ABSTRACT

COPD and asthma are common diseases worldwide and entail high costs for the society. The diseases also cause impairment in quality of life for the patients. Most of the health economic studies of COPD and asthma have been based on registry data. There is a lack of studies using health economic data of representative samples derived from studies of the general population when estimating the burden of illness of COPD and asthma. The aim with this thesis was to estimate the direct, indirect and intangible costs of COPD and asthma using well-defined and representative cohorts of subjects with COPD and asthma in northern Sweden.

Telephone interviews were conducted in order to record the resource use due to asthma and COPD and the resource use due to exacerbations of COPD. Three health-related quality of life questionnaires were used for measuring the quality of life for the patients with COPD.

The total costs for asthma were estimated at SEK 15,919 annually per subject with asthma, and the direct costs accounted to 31% and the indirect costs to 69% of the total costs. The costs for subjects with persistent asthma were more than 10 times higher compared to the costs for subjects with mild intermittent asthma, SEK 27,628 and SEK 2,222, respectively. The total societal costs were estimated at about SEK 3,7 billion (95% CI 1.5-5.7) for asthma in Sweden in the ages from 25 to 56 years.

The annual costs for COPD amounted to SEK 13,418 per subject with COPD. The direct costs accounted to 42% and the indirect costs to 58% of the total costs. Subjects with a severe disease had approximately 3 times higher costs compared to subjects with moderate COPD, and more than 10 times higher compared to subjects with mild COPD. The total societal costs for Sweden were estimated at about SEK 9.1 billion (95% CI 6.1-12.8). As COPD to a great extent is an underdiagnosed disease, the total costs were divided into subjects with and without a physician-diagnosis of COPD. The costs for undiagnosed subjects accounted to approximately 40% of the total costs. Costs for exacerbations of COPD were related to severity of the exacerbations and severity of COPD. Severe exacerbations were on average 10 times more expensive than moderate and 60 times more expensive than mild/moderate exacerbations. The total costs of exacerbations during a 4½ months study period amounted to SEK 13,708 for subjects with a severe COPD compared to SEK 294 for subjects with a very mild COPD. The costs of exacerbations comprised to 35-45% of the direct costs of COPD. Severity of COPD was correlated to health related quality of life but less so to generic quality of life measures.

In conclusion, the thesis shows that asthma and COPD are costly diseases for the society. The costs were found to be strongly dependent of the severity of asthma and COPD. The costs of COPD were strongly affected by impaired lung function and exacerbations.

Keywords: COPD, asthma, epidemiology, quality of life, health economics.

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INTRODUCTION

Today, there are increasing demands on limited health-care resources. As a result of this, health economics has become an important tool for decision-making at all levels of health-care organisations.

As asthma and COPD are two of the main chronic diseases worldwide, it is important to get a better understanding of the societal costs for these diseases, both in terms of costs for health-care resources as well as costs for loss of productivity due to the diseases.

A number of estimations of the costs of asthma and COPD have been conducted both in Europe and USA. However, there are still many questions, which need an answer, as most of the studies have not taken into account all kind of costs that are involved in these diseases. How high are the costs? What kind of costs appears due to asthma and COPD? Do the costs differ between different severity grades of asthma and COPD? Is the health-related quality of life affected by COPD? Is the quality of life dependent on the severity of the disease? There is still a lack of knowledge of the costs of respiratory diseases, especially costs of COPD, where a great underdiagnosis exists.

The Obstructive Lung Disease in Northern Sweden (OLIN) Studies has collected longitudinal epidemiological data of allergy and obstructive pulmonary diseases since 1985. Several cohorts are today included in prospective longitudinal studies. A number of doctoral theses and about 100 scientific articles have been published based on the OLIN Studies. This thesis is based on samples from these studies. The health economics of both asthma and COPD and the quality of life of subjects with COPD will be discussed.

BACKGROUND

Obstructive airway diseases belong to the most common chronic diseases in the world. During the last decades the prevalence has increased both in Sweden and in other parts of the world. In Sweden, only heart diseases are more common nowadays. The prevalence of COPD and asthma are high and the costs for these diseases are huge worldwide. Particularly for diseases with a high prevalence, it is important to get knowledge of the economic implications of the diseases. In a Dutch study using register data based on identified cases, the direct costs for asthma and chronic obstructive pulmonary disease (COPD) were estimated at 1.3% of the Dutch health care budget in 1993 (Rutten van Mölken et al, 1999). In a Swedish register-based study the total costs of both asthma and COPD were estimated at about 1% of the costs for all diseases in Sweden (Jacobson et al, 2000). However, there is a lack of studies using representative samples of subjects derived from studies of the general population when estimating the burden of illness of both COPD and asthma.

The best method to measure the real costs ought to be a prospective collection of real expenses and consumption of health care resources within a cohort of subjects with COPD or asthma. The cohort must be representative for the general population regarding the distribution of age, gender and severity of the disease.

Asthma

Asthma is a chronic lung condition that causes recurring episodes of wheezing and other respiratory symptoms. Chronically inflamed airways are hyperresponsive; they become obstructed and airflow is limited when airways are exposed to various provoking factors, such as allergens, irritants, cold air or exercise. This makes it difficult for the air to move in and out. This narrowing or obstruction can cause one or a combination of symptoms such as wheezing, shortness of breath, chest tightness particularly at night or in the early morning. The attacks vary in severity and frequency from person to person and within the individuals. The exacerbations of asthma are episodic, but airway inflammation is chronically present. For many patients, medicines must be taken every day to control symptoms, improve lung function, and prevent attacks (Global Initiative for Asthma www.ginasthma.com, 2006). The classification of severity of asthma has varied over time and is partly arbitrary. The most recent classification of severity is based on the GINA guidelines. The severity is dependent on a combination of symptoms, lung function and use of medicines Asthma cannot be cured, but can be controlled. The strongest risk factors for developing asthma include a family history of asthma and especially in childhood allergic sensitisation (World Health Organization www.who.int/topics/en/, 2006).

Asthma is a major health problem in society, and the disease seriously affects both children and adults. During the past five decades the prevalence has increased considerably (Bråbäck et al, 2004; Masolo et al, 2004). A similar trend has been found both in studies from Europe and USA (Burney, 1993; Adams et al, 1994; Weiss et al, 2000). The prevalence of physician-diagnosed asthma in 1990's was about 5 - 9% in the adult population in northern and western Europe with variations between both countries and regions within the countries (Burney et al, 1994). This stable increase in the prevalence of asthma during the last decades has also been demonstrated by the OLIN Studies in northern Sweden (Lundbäck et al, 1991; Lundbäck, 1998). It is still unclear why the prevalence of asthma has increased. There are relatively few studies of the incidence of asthma. One study has found that the incidence increased with 20% between 1986 and 1993 (Reijula et al, 1996), while another study showed no clear pattern of changes in incidence (Torén et al, 1999). The incidence of asthma among adults in Sweden seems to be about 2/1,000 persons/year according both to the OLIN Studies (Rönmark et al, 1997; Lundbäck et al, 2001) and the Nordic-Baltic branch, Respiratory Health in Northern Europe (RHINE), of the European Community Respiratory Health Survey (ECRHS) (Torén et al, 2004).

The prevalence among school children has increased during the last decades. About 50 years ago, the prevalence amounted to about 1%. During the 1980's about 3% of the school children had asthma (Åberg et al, 1995) and ten years later the prevalence was 6-7% (Rönmark et al, 1999). This increase can partly be explained by a change in the asthma diagnosis. However, the prevalence has until recently shown a stable increase among children (Magnus et al, 1997). Some recent studies have, however, indicated that the prevalence of asthma may not be increasing any more (Robertson et al, 2004).

There is today considerable interest in the health economic consequences of asthma worldwide (Weiss et al, 2001). Cost-of-illness studies have been performed in different countries, both in Europe and in the USA. Most of them have been register studies or studies of health statistics (Mellis et al, 1991; Weiss et al, 1993; Rutten van Mölken et al, 2001; Godard et al, 2002; Cisternas et al, 2003; Schwenkglenks et al, 2003; Stock et al, 2005;). Also in Sweden, a study based on register data has estimated the societal costs of asthma for the Swedish society (Jacobsson et al, 2000).

However, it is difficult to compare results from studies from different countries due to a number of causes. The definitions of costs differ greatly between the studies and so do the sources of unit costs. It is also difficult to compare studies when the time periods differ. Further, the exchange rates can differ greatly from one year to another. Weiss et al (2001) showed in a review conducted in 2001 that the societal costs due to asthma varied from USD 326 to USD 1,315. Direct costs accounted for

approximately 40-50% of the total costs for asthma. However, in a study from 2003 in the USA the total costs accounted to USD 4,912 (Cisternas et al, 2003).

Some newly performed studies have shown that the costs for asthma are strongly correlated to disease severity (Godard et al, 2002; Cisternas et al, 2003; Schwenkglenks et al, 2003). A study from Switzerland showed that resource use and costs were associated with both severity of asthma and the probability of exacerbations (Schwenkglenks et al, 2003). They also found an interaction between severity and exacerbation status. Direct costs were 2.5 times higher for those with the most severe asthma compared to those in the lowest severity group if there were no exacerbations. Differences in costs were higher if exacerbations were present, and the costs were 5.7 times higher for the most severe group compared to those with the mildest asthma.

The distribution of costs among direct and indirect costs has shown some disparities in different studies. Cisternas et al (2003) showed that the total societal costs of asthma accounted to USD 4,912 per subject. Direct costs were USD 3,180 (65%) and indirect costs were USD 1,732 (35%). The main cost drivers among the direct costs were medications (50%) and hospitalisations (15%). Disability pension was the main cost driver among the indirect costs, 61%. Total annual costs per subject with asthma accounted to USD 2,646 for those with mild asthma, USD 4,530 in moderate asthma, and USD 12,813 in severe disease. In the Swedish study by Jacobsson et al (2000) the total costs amounted to SEK 3 billion, and the direct costs accounted to 35% of the total costs.

Chronic obstructive pulmonary disease (COPD)

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease characterized by limitations in lung airflow that are not fully reversible. COPD is usually a result of cumulative exposure to tobacco smoke, occupational dusts or vapors, and indoor or outdoor air pollution. The diagnosis is confirmed by spirometry, which measures lung function and capacity (World Health Organization www.who.int/topics/en/, 2006). The severity grading of COPD in all recent guidelines is based on the degree of lung function impairment (British Thoracic Society, 1997; Global Initiative for Chronic Obstructive Lung Diseases www.goldcopd.com, 2006).

Chronic Obstructive Pulmonary Disease (COPD) is a common disease among middle-aged and elderly and is a major health problem worldwide (Buist, 1996). The main risk factors of COPD are increasing age, which expresses a “total life time exposure” in addition to normal ageing, and smoking (Doll et al, 1994; Buist, 1996; Silberman et al, 2000; Lundbäck et al, 2003). With increasing age, an

increasing proportion of smokers develop the disease (Bakke et al, 1991; Larsson L et al, 1994; Isoaho et al, 1994; Silberman et al, 2000; Lundbäck et al, 2003; Lindberg et al, 2006a). Moderate and severe COPD is a disabling disease causing high costs for society (Rutten van Mölken et al, 1999; Sullivan et al, 2000) and impairment in general and in health-related quality of life (HRQL) for the patients (Curtis et al, 1994; Engström et al, 1998).

Despite the existence of extensive literature on COPD, there is a lack of data on age-related prevalence-based studies of the general population. A number of population studies from northern Europe have shown that the prevalence of COPD is low in persons below the age of 50 (Bakke et al, 1991; Larsson L et al, 1994; Lundbäck et al, 2003; Kotaniemi et al, 2005). From around the age of 50, the prevalence increases considerably particularly among smokers. Sooner or later 50% or more of smokers develop COPD (Silberman et al, 2000; Lundbäck et al, 2003). Several studies have shown that COPD is underdiagnosed. Subjects with COPD remain undiagnosed for many years, despite having multiple respiratory symptoms (Lindberg et al, 2005a). The subjects are often not correctly identified until late in the disease process (Tirimanna et al, 1996; Sobradillo et al, 1999; Mannino et al, 2000; Lindström et al, 2001; Lundbäck et al, 2003; Lindberg et al, 2006a). As a majority of subjects suffering from the disease has not been identified by the health care system, COPD is a hidden disease. A European study has estimated that only 25% of the COPD cases in the general population are diagnosed (Soriano et al, 2000). As the disease progresses, patients with COPD also experience increasing deterioration of their quality of life.

Incidence of COPD is still poorly studied. As far as now only four publications using updated criteria of COPD have studied incidence of COPD (Vestbo et al, 2002; Johannessen et al, 2005; Lindberg et al, 2005b; Lindberg et al, 2006b). The results from these studies indicate that 1-2% of smokers in the middle ages and elderly develop COPD every year. According to the Swedish studies, the incidence among non-smokers is about ten times lower. The difference between smokers and non-smokers was less pronounced in the study conducted in Denmark (Vestbo et al, 2002).

COPD is in most cases a slowly progressive disease (Bakke et al, 1991; BTS, 1997; Silberman et al, 2000). Acute exacerbations or acute worsening of respiratory symptoms often affect subjects with COPD (Rodriguez-Roisin et al, 2000). These exacerbations differ in severity. One study has estimated that the average COPD patient experiences 1-4 acute exacerbations per year (Hagedorn, 1992). During an exacerbation, the use of health-care resources is usually significantly increased (Gibson et al, 1998; Hilleman et al, 2000; Rodriguez-Roisin et al, 2000; McGuire et al, 2001), and the quality of life is considerably reduced for the subjects

(Seemungal et al, 1998). Data about the economic consequences of exacerbations are still extremely scarce.

Despite the fact that COPD is a costly disease, only a few health economics studies of COPD have been performed (Ruchlin et al, 2001). Most of them have been register studies based on identified cases and health statistics without correction for the large underdiagnosis of COPD (Rutten van Mölken et al, 1999; Sullivan et al, 2000; Jacobsson et al, 2000; Ward et al, 2000). However, the large proportion of unidentified cases complicates the estimation of the burden of the disease. To the best of our knowledge, no information is so far available describing the societal costs of COPD taking into account the costs for subjects without a physician-diagnosis.

Health economics

The term economics deals with society's allocation of scarce resources among alternative uses. Scarcity of resources and the allocation of these resources is the foundation of economic theory. One of the disciplines of economics is health economics, which is applied to the topic of healthcare.

Health economics can be defined as the use of economic principles and techniques to ensure that the limited healthcare resources are used effectively. A health economic evaluation is defined as the comparative analysis of *alternative* courses of action in terms of both their *costs* and *consequences* (Drummond, 1987). Due to increasing demands on limited healthcare resources, health economics has gained an increasing impact in decision-making at all levels of healthcare organisations.

Cost-of-illness studies examine the economic impact of illness on society (Luce et al, 1990). The basis of cost-of-illness studies is that resources, which are used for health care, have an alternative use. The goods and services, which one has to give up to carry out a certain project are called the opportunity cost of the project. Loss of productivity due to death, permanent or temporary illness due to a disease is also included in these types of costs. The opportunity cost is a fundamental idea within economic theory, and assumes that all resources are scarce, which means that there is always an alternative use for the resources used for a specific purpose. This is the basis for all cost-of-illness studies, although sometimes only some of the societal costs are estimated.

There are great differences between different cost-of-illness studies both in estimating the resources used for a certain disease and also what kind of data sources that are used. These differences in methods and data are some of the factors that make it difficult to compare different cost-of-illness studies. Further,

there are difficulties when comparing studies performed in different countries and different years.

The existing literature in economic evaluation in health care classifies costs as direct, indirect, or intangible (Lindgren, 1981; Luce et al, 1990; Drummond et al, 1997). Direct costs have been used to denote the resources consumed when compared to an alternative. Mainly these would be resources in the health care sector, but sometimes patients´ out-of-pocket costs also are included. However, direct costs are not used consistently across studies, which sometimes cause confusion when comparing different studies. Indirect costs have been used to denote the time of patients consumed. Mainly the focus has been on work time, and indirect costs have been synonymous with losses of productivity. Consequences that are difficult to measure and value have been classified as intangible costs. This term has been used when valuing improved health, and the pain and suffering associated with the disease. These consequences are often measured and valued through the utility or willingness-to-pay approach.

A cost-of-illness study is based on one of two common epidemiological approaches, incidence or prevalence (Rice, 1996). When using the incidence approach, all future costs for a person who has been diagnosed as having a disease are estimated, while using the prevalence approach, the costs for all persons with a disease are estimated during a specific period, usually one year. The prevalence approach is the most commonly used when measuring the costs. This is true mainly for rare diseases. The incidence approach in that case would be too costly and take a very long time to conduct.

The data, which are used in a cost-of-illness study, can either be general data or partial data. General data covers the total population or data from representative samples of the general population. Partial data are data from clinical or other studies of a defined sample of the population. General data are often available in different registers.

A top-down distribution of the societal costs is usually used in cost-of-illness studies, which are based on general data. The total costs for all diseases divided into different direct and indirect costs are firstly conducted. A division of these costs are then made into different categories of diseases and specific diseases, as for instance asthma and COPD.

Representative data from a defined sample of the population, partial data, can also be used for analyses of the societal costs for a disease. In studies consisting of partial data, it is possible to choose which data that ought to be collected. A disease can be divided into different severities, and multiple diagnoses can be considered. There are also possibilities to use more variables compared to those that are

available in official registers. Studies using partial data are usually called bottom-up estimations, where results from a defined sample of the population are multiplied with the prevalence in order to get societal costs for the total population in a country.

Health-related Quality of Life

Health-related Quality of Life has today become an important and popular tool when effects of a disease are described and when treatment effects are measured. This tool has to a great extent complemented or even replaced the objective physiological evaluation variables that were solely used earlier together with symptoms.

Health-related Quality of Life represents the functional effect of an illness and its consequent therapy upon a patient as perceived by the patient (Schipper et al, 1996). Health-related Quality of Life can be described as a physical, social, and emotional condition of health, which is relevant and important to the individual. It is the patient's own experiences that are important. There are a number of reasons why it is important to measure the quality of life in persons having a disease. They include the effect of a medical treatment, the evaluation of the quality of the health-care sector, and the understanding of reasons to and consequences of differences in health.

Three different kinds of questionnaires are available when performing a study of quality of life; generic, disease specific, and utility questionnaires. Generic instruments are not disease specific, and show a general view of how the disease affects the subjects and contain several items, which can affect the quality of life. These questionnaires are also possible to use for comparing different diseases. Examples of generic questionnaires are The Medical Outcomes Study Short Form 36 (SF-36) (Ware et al, 1992), Sickness Impact Profile (SIP) (Bergner et al, 1981), and Nottingham Health Profile (NHP) (Hunt, 1986).

The characteristics of disease specific questionnaires are their adaptation to the patients under study. They are clinically sensitive, and the answers are often more reliable compared to generic instruments. When measuring the quality of life of subjects with COPD, there are two instruments available that are widely used: The St George's Respiratory Questionnaire (SGRQ) (Jones, 1991), and Chronic Respiratory Questionnaire (CRQ) (Guyatt et al, 1987). Two instruments commonly used in measuring the quality of life in asthma are Asthma Quality of Life Questionnaire (AQLQ) (Juniper et al, 1992), and Living With Asthma Questionnaire (LWAQ) (Hyland, 1991).

The utility questionnaires are based on quantification of preference for a state of health. They can be used both for generic and specific states of health. The obtained value is useful when performing cost-effectiveness analyses. Two of the most commonly used generic utility instruments are EuroQol 5D (EQ-5D) (Kind, 1996) and Health Utilities Index (HUI) (Boyle et al, 1983; Feeny et al, 1992). A new specific utility instrument for COPD is Health State-COPD (HS-COPD) (Schunemann et al, 2004).

There are a number of advantages in using questionnaires to measure quality of life. It is a standardized way to administrate, and limited bias is occurring. There are also possibilities to compare different groups of subjects and/or results from different studies.

It is of great importance that the administration of quality of life questionnaires always is conducted in a standardized way. When the subjects are answering the questions, no help is permitted from the physician or the nurse. The questionnaire should also be answered immediately when the patient has arrived to the clinic. The patient also has to sit alone in a quiet part of the clinic without disturbance. The administrator of the questionnaire also has to control that the patient has answered the questions before the patient is leaving. There are also recommendations in which order the instruments shall be used.

It is important to measure the quality of life in a disease like COPD. Firstly, previous studies have found that there is no or a poor correlation between lung function and quality of life. Furthermore, cough and sputum can be considered as a social problem, and a decrease in lung function can result in depression. There is also no other objective way to measure dyspnoea, and the different dyspnoea scales can be regarded as measures of quality of life and not only degrees of severity of symptoms (Mahler, 2000).

Summary

In summary, most health economic studies of airway diseases have so far been based on register data. However, in diseases like COPD where the underdiagnosis is large, these methods probably result in an underestimation of the societal costs. Due to the great underdiagnosis of COPD, more valid data will be presented if population based data are used. As a result of this thesis, methodological aspects have been developed taken into account the impact of underdiagnosis of diseases. The way of using population studies for studies of health economics is not conventional and at least in part new.

AIMS

The overall aims with this thesis were to estimate the societal burden of COPD and asthma in terms of direct, indirect and intangible costs, using well-defined and representative cohorts of subjects with COPD and asthma, respectively.

The aims were split into following specific aims:

* To estimate the direct and indirect costs of adult asthma.

* To estimate the costs of adult asthma by disease severity and age.

* To identify the key cost drivers for direct and indirect costs of adult asthma.

* To estimate the direct and indirect costs of COPD.

* To estimate the costs of COPD by disease severity.

* To identify the key cost drivers for direct and indirect costs of COPD.

* To examine the differences in costs of COPD among diagnosed and undiagnosed subjects with COPD.

* To examine the costs of COPD exacerbations in relation to the severity of exacerbations and severity of COPD.

* To evaluate the association between quality of life and severity of COPD.

* To evaluate and discuss the consequences of the results for Sweden as a whole assuming the prevalence, disease severity and cost items of asthma and COPD is similar in Norrbotten compared to Sweden as a whole.

MATERIAL AND METHODS

The thesis is based on samples of the general population in Northern Sweden from The Obstructive Lung Disease in Northern Sweden (OLIN) Studies. Well-defined and representative cohorts of subjects with COPD and asthma from the OLIN Studies are used. The cohorts are described in the *study population* section.

Study area

The county of Norrbotten is the largest county in Sweden by area and represents about a quarter of Sweden's total area. Belgium, the Netherlands and Luxembourg combined account only to 75% of the county's area. Norrbotten is located in the most northern part of Sweden consisting of the Province of Norrbotten and the northern part of the Province of Lapland. It consists of both a coastal area and also highland areas and mountains. Most of the population lives along the coast, where for instance the two cities Luleå and Piteå are situated. Despite that Norrbotten accounts for 25% of the area in Sweden, less than 3% of the population of Sweden live in the area.

Norrbotten is a county of contrasts. The highest mountain in Sweden, Kebnekaise at 2,107 metres, is located in Norrbotten, and also Sweden's deepest lake, Hornavan, 232 metres deep. While there is permafrost in the mountains, there are many tourists staying in the bathing resorts at the Gulf of Bothnia. Norrbotten is also a multi-cultural and multi-lingual county. Not only Swedish but also Finnish and Saami are spoken here. The county also has three of the four protected rivers in Sweden, the Torne, Kalix and Pite rivers.

Norrbotten has a somewhat lower proportion of men and women in the ages between 20 and 39 years, while the area has a larger proportion of its population in the age range between 40 and 70 years. Norrbotten also has a lower proportion of men and women aged 80 years and older compared to Sweden as a whole. The population has decreased by about 7,000 since 1968. The structure of the population has changed with a decrease in the young age groups and an increase in elderly people. Especially young men between 21 and 35 years, and young women in the ages from 18 to 29 years move to other counties in Sweden.

The climate is sub-arctic with winter and snow lasting for at least 6 months. The average annual temperature was 3.1 C in Luleå in 2003 and -0.6 C in Kiruna, compared to 7.7 C in Stockholm.

Heavy industry has historically been the main branches, but today the importance of heavy industry has declined. However, the greatest subterranean mine of the

world is located in Norrbotten. Today, jobs in the public sector, including health care and education, and also trade and tourism has become more important. The greatest international centre for peaceful exploration of space in Western Europe is located at Esrange, near Kiruna.

Study population

Large-scale population studies on the epidemiology of obstructive airways diseases and type-1 allergy in northern Sweden, the Obstructive Lung Disease in Northern Sweden (OLIN) Studies, started in 1985 (Lundbäck, 1993; Rönmark, 1999). Today, longitudinal studies of a number of cohorts are in progress, including a total of approximately 50,000 children, adults, and elderly persons. All five papers in this thesis are based on two of the study cohorts.

The first cohort was based on 6,610 persons born in 1919-20, 1934-35, and 1949-50 in eight different areas of Norrbotten. In 1985-86, a questionnaire was sent to these subjects. This cohort, stratified by age, has been followed longitudinally, and a number of follow-up studies have been implemented. Data have been collected by questionnaires in 1985, 1992, and 1996. All subjects with respiratory symptoms in 1986 were identified and structured interviews and spirometries have been performed in 1986, 1996, and 2003. The second cohort consisted of 6,434 persons in the same ages (born in 1925-26, 1940-41, and 1955-56) and was living in the same areas as the subjects from cohort 1 at the first survey in 1985-86, but they were examined six years later. In addition, subjects born in 1970-71 were also included in cohort 2.

In paper 1, which is focused on the societal costs of adult asthma, the sample was derived from cohort 2. All subjects reporting respiratory symptoms or diseases were invited to lung function tests and structured interviews in 1993-94, and about 1,400 subjects born in 1925-26, 1940-41, 1955-56 and 1970-71 participated. The subjects who had reported either a physician-diagnosed or a self-reported asthma, and in addition used asthma medications and had symptoms common in asthma, such as attacks of shortness of breath or recurrent wheeze, comprised 352 subjects, or 5.5% of the study sample.

A random sample of these 352 subjects was drawn from each age group in order to obtain a study sample of sufficient size to allow measures of total societal costs, and thus 129 asthmatics were invited, and 115 (59% women) participated in the study of cost-of-illness of asthma. Of them, 46% had mild intermittent asthma, and 54% had persistent asthma. Persistent versus mild intermittent asthma was classified based on use or not use of inhaled cortico-steroids. Women were more frequent than men in both severity grades.

In papers 2 and 3, which were focused on the societal costs of COPD, the study sample was derived from two surveys using clinical methods performed between 1993 and 1998, and comprised subjects classified as having COPD. The first survey was the survey referred to in the paragraph above. The survey included the second cohort of the OLIN Studies with lung function tests and structured interviews and was performed from year 1993 to 1994 on 1,997 subjects born in 1925-26, 1940-41, 1955-56 and 1970-71 (Lindström et al, 2001). The other survey was the third survey of the first cohort of the OLIN Studies performed in 1996-98. The same method was used, i.e. structured interviews and lung function tests, and 2,694 subjects participated (Rönmark, 1999; Lundbäck et al, 2003).

In total, the above-mentioned surveys (Rönmark, 1999; Lindström et al, 2001; Lundbäck et al, 2003) identified about 800 subjects aged 28-80 years fulfilling the criteria for COPD; however, when stratifying by disease severity, some strata contained a limited number of subjects. Accordingly, all subjects with an FEV_1 <60% of predicted values were included in the present study cohort. From subjects with an FEV_1 ≥60% of the predicted value, a random sample was drawn from each stratum in order to obtain a study cohort of a sufficient size to allow measures of significant differences between different groups of severity. By subsequently assigning weights based on prevalence to our strata, bias originating from the selection could be avoided, since the weighted strata generated the weighted results according to the prevalence of subjects with corresponding age and degree of severity.

A study cohort of 261 subjects was selected, and 212 (43% women) participated in the study. Due to a number of reasons, 38 persons could not be traced, i.e. they were not living at the given address, could not be reached by telephone, or did not speak Swedish. A number of 11 individuals refused to participate in the study. There were no significant differences in terms of age, gender, smoking habits, area of residence, or FEV_1 between the 49 persons in the original study sample who did not take part in the study and the 212 participating subjects.

Methods

In all papers dealing with costs, data were collected by regular telephone interviews using specially designed and pilot-tested questionnaires. An English and Swedish version of the questionnaire used in the study of costs of COPD is found in the *Appendix.* The questionnaire used in the study of costs of asthma is similar with very small differences when compared to the questionnaire used in the health economic study of COPD. A Swedish version of the questionnaire used for the costs of exacerbations of COPD is also shown in the *Appendix.* No official English

version is available. Before the interviews started, an information letter was sent out to all participating subjects in each study. In every paper, the same person carried out all the interviews, respectively, and the interviews lasted up to 45 minutes each. In the Quality of Life study, data were collected from three different questionnaires that the subjects responded.

Health economic investigations

Asthma

Costs of adult asthma were estimated in a study using telephone interviews. The structured questionnaire retrospectively covered resource use for one year. The questionnaire included questions regarding number of visits to the health-care sector, number of days in hospital, use of medications, number of days off work, and early retirement. The telephone interviews took place in 1996. Both respiratory-related healthcare utilisation and healthcare utilisation due to other reasons were recorded, but only costs due to asthma and asthma-related conditions were used in the estimations. The interviews lasted 15-45 minutes each and were carried out by the same person (SAJ).

COPD

The societal costs of COPD were recorded in telephone interviews with persons classified as having COPD. All participating subjects were interviewed on four occasions during 1999 (March, June, September, and December), and the interviews covered resource use during the preceding 3-month period. Both respiratory-related healthcare utilisation and healthcare utilisation due to other reasons were recorded, but only costs due to respiratory-related diseases were used in the analyses. Due to the risk of recall bias, a period of 3 months was considered to be a suitable time. A patient diary was also used after the first interview in order to eliminate the risk of recall bias. In the patient diary, the subjects were told to make a note of dates when they had visited outpatient care, dates when they had been hospitalised, and dates when they had been home from work due to COPD. During the one-year period, 5 subjects died and 6 subjects did not want to take part in all interviews. Costs for those who did not complete the study were estimated according to the patient-year approach (Rutten-Van Mölken et al, 1994). Costs for those subjects were estimated as the average costs for their previous study periods. For subjects who died during the study, the costs were assigned to zero after death. This method has been used in papers 2 and 3.

COPD-exacerbations

The costs of exacerbations were also estimated using the same study sample as in papers 2 and 3. Also in this study a structured and pilot-tested questionnaire was used. A registered nurse interviewed the subjects who fulfilled the inclusion criteria to the study. The questionnaire was only focused on use of extra resources due to exacerbations. Only incremental costs due to exacerbations were included in the estimations, while costs appearing daily due to COPD were excluded. In this study, the patient records were used to verify healthcare visits and hospitalisations, as these cost items are the main cost drivers worldwide (Rutten-van Mölken et al, 1999; Guest, 1999; Sullivan et al, 2000; Jacobson et al, 2000). This method has been used in paper 4.

Quality of Life investigations

The same study sample as in paper 2 and 3 was also taking part in the Quality of Life study. A qualified specially trained nurse initially instructed the subjects. The subjects were then responding the questionnaires in the following order: SF-36, SGRQ and EQ-5D. A few subjects did not complete all the questionnaires. A division of the subjects was made into four severity groups according to FEV_1 per cent of predicted normal using two different guidelines, GOLD (Pauwels et al, 2001) and BTS (British Thoracic Society, 1997).

Lung function investigations

Lung function tests have been performed since 1986 within the OLIN Studies. Four parallel sets of the dry volume spirometer, Minjhard Vicatest 5, the Netherlands have been used. Vital capacity (VC) has been defined as the best values of forced vital capacity (FVC) and slow vital capacity. Swedish normal values for FEV_1 have been used (Berglund et al, 1963). These values have been considered as applicable for the adult population in Norrbotten (Lundbäck et al, 1994; Lindberg, 2004). Most of the subjects in the studies have been taking part in at least two or three lung function measurements before the studies started. During the study a validation of the lung function values was performed.

Definitions

The following definitions were used in the four different studies.

Physician-diagnosed asthma: Subjects answer "yes" to the question: "Have you been diagnosed as having asthma by a physician?"

Self-reported asthma: Subjects answer "yes" to the question: "Have you ever had asthma?"

Asthma: Subjects who had either a physician-diagnosed or a self-reported asthma, and in addition used or had used asthma medications, and had symptoms common in asthma such as attacks of shortness of breath or recurrent wheeze.

Mild intermittent asthma: Asthma in subjects not using inhaled cortico-steroids.

Persistent asthma: Asthma in subjects using inhaled cortico-steroids.

COPD: Defined according to the British Thoracic Society (BTS) criteria: FEV_1/VC ratio <70% and FEV_1 <80% of predicted values. COPD is divided into mild, moderate and severe disease (British Thoracic Society, 1997). In addition, persons with an FEV_1/VC ratio <70% and an FEV_1 ≥80% of the predicted value, which corresponds to the GOLD criteria for mild COPD (Global Initiative for Chronic Obstructive Lung Diseases www.goldcopd.com, 2006), were also included in the study (labelled as *very mild* COPD in this thesis). Persons with chronic airways obstruction who referred themselves as asthmatics were included, an approach that is supported by the BTS guidelines. Subjects with other diseases that explained their impaired pulmonary function were excluded.

Severity of COPD:

The BTS guidelines and the grading of severity conform to guidelines that were developed for Sweden some years after our study was performed (Svensk Lungmedicinsk Förening www.slmf.se/kol, 2006). During the late 1990s was discussed whether or not subjects with a pathological ratio (FEV_1/VC ratio <70%) but a normal FEV_1 should be included within COPD. We thus included these subjects. Later on this group of subjects were included in the Global Initiative for Chronic Obstructive Lung Diseaseas, GOLD, guidelines as having COPD, and the severity degree of them was defined as *mild* COPD according to GOLD (Global Initiative for Chronic Obstructive Lung Diseases www.goldcopd.com, 2006).

Severe (BTS):	FEV_1/VC <70% and FEV_1 <40% predicted.
Moderate (BTS):	FEV_1/VC <70% and FEV_1 40-59% predicted.
Mild (BTS):	FEV_1/VC <70% and FEV_1 60-79% predicted.
Very mild (Mild GOLD):	FEV_1/VC <70% and FEV_1 ≥80% predicted.

Physician-diagnosed COPD: Subjects answer "yes" to the question: "Have you been diagnosed by a physician as having COPD, chronic bronchitis, or emphysema? "

Severity of exacerbation:

Exacerbations of COPD were classified in this thesis by degree of severity, but not using symptom-based definitions, which was common during the 1980s (Anthonisen et al, 1987). Instead the new definitions of exacerbations based on the measures that patients and the health-care sector have to take during an exacerbation were used. These were later summarised and reviewed by Rodriguez-Roisin, (2000). The latter classification is nowadays the most commonly used.

Mild: Self-managed by the subject by increasing the dose of the current medication (including adding over-the-counter medication).

Mild/moderate: Required telephone contact with a health-care centre, other health provider and/or treatment with antibiotics or systemic corticosteroids.

Moderate: Required visit to a general practitioner or to an outpatient clinic.

Severe: Required hospital admission or emergency visit to an accident and emergency department.

Costs

Direct costs of asthma: Costs for health-care visits and contacts, hospitalisations and medicines.

Indirect costs of asthma: Costs for loss of productivity due to disability pensions and absence from work due to sick leave.

Direct costs of COPD: Costs for hospitalisations, medicines, planned and acute healthcare visits and contacts, oxygen therapy and equipment used as aids, such as wheel-chairs.

Indirect costs of COPD: Costs for loss of productivity due to absence from work and disability pensions.

The cost items are described in detail in the different papers in this thesis.

Analyses and statistical methods

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) for Windows version 10.0 and 11.0. Both standard deviation and confidence intervals were used in frequency distributions. A p-value less than 0.05 was considered to be statistically significant. In the cost-of-illness study of asthma, chi-squared test was used for bi-variate comparisons and one way ANOVA for tests for trends. A multiple logistic model was created with costs as a function of age, sex, smoking habits, and severity of asthma (i.e. persistent or mild intermittent asthma).

As a means of testing the influence of degree of severity on costs while controlling for covariates in studies of cost-of-illness of COPD, multiple linear regression was applied with direct and total costs as dependent variables. Since the disease severity divides subjects into four ordered groups with six possible comparisons, this regression approach is a straight-forward way to perform the task of analysing the dependency between FEV_1 and costs. Due to the skewness of cost data, we tried different transforms. A log transformation of the costs was finally used. The model for direct costs examined 100% - FEV_1 % predicted, 100 % - FEV_1 % predicted squared, and controlled for explanatory variables. In addition, each separate cost component alone was subjected to the same analysis. The sole purpose of these models was to analyse the relationship between costs and lung function, i.e. none of these models were used for predicting costs.

In paper 3, sensitivity analyses were also performed, first by including the subjects referring themselves as asthmatics in the group with a diagnosis, i.e. either COPD or self-reported asthma, and then by excluding all subjects with FEV_1 $\geq$80% of predicted. The average cost per patient estimates in the severity groups were weighted using prevalence weights by severity group, and estimated proportions with and without a physician-diagnosed disease by severity group, in order to get the societal costs for COPD in Sweden among those with and without a physician-diagnosed disease.

RESULTS

Costs of asthma (Paper 1)

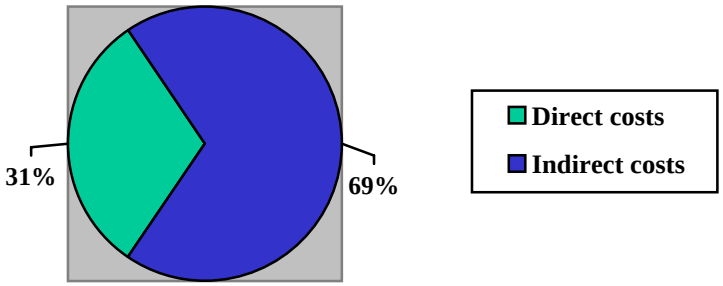
Resource use

There were great differences in resource use among the asthmatics both according to age and severity of asthma. Number of visits to the healthcare sector and number of days in hospital were higher in the oldest age group compared to the two younger age groups. The same pattern was found in the different severity grades of asthma, where subjects with persistent asthma had more visits to the health-care sector and had a higher degree of hospitalisations compared to subjects with mild intermittent asthma. Absence from work due to sick leave and disability pensions showed a similar pattern. All resource units consumed increased with age and severity of asthma.

Total costs

The average total societal costs were estimated at SEK 15,919 annually per subject with asthma. The indirect costs were higher than the direct costs, 69% of the total costs compared to 31% for the direct costs. The distribution of total costs is illustrated in Figure 1. The total costs differed a lot between the different age groups and the two severity grades of asthma. Among the three different age groups, the highest costs were found in the oldest age group. The indirect costs were higher than the direct costs in the oldest age group, while the direct costs were higher in the two younger age groups. There was also a significant difference in costs by severity of asthma. The costs for subjects with persistent asthma were more than 10 times higher compared to the costs for subjects with mild intermittent asthma, SEK 27,628 and SEK 2,222, respectively ($p<0.001$).

Figure 1. The percentage distribution of total costs for asthma.



Direct costs

The average direct costs accounted annually to SEK 4,931 per subject with asthma. The distribution of the direct costs was similar to the total costs. Subjects in the oldest age group and subjects with persistent asthma had higher costs compared to the other age groups and to subjects with mild intermittent asthma. Medications were the main disease-related cost driver among the direct costs, 56%, followed by outpatient care and hospitalisations. The distribution of the direct costs is presented in Figure 2. As there were no hospitalisations in the two youngest age groups, medicines were a more prominent cost driver in these age groups. Costs for visits and contacts with the health-care sector were also higher in the oldest age group compared to the two younger age groups. The differences found in the direct costs between the age groups are to a large extent explained by costs for hospitalisations. The distribution of direct costs among the different age groups is shown in Figure 3.

Figure 2. The percentage distribution of direct costs for asthma.

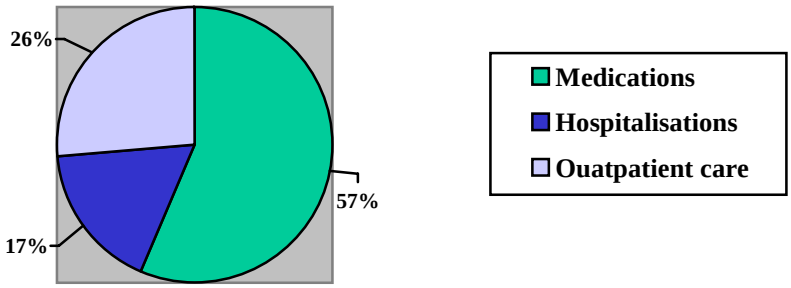
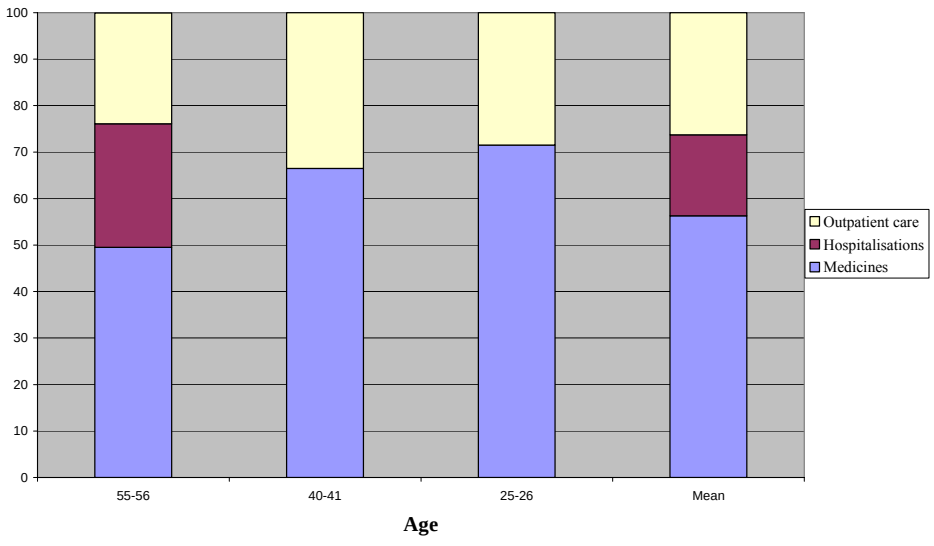


Figure 3. The percentage distribution of direct costs in the different age groups.



Indirect costs

The indirect costs were estimated at SEK 10,988 annually per subject with asthma. Loss of productivity due to disability pension was the main cost driver among the indirect costs. The costs accounted to SEK 8,644 per subject with asthma (83% of the indirect costs). Subjects who had disability pension were only found in the oldest age group. In the other age groups, all indirect costs consisted of costs for absence from work due to sick leave. Persons in the oldest age group had also more days off from work due to sick leave, and consequently the costs were higher in this age group compared to the two younger groups. The same pattern was found when comparing the two severity grades of asthma. Subjects with persistent asthma had the highest indirect costs, and costs for disability pension was the main cost driver. Also costs for absence from work due to sick leave were higher in subjects with persistent asthma.

Costs to society

Assuming that the prevalence, severity, medications and economic consequences of asthma were similar in Norrbotten as in Sweden as a whole, the annual total costs for the society would amount to SEK 3.7 billion (95% CI 1.5 - 5.7) for all subjects with asthma in Sweden in the ages between 25 and 56 years. The direct costs were SEK 1.1 billion and the indirect costs amounted to SEK 2.6 billion. The total societal costs for Sweden would probably be approximately twice as high because this study was based only on subjects aged 25-56 years.

Costs of COPD (Papers 2 and 3)

Of the study sample used for the studies of cost-of-illness of COPD, 76 subjects had COPD diagnosed by a physician, while 136 persons had not. Most of the subjects without a physician-diagnosis had a mild or very mild disease (65.5%), while only 7.4% had a severe COPD. For those who had a physician-diagnosed disease, mild and very mild disease accounted to 30.3%, while 23.7% had a severe COPD.

Resource use

Large differences in resource use were found in the four different severity grades of COPD. Subjects with a severe disease consumed considerably more healthcare resources and medicines compared to persons with moderate and mild and very

mild or very mild COPD. The same pattern was found for disability pensions and absence from work due to sick leave.

There were a greater consumption of healthcare resources and medicines among those with a physician-diagnosed COPD compared to those without a diagnosis. A greater proportion of them had disability pensions and absence from work due to respiratory diseases.

Total costs

The average annual costs accounted to SEK 13,418 per subject with COPD. The direct costs were estimated at 42% of the total costs. In all severity grades of COPD, except in the very mild group, the indirect costs were higher than the direct costs. The distribution of costs among the different severity grades of COPD is illustrated in Table 1. Costs for subjects with a severe disease were approximately three times higher compared to the costs for subjects with a moderate disease and more than 10 times higher than the costs for subjects with mild and very mild COPD. The variations in total costs between the different severity grades are shown in Figure 4.

The differences in costs between the different severity grades of COPD were highly significant. The total costs were also skewed with few subjects who were very costly, while most subjects had moderate costs (Figure 5).

The total costs for those with a physician-diagnosis were approximately twice as high compared to subjects without. In all disease severities, the costs were higher for those with a diagnosis ($p=0.002$). The indirect costs were higher than the direct costs both for those with and without a physician-diagnosis of COPD, 58% and 55%, respectively.

Table 1. Average annual societal costs per patient with COPD according to severity of disease.

FEV_1-categories	Direct costs SEK (%)**	Indirect costs SEK (%)**	Total costs
<40%	44,480 (41.2)	63,512 (58.8)	107,992
40-59%	13,546 (31.6)	29,310 (68.4)	42,856
60-79%	4,007 (48.4)	4,270 (51.6)	8,277
>79%	1,803 (71.7)	711 (28.3)	2,513
Mean *	5,592 (41.7)	7,828 (58.3)	13,418

* prevalence-weighted mean
** refers to the proportions within each severity group

Figure 4. The relationship between costs and severity of COPD.

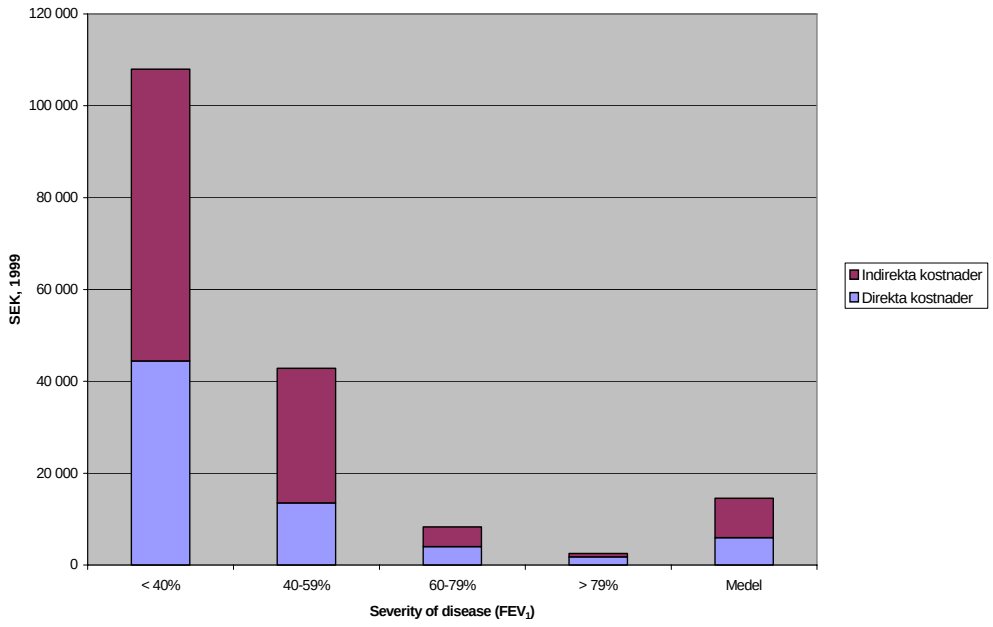
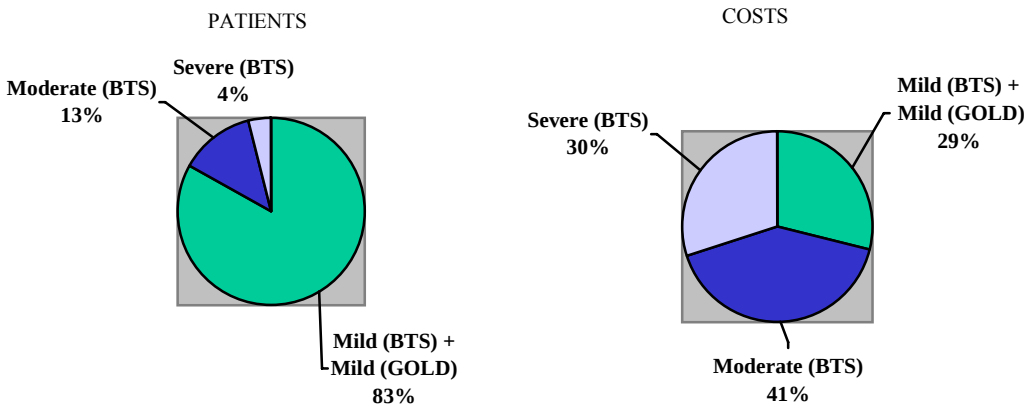


Figure 5. The distribution of weighted severity grades of COPD among patients and costs.



Direct costs

The direct costs accounted to SEK 5,592 annually per subject with COPD. Medicines and hospitalisations were the main cost drivers, 40% and 37%, respectively. In moderate and severe disease, hospitalisations were the main cost drivers, while in mild and very mild COPD, medicines and costs for health-care visits and contacts were the main cost drivers. As found for total costs, the costs were skewed also for direct costs. Subjects with severe COPD had more hospitalisations compared to subjects with moderate and mild or very mild disease. A proportion of 21% of subjects with severe disease were hospitalised for at least 1 night, while the corresponding figures were 5%, 1% and 0% for subjects with moderate, mild, and very mild COPD. The main explanation for higher costs in severe disease was the use of medicines and hospitalisations. As very few subjects used oxygen therapy, the costs amounted only to SEK 116 per subject with COPD. However, the average cost per subject who used oxygen therapy amounted to SEK 9,772.

The direct costs were higher for subjects with a physician-diagnosis of COPD compared to subjects without a diagnosis, SEK 7,646 and SEK 4,198, respectively.

The main cost driver was medicines in both groups, 48% and 41%, respectively. Different cost drivers were found in the group with a diagnosis compared to the group without. In the diagnosed group, hospitalisations were the main cost driver, while medicines were the main cost driver among those without a COPD-diagnosis. The costs were higher for subjects with diagnosed COPD than for those without for all COPD severity levels ($p=0.003$). The direct costs were positively correlated to disease severity independent of presence or absence of physician-diagnosis ($p<0.001$).

Indirect costs

The indirect costs were estimated at SEK 7,828 annually per subject with COPD. Loss of productivity due to disability pension was the main cost driver amounting to 90% of the indirect costs. Costs for disability pension were considerably higher in all severity grades of COPD, except in the very mild group, where no subjects with disability pension were found. The costs for loss of productivity due to sick leave accounted to SEK 749 per subject with COPD, and persons with a severe disease had the highest average costs (SEK 3,150). As the majority of subjects with moderate and severe COPD were quite old, only a few persons were employed in these groups.

The indirect costs were twice as high for those with a physician-diagnosed COPD compared to those without, SEK 10,606 and SEK 5,129, respectively. Loss of productivity due to disability pension was the main cost driver in both groups. A significant correlation was found between costs and disease severity both among those with and without a physician-diagnosis.

Costs to society

Assuming that the prevalence, severity, medications and economic consequences of COPD were similar in Norrbotten as in Sweden as a whole, the total societal costs for the Swedish society were estimated at about SEK 9.1 billion (95% CI 6.1 - 12.8). The direct costs amounted to SEK 3.8 billion and the indirect costs were SEK 5.3 billion. The costs were skewed with severe disease accounting for 30% of the total costs but only comprising about 4% of the persons with COPD. The costs for those with moderate disease accounted for 41% of the total costs and comprised 13% of the subjects. Persons with mild or very mild disease accounted for 29% of the total costs although 84% of subjects with COPD had a mild or very mild disease (Figure 5).

Costs of exacerbations in COPD (Paper 4)

Exacerbations in relation to demography

No significant differences were found in terms of age, gender and smoking habits between those who reported exacerbations and those who did not. However, subjects with exacerbations had a lower FEV_1 of predicted value compared to those who did not experience an exacerbation during the study period ($p=0.028$). Subjects without exacerbations were to a greater extent part of the labour market. Disability pensions were more common in subjects with exacerbations compared to subjects who did not experience exacerbations, 21% and 5%, respectively ($p<0.001$). Exacerbations were more common among those with severe COPD compared to those with moderate, mild and very mild COPD. Half of those with severe disease had experienced one or more exacerbations during the study period compared to only 21% for those with mild and very mild COPD.

Exacerbations in relation to costs

Resource use for the four different types of exacerbations differed. The average number of medicines used during a mild exacerbation was significantly lower than during mild/moderate, moderate and severe exacerbations. For moderate exacerbations the number of healthcare visits amounted to 1.56 compared to 0.65 for severe exacerbations. The costs of treating COPD exacerbations were positively correlated to the severity of exacerbations. A severe exacerbation was on average 10 times more expensive than a moderate and 60 times more expensive than a mild/moderate exacerbation. The main cost driver among the costs of exacerbations was hospitalisations, which accounted for 67% of the total costs.

Exacerbations in relation to severity of COPD

The average total costs due to exacerbations varied from SEK 13,708 in subjects with severe COPD to SEK 294 for those with very mild COPD. The significantly higher costs for those with severe COPD compared to those with moderate, mild and very mild disease were due to a higher degree of severe exacerbations among subjects with severe COPD. The average prevalence-weighted costs for exacerbations amounted to SEK 940 during the 4.5-month winter period. Using recent prevalence estimates for each severity of COPD and official population data and assuming no seasonal variations, the total costs for exacerbations could be estimated at about SEK 1.7 billion for all subjects with COPD in Sweden.

Health-related Quality of Life in COPD (Paper 5)

Health-related quality of life in relation to COPD severity according to GOLD

SF-36, Physical Component Summary showed a statistical difference between the different severity grades ($p = 0.006$). The scores were 42 in the mildest group, stage I, and 29 in the most severe group, stage IV. However, no significant association was found for the Mental Component Summary scores of SF-36 and COPD severity. The scores were 55 and 48 in the mildest and most severe group, respectively ($p=0.19$). A statistically significant difference was found between the different severity grades and the SGRQ scores ($p<0.001$).

Health-related quality of life in relation to COPD severity according to BTS

The COPD severity grades according to BTS also affected the SGRQ scores varying from 25 to 45 ($p=0.002$). SF-36, Physical Component Summary showed no statistical difference between the different severity grades of COPD according to BTS ($p = 0.03$). The scores were 42 in the mildest group, stage I, and 35 in the most severe group, stage IV. The corresponding scores for SF-36 MCS were 55 and 50 in the mildest and most severe group ($p=0.29$).

Influence of age, gender, smoking status and socioeconomic group

SF-36 PCS and SF-36 MCS showed no statistically significant difference between the different age groups. However, the scores for SGRQ were statistically significant ($p=0.005$) with the scores varying from 29 in the youngest age group to 44 in the oldest age group. No statistically significant difference between the age groups was found for EQ-5D VAS and EQ-5D.

Only one instrument, SF-36 PCS, showed a statistically significant gender difference with scores 44 and 35 for men and women, respectively ($p<0.001$). No significant differences in health-related quality of life were found with regard to smoking status and socio-economic group.

DISCUSSION OF METHODOLOGY

In this section, the methods and study designs used in the five papers will be discussed. Advantages and disadvantages compared to other methods and study designs will be analyzed. Furthermore, different types of biases, which may have influenced the results, will be discussed. Non-response will not be discussed, as the response rate was high in all studies the papers in this thesis are based on as well as in the epidemiological studies from which the samples with COPD and asthma were derived from (Rönmark, 1999; Lindberg, 2004).

Population-based studies versus register-based studies

There are different methods for performing a cost-of-illness study. One commonly used study design is based on register data. These types of studies are usually called top-down studies. The method is useful when the diagnoses made by clinicians are clear, as is the case for instance with cancer. For many diseases it is difficult to distinguish a symptomatic subject from a subject with the disease under study. This is especially common for COPD, as subjects with COPD often do not seek health care for their symptoms early in the disease process and adapt their lifestyle and activity levels to their disease. Furthermore, subjects who are contacting health care do not always get the correct diagnosis. As a result of this, information about undiagnosed subjects will not be found, and the costs will to a great extent be underestimated. Another problem with top-down studies based on statistical databases and registries is that several costs are usually not found in these registries in most countries, and the total costs will therefore be underestimated. Examples of such costs include among others costs for sick leave and transportation costs to hospital and health-care centres.

In so called bottom-up studies, costs are collected directly from a patient sample, either retrospectively by using questionnaires, or prospectively by following the sample over a specific time period, usually one year. Studies based on representative samples from the general population can be in the form of postal questionnaires or interviews of the subjects in the studied samples. Interview-based studies must be considered to be more valid than studies based on postal questionnaires, as it is possible to coach the subjects during the interviews.

In bottom-up studies based on interviews, a structured questionnaire must be used to record resource use of healthcare utilization in order to avoid inter-individual and inter-observer bias. The interviews can either be performed by using telephone or by meeting the subjects personally. In population-based studies it is possible to provide information from previously undiagnosed subjects, which is not possible in register-based studies.

Strengths and weaknesses

There are both strengths and weaknesses with population-based studies compared to register-based studies. Some biases may occur in the different types of studies, which may lead to distortion of the results. Bias is commonly classified into selection bias, information bias, and confounding bias. Two common types of information bias are recall-bias and interviewer-bias.

Data collected in structured interviews are more detailed compared to data from register-based studies. However, there may be a risk of recall bias when subjects are asked about events that have occurred some months ago. A number of studies have reported that there is a risk of recall bias in patients' self-reports (Revicki et al, 1994; Evans et al, 1999).

Various ways to minimize that risk were used in the different studies. The results in paper 2 and paper 3 were based on structured interviews performed on four occasions. Each interview covered a period of three months. A patient diary was also used during the last nine months in the studies. When estimating utilization of medications (4 papers), the subjects were asked to bring their medications to the telephone in order to obtain the correct doses and strengths. When asking questions about visits to the health care sector and hospitalizations during the last year, we also asked when and where the patients had visited the health care sector or had been hospitalized.

In the exacerbation study, the potential for recall bias could have influenced the study in two ways. Firstly, the subjects were sent a letter in March 2000, in which they were asked if they had experienced some additional respiratory problems during the previous winter season (November-March). Most of the subjects were elderly, so it is possible that some early disease events could have been forgotten. Further also if the actual incident was recalled, some resource use could have been forgotten, for instance telephone calls to healthcare centres. This recall bias is not a major problem for the severe and moderate exacerbations, as probably all major resource use was verified by the patients' health-care records. Furthermore, visits and hospital admissions accounted for more than 85% of the total costs for exacerbations.

Another disadvantage in using individual interviews is the possibility that the study will be based on too few subjects. This can result in samples, which are not representative for the study population. However, the study samples in the five different studies include well-defined and stratified samples from the OLIN Studies. All subjects with COPD and asthma have been identified from two different study cohorts including about 6,000 subjects each.

It is also of great importance that the questionnaire contains clear questions that are easy to understand in order to minimize the risk of errors. When the study sample mainly consists of elderly people, as in a COPD population, there is an obvious risk that the questions could be misunderstood. It is also a risk that the questions can be formulated in different ways if there are several persons, who are interviewing. In each paper, the same person carried out all the interviews.

As most of the subjects with severe COPD are elderly, there is also a risk that this group will be underrepresented in population-based studies. They are often hospitalised and may also have difficulties to participate in a study. This will underestimate the costs in a population-based study compared to a register-based study. However, the participation rate has been high in our studies, especially among the elderly subjects. The proportion of subjects who were using oxygen therapy corresponded also well with the reported proportion from the hospital that managed this therapy in the study area.

However, a prospective study following a study sample daily by diary cards or weekly by interviews during one year is the study design that probably would lead to very valid results. This type of study is, however, very costly.

Other possible causes of bias

We are convinced that the results are quite valid for the area of Norrbotten. However, there are uncertainties when transforming the results to Sweden as a whole. Studies of COPD are very few, and the only published study of prevalence in Sweden is conducted within the OLIN Studies in Norrbotten. Several studies have shown that the prevalence of asthma is somewhat higher in Norrbotten compared to Sweden as a whole. The quota has been found to be 1.2/1.4 greater than the prevalence in central and southern parts of Sweden (Larsson L et al, 1994; Lundbäck, 1998; Larsson M et al, 2001; National Board of Health and Welfare (Socialstyrelsen), 2001; Pallasaho et al, 2002). However, there are no results showing if severe asthma is more common in Norrbotten. The distribution of severity grades of asthma is quite unknown, but about half of the asthmatics are supposed to have mild intermittent asthma.

The age groups of the subjects in the studies can also have biased the results. This has been discussed previously in a number of studies within the OLIN Studies and has not been found to have a major impact on the results. The prevalence of COPD is increasing considerably with age. As we have a gap between the different age groups, the estimation of over-all costs of COPD could be affected. In asthma, the prevalence is more homogeneous between the different age groups. The prevalence is slightly higher among young adults and among elderly compared to middle-aged

subjects. As the subjects in our study were between 25 and 56 years, the age groups of the participating subjects could not have had any major impact on the results.

Validity of the results

The validity of the results in a study is of great importance, and the concept deals with to what extent the conclusions are correct or not. It is important that the results as truly as possible reflect the situation of the studied population.

The data in these five papers should be considered as fairly valid, as they reflect a real-life setting with a random sample from a large-scale population study. The studied sample can be considered as representative for subjects with COPD and adult asthma in the general population of Norrbotten in northern Sweden. Further, the studied COPD-sample was stratified by age and severity of disease thus allowing prevalence-weighted estimates. However, there is a risk that the costs for the undiagnosed subjects could have been somewhat biased, as some subjects may have been diagnosed as having COPD by a physician without having been informed. In the study of costs of asthma the proportion of subjects with mild intermittent asthma reflects well this proportion in society.

The participation rate is also very high in all five papers, which indicates that there is no or limited risk for selection-bias. Furthermore, all the interviews in papers 1-3 were carried out by only one person (the author of this thesis) aiming to eliminate the risk of inter-observer bias. In paper 4, the subjects were guided by an experienced nurse during telephone interviews, and all visits to the health-care sector and all hospitalisations were verified by patient records.

Keeping in mind possibilities of uncertainty and pitfalls including wide confidence intervals, we have transformed the results in our studies to Sweden as a whole, assuming that there are no major differences between subjects with COPD and asthma in northern Sweden compared to subjects with these diseases under study in central and southern Sweden in terms of prevalence, treatment patterns and early retirement. No data support the view that clinical treatment patterns are different in Norrbotten compared to Sweden as a whole. However, public statistics show that the proportion of disability pensions is somewhat higher in Norrbotten compared to Sweden as a whole. This has also been discussed in *Discussion of main results.*

DISCUSSION OF MAIN RESULTS

In this section the results of the papers included in this thesis, will be discussed. The results will be compared with results from other studies and further, how differences in results can be influenced by different methods. The discussion starts with the results from the studies of costs of asthma and COPD followed by a discussion about costs of exacerbations of COPD. In the last part, the results from the quality of life paper will be discussed.

Costs of asthma and COPD

The societal costs of adult asthma and COPD were estimated. The analyses were implemented at an individual level, and we also examined the relationship between costs and age, and between costs and severity of asthma. An aggregation of the costs to the whole of Sweden was then made using the estimated prevalence of the diseases divided into different severity grades. We found that asthma and COPD are costly diseases for the Swedish society.

The total per capita annual costs amounted to SEK 15,919 (USD 1,592; Euro 1,768) per subject with asthma and SEK 13,418 (USD 1,284; Euro 1,448) per subject with COPD. There was a substantial difference in costs by severity of the diseases. The costs for subjects with persistent asthma were ten times higher compared to asthmatics with mild intermittent asthma. In subjects with COPD, the costs were three times higher for subjects with severe disease compared to subjects with moderate disease and more than 10 times higher than in mild and very mild COPD.

Asthma

The interest of the burden of asthma in society worldwide has been evidenced by a number of cost-of-illness studies (Weiss et al, 2001). There are, however, difficulties to compare different studies due to different study designs, time periods, and cost items. The main part of the studies of cost of asthma has been register-based studies (Mellis et al, 1991; Weiss et al, 1993; Rutten van-Mölken et al, 2001; Godard et al, 2002; Cisternas et al, 2003; Schwenkglenks et al, 2003; Stock et al, 2005). The average annual societal cost has ranged from USD 326 to USD 1,315 per subject in studies performed in United States, United Kingdom, Australia, and Europe (Weiss et al, 2001), all somewhat lower than in our study. However, a recent study in the United States found the total annual costs to be USD 4,912 (Cisternas et al, 2003), which are more than twice as high than the total costs found in our study. A correlation between costs and severity of asthma has

also been found in several studies (Godard et al, 2002; Cisternas et al, 2003; Schwenkglenks et al, 2003).

The key cost driver in our study among the direct costs both in persistent and in mild intermittent asthma was medicines. Studies performed in the Netherlands, the United States and Germany have shown a similar pattern in the distribution of the direct costs with asthma medicines being the main cost driver (Rutten van-Mölken et al, 2001; Cisternas et al, 2003; Stock et al, 2005).

Among the indirect costs in our study, disability pension was the main cost driver. However, there was a difference in the different severity grades of asthma. In mild asthma, the costs for sick leave due to asthma were higher than the costs for disability pension. Most studies from other countries show the same pattern. In a study conducted in the United States, the costs for disability pension accounted to 61% of the indirect costs (Cisternas et al, 2003). However, in one study conducted in Germany, the results were opposing with higher costs for sick leave than costs for disability pension (Stock et al, 2005). This result could be explained by the fact that the German study included also children.

Assuming that the prevalence, severity, medications and economic consequences of asthma were similar in Norrbotten as in Sweden as a whole, the total costs for the Swedish society could be estimated at about SEK 3.7 billion (95% CI 1.5 - 5.7) for all asthmatics from the age of 25 to 56 years. The direct cost amounted to SEK 1.1 billion and the indirect costs were SEK 2.6 billion. The results indicate that the total costs for asthma in all age groups would presumably be estimated at approximately twice as high. However, the prevalence in northern Sweden is somewhat higher than in other parts of Sweden (Larsson L et al, 1994; Lundbäck, 1998). On the other hand, the selection procedure may have resulted in a loss of subjects with mild intermittent asthma. Whether or not differences in severity of asthma exists between Northern and Southern Sweden is not known, but severe asthma could be somewhat more common in Northern Sweden. Above that there may still be underdiagnosis of asthma as indicated by Nathell et al (2003). Nathell et al found that several persons on sick leave had a number of different diagnoses other but asthma as the causes for the sick leave although it was obvious that they were suffering from exacerbations of asthma.

One Swedish study based on register data (Jacobsson et al, 2000) has found that the societal costs of asthma in Sweden amount to SEK 3 billion and the direct costs accounted to 35% of the total costs. This distribution corresponds well with the results in this thesis, where the direct costs amounted to 31% of the total costs. However, we found the total societal costs to be considerably higher than the estimations from the study by Jacobsson et al (2000). The higher costs in this thesis could be explained by a higher prevalence in the north of Sweden. Further, as our

study was performed later, the costs of medicines and costs for different health-care contacts have also increased steadily and the prevalence of asthma may have increased. As our estimations were based on samples of the general population, and the diagnosis of asthma had a high specificity, 99%, our results can be considered as valid (Lundbäck, 1993; Lundbäck et al, 2001). One important reason for the higher costs in this thesis compared to the results from the previously performed Swedish study could also be underdiagnosis, which cannot be corrected for in register studies. Another contributing explanation to the differences in costs is that all costs were not included in the Swedish register based study. Costs for health care provided by private physicians and clinics and costs for sick leave are included in this thesis but not in the register based study.

The only published comparable data from the Nordic countries that the author of this thesis has found are from Denmark. The results from the two studies are based on interviews of asthmatics outside pharmacies when the subjects were collecting their medicines. The number of participants in the two studies is between 100 and 200 subjects, comparable with the study sample in our study. It can of course be discussed if the study samples in the Danish studies can be regarded as representative for asthmatics in Denmark. Assuming that prevalence of asthma is similar in Denmark with the prevalence in Sweden, the costs for a country with a population of Sweden would amount to SEK 3-4 billion and SEK 6-7 billion, respectively, according to these two Danish studies. Taken into account uncertainties including wide confidence intervals, the results are not far from what we found.

COPD

We found that the key cost drivers for direct costs were costs for medicines (40%) and hospitalisations (37%). In the very few studies available from other parts of the world, hospitalisations have been the main cost driver, while medicines have not been a major cost driver (Rutten-Van Mölken et al, 1999; Sullivan et al, 2000; Ward et al, 2000). Another large difference was found in costs for oxygen therapy, as only 2% of our study sample needed oxygen therapy. Costs for oxygen therapy were considerably higher in studies conducted in United Kingdom and the United States, 18% and 35% of the direct costs, respectively (National Health Service Executive, 1996; Ward et al, 2000). The main reason for these differences is probably a result of how the samples have been composed in the different studies. The results from United Kingdom and the United States indicate that the disease severity in their samples must have been much different compared to our sample.

There are, so far, limited data on costs of COPD worldwide. Studies in the United States have estimated the annual total cost at USD 1,522 per patient with COPD

(National Heart, Lung, and Blood Institute, 1996), which is close to our result. A study in the Netherlands has found that the costs would amount to USD 876 per patient with COPD (Rutten-Van Mölken et al, 1999).

The relationship between severity of COPD and costs has been analysed only in a few studies (Strauss et al, 1986; Vestbo et al, 1989; Decramer et al, 1997; Hilleman et al, 2000). A similar relationship between severity of disease and costs was found in a study from USA (Hilleman et al, 2000). In contrast to these results, Decramer et al (1997) did not find any relationship between severity of COPD and costs. However, the main explanation to these results is that only subjects with severe COPD were included in that study. As for quality of life, there is probably no relationship between lung function results and costs within a defined severity grade of disease, while a relationship can be found when subjects with a wide range of FEV_1-values are included in the study.

The total costs for Sweden were estimated by multiplying the estimated prevalence weighted by severity with the costs per subject with COPD. We assumed that the prevalence in Norrbotten was similar to the prevalence in Sweden as a whole. Still no Swedish study has estimated neither the prevalence of COPD nor the prevalence by disease severity except the OLIN Studies (Lundbäck et al, 2003; Lindberg et al, 2005a; Lindberg et al, 2006b). Prevalence data including pulmonary function tests have only been found in one other Swedish study, where the prevalence of chronic bronchitis was similar to the results in the OLIN Studies (Larsson L et al, 1994). Swedish questionnaire data have not shown any major differences in prevalence rates of chronic symptoms between different parts of Sweden, and smoking habits are not different in Norrbotten compared to Sweden as a whole (Larsson L et al, 1994; Lundbäck et al, 1994; Björnsson et al, 1994; Lundbäck, 1998). We can thus assume that the prevalence of COPD does not differ considerably between Norrbotten and Sweden as a whole.

The total costs for the society in Sweden were estimated at approximately SEK 9 billion. There is only one Swedish study based on registry data so far that has estimated the societal costs of COPD (Jacobsson et al, 2000). The results from that study indicated that the total costs would amount to SEK 2.8 billion: direct costs accounting to SEK 1.1 billion and indirect costs to SEK 1.7 billion. The distribution of the costs into direct and indirect costs was similar as was found in our study, 42% and 58%, respectively. The great difference in total costs could to a large extent be explained with the different study designs. As there is a great underdiagnosis in COPD, a register-based study like the study by Jacobson et al (2000), cannot register the costs for all subjects with COPD in the society, as the majority is undiagnosed. Another explanation to the difference in costs could be that in the beginning of the 1990s medications prescribed for asthma were free of charge, but not medications for COPD. This may have provided an incentive to

report the diagnosis as asthma rather than COPD, as the same medicines are commonly used in the two different diseases. Further, our estimations were performed 10 years later, and as for asthma the costs have become higher during these years.

One important factor to the differences in costs could be explained by the geographical area studied, Norrbotten. Public statistics show that the degree of disability pension is somewhat higher in Norrbotten compared to other parts of Sweden. In 1999, the proportion of disability pension was 9.4% in Norrbotten compared to 7.7% in Sweden as a whole. Respiratory diseases accounted for 3% of all disability pensions in Norrbotten compared to 2% in Sweden as a whole. Disability pensions accounted to a half of the total costs for COPD in our study. The discrepancy in the proportion of disability pensions would reduce the annual cost per subject from SEK 13,418 to SEK 12,138. The total costs for the Swedish society would then be reduced from SEK 9.1 billion to SEK 8.2 billion.

As COPD is a disease with a great underdiagnosis, it is important to study the differences in costs between subjects with a physician-diagnosis and subjects without a diagnosis. A more complete understanding how the costs are distributed among different subjects with COPD can then be described. Undiagnosed subjects also often seek health-care as shown by epidemiological studies (Lindberg et al, 2005a). No previous study has so far analysed the costs for subjects with and without a physician-diagnosis. We found that the individual costs differed a lot between diagnosed and undiagnosed subjects. The costs for subjects with a diagnosed COPD were twice as high compared to subjects without a diagnosis. This difference can to a great extent be explained by the fact that subjects with a severe COPD are more often correctly identified by the health-care sector.

However, when multiplying the costs for subjects with and without a diagnosis with the estimated prevalence in the different groups, we found that the costs for undiagnosed persons with COPD accounted to about 40% of the total costs for COPD. These results are in accordance with well-known data of underdiagnosis of COPD in society (Tirimanna et al, 1996; Sobradillo et al, 1999; Soriano et al, 2000; Mannino et al, 2000; Lindström et al, 2001; Lundbäck et al, 2003; Lindberg et al, 2006a). The limited use of spirometry is the main explanation of the large underdiagnosis of COPD.

The statistical analysis showed that both severity of disease and having a diagnosis of COPD affected both the total and the direct costs. On the other hand, both age and smoking status did not significantly influence the costs. The costs are not related to the causes of the disease but solely to the severity of the disease.

As discussed above, the great differences in costs of COPD between this study and the previously performed register-based Swedish study (Jacobson et al, 2000) may to a great extent be explained by the large number of undiagnosed subjects. Assuming that the prevalence is similar in Norrbotten as in Sweden as a whole, underdiagnosis would result in an underestimation of the costs of about SEK 3-4 billions. During the almost ten years between the register-based study and our study the prevalence and the impact of COPD has increased particularly in women. Furthermore, some of the cost components in our studies were not possible to measure in the register-based study including absence from work, equipment aids, and oxygen therapy.

Exacerbations of COPD

The results showed that there was a difference between subjects, who reported exacerbations and those who did not. Those who had experienced one or more exacerbations during the study period had a more severe COPD and were to a less extent working. Subjects with lower lung function had more exacerbations, and the exacerbations among them were also more severe. There were also great differences in costs between the different severities of exacerbations. The costs for a severe exacerbation were more than 10 times higher compared to the costs for a moderate exacerbation and about 60 times higher than for a mild/moderate exacerbation. The costs for exacerbations were also strongly correlated to severity of COPD. Subjects with severe COPD had more than 45 times higher costs for exacerbations compared to subjects with a mild and very mild disease.

The correlation between impaired lung function and the number of exacerbations and the severity of exacerbations have also been found in other studies (Rodriguez-Roisin, 2000). A study conducted in Spain showed that lung function was an explanatory variable in their models (Miravitles et al, 2000).

Costs of exacerbations are poorly studied worldwide, but the very few data that are available correspond well with our results. Data from a randomised pharmaceutical study using definitions of exacerbations that are similar to ours showed that the distribution of costs in different severities of exacerbations were similar to our study (Price et al, 1999). One study conducted in French subjects with chronic obstructive bronchitis found that 60% of the costs for exacerbations were hospital-related (Pechevis et al, 1996).

Also in our study, the key cost driver in exacerbations was hospitalisations, which accounted for 67% of the prevalence-weighted costs of SEK 3,136. When transforming the weighted cost per exacerbation to Sweden as a whole, the costs for exacerbations due to COPD would amount to SEK 1.7 billion annually, which

accounts for about 40% of the direct costs of COPD. However, in our study, we have not considered the possibility of seasonal variations in the frequency of exacerbations. One study has shown that the number of hospitalisations due to chronic bronchitis was highest during the first quarter of the year (Niederman et al, 1999). If we, for instance, assume that the number of exacerbations is twice as high in our study period, the winter, compared to the rest of the year, the societal costs would be SEK 1.3 billion per year and still very high.

There are difficulties in measuring the duration of an exacerbation. As most of the subjects were elderly and to a great extent had symptoms of varying severity every day, it was difficult for them to estimate how many days the exacerbation lasted. However, we found that the subjects' estimations of the duration were closely related to the duration of a given prescription. Another problem is the patients' self-reports of exacerbations. One study on the effects of exacerbations on quality of life has shown that subjects did not report 50% of the exacerbations (Seemungal et al, 1998).

In future studies, the study samples need to be larger than in our study. However, when we planned this study, there was little information of the frequency of exacerbations. Some other studies have shown that the frequency of exacerbations was higher compared to our results. (Anthonisen et al, 1987; Seemungal et al, 1998; Miravitles et al, 1999). The main explanation to the lower frequency of exacerbations in our study may in part be due to different definitions, but the main reason is probably the fact that our study sample included a large proportion of subjects with mild and very mild disease. According to the literature one study has shown that only about 30% of the subjects had experienced an exacerbation during a study period (Paggiaro et al, 1998), which is in accordance with the results from our study.

Health-related Quality of Life in COPD

The results from our study confirm that HRQL is affected by disease severity and age among subjects with COPD. A strong correlation was found between impaired lung function and HRQL. On the other hand, no relationship was found between gender, smoking status, socio-economic status based on occupation and impaired quality of life. Some previously conducted studies have not found any correlation between severity of COPD and HRQL (Ståhl et al, 2001). Pharmaceutical studies have often limitations and narrow windows for inclusion of subjects to the studies, and study samples are relatively homogenous. The possibilities to find correlations between lung function and quality of life in such studies are thus limited. The relationship between disease severity and HRQL is only rarely studied in population studies. Our findings are, however, supported by two other studies. One

study showed that the GOLD stages of COPD severity differed significantly in SGRQ (Antonelli-Incalzi et al, 2003), and another study found a significant relationship between severity of disease and HRQL (Ferrer et al, 1998).

Smoking status and impaired HRQL did not correlate in our study once COPD had been established. Different studies have shown different results for the association between smoking status and HRQL. One study has shown that subjects who are ex-smokers have a better HRQL compared to those who continue to smoke (Prigatano et al, 1984). However, contrary results were found in another study, and those who were smokers had a better HRQL (Wijnhoven et al, 2001). The explanation given to these results was the fact that those who continue to smoke often have a less severe COPD.

CONCLUSIONS

The total per capita annual costs amounted to SEK 15,919 per subject with asthma of which direct costs accounted to 31% and indirect costs to 69%.

A strong correlation was found between costs and severity of asthma and between costs and age. Subjects with persistent asthma had more than ten times higher societal costs compared to subjects with mild intermittent asthma. The costs for subjects in the oldest age group, 55-56 years, were considerably higher compared to the costs for subjects in the younger age groups.

The key cost driver among the direct costs both in persistent and in mild intermittent asthma was medicines. Among the indirect costs, disability pension was the main cost driver. However, there was a difference in the different severity grades of asthma. In mild asthma, the costs for sick leave due to asthma were higher than the costs for disability pension.

The total per capita annual costs amounted to SEK 13,418 per subject with COPD of which direct costs accounted to 42% and indirect costs to 58%.

Large variations were found in costs between the different severity grades of COPD. The costs for persons with severe COPD were three times higher than the costs for persons with moderate disease and more than ten times higher than for those with mild or very mild disease.

The key cost drivers among the direct costs were costs for medicines (40%) and hospitalisations (37%). In moderate and severe disease, hospitalisations were the main cost drivers, while in mild and very mild COPD medicines and costs for health-care visits and contacts were the main cost drivers. Among the indirect costs, loss of productivity due to disability pension was the key cost driver amounting to 90% of the indirect costs.

The societal costs of COPD differed considerably between those with and without a physician-diagnosis of COPD. The per patient costs for those with a diagnosis were on average twice as high as for those without a diagnosis, but when estimating the total costs for the society, the undiagnosed subjects accounted for approximately 40% of the total costs.

Great differences were found in costs between the different severity grades of exacerbations. The costs for severe exacerbations were more than ten times higher compared to the costs of moderate exacerbations and about 60 times higher than

for mild/moderate exacerbations. The costs for exacerbations were also strongly correlated to severity of COPD.

An association was found between health-related quality of life and the severity of COPD. A strong correlation was found between impaired lung function and health-related quality of life, but less so between impaired lung function and generic quality of life measures.

Assuming that the prevalence, severity, medications and economic consequences of asthma and COPD were similar in Norrbotten as in Sweden as a whole, the total costs for the Swedish society could be estimated at about SEK 3.7 billion (95% CI 1.5 - 5.7) for all asthmatics from the age of 25 to 56 years and at about SEK 9.1 billion (95% CI 6.1 - 12.8) for all subjects with COPD.

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