young adulthood the impact of allergic sensitization in terms of risk for asthma is significant [32,82,83], but with increasing adult age its impact decreases [34].

The relationship between asthma and smoking is unclear. Smoking has been observed as a risk factor for incident asthma in some studies [75,84,85], while others have found no association [86]. Associations between ex-

smoking or ever-smoking and asthma have been found in some cross-sectional prevalence studies [64,87] but not in others [88,89].

Regional differences in asthma prevalence between Eastern and Western Europe [90-92] and rural versus urban areas [93] have been observed, where differences in both life-style and environmental factors [94] probably contribute. Despite the extensive number of studies on this topic, the underlying causes for regional differences in prevalence and the increasing worldwide prevalence-trend still remain unknown [95].

COPD

Historical overview - COPD

In contrast to asthma, COPD is a young term first mentioned in the beginning of the 1960s as "chronic obstructive broncho-pulmonary disease" by Mitchell and Filley [96] and in 1965 with the final labelling "chronic obstructive pulmonary disease" by Briscoe and Nash [97].

Just as the symptoms of asthma have been described since thousands of years, symptoms of bronchitis have also long been described. The term bronchitis was first used by Badham [98] and sub-types similar to the classification of bronchitis were described from the 1960s and onwards [99]. During the 17th and 18th centuries, autopsies became more common than previously, and anatomists and others in France, Switzerland, Italy and England reported about voluminous lungs. The first description of emphysema was made by the French physician Laennec in the beginning of the 19th century [100]. Laennec suffered from tuberculosis and died young, but had already made enormous contributions to the medical science; he invented the stethoscope and described breath sounds of both heart and lung diseases in his novel piece "De 'l'Auscultation mediate" from 1819 [101,102].

The next major breakthrough came in the 1950s. Chronic bronchitis had become recognized as a common and important cause of disability and mortality, especially in England, and occupational exposures and air pollution were identified as important causes. A large symposium on bronchitis was held in 1951 by physicians in Great Britain and Ireland [99] whereafter increasing attention was paid to chronic bronchitis and emphysema [99,103]. In 1952 the London fog catastrophe caused 4-12000 deaths during one single week in December. People with pre-existing lung or heart disease of all ages died in excess when London was covered by smog. This extraordinary event resulted in several activities by the British Medical Research Council [99]: the first validated respiratory questionnaires were

developed, studies of occupational cohorts and communities were initiated [104-106], and classifications of respiratory diseases were more extensively developed [99,107].

These activities also resulted in the first clear classification of the obstructive airway diseases described in detail by Scadding during the 1950s, conclusions he published in 1959 [24]. Asthma was defined mainly by physiological terms i.e. by reversible airway obstruction, chronic bronchitis by a medical history of chronic expectoration, and emphysema by pathological and anatomical terms, i.e. by increased air spaces in the lungs. This classification was generally agreed upon at the previously referred CIBA Guest Symposium [23].

During that time a scientific debate was ongoing between British and Dutch physicians and researchers. The British kept to the theory of three different diseases, i.e. asthma, chronic bronchitis and emphysema, and the British opinion regarding the disease progress, particularly of chronic bronchitis, was that repeated infections and exposures were the main drivers of disease progress. The researchers behind the Dutch hypothesis [108,109], still cited and under debate [110,111], launched the term Chronic Non-Specific Lung Disease (CNSLD) in 1969 which included all obstructive lung- and airway diseases and suggested more genetic predetermination. They argued that CNSLD could develop differently depending on clinical pathways, existence of allergic sensitization and the development of lung function where host factors and exposures influenced the pathway of the clinical presentation and disease progress.

The Brittish theory was thouroughly described by Fletcher et al [99,107,112] who for the first time provided more detailed descriptions of the harmful consequences of smoking and also constructed the frequently cited "Fletcher curve", displayed in Figure B.
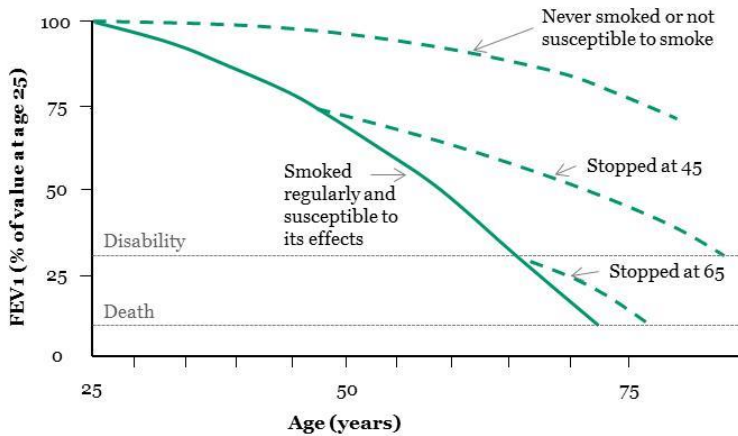
Figure B. Reproduction of the Fletcher curve [112]

Fletcher et al found that among 792 healthy working men, of whom 103 were lifelong non-smokers, ~15% of the ex- or current smokers developed chronic bronchitis with obstruction after an 8-year observation period [99]. This very important result of the effects of smoking resulted in the unfortunate misunderstanding that only 15% of smokers develop COPD, a statement which still today exists in several medical schoolbooks.

The definition of COPD

In the 1990s the first guidelines for both the definition and management of COPD were launched. In 1995 the ATS [113] and the ERS [114] published their policy documents, the British Thoracic Society (BTS) [115] published theirs in 1997 and the Global Initiative for Obstructive Lung Disease (GOLD) in 2001 [116]. Although published wihtin a short period, they all defined COPD differently.

Just as the definition of COPD has changed over time, the definition of a decreased post-bronchodilator FEV_1/FVC ratio (forced expiratory volume in one second/forced vital capacity) is still under debate [117-122]. Two commonly used definitions today are the GOLD [117,123] and ERS/ATS [118,124] definitions of a post-bronchodilator $FEV_1/FVC<0.7$ and $FEV_1/FVC<LLN$ (Lower Limit of Normal), respectively. The simplicity is the main argument for the fixed ratio criterion advocated by GOLD [117,121,123], while the ERS/ATS points out under-diagnosis among younger subjects and over-diagnosis among elderly associated with the fixed ratio criterion

[118,119,122]. The GOLD-criterion has been most frequently used, and is recommended in the 2015 update of the Swedish national treatment guidelines on COPD [125], while the LLN-criterion markedly is gaining ground in more recent epidemiological studies on COPD.

The most commonly used measure of COPD severity has been to analyze FEV_1 as percent of predicted as an indicator for the level of airflow limitation, which in turn is associated with mortality [126]. Also other measures of airflow limitation have been discussed, such as FEV1 Z-scores (standardized residuals) [127]. Recently, the GOLD consortium has presented ABCD groups for guiding of treatment based also on symptoms and exacerbations beside the GOLD grades 1-4 of airflow limitation [123]. Recent publications provide evidence that the spirometric GOLD grades 1-4 predict mortality at least as good [128,129], and they are still widely used in epidemiological studies despite the arbitrary cut-offs.

As a consequence of the high estimates of COPD prevalence when based on the GOLD definition and the fairly good health status and in many cases a good prognosis [130] among subjects with mild COPD (GOLD grade<2) has resulted in a debate on how to introduce other more clinically relevant definitions of COPD. The term "clinically relevant COPD" has been used by several authors, but there is no consensus of the term. Both the ERS White Book about respiratory diseases in Europe [131] and the ERS Monograph on respiratory epidemiology [132] present the prevalence of COPD based on GOLD grades≥2. The debate aims towards the inclusion of clinical aspects more than merely results of spirometry for defining clinically relevant COPD [133-136].

Trends in COPD prevalence

Estimates of prevalence and severity of COPD from studies of general population samples are dependent on e.g. the age distribution of the studied sample, the smoking habits in the area, the definition of COPD and on the reference values for spirometry [132]. Thus results on prevalence vary [4,133,137,138]. The Italian Pisa/Po River Delta studies [139] and the Swedish OLIN Studies [140] have presented results on prevalence based on different definitions of COPD, and as hypothesized, the prevalence varied considerably depending on the choice of definition. Vollmer et al have presented results from the Burden of Obstructive Lung Disease (BOLD) study in ages >40 years using five different criteria for COPD [141]. The GOLD fixed ratio criterion yielded the highest prevalence in all studied areas with a prevalence of 26% in Salzburg (Austria) and more than 20% in Cape Town (South Africa), Krakow (Poland) and London (UK) and close to 20% in

several other areas, while the prevalence in the Asian centres were lower with 12-14% in Guangzhou (China) and Manila (the Philippines). When the lower limit of normal (LLN) 5th percentile was used for defining COPD, the prevalence was on average about 60% lower compared to the GOLD criterion, and about 50% lower compared to GOLD grades≥2 [141]. The LLN-criterion in combination with FEV1<80% of predicted, as well as the LLN-criterion in combination with FEV1<LLN resulted in even lower prevalence ranging from 4-10% for most centres, or about 30-40% of the prevalence based on the GOLD criterion [141].

In the Nordic countries, relatively similar prevalence of COPD has been observed. In the Nordic BOLD study areas the prevalence based on the GOLD criterion was about 18% and 16% in Bergen and Uppsala, respectively [141,142], and a similar prevalence, 18%, has been reported from Copenhagen in age >35 years [143]. These results are fairly in line with previously reported results from the OLIN-studies [140,144]. In Finland, somewhat lower prevalence (GOLD) are reported in ages >20 years; about 10% in northern Finland and 6% in Helsinki [145,146].

A common statement in the literature is that both the prevalence and burden of COPD is increasing worldwide [5] due to increasing smoking prevalence and ageing populations. However, COPD is a "young" disease with clearly defined diagnostic criteria only since 20 years, why long-term time trends are lacking. The definitions of COPD have changed several times during a very short period of time, which makes comparisons troublesome. Nevertheless, there are a few studies in Europe revealing time-trends for COPD in a defined area [4]. In Spain, two studies 10 years apart were performed in partly the same areas, the IBERPOC and the EPI-SCAN [147,148]. An obvious decrease in prevalence of COPD was observed, also when different diagnostic criteria were applied [148]. Further, a large study in Finland found no change in prevalence over 25 years [149]. Thus, the knowledge on current trends in COPD prevalence is limited.

Risk factors for COPD

Smoking is the single most important preventable risk factor for respiratory symptoms, chronic bronchitis and COPD [40,132]. Several epidemiological studies have found that up to 50% of smokers develop COPD if they continue smoking [144,145,147,150-152]. Tobacco consumption is an important risk factor for premature death and disability worldwide [153]. The use of tobacco is rising globally mainly because of an increasing number of smokers in many low and middle income countries [154]. The societal costs of diseases related to tobacco use are substantial; e.g. estimated to more than

4.6% of the Gross Domestic Product of the European Union [155]. In 2008, about one out of three adults in the world smoked [156], and the overall pattern in the World Health Organisation (WHO) European region was similar with 48% of men and 24% of women being current smokers in 2010, although a decrease in smoking prevalence has been observed in several northern and western European countries. In Sweden the prevalence of smoking has decreased during more than three decades [64,157]. Historically, men have smoked more than women in almost all parts of the world, but in Sweden, along with in the UK, smoking has become more common among women than men [51,158].
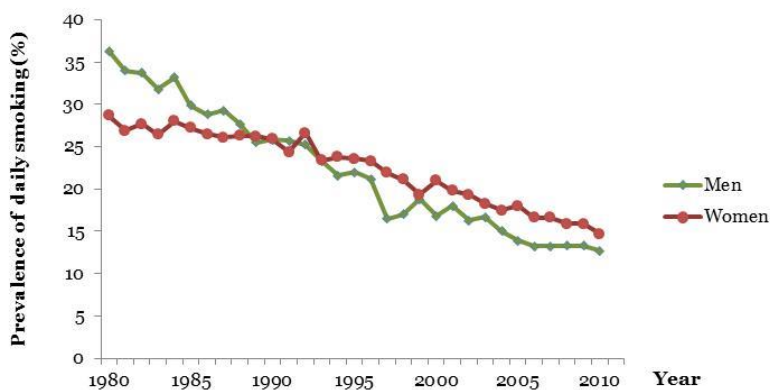
Figure C. Time-trends in the prevalence of daily smoking among men and women 16-84 years in Sweden [158,159].

Further, smoking affects not only the smokers themselves, but also the people around them. Environmental Tobacco smoke (ETS), also labelled passive smoking, has been observed as an independent risk factor for COPD [160-163]

Besides smoking, older age is the other most well-known and important risk factor for COPD [99,132,140]. Occupational airborne exposures [99,164], socioeconomical factors [99,165,166] and heredity [99,167] have also been observed as independent risk factors for COPD. Further, COPD has consistently been observed as more common among men than among women [132,140]. This is to a large extent due to the historically higher smoking prevalence among men. The question is if the risk factor pattern will be altered when the main risk factor smoking decreases substantially in prevalence and when women smoke more than men [159]. Also, the risk factor pattern may be affected by the use of different spirometric definitions of COPD [168].

Reference values for lung function (spirometry)

Historical overview - spirometry

Measurements of lung function play a central role in the evaluation of the pathophysiology of the lungs. In 1846, Hutchinson [169] published the first paper where a spirometer was utilized to measure lung function. It was based on the technique behind the gasometer and measured the vital capacity (VC), thus only volume and not the airflow. Shortly thereafter, water-seal (wet) volume displacement spirometers were developed, and became dominating until the mid 1900s. The first bellows spirometers were developed in the late 1800's, often referred to as dry spirometers to differentiate them from the water-seal spirometers. Tissot developed an exceedingly large water-seal spirometer in 1904 which was manufactured in different versions until the 1980s [170]. Tiffeneau and Pinelli introduced the concept of timed vital capacity as a measure of airflow in 1947 [171], and Gaensler et al the concept of forced vital capacity in the early 1950s [172,173]. In 1952, the Bernstein water-seal spirometer was presented [174] and became commonly used and e.g. in Sweden considered as a state-of-the-art spirometer for a couple of decades.

During the 1960s, the dry spirometers became more commonly used, for instance the Vitalograph bellows spirometer [175] still used today [149]. One of the advantages of the dry Vitalograph versus the water-sealed Bernstein was that it was of lower weight, 6kg versus 35kg, and portable which the Bernstein was not [175]. During the 1970s, a transition from dry but especially from water-seal spirometers to flow measurement systems emerged. Now, more light-weight and portable spirometers could calculate the volumes based on the flow of the exhalation, first based on turbines and subsequently also based on air pressure over a resistance ("screen") in a pneumotach. However, dry volume spirometers are still commonly used, both in clinical work and epidemiology. Within the OLIN studies, the dry Mijnhardt Vicatest 5 volume spirometer has been in use since the 1980s, and the Jaeger Mastersope pneumotach flow/volume spirometer since the late 2000s.

Reference values for spirometry

In order to evaluate if observed spirometric values are normal or abnormal, one must first know what "normal" or "healthy" is. Hutchinson [169] who assessed the VC of 2000 healthy men during the mid 1840s concluded that the VC increased with the subject's height and decreased with the subject's age. This was a startingpoint for today's reference values for spirometry.

It is essential that the sample from which the reference values are derived is representative for healthy subjects in the population in terms of anthropometric, ethnic and environmental factors which can affect lung function [118,176]. The main prerequisites are lack of smoking history, obstructive lung diseases, breathlessness, cough and wheeze [177]. With the startingpoint in Hutchinsons [169] findings, sex-specific linear regression models based on age and height have been commonly used to estimate reference values for spirometry.

There is a large number of published reference values for spirometry available [178-192]. The European Coal and Steel Community (ECSC) reference values [186] have until recently been recommended for European countries by the ERS. In Sweden, two domestic reference values [178,181,182] have been widely used [193] beside the ECSC [186]. The reference values by Berglund were developed in early 1960s [178] and those by Hedenström in the 1980s [181,182]. In 2012, The Global Lung function Initiative (GLI), an ERS task force, presented new multi-ethnic reference values for spirometry within the 3- 95 years age-span which currently are endorsed by several respiratory societies including the ERS and ATS [190]. For Caucasians, the GLI reference values are based on data from asymptomatic lifelong non-smokers from 30 different centres comprising 57,395 subjects of European ancestry from several European countries along with Israel, Australia, USA, Canada, Brazil, Chile, Mexico, Uruguay, Venezuela, Algeria and Tunisia [190].

Abnormal lung function is identified by comparing an observed value such as FEV1 with a reference value. The "percent (%) of predicted" is calculated by dividing the observed value by a reference value and then multiply by 100. Although recently challenged [127,190], FEV1 % of predicted is commonly used to evaluate the severity of obstructive lung diseases. Thus, the accuracy of the evaluation of disease severity depends on the accuracy of the reference values. Also, the ERS/ATS criterion of FEV1/FVC<LLN rely on the reference values. Figure D illustrates the difference between the GOLD fixed ratio criterion and the ERS/ATS LLN-criterion for airway obstruction, for a 180 cm tall man. The possibly false-positives are those which are identified as obstructive by the fixed ratio GOLD criterion but not by the LLN-criterion. The possibly false-negatives are those identified as obstructive by the LLN-criterion but not by the GOLD fixed ratio criterion.
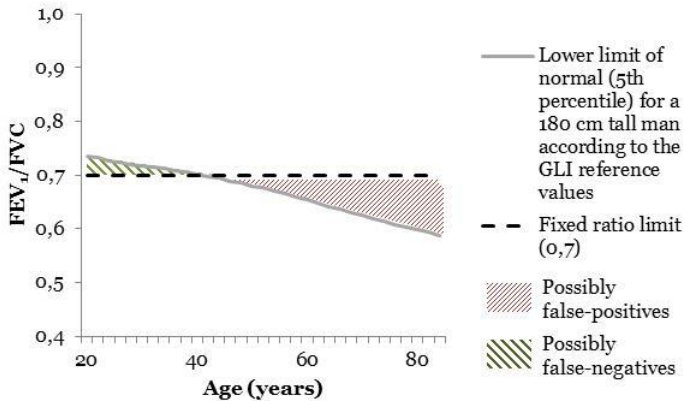
Figure D. Illustration of the difference between the GOLD fixed ratio criterion and the ERS/ATS LLN criterion for airway obstruction based on the GLI reference values [190].

Most spirometric reference values are sex-specific with age and height as predictors, but ethnicity is increasingly recognized as an independent predictor [186,188,190]. It has been observed that subjects of European ancestry (Caucasians) have larger lung volumes compared to subjects of several other races/ethnicities [118,194,195] but it is still debated if this is due to biological or environmental/socioeconomic differences [176]. Height is a proxy for chest size and women have smaller lung volumes than men. Age is a proxy for maturity and lung volumes increase by age during childhood and adolescence followed by a plateau with a subsequent decrease, with a starting point some years post upper teenage but most often before 25 years of age [188,190,196]. Reference values for spirometry are usually derived from spirometric data from healthy lifelong non-smokers identified in random population samples. The spirometric measurements performed by the reference sample should be in line with the contemporary guidelines [118,196-198]. It is also important that reference values for spirometry are evaluated and updated continuously [118,197].

Recently, progress has been made in the area of modelling lung function and the Lambda-Mu-Sigma method (LMS) imbedded in the Generalized Additive Models for Location, Scale and Shape (GAMLSS) models [199,200] is preferred by some authors [192,201]. This method was used to derive the GLI reference values [190,202]. It is increasingly common to use spline-functions to allow both the predicted estimates and the standard deviation (SD) to vary as functions of an explanatory variable [186,190,192,201]. Previous studies have shown that not only the predicted mean but also the standard deviation varies with age, especially when including ages from

childhood to adulthood [190,202], while a large but somewhat older study indicated a more or less constant variance for adults [203].

Reference values for spirometry have historically been labeled inconsistently. Their main purpose is to enable identification of subjects which are likely to be associated with disease or risk for disease, and terms such as "normal", "predicted", "reference" and "healthy" have been used interchangeably despite the somewhat different meanings. In this thesis, the term "reference values", except for in the well-known and commonly utilized expression "percent of predicted", is consistently chosen.

Aims

Paper I: To estimate prevalence trends of respiratory symptoms and asthma among adults in relation to smoking habits by two large-scale cross-sectional studies performed in 1996 and 2006. A further aim was to estimate the proportion of respiratory symptoms and asthma prevalence attributable to smoking.

Paper II: To study changes in prevalence and risk factor patterns of COPD in the same area in Sweden and within the same age-span 15 years apart, in 1994 and in 2009. We hypothesize that the prevalence has decreased due to decreased smoking habits over 30 years in the area. A further aim was to compare outcomes of two different COPD-criteria in terms of prevalence, disease severity and risk factors.

Paper III: To evaluate if the GLI reference values, which are endorsed by several respiratory societies including the ERS and ATS, are applicable for an adult Caucasian population resident in Sweden.

Paper IV: To estimate new up-to-date reference values for spirometry for adults of European ancestry by fitting a multivariable regression model to data from Caucasian healthy non-smokers sampled from the general population of northern Sweden. A further aim was to evaluate the external validity of the new reference values on contemporary data of healthy non-smokers from western Sweden.

Material and methods

In summary:

This doctoral thesis was based on data from population-based samples of adults from the Obstructive Lung Disease in Northern Sweden (OLIN) studies. Postal questionnaires were sent to large cohorts recruited in 1992, 1996 and 2006. The questionnaire included questions on respiratory symptoms and diseases, their comorbidities and several possible risk factors including smoking habits. Structured interviews and spirometry were performed in random samples of the responders to the 1992 and 2006 surveys, of which n=660 (in 1994) and n=623 (in 2009) were within identical age-spans (23-72 years). The trend in asthma prevalence was estimated by comparing the postal questionnaire surveys in 1996 and 2006 within the 20-69 year age-span, and the trend in COPD prevalence was estimated by comparing the samples participating in dynamic spirometry in 1994 and 2009. The prevalence of COPD was estimated based on two different spirometric definitions of COPD, i.e. FEV1/FVC<0.7 and FEV1/FVC<LLN. Commonly used reference values for spirometry were evaluated based on a sample of healthy non-smokers (n=501) defined in clinical examinations of participants in the 2006 postal questionnaire survey. The main focus of the evaluation was the global lung function initiative (GLI) reference values, for which Z-scores and percent of predicted were analysed. New sex-specific reference values for spirometry were estimated by linear regression with age and height as predictors. These new OLIN reference values were evaluated on a sample of healthy non-smokers identified in the population-based West Sweden Asthma Study.

Study area

Norrbotten is the largest and northernmost county of Sweden and is characterized by cold and dry winters and short but warm summers. It is sparsely inhabited with a total population of ~250,000 and a density of 9-10 inhabitants per square km around the time of the millennium shift. The Arctic Circle crosses the county, and Norrbotten is famous for both the midnight sun in the summer and the northern lights in the winter. Most of the inhabitants, about 70%, live in the coastal area within a few dozen kilometres of the largest town, Luleå. Norrbotten shares land border with two countries – Norway and Finland – and the inhabitants speak primarily Swedish, but the national minority languages Meänkieli, Finnish and Sami

are also common. Historically, production of raw materials has been the main driver of Norrbottens' industry, and 90% of Europe's iron ore is extracted from the northern inland region of the county. Today, the traditional industrial branches of iron ore, steel and paper-pulp are to an increasing extent accompanied by branches such as information technology, trade, space research and tourism.
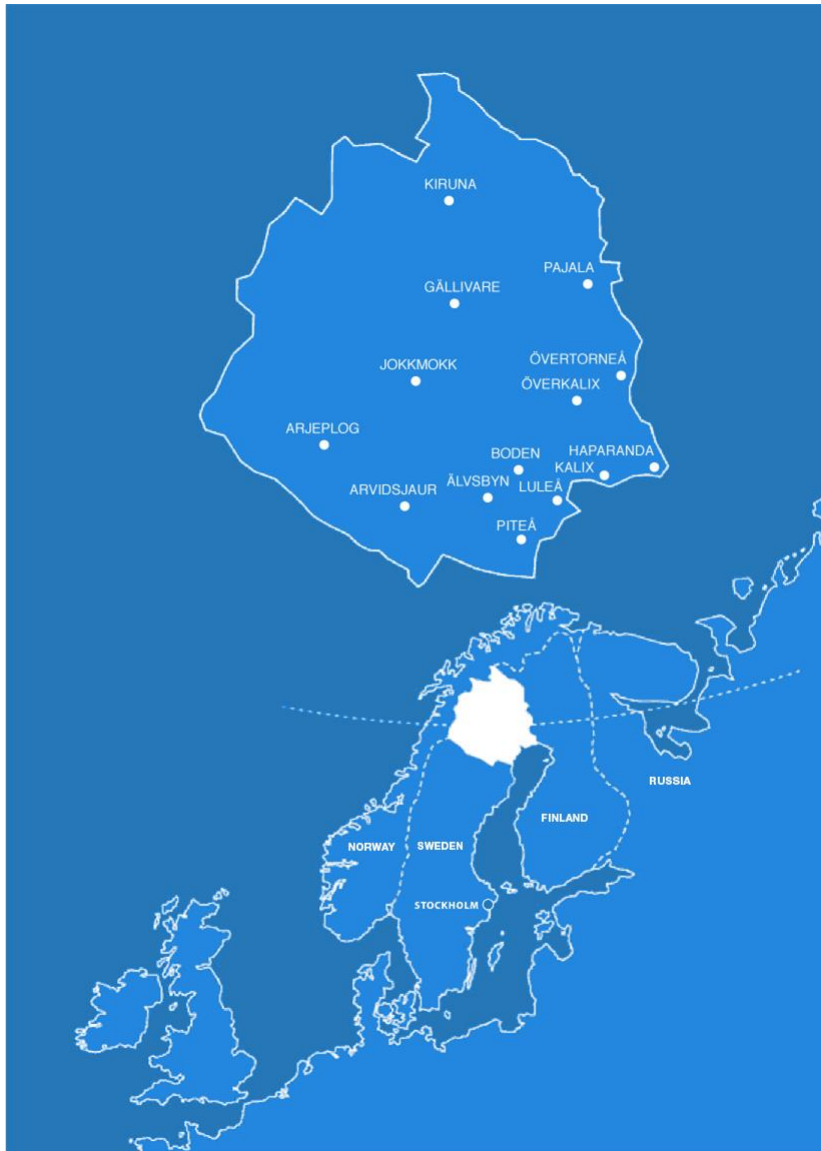

Figure E. Map of Norrbotten county

Study design


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1992        Postal Questionnaire
            Random sample
            N=5682 invited
            N=4851 (85%) participated
            20-69y

1994        Clinical examinations of a
            random sample
1996        N=970 invited
            N=664 (68%) participated          Postal Questionnaire
            n=660 with adequate spirometry    Random sample
            23-72y                            N=8704 invited
                                              N=7420 (85%) participated
                                              20-74y

2006                        Postal Questionnaire        Postal Questionnaire
                            Follow-up of responders     Random sample
                            N=7004 invited              N=7997 invited
                            N=5890 (84%) participated   N=6165 (77%) participated
                            30-84y                      20-69y

2009                        Clinical examinations of a
                            random sample
                            N=1016 invited
                            N=737 (73%) participated
                            n=726 with adequate spirometry
                            21-86y                      Clinical examinations of
                                                        healthy non-smokers*
2011-                                                   N=738 invited
2013                                                    N=448 (61%) participated
                                                        n=433 with adequate spirometry
                                                        25-91y

                                                        *according to the 2006
                                                        questionnaire
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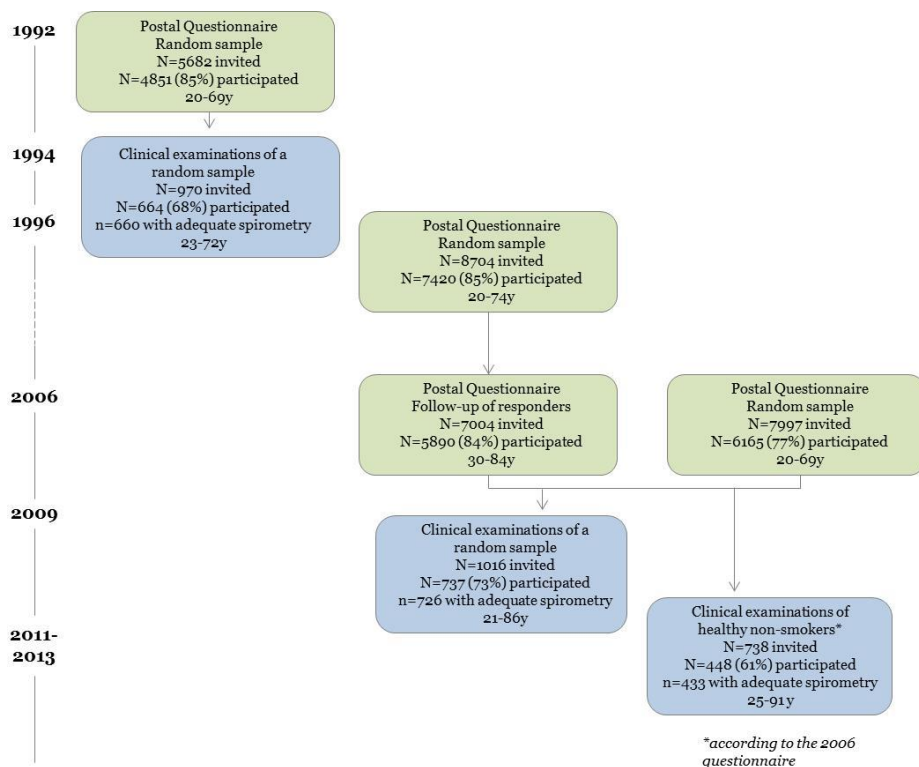
Figure F. Study flow chart

Paper I

In 1996, a random sample of the population of Norrbotten county aged 20-74 years was invited to participate in a postal questionnaire survey, and n=7420 (85%) participated. Of the participants, n=7104 were aged 20-69 years. In 2006, a new random sample of the population of Norrbotten county aged 20-69 years was invited to participate in a postal questionnaire survey with the same questionnaire as in 1996, and n=6165 (77%) participated. In paper I, the prevalence of respiratory symptoms and asthma was estimated in relation to smoking habits and compared between 1996 and

2006. Also, the proportion of respiratory symptom and asthma prevalence attributable to smoking was estimated.

Paper II

In 1992, a random sample of n=5682 subjects from the population of Norrbotten was invited to a postal questionnaire survey, and n=4851 (85%) participated. Of the responders, a randomly selected sample was invited to a structured interview and ckinical examinations including spirometry in 1994. In total, n=660 subjects performed spirometry of adequate quality out of the n=664 (68%) participating subjects. In 2006, two cohorts, of which one had been recruited in 1996 and one in 2006, were invited to participate in a postal questionnaire study, and n=12,055 (80%) participated. N=1016 subjects of the participants were randomly selected after stratification of the age and sex distribution of the general population of Norrbotten, and invited to a structured interview and clinical examinations including spirometry in 2009. In total, n=737 (73%) participated in the clinical examinations, of which n=726 with spirometry of adequate quality. In paper II, COPD prevalence and severity according to different criteria were estimated for the n=660 participants in 1994, and compared to the corresponding estimates for the participants within overlapping ages (23-72 years) in 2009, n=623.

Papers III and IV

Papers III and IV are based on a sample of healthy non-smoking subjects derived from the two population-based adult cohorts participating in the postal questionnaire survey in 2006. Among the participants in the clinical examination in 2009, n=176 healthy non-smokers with adequate spirometry were identified. In order to obtain a sufficient number of healthy non-smokers, an additional sample of healthy non-smokers according to the 2006 questionnaire survey were also invited, and n=433 participated with spirometry of adequate quality in 2011-13. In total, n=501 Caucasians (49% women) were identified as healthy non-smokers with spirometry of adequate quality. In paper III, a number of different reference values for spirometry, with main focus on the Global Lung function Initiative (GLI) reference values, were evaluated based on the sample of n=501 healthy non-smokers. In paper IV, new reference values for spirometry were estimated based on the same sample. In addition, the external validity of the new OLIN reference values was evaluated on a sample from the Swedish region of West Gothia (Västra Götaland), where healthy non-smokers were identified in a general population sample examined by spirometry in 2009-2012.

Methods

The OLIN questionnaire

The OLIN questionnaire for adults consists of a short version for postal questionnaire surveys and an extended version for structured interviews. In summary, it involves questions on respiratory symptoms and diseases, and their comorbidities and factors potentially associated with the conditions. A few of the questions have been somewhat modified throughout the years.

The short postal version [204-206] was developed from a revised version [45] of the British Medical Research Council (MRC) questionnaire [41-44]. It was further influenced by the questionnaires developed by the US National Heart, Lung and Blood Institute, the Tucson Study [47] and the American Thoracic Society (ATS) [50]. From 1996 and onwards questions about chest tightness and wheezing from the International Union against Tuberculosis and Lung Diseases (IUATLD) and the European Community Respiratory Health Survey (ECRHS) questionnaires were included [48,52] along with a slightly modified question about dyspnea from the British MRC [42]. The 2006 questionnaire can be found in in Appendices 1 (Swedish version) and 2 (English version).

The extended version for structured interviews (Swedish version in Appendice 3, English version in Appendice 4) included additional questions from the IUATLD questionnaire [48], and in 2009 also questions from the interview version of the ECRHS questionnaire and a European questionnaire developed for epidemiological studies [207,208]. In addition, it included more detailed questions about respiratory symptoms and diseases, medication use, co-morbid diseases, anthropometric information, lifestyle factors as well as smoking habits and occupational and environmental exposures.

Spirometry

Lung function was measured by dynamic spirometry, including slow vital capacity (SVC), forced vital capacity (FVC) and the volume exhaled during the first second of a forced manoeuvre (FEV1). In the 1994 clinical examination, a dry spirometer (Minjhardt, Vicatest 5, the Netherlands) was used, and in the latter clinical examinations two Masterscope (Jaeger, JLAB version 5.21 software, CareFusion, Würzburg, Germany) spirometers were used. The procedures followed the current ATS/ERS recommendations [209] but with a repeatability criterion of ≤5% [210] instead of ≤150ml deviation from the second highest value, or <100 ml difference if the

spirometric values were <2 Litres. Adequate spirometry was achieved when it successfully followed the recommendations. Further, if the repeatability criterion was not fulfilled, the flow-volume curves were ocularly analysed by trained professionals, either at the time of examination or during the subsequent data management process. Daily quality control of the spirometers was performed the morning on each working day with a 3L syringe. The highest value for FEV1, FVC and SVC, respectively, was used after at least three up to a maximum of eight measurements in order to fulfil the repeatability criterion. The VC was defined as the highest value of FVC and SVC (paper IV). Reversibility testing was performed after 15 minutes using 0.4 mg salbutamol powder via discus in all subjects in 2009 survey, and in subjects with FEV1 <90% of predicted values or a ratio of FEV1/VC<0.7 in 1994. Post-bronchodilator values were defined as the highest values before or after reversibility testing. The date of birth was collected from the Swedish national registry, and age was calculated by one decimal point as the difference between date of birth and date of examination. 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.

Definitions

In this thesis, the following terms are commonly used and defined as follows:

Ever asthma (labelled as ever asthma in papers I, III,IV, but as asthma in paper II): Do you have or have you ever had asthma? *Physician-diagnosed asthma*: Have you been diagnosed as having asthma by a physician? *Asthma medication*: Do you use asthma medication (on a regular basis or when needed)? *Longstanding cough*: Have you had longstanding cough during recent years? *Sputum production*: Do you usually have phlegm when coughing, or do you have phlegm in your chest that is difficult to bring up? *Chronic productive cough:* Bringing up phlegm when coughing on most days during periods of at least 3 months during at least 2 successive years. *Any wheeze*: Have you at any time during the last 12 months had wheezing or whistling in your chest? *Recurrent wheeze*: Do you usually have wheezing or whistling in your chest when breathing? *Asthmatic wheeze:* Wheeze with breathlessness during the last 12 months without having a cold.

COPD (paper II) was defined based on post-bronchodilator values by two different spirometric criteria:

1. FEV1/FVC<0.7
2. FEV1/FVC<Lower Limit of Normal (LLN)

The LLN was defined as the 5th percentile of the corresponding reference value.

The level of airflow limitation (paper II) was measured based on FEV1 as percent (%) of predicted (i.e. observed FEV1 divided by the reference value for FEV1 multiplied by 100). FEV1 % of predicted was stratified according to the cut-offs advocated by GOLD [123] and when COPD was defined by the FEV1</FVC<0.7 criterion, the strata are explicitly labelled as GOLD severity grades 1-4:

GOLD 1. FEV1 ≥ 80% of predicted
GOLD 2. 50% ≤ FEV1 < 80% predicted
GOLD 3. 30% ≤ FEV1 < 50% predicted
GOLD 4. FEV1 < 30% predicted

Smoking habits were stratified into never-smokers (labelled as non-smokers in paper I), ex-smokers and current smokers. Current smokers were defined as those who reported current smoking including those who smoked occasional cigarettes or pipefuls and those who had quit smoking during the last 12 months, while ex-smokers were defined as those who had quit smoking at least 12 months prior to the study. In paper I, the amount of cigarettes smoked each day was reported accordingly by current smokers: <5 cigarettes/day, 5-14 cigarettes/day, or >14 cigarettes/day.

The number of pack-years of smoking (papers III-IV) was calculated among current and ex-smokers by multiplying the number of cigarette packs (number of cigarettes/20) smoked per day by the number of years of smoking.

Healthy non-smokers were defined as subjects without a history of any airway or lung disease, breathlessness, cough, wheeze, ischemic heart disease, rheumatic disorders or a previous life-time exposure of >1 pack-year of smoking (papers III-IV). The Swedish and English versions of the interview questionnaire for healthy non-smokers are found in Appendices 5 and 6.

Ischemic heart disease (IHD) was defined as a history of myocardial infarction, coronary surgery or angina pectoris (papers I-IV).

The classification of socio-economic status (paper II) was based on occupations according to Statistics Sweden classifications: academics and higher civil servants, non-manual employees, manual work in service,

manual work in industry, self-employed other than academics and others (housewives, students, unemployed).

Dyspnea was defined according to a slightly revised version of the modified British Medical Research Council (mMRC) dyspnea scale [211], with values ranging from 0-4, and dichotomized with a value of 2 or higher as cut-off (papers II-IV).

Caucasian ethnicity was defined as a subject of European ancestry.

Statistical analyses

In papers I-III, all statistical analyses were performed by use of the Statistical Package for Social Science (SPSS) software versions 20-22 (IBM, New York, USA). The Chi-square or Fisher's exact tests were used for comparisons of categorical variables in 2*2 contingency tables. The Mantel-Haenzel test for trend was used for comparisons across $2*k$ contingency tables. The student's T-test was used to compare means between two groups. A p-value<0.05 was considered as statistically significant. Multiple linear regression analysis, binary logistic regression analysis and poisson regression analysis was used to test independent associations between covariates and outcome variables. Results from the adjusted analyses are presented as Beta-coefficients, odds ratios (OR) and relative risks (RR), i.e. prevalence ratios, respectively, with corresponding 95 % Confidence Intervals (CI).

In paper I, the population attributable risk (PAR) of current smoking was calculated for both asthma and for a number of other respiratory symptoms. PAR of current smoking was calculated both unadjusted and adjusted for possible confounding factors. Unadjusted PAR was calculated by the following formula:

$$((P_T - P_0)/P_T)*100,$$

where P_T = the prevalence of the condition among all subjects, and P_0 = the prevalence of the condition among non- and ex-smokers. 95% CI for PAR were calculated by the maximum likelihood method [212].

Adjusted PAR of current smoking was calculated in two different ways in this thesis, based on OR from multiple binary logistic regression models and on RR from multiple poisson regression models, both adjusted for age, sex and family history of asthma. The following two formulas were used for the calculation of adjusted PAR:

$$((OR-1)/OR)*P*100$$

and

$$((RR-1)/RR)*P*100,$$

where P=the prevalence of smoking among subjects with the respiratory condition, OR=odds ratio and RR=relative risk [213].

In paper IV, both the SPSS and the BASIC (Basic Software Systems, Texas, USA) software were utilized. Normal Q-Q plots were utilized to evaluate and confirm normal distribution of the spirometric indices. Sex-specific multiple linear regression models were estimated for each of the spirometric indices, with age and height as independent variables. Maximum likelihood estimation was used for the parameters. The relationships with weight were also investigated, but model improvements were absent or negligible why weight was omitted to keep the models parsimonious. Age-dependent spline functions were incorporated in each model to allow the outcome variable to vary smoothly over the age range. The SD was included in the model as a linear function of age.

In papers III and IV, Z-scores were utilized to investigate the distributions of both the observed and predicted values. When based on a linear regression model, the Z-score is calculated as (observed value-reference value)/standard deviation for the reference value. This is how Z-scores are calculated based on the OLIN reference values in paper IV. Z-scores based on the GLI reference values (paper III) are calculated by the software used for the calculation of the GLI reference values (www.lungfunction.org). These GLI Z-scores are not based on linear regression model but on the more recently developed Lambda-Mu-Sigma model [199] imbedded in the R software package GAMLSS [200].

Results

In summary:

Although the prevalence of smoking decreased from 27.4% to 19.1%, between 1996 and 2006, the prevalence of physician diagnosed asthma increased from 9.4% to 11.6%. The prevalence of wheeze did not change significantly between the surveys or tended to decrease, while bronchitis symptoms such as cough and sputum production decreased significantly. The evaluation of the GLI reference values showed that the predicted values were lower compared to the observed values in Norrbotten, which makes the percent of predicted too high. This was especially true for FVC and among women. Further, when using the FEV1/FVC<LLN criterion for COPD, the prevalence may be biased by use of the GLI. New OLIN reference values valid for the Norrbotten sample were modelled and showed a high external validity when applied on the sample from West Sweden. The prevalence of COPD tended to decrease, while the prevalence of moderate to severe COPD decreased substantially, over the 15-year period from 1994 to 2009.

Increased prevalence of physician-diagnosed asthma over 10 years

The prevalence of physician-diagnosed asthma increased from 9.4% (95% CI 8.7% to 10.1%) in 1996 to 11.6%(95% CI 10.8% to 12.4%) in 2006. When adjusted for age group, sex, family history of asthma and smoking habits, the OR for physician-diagnosed asthma in 2006 compared to in 1996 was 1.28 (95%CI 1.14-1.44) (paper I).

When studied by age group, the asthma prevalence increased in all age groups from 20 to 59 years of age, but not in the 60-69 years age group (Figure G). By sex, the prevalence increased from 9.4% in 1996 to 12.4% in 2006 among women, compared to from 9.3% to 10.5% among men. The prevalence of ever asthma, physician-diagnosed asthma and use of asthma medication was significantly higher among women than men in 2006, while only use of asthma medication was significantly more common among women in 1996 (paper I).
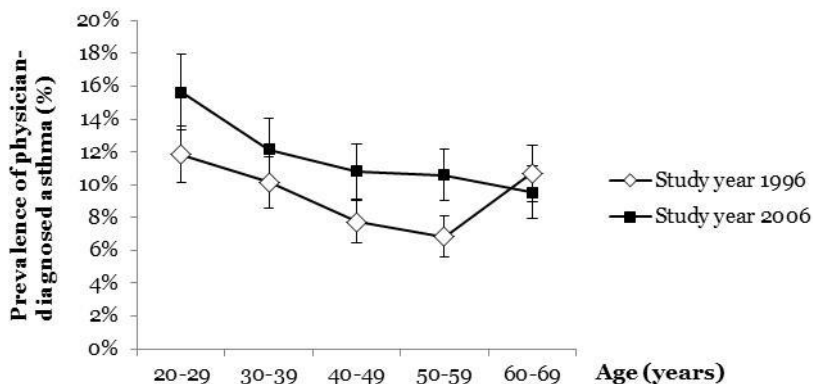
Figure G. Prevalence (with 95% CI) of physician-diagnosed asthma by age group in 1996 and 2006.

A tendency towards decreased COPD prevalence over 15 years

The prevalence of COPD tended to decrease over the 15-year period from 1994 to 2009; from 10.5% to 8.5% (p=0.254) based on the GOLD criterion and from 9.5% to 6.3% (p=0.030) based on the LLN criterion. The prevalence of moderate to severe COPD decreased from 8.5% to 3.9% (p<0.001) based on the GOLD-criterion and from 8.1% to 3.2% (p<0.001) based on the LLN-criterion. In ages >40 years, the corresponding decrease in prevalence of moderate to severe COPD was from 11.6% to 5.6% (p=0.001) based on the GOLD-criterion and from 9.7% to 4.6% (p=0.002) based on the LLN-criterion. The prevalence of moderate to severe COPD decreased significantly by at least half between surveys among men according to both criteria, while the decrease only reached statistical significance for the LLN-criterion among women (paper II). When studied by age group the decreased prevalence was mainly found in ages ≤60 years (Figure H).
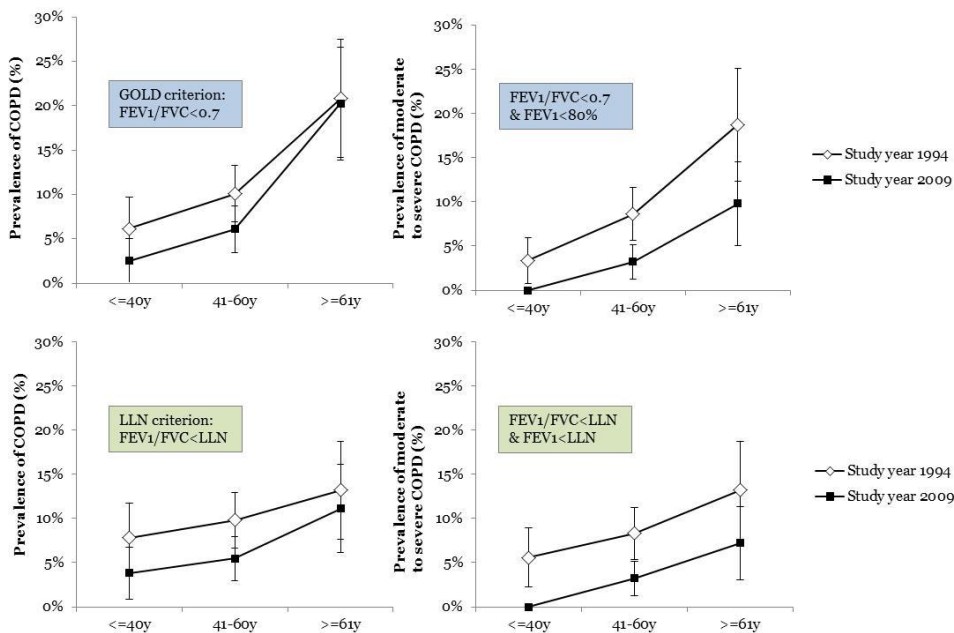
Figure H. Prevalence (with 95% CI) of COPD and moderate to severe COPD according to the GOLD and LLN criteria, respectively, by age group in 1994 and 2009.

Decreased severity of obstructive airway diseases

The prevalence of most respiratory symptoms decreased significantly both among subjects with physician-diagnosed asthma and among subjects with COPD according to the spirometric GOLD criteria. Among subjects with physician-diagnosed asthma, 87% in 1996 and 81% in 2006 reported any respiratory symptom. Among subjects with COPD according to the GOLD criterion, the corresponding figures were 86% in 1994 and 78% in 2009. Among subjects with physician-diagnosed asthma, 74% in 1996 and 66% in 2006 reported use of airway medication during the last 12 months. Among subjects with COPD according to the GOLD criterion, the corresponding figures were 27% in 1994 and 24% in 2009 (Tables 1-2).

Among subjects with COPD according to the GOLD criterion, the level of airflow limitation decreased between the surveys, with a mean FEV1 % of predicted of 67.0% in 1994 compared to 83.4% in 2009 (p<0.001). Also the prevalence of both COPD with FEV1 50-80% of predicted and COPD with FEV1<50% of predicted decreased markedly and significantly. Among subjects with GOLD 1, the proportion reporting a physician-diagnosed

chronic bronchitis, COPD or emphysema was stable around 7% in both surveys, while it increased from 12.9% to 40.0% (p=0.008) among subjects with GOLD≥2. The proportion reporting ever having had asthma did not change significantly between surveys among subjects with COPD (Paper II).

Table 1. Change in the prevalence of symptoms, use of medication for airway disease and smoking habits over 10 years among subjects with physician-diagnosed asthma

	Prevalence change#		Unadjusted			Adjusted##		
	From	To	RR	95% CI		RR	95% CI	
Any respiratory symptom	86.6%	80.9%	**0.93**	**0.89**	**0.98**	**0.94**	**0.90**	**0.98**
Use of medication for airway disease last 12 months	73.9%	66.0%	**0.89**	**0.83**	**0.96**	**0.89**	**0.83**	**0.96**
Ex-smoking	25.5%	26.2%	1.03	0.86	1.23	*	*	*
Current smoking	24.7%	19.9%	**0.81**	**0.66**	**0.99**	*	*	*

#Prevalence change from 1996 to 2006 among subjects with physician-diagnosed asthma, RR=prevalence rate ratio=prevalence in 2006 divided by prevalence in 1996, ##adjusted for smoking habits, bolded figures indicate statistically significant prevalence changes.

Table 2. Change in the prevalence of symptoms, use of medication for airway disease and smoking habits among subjects with COPD over 15 years according to the spirometric GOLD criterion of FEV1/FVC<0.7

	Prevalence change#		Unadjusted			Adjusted##		
	From	To	RR	95% CI		RR	95% CI	
Any respiratory symptom	86.4%	77.5%	0.90	0.74	1.09	0.92	0.76	1.11
Use of medication for airway disease last 12 months	26.7%	24.1%	0.90	0.49	1.65	0.89	0.49	1.62
Ex-smoking	36.0%	37.0%	1.03	0.65	1.63	*	*	*
Current smoking	44.0%	38.9%	0.88	0.58	1.35	*	*	*

#Prevalence change from 1994 to 2009 among subjects with COPD, RR=prevalence rate ratio=prevalence in 2009 divided by prevalence in 1994, ##adjusted for smoking habits, bolded figures indicate statistically significant prevalence changes.

Decreased smoking habits

During the study period, the prevalence of current smoking decreased substantially in the population, from 27.4% in 1996 to 19.1% in 2006 (p<0.001). Meanwhile, the proportion of non-smokers increased, from 51.5% in 1996 to 59.1% in 2006 (paper I). Also, current smokers reported fewer cigarettes smoked per day in 2006, especially male current smokers (Figure I).
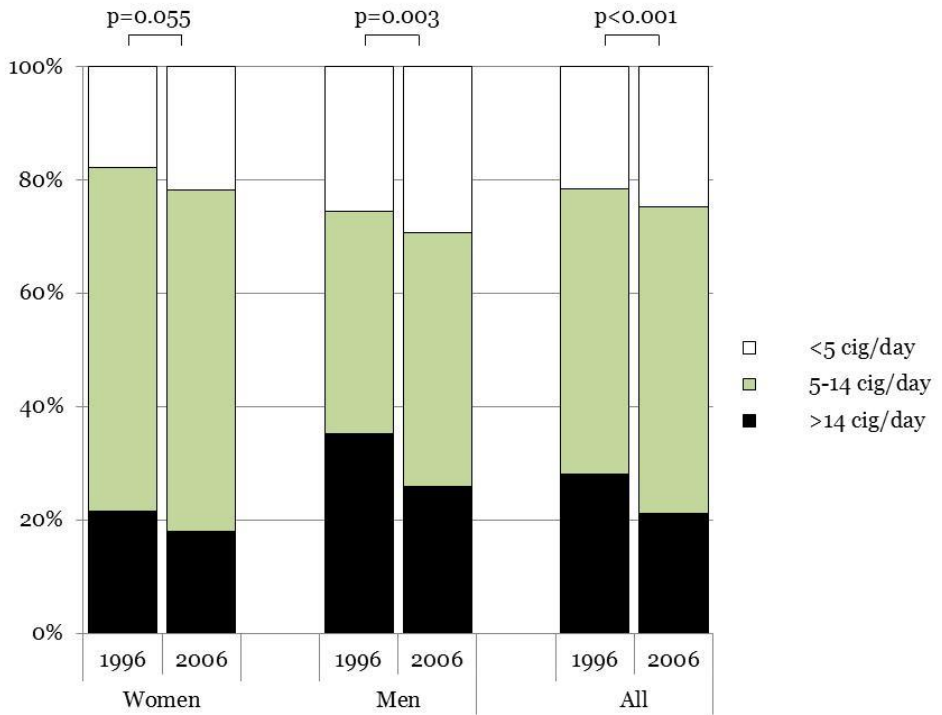

Figure I. Number of cigarettes smoked per day among current smokers in 1996 and 2006, for women, men and all subjects, respectively.

Risk factors for COPD and physician-diagnosed asthma and the population attributable risk of current smoking

For physician-diagnosed asthma, younger ages, a family history of asthma and ex-smoking were significant risk factors in both 1996 and 2006, when adjusted also for sex. Current smoking was not significantly associated with physican-diagnosed asthma when adjusted for age, sex and a family history of asthma, except in 2006 when subjects smoking 5-14 cigarettes/day had an increased risk (paper I).

For COPD, older ages and current smoking were significant risk factors in both 1994 and 2009, when adjusted for sex, ex-smoking, a family history of obstructive airway disease (OAD) and socioeconomic status. In contrast to 2009, the 1994 risk factor pattern also included ex-smoking and a family history of OAD. Additionally, the socioeconomic groups manual workers in industry, non-manual employees and self-employed other than academics, with academics as reference, emerged as more strongly associated with different definitions of COPD in 2009.

There was no significant PAR of current smoking for physician-diagnosed asthma. For respiratory symptoms, PAR of current smoking was significant with the highest value for recurrent wheeze (paper I and Table 3). The PAR of current smoking for COPD ranged between 25-30% depending on definition of COPD, definition of PAR and year of study (Table 3).

Table 3. Unadjusted and adjusted PAR (%) of current smoking for physician-diagnosed asthma, sputum production, recurrent wheeze and COPD according to the GOLD and LLN criteria, by year and different formulas.

		Physician-diagnosed asthma		Sputum production		Recurrent wheeze		COPD GOLD criteria		COPD LLN criteria	
Formula for PAR		1996	2006	1996	2006	1996	2006	1994	2009	1994	2009
$((P_T-P_o)/P_T)*100$	U	-4	1	14	14	23	18	24	27	30	26
$((RR-1)/RR)*P*100$	U	-4	1	14	14	23	18	24	27	30	26
	A	-3	1	15	14	22	18	28	26	32	25
$((OR-1)/OR)*P*100$	U	-4	1	17	16	25	20	26	29	32	27
	A	-4	1	18	17	25	21	31	29	34	27

P_T=the prevalence of the respiratory symptom/condition among all, P_o=the prevalence of the respiratory symptom/condition among non- and ex-smokers, OR=odds ratio, RR=prevalence rate ratio, P=the prevalence of current smoking among subjects with the respiratory symptom/condition, U=unadjusted, A=adjusted for age, sex and a family history of asthma or other obstructive airway disease.

Evaluation of reference values for spirometry

The evaluation of reference values for spirometry showed that the commonly used ECSC reference values are significantly lower than the observed values among healthy non-smokers in the population of Norrbotten. The mean % of predicted for both FEV1 and FVC are thus much higher than the expected mean of 100% (Paper III), especially among women. Similar trends were also found for the GLI reference values but with less deviation from the observed values compared to for the ECSC. The mean GLI Z-scores for men and women, respectively, were 0.20 and 0.22 for FEV1, 0.29 and 0.42 for FVC, and -0.12 and -0.38 for the FEV1/FVC ratio, of which all differed significantly from zero.
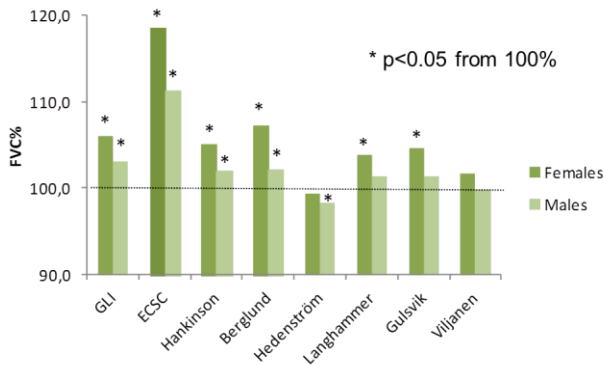

Figure J. Mean FVC as percent of predicted among healthy non-smokers (paper III)

Further, instead of the expected 5% with values below the LLN for the FEV1/FVC ratio, 9.4% (95% CI 5.7%-13.1%) of the healthy non-smoking women and 2.7% (95% CI 0.7%-4.7%) (p=0.002 for difference between sexes) of the healthy non-smoking men had such low values.

Estimation of the OLIN reference values for spirometry

Sex-specific linear regression models were estimated for FEV1, FVC, SVC, VC, the FEV1/FVC ratio and the FEV1/VC ratio with age and height as independent variables. The relationships with weight were also investigated, but model improvements were either absent or negligible why weight was omitted to keep the models parsimonious. Age-dependent spline functions were incorporated, and the standard deviation (SD) was included as a linear function of age in the models. The SD, reference value (mean), and lower

limit of normal (LLN, defined as the lower 5th percentile) for each of the spirometric indices are calculated by the following formulas:

SD: A * B * age
Mean: (B(J) * X(J)) * SD
LLN: Mean -1.645 * SD

Where J ranges from 1 to 5 and age is expressed in years. The coefficients A, B, B1-5 and the variables X1-5, which are unique for each of the spirometric indices, can be found in Paper IV.

OLIN versus GLI reference values for spirometry

A graphical illustration of the differences in FVC for the GLI and the OLIN reference values for a woman and a man of approximately average heights are presented in Figure K. The predicted FVC (solid lines) between ages 22 and 86 years are displayed for the OLIN (in green colour) and the GLI (in grey colour) reference values, along with the LLN for both (dashed lines).
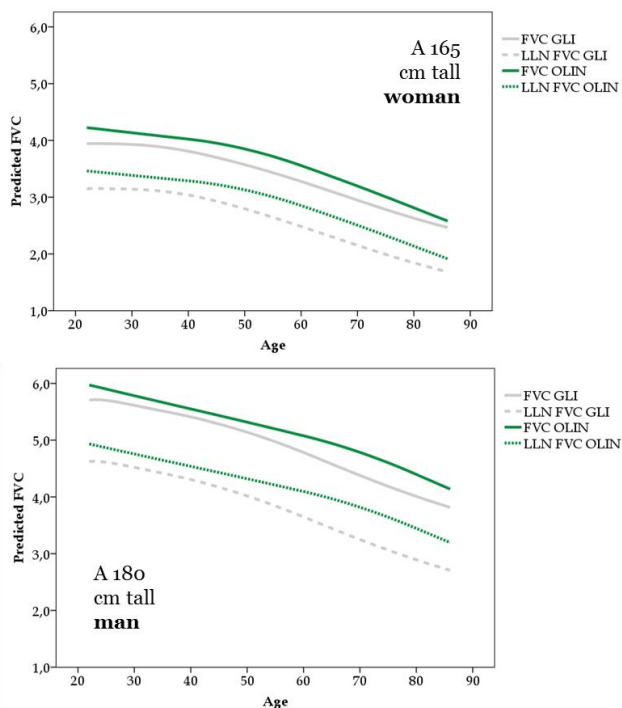

Figure K. Predicted FVC and LLN for FVC, by age, for a woman and a man of approximately average height, according to the GLI and OLIN reference values, respectively

Discussion of methodology

In summary:

The study design with repeated cross-sectional random samples within the same age-span in the same area is appropriate and follows recommendations on how to best study trends in prevalence over time. Also the recommended approach on how to best evaluate reference values for spirometry is adhered, with clinical examinations including spirometry of random population samples where healthy non-smokers are identified. The high participation rates and random sampling strategies propose high validity, although selection bias cannot be ruled out. Further, validated questions in standardized questionnaires were used. Efforts to control for confounding were made both through stratification and by adjustments in multivariate regression models. The spirometric measurements followed recommended guidelines which increase the reliability, although the criteria for reversibility testing differed. Statistical significance proposes reliable results and testing for statistical significance was performed for all main results. A shortcoming in risk factor and PAR calculations is the cross-sectional design where temporal sequences between a certain factor and asthma or COPD cannot be evaluated. The size of the sample from which the OLIN reference values were derived is small compared to the GLI sample but model evaluations implied a high internal validity, and they were also externally validated on a sample from another region in Sweden. The comparison of the OLIN and GLI reference values revealed better validity for the OLIN reference values for the population of Norrbotten.

This section discusses important methodological aspects of the thesis. The terms *internal* and *external validity (accuracy)*, *reliability (precision, consistency)* and potential *bias* are discussed where appropriate.

Study design

To evaluate changes in prevalence in the population over time, repeated measures with identical methods in the same area and within the same age-span are preferred. In addition, the preferred way to study these phenomena is to use population-based data, i.e. representative samples from the population of interest. Data from registers or hospital-populations cannot accurately represent the general population. Instead, they represent the specific subgroups included in the registers or who visits specific hospitals.

Registers are often utilized to study fatal diseases which are commonly diagnosed and where most subjects with the disease are included in registers. Under-diagnosis is common regarding COPD [214], why register-based studies of population prevalence are inappropriate. Thus, studies on prevalence require random samples from the population. Further, the study design should preferably be cross-sectional, not longitudinal, to avoid possible effects of e.g. healthy survivors and systematic reasons for non-response. Concerning paper I on asthma prevalence trends, both samples are large and cross-sectional. The samples in paper II on COPD prevalence trends are smaller; the 1994 sample (n=660) includes randomly sampled participants from a postal survey performed in 1992, whereas the 2009 sample (n=623) includes participants from two separate postal surveys performed in 1996 and 2006 respectively. Although the participants in the 1996 and 2006 postal surveys were almost identical regarding prevalence of asthma, allergic sensitization, respiratory symptoms, use of asthma medication and smoking [215], some healthy-responder effects may still have introduced *selection bias* in this sample.

Systematic bias or errors may have an effect on the *validity* of a study. *Validity* is how accurate a study measures what it intended to measure, and can be affected by *systematic bias such as selection bias, information bias* and *confounding*. The random sampling strategy and the high participation rates reduce the risk for *selection bias*, although it cannot be completely ruled out. The participation rates increased by age, and were lowest among younger subjects, especially among males, in line with other studies [53,205,216], although Rönmark EP et al have shown that the lower participation in younger subjects and also among smokers has minor impact on the epidemiological associations [216]. However, the almost identical prevalence estimates after adjustment for the age and gender distribution in Norrbotten each year imply representativeness of these study samples. The quality control of the spirometric measurements was rigorously thorough and they were performed in line with standardized guidelines. Thus, the *internal validity* is considered to be high. The use of validated questionnaires and standardised methods for the measurements of spirometry increases the *validity* and *reliability* of the measured variables. The *external validity* was tested in paper IV on a sample of healthy never-smokers drawn from another population, i.e. that of western Sweden. This western Sweden-sample could be identified with identical methods as the Norrbotten-sample from which the reference values were derived, since the the main part of the questionnaires were identical. The good concordance between the OLIN reference values and the observed spriometric values in the western Sweden sample propose a high *external validity*. Further, also

the results on asthma, risk factors and smoking prevalence are in concordance with other studies in Sweden [62,64].

Confounding is the effect of a factor which is independently associated with both the outcome and the exposure, and which can lead to over- or underestimation of an association. A *confounding* factor can even change the direction of an association [217], and should be controlled for to reduce potential *bias*. By stratifying the analyses in paper I by smoking habits, the results were controlled for the potential *confounding* effect of smoking. Another way to control for *confounding* is to adjust associations between an outcome and an exposure for potentially *confounding* factors in multivariate regression models. In papers I and II, multivariate logistic regression models were utilized to control for *confounding* factors such as e.g. changes in age and sex-distributions in the population between surveys. Despite these efforts, *bias* due to unknown *confounding* factors may still have occurred.

A number of subjects (n=176) from the 2009 sample (n=726, paper II) were healthy non-smokers and included in the sample of n=501 subjects (paper III) on which the OLIN reference values models are based (paper IV). Although the reference values may be "extra" tailor made for the 2009 sample as compared to the 1994 sample, the observed differences are hardly a result purely due to the methods used. The decrease in the prevalence of FEV1/FVC<0.7 was similar to the decrease in the prevalence of FEV1/FVC<LLN, despite that the latter is dependent on the reference values. Thus, it is not likely that any substantial bias is introduced by the fact that the reference values are tailored specifically for this population.

Questionnaire

The use of standardized questionnaires is a convenient method in studies of large population-based samples. Self-completed questionnaires are less expensive and resource-consuming compared to performing interviews, and reduce the risk of *interviewer bias*. In this thesis, both methods are used. The data quality obtained relies on the *validity* and *reliability* of the questions in the questionnaires, and can be affected by *information bias*. *Information bias* is introduced if there are errors in the information obtained, and *recall bias* if the responders cannot remember the accurate answer. For instance, questions on childhood events are probably affected by *recall bias*. The data *validity* can be evaluated by comparing the response to a question with a separate and independent criterion, and the consistency can be evaluated by comparing the response to the same question at two separate time points. The OLIN questionnaire has recently been validated and compared with the international GA2LEN questionnaire [218].

Since the diagnosis of asthma is arbitrary, it can be difficult to evaluate sensitivity and specificity, which are measures of *validity*, on questions on asthma. The sensitivity of a question is the proportion of those with the disease which are categorized as diseased by the question, while specificity is the proportion of those without the disease which are categorized as non-diseased by the question. For asthma, it is difficult to decide on what to validate a question against. A review study from 1993 on the *validity* of several different asthma questionnaires revealed a high specificity but somewhat lower sensitivity for self-reported asthma compared to the clinical diagnosis by a physician [28]. Within the OLIN-studies, the question on asthma has previously been validated, with high specificity but poorer sensitivity [32,39]. Questions on smoking have not been validated against biological tests, but answers to questions in self-completed questionnaires have been in concordance with those in subsequent structured interviews and the results in follow-up studies show high consistency.

Spirometry

Different types of spirometers were used in 1994 and 2009. To date, no published evaluations of difference in performance between the Minjhardt Vicatest and the Jaeger Masterscope exist, where the first is a dry volume spirometer and the second a flow/volume pneumotach spirometer. The performance of the Mijnhardt Vicatest has been evaluated in 1990 where it got the highest test-grade [219]. The authors of that study evaluated 62 different spirometers, of which the Minjhardt Vicatest was one, although of a somewhat earlier version (version 3) than the one used in the OLIN 1994 study (version 5). Another evaluation study of the Mijnhardt Vicatest also presented positive results, such as "very good linearity over the entire volume ranges" in 1981 [220]. Further, dry volume spirometers are still widely used in epidemiological research, e.g. in the Nhanes [221] and the ECRHS II [222]. Pneumotach spirometers, such as the Jaeger MasterScope, are commonly used in epidemiological research [146,189,223,224], for instance also in the ECRHS II [225]. Further, the spirometers were checked-up on a daily basis and no obvious deviations were observed on either survey. Thus, the *validity* and *reliability* of the spirometric data are assumed to be high.

The repeatability criterion for spirometric measurements aims towards high data *reliability*. The repeatability criterion of <5% difference (or 0.1 Litre if the values are <2 Litres) between the largest and second largest results [210] was identical in the different surveys (papers II-IV) but is not quite in accordance with the <150ml difference criterion currently recommended by

the ERS/ATS [209]. Because the <5% difference criterion was used in 1994 it was preferred over the current ERS/ATS criterion also in 2009, since it enabled less *biased* comparison between the surveys. The <5% criterion is an older and less strict ATS criterion for larger values, but neither the older [210] nor the current [209] recommendations are explicit rules but rather recommendations. There is no "rule" to without further analysis exclude results not fulfilling the repeatability criteria. Instead, the recommendation is to thoroughly evaluate deviating results and make a professional decision if they still are valid or not. In our studies, this was done by trained professionals and the majority of the deviating test results were considered valid. The methods were identical in both surveys, proposing a high *reliability*. Furthermore, the criterion for reversibility testing differed between the surveys. In 1994, subjects with FEV1<90% and/or a FEV1/VC ratio<0.7 performed both pre- and post-bronchodilator spirometry, compared to all subjects in 2009. This could possibly impact the *reliability*, but since it is unlikely that subjects with normal lung function on average would be much affected by bronchodilation there is probably minor impact on the results due to this difference between surveys. A sensitivity analysis based on pre-bronchodilator spirometry revealed similar results as those found based on post-bronchodilator spirometry; moderate to severe COPD decreased from 9.2% to 5.1% (p=0.005) based on the GOLD-criterion and from 8.5% to 4.7% (p=0.007) based on the LLN-criterion, and the mean FEV1 % of predicted increased substantially and significantly among subjects with COPD.

Statistics

A statistically significant result proposes that the same associations would be found if the study was repeated with the same data collection methods. Thus, statistical significance proposes *reliable* results. Statistical significance was consistently determined by p-values <0.05 and 95% Confidence Intervals not including the Figure 1.

A limitation of the chosen cross-sectional study design is the lack of information on temporal sequences of cause and effect between different risk factors and asthma and COPD, respectively. Thus, the statistical associations presented in the four papers reveal e.g. systematic co-existence (or lack thereof) of factors, rather than causal relationships between them. Although the cross-sectional design is preferred for measurements of prevalence which were the main aims of these papers, risk factor analyses based on longitudinal study designs can be informative.

Binomial logistic regression models were used in papers I and II to assess significant associations between different risk factors such as sex, age group and family history of asthma and a binary outcome variable such as asthma/no asthma or COPD/no COPD. All analyses presented had a significant Omnibus test of model coefficients, but since they were not intended to be used as prediction models no Hosmer-Lemeshow tests were performed. Poisson regression models were utilized in the results section of this thesis to assess prevalence ratios, or relative risks (RR), for COPD between 2009 and 1994 and physician-diagnosed asthma, sputum production and recurrent wheeze from 1996 to 2006 adjusted for changes in smoking habits. All analyses presented had significant Omnibus and deviation tests.

The population attributable risk (PAR) for smoking was calculated for several different respiratory symptoms/conditions along with for physician-diagnosed asthma (paper I). The PAR is sometimes called PAF, the population attributable fraction, and the definitions sometimes differ. The PAR can be expressed both in absolute or relative terms, but in this thesis the relative definition is consistently used, i.e. a PAR of smoking with a magnitude of 25% expresses that one fourth of the prevalence in the population can be attributable to current smoking. The cross-sectional study design disables analysis of temporal sequences, and gives no information on whether the smoking habit forewent the debut of the symptoms/condition or not. The decision to study PAR for current smoking instead of for ever-smoking was based on the assumption that current smoking would be more informative when studying current respiratory symptoms and conditions.

Further, both unadjusted estimates of PAR as well as estimates adjusted for age, sex and a family history of asthma or any obstructive airway disease were studied. However, the use of the OR as a proxy for the RR when calculating PAR (paper I) can be criticised. For low prevalences, the OR is a valid proxy for the RR, but the OR is known to perform less accurate for higher prevalences of the condition under study [226]. In Table 3, the differences between the formulas $((P_T-P_0)/P_T)*100$ or, which yields identical unadjusted results, the $((RR-1)/RR)*P*100$ [213], and the formulas based on the OR i.e. $((OR-1)/OR)*P*100$, are illustrated. It is obvious that for unadjusted PAR, the use of OR yields larger PAR estimates compared to the use of the RR. However, although differences were observed, the main messages of these analyses were similar regardless of choice between PAR based on OR or RR (Table 3).

Regarding the sample of n=501 healthy nonsmokers in papers III-IV, selection bias such as including smokers [181,182] or only employees within

certain industries [179] is avoided due to the random sampling from the general population. Compared to the sample size of n>57,000 of the GLI reference values [190], n=501 is a small sample. Quanjer et al [227] has previously shown that 150 subjects of each sex is a sufficient sample size to make a reliable evaluation of the applicability of reference values for spirometry. Our sample size of healthy non-smokers was based on previous sample sizes in studies on reference values for spirometry [178,181,182] and the paper by Quanjer et al [227] rather than on specific sample size calculations. This can certainly be criticised, but the results showed a very good model performance based on the sample of n=244 women and n=257 men.

A measure with the ability to characterise and compare regression models is the bayesian information criterion, today frequently called the Schwarz-Bayesian Criterion (SBC) [228]:

$$SBC = -2*\ln(L) + k*\ln(n)$$

Where L is the likelihood function, k is the number of parameters and n is the size of the sample. The model with the lowest SBC value is preferred and the differences in SBC are characterized as follows: 0-2 units "Not worth more than a bare mention", 2-6 units "Positive", 6-10 units "Strong" and >10 units "Very strong" [228]. A comparison of the regression methods used for the GLI and the OLIN reference values based on the sample of n=501 healthy non-smokers is presented in Table 4. The evaluation shows that the OLIN models are "very strongly" preferred for both FEV1 and FVC among both men and women, while the difference compared to GLI for the FEV1/FVC ratio among men is "not worth more than a bare mention" and GLI is "very strongly" preferred for the FEV1/FVC ratio among women.

Table 4. SBC calculated for the sample of n=501 healthy non-smokers

	SBC for the GLI reference values		SBC for the OLIN reference values	
Variable	Women	Men	Women	Men
FEV1	156.29 +k* ln(n)	374.65 +k* ln(n)	127.72 +k* ln(n)	343.16 +k* ln(n)
FVC	330.34 +k* ln(n)	507.29 +k* ln(n)	290.16 +k* ln(n)	474.05 +k* ln(n)
FEV1/FVC	-707.54 +k* ln(n)	-795.29 +k* ln(n)	-694.47 +k* ln(n)	-794.10 +k* ln(n)

Historically, almost all reference values for spirometry rely on age and height for men and women separately and many also account for race or ethnicity [188,190]. A recent review by Braun et al [195] found that before the millennium shift, 17% of publications on reference values for spirometry accounted for race/ethnicity, compared to 70% after the millennium shift.

In epidemiology, measures of body mass usually include height, weight and BMI which are simple and cost-effective measures. Correlations between BMI and reduced lung function [229] have been found in epidemiological studies of "healthy" subjects with above normal BMI. Collins et al [230] found that in a sample of 42 healthy men of normal weight or mildly obese, several measures of body fat distribution were associated with lung function. In that study, BMI was only significantly associated with FVC and not with FEV1. Further, BMI, body fat (%) and height could together only account for half of the variation in FVC, while, rather illogical, age was not significantly associated with FVC. Further, high body weight has not only been associated with reduced lung volumes, but also with muscularity and improved lung function in young adults [231]. Correspondingly, Ray et al [232] concluded already in 1983 that also among massively obese subjects, standard reference values for spirometry were appropriate although they did not account for BMI or weight in the equations. There were none or minimal associations with weight in the sample of n=501 healthy non-smoking subjects, why weight was excluded from all models in order to keep them parsimonious. Thus, it can be reasonably concluded that no substantial *systematic bias* was introduced by omitting weight from the models.

Discussion of main results

In summary:

Increasing prevalence trends of asthma and COPD have been documented in several parts of the world. The increase in physician-diagnosed asthma is in line with findings from other countries. However, the increase was not supported by increase of symptoms common in asthma, which were on level, why the increase at least partly may be a result of increased awareness of asthma in society, improved recognition by care providers and altered diagnostic practices. In contrast to asthma, the prevalence of especially moderate to severe COPD decreased considerably, in Europe one of the first results showing a decreased prevalence of COPD. Smoking remained as the main risk factor for COPD and the decrease in prevalence is probably due to the substantial decrease in smoking over several decades in Sweden. The evaluation of reference values for spirometry found the OLIN-reference values to be more precise in predicting observed values with mean values higher than those predicted by the GLI, a result in line with results from other Nordic countries. As found by others, samples of single studies reveal less variation around the mean compared to the large all-ages multi-ethnic GLI, which affects the LLN. When considering what reference values to use, it is important to decide if you are interested in the worldwide average on what is normal or abnormal, or if you are more interested in what is normal or abnormal in your specific population.

Increased prevalence of physician-diagnosed asthma over 10 years

The prevalence of physician-diagnosed asthma increased from 9.4% to 11.6% between 1996 and 2006 (p<0.001) (paper I). This prevalence is higher both compared to similar contemporary studies from other countries [88,89,233] and to studies in other Swedish areas using the same questionnaire [64,234] which confirm previous indications of a north-south gradient in asthma prevalence in Sweden [71,235]. The reason for this is unclear, but the cold climate may contribute. However, the World Health Organization has reported contemporary prevalence of physician-diagnosed asthma ranging from 4.3% to 21.0% in different countries, and the observed prevalence in Norrbotten is well within those ranges [236].

When stratified into 10-year age groups, the prevalence of physician-diagnosed asthma decreased by age group in both surveys (paper I), in line

with results from other Swedish studies [62,64]. In 1996 however, in contrast to 2006, there was a higher prevalence of asthma in the oldest age group (60-69 years) compared to those aged 30-59 years. This result might reflect misclassification of COPD as asthma among the elderly in 1996. Also, both asthma and use of asthma medication increased most in the youngest age group, and the younger subjects tended to report more wheeze in 2006. This may imply a true increase of asthma, since misclassification of asthma as e.g. COPD is unlikely among young subjects. On the other hand, it could also be a result of increased awareness of asthma and symptoms common in asthma in the society and of altered diagnostic practices [68].

The odds ratio for physician-diagnosed asthma in 2006 versus 1996 did not change to any significant extent when adjusted for age, sex, smoking habits and a family history of asthma. Thus, it can be assumed that the increase in prevalence probably is not mainly due to changes in these factors. Data on ETS exposure, BMI and occupational exposures [95] would have been valuable, since changes in the presence of these factors may have contributed to the change in the prevalence of both respiratory symptoms and asthma.

So, does the estimated increase in the prevalence of asthma reflect a "true" increase, or is it merely a result of increased awareness and diagnostic habits? The proportion reporting symptoms common in asthma such as wheeze decreased significantly from 1996 to 2006 among subjects with physician-diagnosed asthma. This occurred despite the fact that the proportion of subjects using asthma medicines also decreased significantly among the asthmatics. These data suggest an increased awareness of asthma in the society, improved recognition of asthma in primary care and an increasing diagnostic activity, in particular of mild asthma, a result in line with several other studies [56,62,64]. On the other hand, the lack of over-all decrease in asthmatic wheeze and any wheeze despite the major decrease in smoking, and a parallel increase in the prevalence of allergic sensitization both among children and adults in Norrbotten [237,238], may indicate a true increase in asthma. Thus, the observed increase in asthma could be due to both a true increase in asthma and increased diagnostic activity, which would be a result in line with studies from other countries [57], and it is possible that the increasing trend in asthma prevalence has not levelled off in Norrbotten.

A tendency towards decreased COPD prevalence over 15 years

The prevalence of COPD decreased non-significantly from 10.5 to 8.5% based on the GOLD-criterion and significantly from 9.5 to 6.3% based on the LLN-criterion over the 15-year period from 1994 to 2009 (paper II). The prevalence of moderate to severe COPD decreased substantially and significantly from 8.5% to 3.9% based on the GOLD-criterion and from 8.1% to 3.2% based on the LLN-criterion. The decrease was larger and significant among men but reached statistical significance only for the LLN-criterion among women. Also compared to previous studies in Sweden [140,142,144], these results indicate a decreased prevalence, especially of moderate to severe COPD.

To the best of my knowledge, this is one of few studies revealing a decreasing COPD prevalence in Europe based on repeated surveys in the same area. Correspondingly, a Spanish study [148] found decreasing prevalence trends of both COPD (from 9.1% to 4.5%) and the level of airflow limitation in COPD between 1997 and 2007 in partly the same areas, parallel to only a limited reduction in smoking habits. COPD was defined as FEV1/FVC< 88% of predicted in men and 89% of predicted in women in that study [148] which is an older ERS criterion [114]. These Spanish findings were considered positive but controversial when published in 2010 [4,138]. However, the fact that participants reporting a previous asthma diagnosis were excluded from the analyses [148] may have affected the results of an estimated >50% reduction in COPD prevalence in Spain over ten years.

A large repeated cross-sectional population survey in ages≥30 years in Finland revealed no increase in a quite low COPD prevalence over 25 years based on the LLN-criterion and pre-bronchodilator spirometry [149]. In 1978-1980 versus 2000-2001, the prevalence was 4.7% versus 4.3% among men and 2.2% versus 3.1% among women. In the US, the Nhanes have shown a more or less stable COPD prevalence (based on several different criteria for COPD) while the prevalence of severe COPD has decreased [221,239,240]. Thus, the frequently cited statements that the worldwide prevalence and societal burden of COPD are increasing [3-6] can be challenged, at least in some areas [138,148,149].

Several reviews have presented pooled prevalence estimates of spirometrically defined COPD since the millennium shift. A problem is that the definition of COPD and the age-span of the samples vary. Different definitions of COPD results in prevalence estimates that vary by more than

200% [133,141]. According to Halbert et al, the most commonly used definition has been GOLD severity grade≥2 and most studies have been limited to ages >40 years [241], a definition and age-span used in both the ERS White Book and the ERS Monograph on Respiratory Epidemiology [131,132]. Defined accordingly, the average prevalence has been estimated at about 9-10% [131,132,241,242] which is in line with results from the BOLD study [137], while the prevalence of COPD in GOLD grades 1-4 in the BOLD study exceeded 20% in some European areas [137]. The ERS/ATS standards report 13.5% GOLD grades 1-4 prevalence in ages 25-75 years from the NHANES [124], an age-span similar to the Norrbotten samples. Already in 1994, the prevalence of 9.5-10.5% found in Norrbotten is relatively low, and the prevalence in 2009, 6.3-8.5%, seems even lower in comparison with the estimated average of prevalence in the westernized world [124,131,132,137,241,242]. The relatively low prevalence in the latter survey could be attributed to the long-term decreasing smoking prevalence in Sweden [158,159] which contributes to improved public health in the area. Thus, continuous work with strategies for primary prevention and smoking cessation are still very important.

Decreased severity of obstructive airway diseases

Subjects with physician-diagnosed asthma (paper I) reported less symptoms and somewhat less use of medication for airway disease, results which correspond well to patterns found in other areas [37]. This can possibly be a result of more frequent diagnosis of milder disease [37,38] but also of improved quality in the care of asthma patients [56,59]. An important distinction between paper I on asthma and paper II on COPD is that for subjects with physician-diagnosed asthma, these observations in paper I are representative only for those who have been in contact with care providers and who have received a diagnosis. Further, the diagnostic criteria may have differed between surveys.

In contrary to paper I on asthma, the identification of subjects with COPD in paper II was based on identical physiological criteria in both surveys. All subjects who revealed airway obstruction on dynamic spirometry were identified in paper II, and not only those who had been in contact with health care. Interestingly, subjects with COPD defined by the spirometric GOLD criterion (paper II) reported less symptoms and somewhat less use of medication for airway disease in the latter survey, and the mean FEV1 percent of predicted was higher among subjects with COPD. This decreased disease severity could be a result of the decreasing smoking habits in the population during several decades prior to the study period [158,159]. Also, the markedly increased proportion reporting a physician-diagnosed chronic

bronchitis, COPD or emphysema in the latter survey among subjects with GOLD severity grade≥2 implies an increased recognition of moderate to severe COPD in the health care and perhaps increased help with smoking cessation in this group.

In 1994, 22.7% of the subjects with COPD according to the GOLD criterion reported a physician-diagnosed asthma (paper II). When only studying subjects at least 60 years old, the corresponding figure increased to 26.7%. The pattern was the opposite in 2009, where 27.8% of the subjects with COPD according to the GOLD criterion had a physician-diagnosed asthma, but for subjects at least 60 years old this figure decreased to 19.4% (paper II). As previously stated, the asthma prevalence had increased in all age groups except for among 60-69 year old subjects in 2006 (Figure G). Altogether, these findings point towards a misclassification of COPD as asthma among the elderly during the mid 1990s.

Decreased smoking habits

Current smoking decreased by ~30% in the population from 1996 to 2006 in paper I (27.4% vs 19.1%), and by ~40% from 1994 to 2009 in paper II (26.6% vs 16.1%). The decrease was significant in all age groups, in both sexes, and in the proportion of smokers consuming >14 cigarettes/day (paper I), results well in line with the estimations of an on-going decrease in smoking habits since several decades in Sweden [158,159].

It is of great importance for preventive decisions to identify effects of changes in smoking habits on respiratory health in the population. In 2005, legislation was implemented in Sweden to reduce smoking and environmental tobacco smoke exposures in restaurants. More women than men smoked already in 1985 [51], and the decrease in smoking prevalence observed in papers I and II was more pronounced among men than among women. Worryingly, increased smoking habits and symptoms of bronchitis have been observed among teen-age girls in Sweden [243]. It is of great importance to establish a decrease in cigarette consumption also among women, especially since women are more susceptible to the effect of cigarette smoke than men [244,245]. However, Statistics Sweden estimated that 11.7% of the men and 12.1% of the women in Sweden were daily smokers in 2014 [159] which imply not only a further reduction of smoking habits but also that the gender differences more recently may be diminishing.

Risk factors for COPD and physician-diagnosed asthma and the PAR of smoking

Stratified by smoking habits, the highest prevalence of physician-diagnosed asthma (paper I) in both 1996 and 2006 was observed among ex-smokers, a result which conforms well with other cross-sectional studies [64,87]. It has previously been observed that a diagnosis of COPD impacts smokers to quit smoking [246] and previous studies have shown similar results for smokers who get an asthma diagnosis [75]. In paper II, the highest COPD prevalence was found among current smokers in both surveys and according to both criteria for COPD, the second highest prevalence among ex-smokers and the lowest among never-smokers, which is in line with other studies [214,247]. However, as is well-described in the litterature, the impact of smoking is considerably higher for COPD than for asthma [247,248].

All respiratory symptoms were strongly associated with smoking (paper I), and the proportion of respiratory symptoms attributed to smoking (PAR of smoking) varied from 10% to 25%. The decrease in smoking prevalence was greater than the decrease in prevalence of symptoms, and a tendency of a decrease in PAR of smoking from 1996 to 2006 was observed for most respiratory symptoms. In contrast, the PAR of smoking was non-significant for physician-diagnosed asthma in both surveys (paper I). The PAR of smoking tended to decrease for COPD (for both the GOLD and LLN criteria) (Table H), most likely due to the decreased smoking habits and the amount of cigarettes smoked/day.

The decrease in the prevalence of bronchitis symptoms (paper I) is probably mainly a result of the decrease in smoking prevalence, but also of some other factor since a decrease also was observed among non-smokers. The decrease among non-smokers could be related to a reduction of ETS, which followed the stricter Swedish smoking legislation in 2005. The over-all increase in use of asthma medication in 2006 may also contribute to a decrease in symptoms (paper I).

Wheeze is strongly related to smoking and is a common symptom for subjects with obstructive airway diseases [62,64,140]. In contrast to bronchitis symptoms, the prevalence of any wheeze and asthmatic wheeze (paper I) remained at a similar level in 2006 compared to 1996 while recurrent wheeze decreased slightly. Since PAR of smoking was largest for recurrent wheeze, with smoking explaining about one fifth of the symptom prevalence (paper I), a decrease in the prevalence of recurrent wheeze was expected due to the decrease in smoking prevalence. Actually, a pronounced

decrease in the prevalence of all wheeze symptoms was expected due to the substantial ~30% decrease in smoking prevalence. One hypothesis that would explain the lack of an overall decrease in wheeze symptoms is that a parallel increase in asthma prevalence levels the prevalence of wheeze.

The substantial decrease in smoking habits, both in terms of prevalence of current smoking and in the number of cigarettes smoked/day (paper I), is the most likely contributor to the altered risk factor pattern for COPD observed in 2009 as compared to 1994 (paper II). A weakness is the lack of data on pack-years in 1994, why possible changes in pack-years could not be analysed. Although smoking and age remained as important risk factors, the socioeconomic groups manual workers in industry, non-manual employees and self-employed other than academics, with academics as reference, emerged as more strongly associated with different definitions of COPD in 2009, while ex-smoking and a family history of obstructive airway diseases lost its significance. For physician-diagnosed asthma, the risk factor pattern was not substantially altered between 1996 and 2006 (paper I). Younger ages, a family history of asthma and ex-smoking remained significantly associated with physician-diagnosed asthma also in the latter survey.

Evaluation of reference values for spirometry

Since the publication of the GLI reference values in 2012, they have yielded much attention, been endorsed by the ERS, ATS and several other respiratory societies [190,249,250] and are today frequently used. Because of the ERS task force recommendation to use the LLN as criterion for airway obstruction in COPD [251], it may be interpreted that LLN:s based on the GLI reference values are endorsed as well. Swanney et al [252] argue that adopting the GLI reference values in clinical practice worldwide is essential and urgent in order to reduce the confusion regarding which reference values to use. In essence, Swanney et al. argue that the use of GLI worldwide is preferable to local specific reference values obtained with different techniques, and similar matters have also been argued by Stanojevic et al. [196]. However, the ERS/ATS also recommends that reference values for spirometry should be reviewed regularly in the areas where they are applied [118,197,209].

The GLI reference values represent the average of the data they are based on and may thus not be quite in concordance with the included subpopulations if they differ from each other. There are substantial differences in e.g. occupational exposures and environmental pollution which may affect lung function between countries and regions populated by Caucasians, why differences in lung function may be expected. Only n=123 (0.2%) subjects

were Swedish of the n=57,395 subjects on which the GLI reference values for Caucasians are based. Caucasians are defined as subjects with "origins in any of the original peoples of Europe, the Middle East or North Africa" by the GLI [190]. Since Sweden and e.g. North Africa differ in terms of environmental, anthropometric and socio-economic factors, an evaluation of the fit for Swedish subjects is both justified and required. The GLI reference values have been evaluated and considered applicable for the Norwegian population in ages 12-95 years [253] and for both Australasian adults and British children [254,255]. However, despite the fact that the GLI reference values may be applicable for Caucasian populations in several countries, they still should be evaluated in the areas where they are utilized. Publications from Tunisia in 2013 [256], Japan in 2014 [257], Finland in 2015 [258] and also from western Sweden in 2016 [259] conclude that the applicability of the GLI is unsufficient compared to observed values in the population and/or to local reference values.

The evaluation of the GLI reference values (paper III) based on the n=501 healthy never-smoking subjects from Norrbotten revealed differences between the GLI and the observed values in the population. Regarding FEV1 and FVC, the GLI reference values were lower than the observed values, and more pronounced so for FVC and especially among women. For the FEV1/FVC ratio, the patterns differed between men and women. For men, the observed values of the FEV1/FVC ratio were higher than the GLI while they were lower for women. In combination with a lower variability than for the GLI reference values, the GLI LLN (5th percentile) was not in concordance with the limits identifying the lowest 5% of the observed values. Instead, the use of GLI LLN as a limit for airway obstruction may lead to an overestimation of airway obstruction among women and an underestimation among men in Sweden. A perfect fit for the GLI reference values would have yielded a 5% prevalence of airway obstruction for both men and women, with no sex-differences, but 9.4% (95% CI 5.7%-13.1%) of the healthy non-smoking women and 2.7% (95% CI 0.7%-4.7%) (p=0.002) of the healthy non-smoking men were identified as obstructive. Further, as the classification into severity grades of airway and lung disease often relies on FEV_1 or FVC as percent of a reference value, the use of GLI may lead to invalid classification of disease severity in Sweden.

The evaluation of other reference values besides the GLI revealed that the ECSC reference values which still are commonly used in Sweden [193] are the most inappropriate. This is previously confirmed by several studies [189,197,260,261]. Thus, it is of utmost importance that health care providers receive this information and switch from the ECSC to more updated reference values. The Hedenström reference values from the 1980s

[181,182], endorsed by the Swedish Respiratory Society until 2014, seem more appropriate for Norrbotten especially compared to the ECSC but also to the GLI, although the fit seems somewhat questionable for women (paper III). Thus, the new updated OLIN reference values for spirometry are of interest.

Estimation of the OLIN reference values for spirometry

Historically, multivariable linear regression has commonly been used to model spirometric outcomes. However, traditional multivariable linear regression modelling does not incorporate the dependence that exists between the dispersion around the spirometric outcome and age [197], i.e. one of the independent or explanatory variables, or the non-linear decline in the spirometric indices with increasing age. In paper IV, we found all spirometric outcomes in the sample of n=501 healthy never-smoking subjects to be reasonably normal distributed. An approach to the modelling of spirometric outcomes by linear regression is presented where the sex-specific spirometric outcomes are predicted by age and height with spline-functions providing a smooth fit over the entire age-span, and where the standard deviation around the mean is allowed to linearly depend on age.

The modelling approach in this study produced unbiased estimates of mean observed values in the reference sample from Norrbotten (paper IV). The model evaluations revealed accurate predictions of both mean values and the LLN defined as the 5th percentile. Further, the results indicate a high external validity when evaluated on a sample from south-western Sweden. The differences in lung function between the samples from northern and western Sweden (paper IV) could possibly be due to minor technical or procedural differences, which are not uncommon [227], while substantial biological or environmental differences are more unlikely.

OLIN versus GLI reference values for spirometry

Undoubtedly, the all-ages GLI reference values are an extremely valuable contribution to the field of reference values for lung function and provide the opportunity to compare a subject or a population to the worldwide average within each ethnicity group. This may be of substantial value for e.g. international multi-centre studies. The differences between the worldwide averages, both in terms of predicted mean values and LLN, and the local averages which we found in the population of Norrbotten (paper III) can most likely be reasonably expected [227].

The GLI reference values are ethnicity-specific for Caucasians, African-Americans, North Asians and South-East Asians [190]. It has been shown that Japanese from Japan have lower spirometric values than Japanese from USA, and that immigrant Asian Indians have lower spirometric values than US-born Asian Indians [262,263]. This implies that environmental factors play an important role in the development of lung function, and that genetics are not the whole explanation for observed differences between different ethnicities [176,194,264,265]. It has recurrently been argued that differences in social class, income level, exposure to toxic environments and access to health care play an important role [176,195,264,265]. Burney and Hooper [264,266] conclude that the lower lung volumes observed in some ethnic groups are not "normal" but instead may be an explanation for the higher mortality rates in low income countries where they reside. They further state that reference values for spirometry should not correct for ethnicity, an opinion supported also by others [195,267]. As previously argued, there are substantial differences between regions populated by e.g. Caucasians in terms of environmental and socio-economic factors which can affect lung function [166], and perhaps these should not be neglected.

So, are international all-ages multi-ethnic reference values preferred over local more specific reference values with shortcomings such as e.g. smaller sample sizes? It all comes down to the definition of "normal", or maybe more importantly to the definition of "abnormal". If you are interested in the worldwide average within each ethnic group, the GLI is certainly preferred. On the other hand, if you are more interested in your specific population or area, local reference values may be preferred.

Conclusions

Paper I: Respiratory symptoms, in particular bronchitis symptoms, decreased parallel to a decrease in smoking over a 10-year period from 1996 to 2006. In contrast, the prevalence of physician-diagnosed asthma increased during the same period. The hypothesis that the observed increase in asthma reflects a "true" increase in asthma prevalence has to be confirmed by clinical studies. Additionally, up to one fourth of the respiratory symptom prevalence in the population was attributable to smoking.

Paper II: Changes in both prevalence and risk factor patterns of COPD were observed from 1994 to 2009. The prevalence of COPD, especially moderate and severe COPD, decreased and the severity of airflow limitation decreased substantially among subjects with COPD according to both the GOLD and the LLN criteria. Apart from the known risk factors smoking and older ages, the risk factor pattern was altered in 2009, when the socio-economic group academics had a lower risk for COPD as compared to other groups.

Paper III: The GLI reference values are preferable compared to the ECSC for Swedish adults. However, among non-smoking healthy men and women in northern Sweden, the mean values of FEV_1 were somewhat higher compared to those predicted by the GLI. A greater discrepancy was found for FVC, especially among women. The use of the LLN criterion for airway obstruction based on the GLI reference values for the FEV_1/FVC ratio may lead to biased prevalence estimates of airway obstruction in Sweden. These results demonstrate the importance of validating the GLI reference values in different countries.

Paper IV: The evaluation of the OLIN reference values based on the reference sample of healthy non-smokers from northern Sweden shows that the models are valid. Further, the evaluation based on the healthy non-smokers from western Sweden indicates a high external validity of the models. The comparison with GLI implies that local population-specific reference values may be preferred.

Future perspectives

Epidemiology is important as a starting point for translational research. Further, population-based research presents knowledge regarding the status in a population and not only regarding the "tip of the ice berg" which for some diseases is in contact with health care providers. This is true particularly for COPD, and to some extent also for asthma.

It is important to continue studying if the increase in asthma prevalence still continues and if so why? As asthma is a heterogenous condition, it is also important to identify different phenotypes and their prevalence trends and risk factor patterns. Epidemiology can contribute to identify such clinically relevant phenotypes. Since cross-sectional data cannot evaluate temporal sequences, risk factor patterns should preferably be studied within longitudinal settings. Despite the huge number of studies, we still have limited knowledge on how to prevent the development of asthma.

It is also important to continue studying prevalence trends of COPD, e.g. if the observed decreasing trend in Sweden continues. Continuous work with primary prevention and smoking cessation interventions is of utmost importance as further decreased smoking habits in the population may reduce the magnitude of both prevalence and severity of COPD and increase the general public health. An important issue for the future is the evaluation of different spirometric and other criteria for COPD and the determination of the clinically most relevant criterion. Further, substantial improvements in the recognition of moderate to severe COPD were observed but under-diagnosis is still common and important to address.

The GLI has put reference values for spirometry in the spot light perhaps more today than ever before. We are planning on offering the GLI team the data from our sample of healthy non-smokers. The GLI are an extremely valuable contribution to the field of lung function. However, weaknesses should not be neglected and it is important to continue studying the clinical implications of the use of different reference values in different areas. Previous evaluations have shown how poorly the commonly used ECSC reference values reflect the values of healthy nonsmokers of today in several different countries, which now is known to be true also in Sweden. To conclude, it is important that correct reference values are used both in clinical practice and epidemiology.

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Appendices 1-6

Appendice 1

The Swedish version of the OLIN postal questionnaire from 2006

Appendice 2

The English version of the OLIN postal questionnaire from 2006

Appendice 3

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

Appendice 4

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

Appendice 5

The Swedish version of the OLIN questionnaire for structured interviews of healthy non-smokers from 2011

Appendice 6

The English version of the OLIN questionnaire for structured interviews of healthy non-smokers from 2011