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THE SOCIO-ECONOMIC COST OF ASTHMA, COPD AND CHRONIC BRONCHITIS IN EUROPE

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Chapter 1

Cost-of-illness studies

The cost-of-illness (COI) analysis [1] is the first and most commonly used method of health monetary assessment for evaluating the economic impact of a disease on the society, with regard to both the consumption of health resources and productivity losses.

Although some COI studies were carried before the 1960s, the fundamentals of the COI methodology were described in detail for the first time in the work of Dorothy Rice in the United States [2]. Since then, many data on the cost of diseases have been published for several countries. However, there are still debates on the reliability and validity of this methodology among the insiders. A few years later the Rice's work, Hodgson and Meiners [3] provided detailed guidelines for undertaking COI studies, which still continue to be the most cited in works where technical methods are at issue.

The main criticisms raised by economists are that COI studies are not based on welfare economic theories and that other forms of economic assessment (i.e. cost-effectiveness and cost-benefit analyses) could be more useful for decision-makers.

On the contrary, COI studies, if considered as descriptive analyses, can

represent an excellent economic tool to inform decision-makers and to support the political process and the management functions at different levels of health organizations [4].

To be effective, a COI study should make it possible to measure the true cost for the society, to estimate the main cost components and their impact on the total cost, and to explain their variability.

1.1 Disease-specific and general COl studies

COI analyses have been classified in two main categories, disease-specific and general studies [5], even if literature is mostly represented by the first ones. In the disease-specific COl studies, all costs relevant to the disease of interest are combined to obtain an estimate of the total cost. To fulfil this purpose, patient-based information on healthcare consumption and productivity losses, and the corresponding unit prices, are used (bottom-up approach). Such studies can have a cross-sectional or longitudinal design. While the former is based on data regarding the expenditures of the different cost components in a given year, the longitudinal approach provides estimates of the lifelong expenditures by following patients over time.

General COI studies have a cross-sectional design and are aimed at describing the overall economic impact of all the diseases classified in the International Classification of Diseases (ICD), in a given year. As the diseases are aggregated into major categories, much broader disease definitions are used than in disease-specific studies. General COI studies are usually based on aggregated data on healthcare utilization obtained from national registries and other official sources (top-down approach) [6].

1.2 Prevalence- versus incidence-based COI studies

COI studies can be based on incidence or prevalence [7,8].
Prevalence-based COI studies provides estimates of the economic burden of a disease in a predefined period of time, usually a year, by quantifying the value of the resources used by all cases (both prevalent and incident) during that time. On the other hand, incidence studies evaluate the lifetime costs attributable to the new cases of a disease, who had their onset in a given period. The main difference between these two methodologies [7] is that, while under the prevalence approach both the direct and the productivity costs due to the disease are assigned to the year in which they occurred, the principle of the incidence study is to evaluate and assign all the costs to the year in which the disease made its debut [8,9].

The cost estimates obtained by applying the two different approaches are different when chronic conditions are considered, the estimates computed under the prevalence approach being generally greater than those computed under the incidence approach.

Disease-specific studies can be based either on prevalent or incident cases, while general studies are always cross-sectional and, therefore, based on prevalent cases. The prevalence-based approach is more appropriate if an estimate of the cost components or cost containment policies within a limited period of time are needed. Indeed, this approach provides decision makers with a picture of the global burden and of the main components of current healthcare expenditure, where cost containment policies would have the greatest impact [4].

If, on the other hand, the objective is to make decisions about the choice of which treatment or public health strategy should be adopted to obtain the maximum effectiveness, the incidence method is more appropriate as it

makes possible to obtain predictions of the possible cost savings deriving from programs that can reduce the incidence and improve the health status. The incidence approach is also useful to evaluate the cost distribution during illness progression and it allows the development of clinical/therapeutic guidelines aimed at increasing the effectiveness and the efficiency of the disease management and of each single step of the clinical therapeutic pathway [6].

1.3 Top-down versus bottom-up approaches

A top-down analysis is performed in general COI studies "from the top-down", allocating portions of a known total expenditure obtained at the national level to each of several broad disease categories. On the contrary, both the prevalence and incidence approaches in disease-specific COI studies require a "from the bottom-up" procedure for collecting input data. Under the bottom-up approach [6], variables are measured at the individual level and costs are calculated by multiplying the quantity of healthcare services used and the amount of productivity losses that each subject reported, by their unit costs.

1.4 Prospective versus retrospective COI studies

Incidence-based COIs can be prospectively or retrospectively performed depending on the temporal relationship between the start of the study and data collection.

Whilst in retrospective COI analyses all relevant events have already occurred at the beginning of the study, in prospective COI studies the relevant events have not yet occurred when the study starts. Prospective COI studies

imply that data are collected by following-up the patients over time and can only be carried out when sufficient data are available, but this is not often the case as data could have been collected for different purposes from those of a COI study.

Retrospective COIs are especially effective to investigate chronic diseases with a long duration and they are less expensive and time consuming than those performed prospectively because all relevant events have already occurred at the time the study is initiated. Vice versa, under a prospective COI approach, it is possible to plan data collection, for example by designing ad hoc questionnaires to be answered by patients. This allows, for example, to obtain complete data even for those cost components that are usually not registered by the healthcare organizations [6].

1.5 Cost components

The quantifiable economic burden of a disease is typically divided into two major cost components: "core costs" are those directly resulting from the illness and "other disease-related costs" include non-healthcare costs due to the disease. Within each category, we can identify direct and indirect costs [10].

Direct costs are those for which payments are made and refer to the healthcare costs associated with medical expenses for the diagnosis and treatment of a disease, and to the non-healthcare costs related to the consumption of other resources (e.g. the time dedicated by family members or volunteers to the patients care, or to their transport to and from health providers).

Indirect costs, also known as productivity costs, are those for which resources are lost and consist in cessation or reduction of work productivity due to illness or death [11]. Indirect costs are therefore associated with mor-

bidity and mortality and can be further classified as absenteeism (withdrawal from work) or presenteeism (inefficiency in work due to impairment) [12].

The indirect costs can also be calculated by evaluating the leisure time forgone as a result of illness. Despite this cost component is rarely considered in applied studies, it has a huge value to individuals. The parameter of monetization of leisure time forgone is given by the net salary that an individual could receive if he/she were employed. An alternative way to evaluate the loss of productivity is therefore to refer to the remuneration of an individual employed in an activity similar to that of the unpaid worker or to consider the wage of part-time help as replacement value.

Some medical and non-medical cost items (for example the costs associated with home care or to the pain and psychological distress of patients) are difficult to classify into the classic cost components and for this reason are often defined as "other indirect costs".

Although these "other indirect costs" represent an important part of the total cost attributable to the disease [13,14], they are rarely considered in COI studies because they are hardly quantifiable in monetary terms.

1.6 Human Capital Approach

Under the Human Capital Approach (HCA) it is possible to estimate the productivity costs due to morbidity and mortality, assuming that the expected future earnings reflect the potential contribution of the individual to the economy, or more precisely, that a worker's salary is equivalent to the value of his marginal product.

Although its basic principles were known at least since the seventeenth century [15], the HCA approach was developed mainly at the beginning of the 1960s, a period in which economists have focused more on human resources,

until then neglected and underestimated in the US economy [16].

As suggested by Mushkin [17], wages and salaries are paid in exchange for a direct return on services and therefore they correspond to the actual individual contribution to production. In COI analyses, morbidity indirect costs are estimated multiplying average wages by the number of working days lost and the number of days with reduced efficiency at work in the reference period. Instead, mortality indirect costs measure the lost productivity (i.e. number of working days) due to premature death in the reference period. For some categories outside the labor market such as housewives, the "replacement value approach", which estimates the services provided on the basis of their corresponding market value, is used. Another approach is the "opportunity cost", which assumes that the economic value of unpaid work is at least equal to the wage that the same person should have on the market [18,19]. However, this approach is inconsistent with that used on the working population, which is assessed on the actual work carried out, rather than on what could be done [8].

Similarly, people who were too sick to work or keeping house were considered as following the same labor force experience as the general population.

Therefore, it is assumed that if these people had entered the labor market, the employment rate and the level of earnings would not have diminished. Given the high rates of unemployment, it could be also supposed that people suffering from chronic illnesses, even if they were no longer ill, would probably not have worked anyway and therefore should not be considered in the calculation of productivity costs. Both positions are extreme because assuming a situation of full employment is not realistic even in a period of economic growth and, in the same way, the hypothesis of non-employment for chronically ill patients (even if no longer sick) is too pessimistic. At this

point a solution could be to apply the national unemployment rate to those patients who are too ill to work, albeit potentially in the active labor force, and to assume that the production losses refer only to the remaining part of the patients.

Other health economists [21-26] also questioned the reliability of the HCA in estimating production losses due to the disease. In fact, it is believed that the HCA overhangs the indirect costs in an economy with less than full employment.

In general, production losses can result from short- and long-term work absences.

For short-term absences, a person's work can be covered by others or compensated by the patient on his return to work, thus representing a cost to the individual but not to society.

The time required to replace a sick worker or to reorganize the production process, called the attrition period, depends on the availability of qualified personnel within companies, the labor market and the level of unemployment. As a result, productivity costs are directly proportional to the duration of this period.

1.7 Willingness-to-Pay Approach

The COI studies conducted under the HCA approach represent an excellent tool for providing decision makers with an assessment of the current allocation of resources.

However, HCA does not aim to estimate the economic value of human life but it only attempts to measure the loss to society deriving by disease morbidity and mortality that cause persons to lose time from work and other productive activities. Indeed, the HCA approach measures the lost wages

not considering the individuals' willingness to pay (WTP) to reduce the risk of getting ill.

In contrast, WTP makes it possible to evaluate the change in defensive expenditures and to overcome the problem of incorporating non-monetary information on quality of life into the economic calculus [27]. Therefore, by providing a comprehensive estimate of the value attached to a reduction in risk of illness, WTP quantifies the intangible costs that conversely remain rather intractable with the HCA approach.

1.8 Role of the cost-of-illness studies in health economics

Undoubtedly, COI studies are a very important decision-making tool and play a key role in health economics. The criticisms made by economists about the fact that COI studies are far from fully representing the welfare economy, and the need to make them more reliable by including WTP techniques [28] in the computations of intangible costs, are fundamentally based on the serious mistake that arises from considering them as a sort of cost-benefit analysis (CBA). The COI analysis is essentially a descriptive study that differs from all other types of economic evaluation, as it does not compare the costs with the results, and that could assume an enormous value if considered from the right perspective.

The principal aim of a COI analysis is to evaluate the economic burden of a disease for society. Therefore, COI studies succeeding in quantifying the resource utilization due to an illness may allow the classification of diseases according to their global burden, along with epidemiological data on their morbidity and mortality.

Another great advantage of this type of analysis is the possibility of quantifying the main cost components and assessing their impact on the total cost. This is of fundamental importance in the field of health policies as they enable decision makers both to focus interventions on cost items that have a greater impact on the total cost and to evaluate the effectiveness of previously adopted health policies. The evidence obtained from COI studies may represent the basis for the redesign of individual medical services or of entire therapeutic models that have proved ineffective, enabling the disease clinical management to be improved and optimized through targeted interventions.

A further strong point of this approach is that it makes possible to estimate the variability of costs determined by factors related to the disease (e.g. severity), to the patient (e.g. demographic characteristics) or to the services providing health care (e.g. hospital centers). An assessment in this sense would provide decision-makers with very useful detailed information in order to plan the provision of health services in a tailored way.

To achieve these objectives, COI studies should therefore be conceived as observational bottom-up studies and the top-down approach should not be adopted.

Chapter 2

Asthma

According to the Global Initiative for Asthma (GINA) international guidelines on the disease management and prevention [29], asthma is a chronic disease of the airways characterized by (i) a more or less accessory bronchial obstruction usually reversible spontaneously or following therapy, (ii) bronchial hyperreactivity and (iii) an accelerated decline in respiratory function that may evolve, in some cases, into an irreversible airway obstruction. Bronchial asthma is therefore defined as a pathology characterized by peculiar clinical, physiological and pathological aspects. The infiltration of inflammatory cells, the release of mediators and the airways remodeling constitute the main pathogenetic mechanisms of the disease [30]. In asthma, inflammation is present even if the symptoms are episodic and the correlation between asthma severity and the intensity of inflammation has not yet been established. The inflammatory reaction causes a variable obstruction of the airways, rupture of the epithelium, infiltration in the airways of eosinophils and lymphocytes, vasodilation and finally remodeling of the airways, with trophic variations such as hyperplasia and hypertrophy of the smooth muscle, vascular neoformation, increase in the number of epithelial goblet cells

and deposit of interstitial collagen below the epithelium.

Asthma is the result of a complex interaction between the genetic and environmental factors, and its pathogenesis is not entirely clear [31]. These multiple factors interact with each other leading to a variable narrowing of the airways. Since asthma can be configured with extremely different clinical, biological and functional patterns, in recent years a new vision of the disease has been consolidated, in which its heterogeneous character is emphasized. The extreme heterogeneity of asthma allowed to identify different phenotypes and endotypes of the disease, in which a specific pathogenetic mechanism corresponds to a biological framework and to its consequent clinical manifestations [32]. The characterization of the disease endotype mainly recognizes two mechanisms underlying the inflammatory process: the activation of the Th2 inflammatory cascade, implicated in the allergic pathogenesis, whose activation will lead to the release of specific pro-inflammatory cytokines, with the eosinophilic granulocyte as the final mediator of the inflammatory process; and the Th1 mediated mechanism, which generally recognizes different inducing factors (pollutants, smoke, viruses, etc.) and is characterized by a different activation of the cytokine pattern, with the neutrophil granulocyte as the ultimate effector. Airway remodeling is thought to be the mechanism underlying the chronicity and progression of asthma. It is characterized by structural alterations both at the level of the large and the small airways and consists in the aberrant repair of the epithelium and in the accumulation of myofibroblasts that contribute to the deposition of extra-cellular matrix proteins and ultimately to the development of persistent bronchial obstruction. The main structural alterations in remodeling are sub-epithelial fibrosis, bronchial smooth muscle mass augmentation and angiogenesis.

From a clinical point of view, asthma is characterized by dyspnea, wheez-

ing, coughing and a feeling of chest tightness; all these manifestations are generally related to the extent of bronchial obstruction. Symptoms often occur at night or early in the morning and can be perceived differently between individuals and during different stages of the disease. During asthma attacks, patients generally have some characteristic clinical signs: cyanosis, numbness, speech reduction, tachycardia, pulmonary insufflation, use of accessory muscles and retraction of intercostal muscles during breathing.

2.1 Asthma epidemiology

Asthma is one of the most common diseases in the world [33], it is present in all countries but its prevalence varies considerably from nation to nation and can also show differences within the same country. According to the GINA guidelines [34], there are as many as 300 million people in the world suffering from the disease, one in every 20, and over 30 million asthmatics in Europe. The lack of a precise and unambiguous definition of asthma implies the difficulty to precisely estimate the prevalence of this disease in the world. However, through the application of standardized methods to measure the prevalence of asthmatic symptoms in children and adults, it seems that the global prevalence of asthma is between 1% and 18% of the population in different countries.

In most European countries, the prevalence and the incidence of asthma increased substantially between 1950 and 2000, but in the past decade, at least in Western Europe, this increase has levelled off [35]. In general, in the 28 countries from the European Community, it was estimated that there are more than 30 million of asthmatics (mean asthma prevalence of 7%), that account for a total expense of more than EUR 20 billion in the European population aged from 15 to 64 years [35].

The prevalence trend in adults is still controversial: some studies suggest stabilization or decrease, while others describe a further increase. However, the stabilization of the prevalence trend seems to be due to the improvement of anti-asthmatic treatments, and the incidence plateau seems to be due to the saturation phenomenon: the development of the disease has been achieved in all susceptible subjects.

Unfortunately, few studies reported a reliable assessment of the trend of asthma prevalence, as it requires repeated cross-sectional studies on different occasions on the same population and the use of an identical study design over an adequate period of time. A study with these characteristics [36], carried out on the adult population of Italy, reported an increase of the median prevalence of current asthma from 4.1% in 1990 to 6.6% in 2010.

According to a recent paper [37] that evaluated the rates of asthma incidence and remission in Italy from 1940 to 2010, the rates of asthma incidence linearly increased, with a percent-age increase of +3.9% (95%CI: 3.1-4.5), from 1940 up to the year 1995 and underwent a substantial stabilization in the late 90s. The stabilization of asthma incidence was explained by the authors to be due to a decrease in the rates of atopic asthma after 1995, while non-atopic asthma has continued to increase. This study also pointed out that, despite remarkable improvements in the treatment of asthma, the overall rate of remission (43.2/1000person-years) did not vary significantly in the last seventy years in Italy.

The prevalence of asthma tends to be higher in northern and western nations and, in general, in the developed compared to the developing countries [38].

In the developed countries the prevalence is higher among the poorest population, which probably has not a complete access to treatment, while

in the developing countries it is higher in the richer population, probably because of major differences in lifestyle (such as the different exposure to allergens, the possibility of treating the most serious diseases). In addition, the prevalence of asthma varies according to ethnic and racial differences, linked to underlying genetic variants, and to socioeconomic and environmental factors.

The interaction mechanism between genetic and environmental factors that causes the clinical manifestations of asthma is complex and not entirely known. Individual risk factors (e.g. genes, obesity, sex) predispose the individual to asthma [38]. Many genetic polymorphisms have been shown to be involved in the pathogenesis of asthma with differences in various ethnic groups. In particular, they are related to the production of allergen-specific IgE (atopy), the expression of bronchial hyperreactivity, the production of inflammation mediators and growth factors or the determination of the Th1/Th2 ratio in the immune response. Male sex is a risk factor for asthma in children, as the prevalence of asthma in males is about twice that of females up to 14 years of age. Over lifetime the difference between the sexes is reduced and in adulthood the prevalence of asthma is higher in females. On the other hand, environmental factors (e.g. allergens, tobacco smoking, occupational exposures, pollutants) may influence the possibility of developing asthma in predisposed subjects, triggering exacerbations and/or causing the persistence of symptoms. The relationship between allergen exposure and the onset of asthma is not clear, in any case it depends on the type of allergen, the dose, the exposure time, the age at the time of exposure and genetic factors. Smoking is associated with an accelerated decline in lung function in patients with asthma, may increase the severity of symptoms and makes patients less responsive to inhaled and systemic corticosteroid

therapy.

2.2 Asthma severity

Asthma can be classified according to its etiology and severity. Based on etiology, classical differentiation is between extrinsic (allergic) asthma, in which symptoms are triggered by an allergen (such as dust mites, pet dander, pollen or mold), and intrinsic (non-allergic) asthma, which tends to start later in life, is more common in females, and is typically more severe. Apart from some clinical differences concerning the onset, the severity and the natural history, the two forms are quite similar from a pathological, physio-pathological and pharmacological point of view. However, it is important to make an accurate etiological investigation for prevention purposes.

Instead, there are significant differences in terms of disease severity and exacerbations. The classification of asthma severity proposed by the "World Asthma Project" established by the National Heart, Lung and Blood Institute (NHLBI) and the World Health Organization (WHO) is based on the combination of different types of characteristics, such as symptoms, respiratory function and pharmacological dosage necessary for keeping asthma under control. In clinical practice, a correct classification of severity is needed for adapting treatment to the clinical needs of the asthmatic patient. The fundamental difference is between intermittent asthma with occasional episodes, which requires occasional treatment with symptomatic drugs, and persistent asthma with close episodes, which requires a background treatment with a dosage appropriate to the presence of a mild, moderate or severe form [38]. Severity should be reassessed periodically, usually every 3 months. Patients with clinical-functional characteristics of severe asthma require greater control because of the risk of fatal exacerbations. Asthmatic

exacerbations are defined as a worsening of symptoms associated with acute limitation of airway flow, due to inadequate treatment of a causal stimulus.

2.3 Asthma control

Asthma control is assessed on the basis of symptoms and the quality of daily life. It also includes the probability of loss of control, exacerbations, decreased respiratory function and side effects of treatment. The goal of asthma treatment is to achieve and maintain control of clinical manifestations of the disease over prolonged periods. Asthmatic patients can achieve various levels of asthma control, depending on several factors including disease severity, exposure to triggers, treatments and patient compliance. The GINA network has established guidelines for the assessment and management of asthmatic patients by health professionals. The GINA guidelines [39] classify asthma control levels as "well controlled", "partially controlled" and "uncontrolled", on the basis of daytime symptoms, night awakenings, normal activities affected by symptoms, and relief inhalers use. However, despite the GINA recommendations and other local guidelines, there is no standard management protocol for asthmatic patients throughout Europe.

2.4 Asthma burden

According to the WHO [33] 4.3% of the global population of younger adults aged 18-45 years, reported a doctor's diagnosis of asthma, 4.5% reported either a doctor's diagnosis or that they were taking treatment for asthma, and 8.6% reported that they had experienced attacks of wheezing or whistling breath (symptoms of asthma) in the preceding 12 months. Australia, Northern and Western Europe, and Brazil had the highest prevalence.

Because of its high prevalence among younger working age groups, evidence suggests an upward trend of the per-patient costs mainly due to productivity losses. Recently, several papers have been published on the economic burden of asthma, but the estimates of the cost components generally vary between different countries. This may depend in part by the fact that while some studies included patients representative of all age groups [40-45], others applied age cut-offs [13,46-49]. However, most of the differences between studies depend on the different study design adopted. Indeed, some studies analyzed administrative health data [42-44,47,48,50] whereas others were designed as survey-based studies. Administrative health data regularly record the use of health resources but they generally consider only a limited amount of cost items. On the other hand, survey-based studies [13,40,41,46] may have a high degree of representativeness and external validity, but at the same time they may suffer from recall bias, which can alter the estimates of the burden. Nevertheless, a good agreement between self-reported and administrative data was assessed in terms of direct costs.

Despite the asthma costs vary widely from country to country it was estimated that the mean cost per patient per year is $USD 1,900 and $USD 3,100 in Europe and in USA, respectively [51].

With regard to cost components, literature reports that medication represent the major burden among direct costs both in North America and Europe, ranging from 51% in the United States [42] to 68% in Canada, and from 45% (Spain) to 84% (Germany) in 11 European countries during 1999-2002 [46]. Whilst cost of medications are increasing over time in the United States and Canada [41,42,47], in the Middle-East and South-East Asia, out-patient costs were responsible for a greater proportion of the total costs [43,44,49]. Probably, this may be explained by the lack of access to

the more expensive combination inhalers, which can result in higher rates of poorly controlled asthma, causing frequent visits to care providers. In North America the costs of in-patient care and of physician visits demonstrated a decreasing trend [42,47], whilst one study reported that the costs of out-patient visits and ED visits increased by 3% and 8%, respectively [41]. As demonstrated by a review on the asthma burden, in general, the loss of working days represents a higher cost compared to direct costs [52]. Few studies have reported information on the indirect costs of asthma and, among these, the results vary widely between the various jurisdictions. The lowest and highest estimates come from the same country (Republic of Korea) [44,48] and this could be partly due to different definitions and measurement methods among the studies. Indeed, in the study with the highest estimated indirect costs, all sources of productivity loss (work/school days lost, early retirement and work absenteeism) have been considered.

Asthma can be a controllable condition in most patients [53]. Studies that report data on the potential reduction in the costs of asthma when an individual moves from uncontrolled to controlled status are useful from a clinical and public health perspective. In fact, asthma exacerbations require the consumption of healthcare resources and productivity losses, and therefore increase the economic impact of the disease. However, in order to assess the association between the level of asthma control and costs, studies should consider the effect of potential confounding variables, such as asthma severity and socio-economic status. Unfortunately, among the studies reporting costs across different levels of asthma control [46,48,54-57], only few of them used regression-based methods to derive an adjusted estimate of the impact of the lack of control on the costs of the disease [54-56].

Two COI studies that evaluated the costs of asthma according to the

degree of disease control and considering the effect of potential confounding variables were published by Accordini et al in 2006 and 2013 [46,58]. The first COI study was carried out on current adult asthmatics (20-44 years) from the general population in Italy and demonstrated that asthma-related costs were substantial even in unselected patients, were largely driven by indirect costs and that about half of the total cost was due to a limited proportion of poorly controlled asthmatics. The more recent study published in 2013 by the same author, was conducted in adult patients (30-54 years) with persistent asthma, who were identified in general population samples from 11 European countries and examined in clinical settings in the European Community Respiratory Health Survey II between 1999 and 2002. This study demonstrated that among European adults, the cost of persistent asthma drastically increases as disease control decreases suggesting that substantial cost savings could be obtained through the proper management of adult patients.

Chapter 3

Chronic obstructive pulmonary disease (COPD)

COPD is one of the most common chronic and disabling inflammatory diseases worldwide [59, 60]. It causes obstructed airflow from the lungs and the related symptoms include breathing difficulty, cough, mucus (sputum) production and wheezing. Most people with COPD have a combination of both chronic bronchitis, which involves a long-term cough with mucus, and emphysema, which involves damage to the lungs over time. COPD is caused by the long-term exposure to irritating gases or particulate matter, most often from cigarette smoke, and it increases with age. It is associated with substantial morbidity and mortality. Indeed, subjects with COPD are at an increased risk of developing heart disease, lung cancer and a variety of other conditions.

The first objectives to pursue for a successful management of COPD are to early diagnose the disease and to prevent its progression. The assessment of COPD is based on a history of exposure to risk factors and the presence of airflow limitation that is not fully reversible, with or without the presence of

symptoms. Spirometry test represents the gold standard as it is the most reproducible, standardized, and objective way of measuring airflow limitation. In order to prevent the onset and progression of COPD an important goal is the reduction of total personal exposure to occupational dusts and chemicals, and indoor and outdoor air pollutants. In particular, smoking cessation represents the single most effective and cost-effective way to reduce the risk of developing COPD and to stop its progression. To effectively manage stable COPD, it should be adopted a stepwise increase in treatment, depending on the severity of the disease. However, none of the existing medications for COPD has been shown to modify the long-term decline in lung function and bronchodilator medications (e.g. 2-agonists, anticholinergics, theophylline, and a combination of one or more of these drugs) are used to decrease symptoms and complications. Exacerbations of respiratory symptoms requiring a medical intervention are important clinical events in COPD and they can be caused by an infection of the tracheobronchial tree and air pollution, though the cause of about one-third of severe exacerbations cannot be identified. Inhaled bronchodilators are the election treatment of exacerbations thought patients with clinical signs of airway infection (e.g. increased volume and change of color of sputum or fever) may benefit from antibiotic treatment.

Because of the heterogeneity and complexity of the disease, the concept of endotypes (e.g. COPD with alpha-1-antitrypsin deficiency, persistent pathogenic bacterial colonization or persistent systemic inflammation) was introduced over the past few years, referring to patients' subtypes defined by a distinct pathophysiological mechanism. The correct identification of the different subtypes of the disease could allow a targeted treatment and a personalised management of patients. Within this complexity, a key role is played by the typical coexistence of other medical conditions beside COPD

that can worsen the severity of the disease in individual patients by increasing both morbidity and mortality. Therefore, the management of COPD should have a holistic approach considering the assessment and the treatment of comorbidities along with the traditional pharmacological therapy focused on treating chronic airflow limitation. Comorbidities commonly associated with COPD are: cardiovascular diseases, skeletal muscle dysfunction, ostheoporosis, psychological disturbances, gastro-oesophageal reflux disease, obstructive sleep apnoea, diabetes/metabolic syndrome, renal insufficiency, lung cancer and infections. It was estimated that up to 90% COPD patients can have at least one of these comorbidities [61].

3.1 COPD definition and severity

So far, the published epidemiological studies on COPD are based on different definitions that consider either symptoms, a diagnosis made by a doctor and/or spirometric data. The International Union against Tuberculosis and Lung Disease and the European Community Respiratory Health Survey (ECRHS) provided questionnaires on respiratory health, which include questions on the clinical definition of chronic bronchitis.

The most used spirometric definition of COPD is that recommended by the Global Initiative for chronic Obstructive Lung Disease (GOLD), which considers a post-bronchodilator Forced Expiratory Volume in 1 second (FEV1)/Forced Vital Capacity (FVC) ratio less than 0.70, whatever the age and the sex of the patients [60]. However, multiple studies have shown that the GOLD definition tends to overdiagnose COPD in the elderly as the FEV1 value decreases more quickly with age than FVC. The international Burden of Obstructive Lung Disease (BOLD) study suggested a definition based on a FEV1/FVC ratio less than the lower limit of normal (LLN), and

FEV1 either less than 80% or below the LLN. Using the LLN, based on age- and sex-stratified pre-bronchodilator cut-off values of the FEV1/FVC ratio, is one way to minimise the potential misclassification by considering abnormal only the values lower than the 5th percentile of a healthy, non-smoking population. Afterwards, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) recommended to replace the fixed cut-off criterion (FEV1/FVC<0.70) with the LLN. As spirometry is the most reproducible way of measuring airflow limitation and FEV1 is the variable most closely associated with prognosis [62], the degrees of COPD severity are usually assessed according to FEV1. The GOLD guidelines categorize airflow limitation for patients with FEV1/FVC<0.70 into four different stages: mild (FEV1>=80% predicted), moderate (50%<=FEV1<80% predicted), severe (30%<=FEV1<50% predicted) and very severe (FEV1<30% predicted), where the FEV1 predicted is defined as FEV1% of the patient divided by the average FEV1 in the population for any person of the same age, height, gender, and ethnic group.

Using data from a large cohort of young adults (20-44 years), followed for nine years during the 1990s as part of the European Community Respiratory Health Survey (ECRHS) I, Cerveri et al [63] demonstrated the importance of using statistically derived spirometric criteria to identify airflow obstruction. In this study, the LLN equations for young adults were obtained from the normal non-smoking participants in the ECRHS I and clinical and functional characteristics and longitudinal outcomes of the subjects identified as "normal" by the fixed ratio but abnormal by the LLN were investigated. The authors showed that the 70% fixed cut-off identified less than 50% of young subjects who had evidence of airflow obstruction using the LLN criteria.

In addition, a study published by de Marco et al in 2009 [64] determined

that COPD was associated with poor long-term outcomes in smokers and in symptomatic subjects only and suggested that definitions of COPD based exclusively on the presence of airflow obstruction assessed by spirometry may include a non-negligible percentage of subjects with no clinically relevant disease (asymptomatic nonsmokers).

Different studies investigated whether the presence of chronic symptoms can predict the future occurrence of COPD, after adjusting for the well-known risk factors, such as smoking habits, giving contrasting results [65-67].

In order to test whether chronic cough/phlegm and dyspnea are independent predictors of the subsequent occurrence of COPD, de Marco et al [68] evaluated, using the GOLD staging system, the incidence of COPD in a cohort of young adults identified in 1991-1993 in the ECRHS I and reassessed in 1999-2002 in the ECRHS II.

The results of this study showed that the incidence of COPD was substantial even in young adults and that the presence of chronic cough/phlegm identified a subgroup of subjects with a high risk of developing COPD, independently of smoking habits.

3.2 COPD epidemiology

COPD is a complex and heterogeneous condition characterized by a huge morbidity and mortality burden. Indeed, it is predicted that by 2020 it will become the third leading cause of death accounting for over 6 million deaths annually worldwide. The Global Burden of Disease Study [69] reported that globally, from 1990 to 2015, the prevalence of COPD increased by 44.2%, whereas age-standardised prevalence decreased by 14.7%.

Although the prevalence of COPD has been well studied, few population-based studies investigated its incidence. Overall, studies reported a wide

range in incidence rates varying between 2-16/1000PY depending on the COPD definition being used and the population being studied [68,70-78].

From 1991 to 2002 the incidence of COPD in an international cohort of young adults from 12 European countries, was 2.8 cases/1,000/yr (95% CI: 2.3-3.3) [68].

Afonso et al estimated that three out of 1000 subjects per year were diagnosed with COPD in the Netherlands and that the incidence, higher in men than in women, increased rapidly with age [79].

In addition, in a more recent prospective population-based cohort study (Rotterdam Study) the overall incidence of COPD was 9.4/1000 PY, with a higher incidence in males and in smokers [80].

However, it has been estimated that only 10-15% of all COPD cases are identified. A study [81] conducted in the United Kingdom on 39,000 patients with a COPD diagnosis has shown the failure of physicians and patients to recognise the significance of symptoms, which results in a missing opportunity for an earlier diagnosis.

3.3 COPD burden

As for asthma, the costs of COPD vary largely in different regions of the world.

Indeed, according to a recent review [82] the average total direct costs of COPD per person-year range from $USD 536 to $USD 6,213 in North America and from $USD 679 to $USD 2,865 in Europe. The same review reported that the indirect costs of COPD per person-year range from $USD 227 to $USD 985 in North America and from $USD 124 to $USD 3,754 in Europe.

This may depend on both an actual variability in COPD costs and on

differences in costing methods. For example, a critical factor is represented by the quantification of the economic impact of comorbid conditions. In fact, a US study [83] showed a reduction in the estimate of direct costs from $USD 6,213 to $USD 536 per patient in a year after the statistical adjustment for demographic variables and 19 comorbidities. Though it is difficult to discriminate COPD attributable costs from the costs due to comorbid conditions [84], it is also true that these conditions contribute to the pathophysiological process of COPD and, therefore, should be included in the computations of the COPD burden. In addition, as in the case of asthma, the published studies on COPD costs vary substantially in terms of patients' age (i.e. working age groups [45,49] or younger adults [13,50]) or the methodological approach (i.e. population-based survey [18,49,50] or administrative health data [83-88]). Moreover, fundamental differences between studies exist in the level of disease severity [14] (only patients with moderate or with severe COPD) or duration [85,86] (i.e. patients with newly diagnosed COPD). The above-mentioned factors, together with the fact that COPD is often underdiagnosed in many countries, make difficult to compare costs across the different studies.

Chapter 4

Chronic bronchitis

Chronic bronchitis is defined as an inflammation of the lining of the airways leading to narrowing and obstruction, and resulting in daily cough with sputum production that lasts for at least three months, two years in a row. Although people of any age can develop chronic bronchitis, the majority of people diagnosed with the disease are 45 years of age or older. Chronic bronchitis is characterised by the loss of the airway cell's cilia, whose function is to maintain the airways clear of particles and fluids, and their replacement by goblet cells that secrete mucus into the airway. The mucus represents an excellent medium for growing bacteria and often becomes infected causing an inflammation that can significantly inhibit the airflow to and from the lung alveoli by narrowing and partially obstructing the bronchi and bronchioles. The airway irritation can stimulate the muscles surrounding the airways causing a bronchospasm that can result in further airway narrowing. As chronic bronchitis is characterised by a long-standing inflammation, the muscular spasm can result in a fixed, nonreversible narrowing of the airway, namely COPD. Indeed, it is generally difficult to separate these conditions as patients often have components of each disease. In chronic bronchitis, the

fixed airway obstruction and inflammation can cause an impairment in the blood oxygenation and in carbon dioxide removal. The main symptoms of chronic bronchitis are cough and sputum production, dyspnea and wheezing. If these symptoms worsen or become more frequent, they often require antibiotics, an increase in respiratory inhaled medications or steroid treatment. Chronic bronchitis is commonly caused by cigarette smoking or by other inhaled repeatedly bronchial irritants. Though chronic bronchitis is a progressive condition, it could often have a good prognosis for many years if it is diagnosed before bronchial damage occurs and if risk factors (smoking, exposure to airborne chemicals and secondhand smoke, dust, and other bronchial irritants) are avoided.

The prevalence of chronic bronchitis and the distribution of its risk factors vary widely both across and within countries and most epidemiological studies report chronic bronchitis data only in elderly people [89-91].

An European study (ECRHS) [92] carried out on 18,000 subjects aged 20-44 yrs evidenced that the median prevalence of chronic bronchitis was 2.6%. In addition, this study pointed out that the prevalence of chronic bronchitis varies widely across countries (0.7-9.7%) and that only 30% of this geographical variability in prevalence was explained by differences in smoking habits, suggesting that other environmental and/or genetic factors may play an important role.

Chapter 5

Aims

Despite in recent years literature on the socioeconomic burden of asthma has increased, most studies derived their estimates from official statistics or from clinically selected samples, which do not permit to evaluate the whole range of disease severity and control. Most studies have been focused on estimating average costs of asthma only in a defined period and they have not analysed the trend of the socio-economic burden over time according to the level of disease severity and control. In addition, very few COI analyses are recent and have been carried out at an international level in the general population in Europe on the differential costs of asthma and other respiratory diseases. Furthermore, there is few information on the socio-economic burden of chronic bronchitis, also in relation with the presence of comorbidities.

In order to investigate the mentioned points, the objectives of the present thesis are:

- **Study 1: Cost of asthma, COPD and chronic bronchitis**

  To evaluate the differential cost of asthma, COPD, and chronic bronchitis among adult subjects from the general population in Europe, who were identified at the ECRHS III (2010-2013).

- **Study 2: Cost variations of asthma over ten years**

  To estimate the ten-year variation of asthma costs in the adult asthmatics who were identified at the ECRHS II (1998-2002) and participated in the ECRHS III (2010-2013).

Chapter 6

Source of data

The ECRHS is the first international multi-centre survey of the prevalence, incidence, determinants and management of asthma and COPD in the general young adult population. It started during the 1990's in response to the global increase in asthma prevalence observed during the previous decades and, though it was originally designed to cover most areas of the European Community, it also included other countries outside Europe. The ECRHS used standardised protocols for physician-led interviews, the assessment of atopy through skin prick tests and the measurement of serum specific IgE to common allergens, lung function measurements, tests of airway hyperresponsiveness, and blood and urine collection.

Between 1991 and 1993, 56 centres from 25 countries across Europe and other parts of the world took part in the first survey (ECRHS I) [93]. A community-based random sample of young adults aged 20-44 was identified from available population based registers and was invited to complete a short postal screening questionnaire (stage 1). Between 1991 and 1994, a random sample of the responders to the screening questionnaire was invited to attend the local clinical centre (stage 2), where the selected subjects provided more

detailed information on their health status and risk factors for asthma and allergic disease (family history of disease, occupation, childhood and current exposure to pets, exposure to tobacco smoke, dampness, ventilation, use of soft furnishings and use of gas appliances). Blood samples were taken and serum was tested for specific IgE to house dust mite, cat, grass and Cladosporium herbarum. Pre-bronchodilator forced expiratory volume in one second (FEV1) and forced vital capacity (FVC), and bronchial reactivity to methacholine were measured. In addition, most centres enriched their random sample with a symptomatic sample of the individuals who had reported symptoms suggestive of asthma (being woken by breathlessness or asthma attacks in the last 12 months) and/or current use of asthma medication, but who had not been selected as part of the random sample at the screening stage. Around 200,000 participants completed the screening questionnaire (stage 1) and around 26,000 from 45 centres participated in the clinical stage (stage 2).

Between 1998 and 2002, twenty-nine of the initial 56 study centres performed a follow-up investigation (ECRHS II) [94]. All participants in the clinical stage of the ECRHS I (from both the random and symptomatic samples) were asked to take part in the ECRHS II. About 10,000 subjects were assessed in the clinical centres, where detailed information on their health status, risk factors, lung function tests and blood and urine samples were collected. Fourteen centres from 6 European countries also agreed to measure indoor and outdoor NO_2 at the participants' home using passive diffusion samplers (Passam, AG, Switzerland).

Twenty-nine centres from 14 countries (mostly European) carried out a further follow-up contact (ECRHS III). Individuals who had participated in the clinical stage of the ECRHS I were sent a short screening questionnaire

and, in 27 centres, those who responded were invited to a local clinical centre for a detailed interview, and for the assessment of lung function, FeNO, venepunctures for specific and total IgE testing. ECRHS III [95] started in 2010 and was completed in 2013 with over 6,000 participants from the original random sample and over 900 participants from the original symptomatic sample (Figure 13.1). The full research protocol can be found at `http://www.ecrhs.org`.

Chapter 7

Study 1: Cost of asthma, COPD and chronic bronchitis

7.1 Methods

7.1.1 Study participants

The study population was recruited from 26 centres in 12 European countries (Belgium, Denmark, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, Switzerland and the United Kingdom) and comprised adult subjects (aged 39-68 years) who had participated in the ECRHS III. The present study included 1,489 subjects with complete information on their disease status and with information on the cost components due to their illness. These patients were identified as having current asthma (n=781), COPD (n=181) or chronic bronchitis (n=527). Ethical approval was obtained for each centre from the appropriate ethics committee and written consent was collected from all participants.

7.1.2 Definitions

Asthma.

The subjects with current asthma were those who had reported a physician diagnosis of asthma during their life and at least one respiratory symptom (wheezing, nocturnal tightness in the chest, attacks of shortness of breath (SoB) following strenuous activity, SoB at rest, or SoB at night time) or at least one attack of asthma or use of medicines because of breathing problems in the past 12 months, at the clinical interview. According to the 2002 GINA guidelines, asthma severity was classified as "intermittent" or "persistent" considering a composite classification of clinical severity and daily medication regimen (Figure 13.2) [96,97]. In particular, clinical severity was subdivided into four increasing steps according to the frequency of diurnal/nocturnal symptoms in the past 3 months and to FEV1% predicted, the FEV1 value of a patient divided by the average FEV1 in the population for any person of the same age, sex and height (step 1: rare symptoms and FEV1>=80% predicted; step 2: occasional symptoms and FEV1>=80% predicted; step 3: frequent symptoms and 60%<FEV1<80% predicted; step 4: continuous symptoms and FEV1<60% predicted). Daily medication regimen was subdivided into four increasing steps according to the reported daily use in the past 3 months (step 1: no controller; step 2: low-dose inhaled corticosteroid [ICS], leukotriene modifier, theophylline, or cromones; step 3: low/medium-dose ICS combined with long acting beta-2-agonists [LABA], or medium dose ICS combined with leukotriene modifier or theophylline, or high-dose ICS alone; step 4: high-dose ICS combined with LABA or with leukotriene modifier). The subjects who had reported to have used oral steroids either in short courses or continuously in the past 12 months were classified in the step 4 of treatment. Finally, the level of asthma severity was defined by

combining the two independent classifications of clinical severity and daily medication regimen (intermittent: step 1 of both clinical severity and daily medication regimen; persistent: all the other combinations). In addition, the subjects who had reported at least one night spent in a hospital or at least one Emergency Department (ED) visit in the past 12 months were classified as persistent asthmatics.

The asthmatic subjects were further classified according to the level of asthma control using the GINA guidelines, version 2006 [39]. The components of asthma control were clustered into two groups:

Group 1:

- asthma attacks (at least one in the last 3 months) and/or daytime symptoms (at least once a week in the last 3 months)
- nocturnal symptoms (at least one in the last 3 months)
- activity limitations (at least 4 working days lost/days with impaired daily life activities because of asthma, wheezing or shortness of breath in the last 12 months)
- reliever treatment (short acting beta2-agonists used more than twice a week in the last 3 months) and/or rescue treatment (oral steroids used in the last 12 months)
- FEV1 $<$80% predicted

Group 2:

- hospitalizations and/or ED visits due to breathing problems (at least one in the last 12 months)
- oral steroids (daily use or short courses in the last 12 months)

- asthma attacks (more than 12 in the last 3 months)

The patients with asthma were defined "controlled" if they had reported no component from both group 1 and group 2, "partially controlled" if they had reported 1 or 2 components from group 1 but no component from group 2, "uncontrolled" if they reported >=3 components from group 1 or at least 1 component from group 2. A "disease status" variable was defined as follows: "persistent uncontrolled" (i.e. subjects with a persistent uncontrolled asthma), "persistent controlled/partially controlled" (i.e. subjects with a persistent controlled or partially controlled asthma), "intermittent" (subjects with an intermittent asthma)

COPD.

The COPD patients were those without asthma who had post-bronchodilator FEV1/FVC below the lower limit of normal (LLN; according to the Quanjer's equations [98]). The best values of FEV1 and FVC were selected based on up to five technically acceptable manoeuvres.

Chronic bronchitis.

The subjects with chronic bronchitis were those who had reported cough and/or phlegm episodes for more than three months a year and for at least two consecutive years at the clinical interview, and who did not have either asthma or COPD.

7.1.3 Cost estimation

During the clinical interview, all subjects provided detailed information on the direct healthcare costs (number of specialist and general practitioner visits, type and number of laboratory tests, medication regimen, type of vaccinations, number of ED visits and nights spent in a hospital per type of ward and diagnosis) and on the indirect costs (premature retirement,

number of lost working days and number of days with limited, not work-related activities, such as looking after children, housework or studying) due to their breathing problems in the past 12 months. The number of doses of each drug consumed was collected for the previous 3-month period and was multiplied by 4 on the assumption that drug consumption in the past 3 months was representative of the entire year. The information on oral steroids was collected for the previous 12-month period.

The monetary unit value of each cost component (Table 12.1) was calculated in Euro on the basis of rates, wages and prices in 2013 obtained at the national level from official sources in 9 European countries (Estonia, France, Germany, Iceland, Italy, Norway, Sweden, Switzerland and the United Kingdom) (listed in the Appendix). When the national monetary values were not available for the reference year, they were converted to the 2013 figures using the corresponding Harmonized Indices of Consumer Prices (HICPs) as annual average inflation rates (Eurostat, `http://epp.eurostat.ec.europa.eu`). Due to the variability of the monetary figures among the ECRHS countries and to the differences among their health systems, the monetary unit value of each cost component was computed as the median of the national figures and adjusted for the purchasing power parity (PPP).

The economic evaluation was carried out from the societal perspective and the cost components were estimated following the bottom-up approach, by multiplying the number of times each patient resorted to healthcare services, the number of doses of each drug consumed, the number of lost working days and the number of days with limited, not work-related activities reported by each subject, by their proper monetary unit value (Table 12.1).

7.1.4 Statistical analysis

The mean annual cost per patient (with the 95% confidence interval [95%CI]) was provided for each cost component. Confidence limits were computed by the bias-corrected and accelerated bootstrap method [99] considering 20,000 replications. In order to minimize information losses due to missing values, the mean total cost per patient was obtained by summing up the estimates of all the cost components.

Multivariable analyses of the association among the individual total cost (computed as the sum of the available cost components for each subject, rounded to the nearest integer) for each disease (asthma, COPD and chronic bronchitis) and a set of potential determinants were performed by using 2-level random-intercept negative binomial regression models (subject: level 1 unit; centre: level 2 unit). This type of model was chosen for modelling the overdispersed count data and the hierarchical structure of the ECRHS data. The following potential determinants were included in the different models:
- cost of asthma: gender, age (5-year increase), body mass index (1-unit increase), smoking habits (past/current vs never smoking), disease status (persistent uncontrolled vs intermittent; persistent controlled vs intermittent), age at onset (>=20 vs 0-9 years; 10-19 vs 0-9 years), coexistence with chronic bronchitis;
- cost of COPD: gender, age, body mass index, smoking habits, coexistence with chronic bronchitis;
- cost of chronic bronchitis: gender, age, body mass index, smoking habits, coexistence of comorbidities (presence of at least one of the following: stroke, angina, heart attack, heart failure, coronary heart disease, hypertension, arythmia, gastritis, gastric ulcers, gastro-oesophagel reflux, hiatus hernia, oesophagitis, Crohn's disease, type 1 and 2 diabetes, hypothyroidism, sleep

apnea syndrome, pulmonary embolism, osteoporosis, migraine and depression), coexistence with allergic rhinitis.
The results of the multilevel negative binomial regressions were summarized as incidence rate ratios with the 95% confidence interval (CI).

The statistical analyses were performed using STATA software, release 15.1 (StataCorp, College Station, Texas, USA) and the R statistical software (version 3.5.0).

7.2 Results

7.2.1 Main characteristics of the subjects

Out of the 781 asthmatic subjects included in the analysis, 46% had an intermittent asthma, 31% had a persistent controlled/partially controlled asthma and 23% had a persistent uncontrolled asthma (Table 12.2). The intermittent asthmatics were on average younger than the patients with persistent asthma. In addition, the subjects with uncontrolled asthma had a median BMI of 28.4 and 49% of them reported chronic cough or phlegm..

The COPD sample was mainly represented by individuals with a mild/ moderate disease (96%) (Table 12.3). These patients had a median BMI of 26.1 (IQR: 23.1-29.6) and were more often current or past smokers (82%). About one COPD patient out of four reported the coexistence of chronic cough or phlegm.

More than sixty percent of subjects with chronic bronchitis reported coexisting comorbidities (Table 12.4). These patients were older on average (p-value$<$0.0001) and had a higher BMI (median: 27.6) than the subjects without comorbidities (p-value $<$0.001).

7.2.2 Cost of the diseases

Asthma

The mean annual cost per patient increased as the degree of disease control decreased, ranging from EUR 143 (95%CI: 94-204) and EUR 398 (95%CI: 345-457) for the subjects with an intermittent and a persistent controlled/partially controlled asthma, respectively, to EUR 5,050 (95%CI: 3,296-6,275) for the subjects with a persistent uncontrolled disease (Tables 12.5-12.7). The distribution of the cost components differed according to the disease status (Figure 13.3). Among the intermittent asthmatics, the direct medical costs represented 41% of the total cost generated by the disease (EUR 58), whereas the remaining 59% was due to the indirect non-medical costs (EUR 85). These figures were 95% (EUR 380) and 5% (EUR 18) for the patients with a persistent controlled/partially controlled asthma, and 20% (EUR 992) and 80% (EUR 4,058) for the patients with a persistent uncontrolled disease, respectively. In addition, in the patients with persistent asthma, drug costs accounted for 82% and 8% of the total cost when the disease was controlled/partially controlled and uncontrolled respectively. In the latter group of patients, hospital costs represented 9% of the individual burden.

At the multivariable analysis, in patients with asthma, the lack of control of a persistent disease was the strongest determinant of the individual total cost, which was about 27-fold higher compared to the cost of an intermittent asthma (IRR=26.80, 95% CI: 16.82-42.69) after adjusting for the effect of the other potential predictors (Table 12.8). The individual annual cost significantly increased (IRR=1.56, 95% CI: 1.07-2.28) with the coexistence of chronic cough or phlegm and with age (5-year increase: IRR=1.18, 95%

CI: 1.04-1.34). Predictive margins were EUR 166 [95% CI: 115;217], EUR 456 [95% CI: 282;631] and EUR 4,446 [95% CI: 2,720;6,171] for intermittent, controlled and uncontrolled asthma, respectively.

COPD

In the patients with COPD, the mean annual cost was EUR 694 (95%CI: 198-1,253) (Table 12.9). Most of the cost (80%) was represented by indirect nonmedical costs followed by drugs (10%), hospital services (7%) and doctor visits/laboratory tests (3%) costs (Figure 13.3). At the multivariable analysis, the individual annual cost significantly increased (IRR=17.10, 95% CI: 3.04-96.22) with the coexistence of chronic bronchitis (Table 12.10).

Chronic bronchitis

In the patients with chronic bronchitis, the mean annual cost largely increased from EUR 94 (95%CI: 38-166) to EUR 642 (95%CI: 249-1,131) according to the presence of comorbidities (Tables 12.11 and 12.12). The total cost was mainly driven by the indirect nonmedical costs and the distribution of the other cost components differed according to the presence or absence of comorbidities (Figure 13.3). Indeed, as compared to the patients without comorbidities, those who reported the coexistence of other diseases showed an increase in hospital costs but decreasing costs due to doctor visits/laboratory tests and drug utilization. After adjusting for the effect of the other potential predictors, the individual total cost was more than 3-fold higher among patients with comorbidities compared with those with only chronic bronchitis (IRR=2.88, 95% CI: 1.10-7.55). In addition, the individual total cost significantly increased with the presence of allergic rhinitis (IRR=3.50, 95% CI: 1.37-8.91) and with age (5-year increase: IRR=1.70,

95% CI: 1.20-2.39) (Table 12.13). The predictive margins were EUR 198 [95% CI: -23;418] and EUR 570 [95% CI: 125;1,015] for chronic bronchitis without and with comorbidities, respectively.

Chapter 8

Study 2: Cost variations of asthma over ten years

8.1 Methods

8.1.1 Study participants

The present study included the subjects aged 29-56 years at the ECRHS II, who had been recruited from 25 study centres in 11 countries (Belgium, Estonia, France, Germany, Iceland, Italy, Norway, Spain, Sweden, Switzerland and the United Kingdom) and who had been identified as having physician-diagnosed current asthma at both the ECRHS II and ECRHS III. Only the 410 asthmatics with complete information on their disease status and with information on the cost components due to their illness at both examinations were included in the present analysis (Figure 13.4).

8.1.2 Definitions

The current asthmatics were those who had reported a physician diagnosis of asthma during their life and at least one respiratory symptom (wheez-

ing, nocturnal tightness in the chest, attacks of SoB following strenuous activity, SoB at rest, or SoB at night time) or at least one attack of asthma or use of medicines because of breathing problems in the past 12 months, at the clinical interview. These patients were further classified according to their "disease status" as in the Study 1 ("intermittent", "persistent controlled/partially controlled" and "persistent uncontrolled"; see Section 7.1.2) [38,96] at both the ECRHS II and ECRHS III. The asthmatic patients were categorised into three different groups according to the variation in their disease status from the ECRHS II to the ECRHS III:

- "intermittent": intermittent asthma at both the ECRHS II and ECRHS III;
- "improved": (i) persistent uncontrolled asthma at the ECRHS II and intermittent asthma at the ECRHS III; (ii) persistent uncontrolled asthma at the ECRHS II and persistent controlled/partially controlled asthma at the ECRHS III; (iii) persistent controlled/partially controlled asthma at the ECRHS II and intermittent asthma at the ECRHS III; (iv) persistent controlled/partially controlled asthma at both the ECRHS II and ECRHS III;
- "worsened": (i) intermittent asthma at the ECRHS II and persistent controlled/partially controlled asthma at the ECRHS III; (ii) intermittent asthma at the ECRHS II and persistent uncontrolled asthma at the ECRHS III; (iii) persistent controlled/partially controlled asthma at the ECRHS II and persistent uncontrolled asthma at the ECRHS III; (iv) persistent uncontrolled asthma at both the ECRHS II and ECRHS III.

8.1.3 Cost estimation

The asthmatic subjects provided detailed information on the direct healthcare costs and the indirect costs due to their breathing problems in the past

12 months (see Section 7.1.3) at both the ECRHS II and ECRHS III. The monetary unit value of each cost component (Table 12.14) was calculated in Euro on the basis of rates, wages and prices in 2013 obtained at the national level from the official sources in 9 European countries (Estonia, France, Germany, Iceland, Italy, Norway, Sweden, Switzerland and the United Kingdom) and used for the Study 1 (listed in the Appendix). The monetary unit values obtained for the reference year (2013) were used for quantifying the economic costs at both the ECRHS II and ECRHS III. The economic evaluation was carried out from the societal perspective and the cost components were estimated following the bottom-up approach, as described in the Study 1.

8.1.4 Statistical analysis

The mean annual cost per patient was estimated for those components available at both the ECRHS II and ECRHS III (Table 12.14), and the individual total cost was calculated at both the examinations. The 10-year variation in the mean annual cost per patient according to the change in the subject's disease status ("intermittent", "improved" and "worsened") was computed as the difference between the individual costs at the ECRHS II and at the ECRHS III. Cost variations were estimated by using a 2-level random-intercept Laplace quantile regression model (subject: level 1 unit; centre: level 2 unit), adjusting for the effect of sex, age, ever smoking and low socio-economic status. The statistical analyses were performed using STATA software, release 15.1 (StataCorp, College Station, Texas, USA) and the R statistical software (version 3.5.0).

8.2 Results

Thirty percent of our sample was represented by intermittent asthmatics at both the examinations (n=128), whilst 33% (n=136) and 36% (n=146) of the subjects reported an improved and a worsened disease status after a 10-year period, respectively. The group of patients with a worsened disease status showed a higher percentage of subjects with chronic cough or phlegm at the ECRHS II (37%), as compared with the intermittent (16%) and the improved (22%) patients (Table 12.15).

In the "intermittent" group, the mean annual cost per patient at the ECRHS II (EUR 166; 95%CI: 107-227) was similar to the value observed at the ECRHS III (EUR 157; 95%CI: 70-292) (Table 12.16). The indirect costs accounted for about 73% of the total cost at both the examinations, whereas the contribution of drug costs to the whole burden increased from 9% to 17% (Figure 13.5).

In the "improved" group, the mean annual cost per patient decreased from EUR 1,058 (95%CI: 752-1,423) at the ECRHS II to EUR 308 (95%CI: 227-405) at the ECRHS III (Table 12.17). Moreover, the distribution of the cost components was largely different at the two examinations: at the ECRHS II, the indirect costs were the main cost driver of the total cost (50%) and the hospitalizations costs accounted for 16%; at the ECRHS III, 67% of the total cost was due to pharmacological treatment (Figure 13.5).

In the "worsened" group, the mean annual cost per patient increased from EUR 2,137 (95%CI: 935-3,753) at the ECRHS II to EUR 4,023 (95%CI: 2,419-5,530) at the ECRHS III (Table 12.18). The avoidable costs (indirect nonmedical costs and the costs due to hospital services) accounted for about 87% of the total costs, even if hospital costs at the ECRHS II are due to the presence of a single patient with a high number of nights spent in a hospital

(Figure 13.5).

At the multivariable analysis, after adjusting for a set of potential confounders, the patients with an improved or worsened asthma from the ECRHS II to the ECRHS III showed reduced [-145 (95%CI: -275;-15) EUR; p-value=0.029] and increased [185 (95%CI: 59;311) EUR; p-value=0.005] mean annual costs, respectively, compared to the patients with an intermittent disease status at both the examinations (Table 12.19).

Chapter 9

Discussion

In recent years, literature on the socioeconomic burden of common chronic respiratory diseases, in particular asthma and COPD, has multiplied in industrialized countries, pointing out that these disorders place a huge burden on society not only in terms of disability and premature mortality, but also in terms of the direct costs due to the use of health services and the indirect costs due to productivity losses and leisure time forgone. Nevertheless, there are major gaps in cost estimates in literature, as very few COI analyses on these diseases have been carried out at an international level in the general European population. In addition, few COI studies have evaluated both direct and indirect costs and have estimated the socioeconomic impact of asthma according to the level of disease severity and control. Furthermore, there is few information on the socioeconomic burden of chronic bronchitis, also in relation with the presence of comorbidities, and on the change over time in asthma costs. This thesis aimed at investigating these mentioned areas of concern.

The main findings from these two studies on patients identified in the general European population are:

Asthma: (i) the economic cost was impressive in subjects with persistent uncontrolled asthma; (ii) in this group of patients, the individual total cost was largely driven by indirect non-medical costs; (iii) the individual total cost was increased by coexisting chronic cough or phlegm; (iv) the mean annual cost per patient significantly increased/decreased when the disease status worsened/improved over 10 years.
COPD: the mean annual cost per patient was not negligible even in patients with a mild/moderate form of the disease.

Chronic bronchitis: the mean annual cost per patient was high only when comorbidities were present.

Compared to the patients with an intermittent or a controlled/partially controlled persistent asthma, those with an uncontrolled persistent disease showed an impressively higher annual total cost. After adjusting for a set of potential confounding variables, the disease status was the main determinant of the individual total cost among adult asthmatics in Europe. Since uncontrolled persistent asthmatics are not a negligible group of subjects (23% of the individuals in our sample), this result points out that the economic burden of asthma could be largely reduced by proper management of these high-cost patients. These findings are in accordance with the results obtained in previous COI studies in different countries [46,52,58,100], in which poor asthma control was associated with an increase in socio-economic costs. However, most studies in literature reported estimates of the asthma costs across the levels of disease control without adjusting for the effect of confounding factors.
In the uncontrolled/persistent patients, the main determinant of the economic cost was represented by the indirect non-medical costs, which largely exceeded the direct medical expenditures. Given that asthma also affect

young adults, the contribution of productivity losses to the total cost can be substantial. This result is consistent with other studies [46,52], which demonstrated that the loss of productivity is the largest component of the total cost in Europe. Unfortunately, the majority of the studies fail to consider the contribution of premature retirement and leisure time forgone to the indirect costs, which instead was addressed in this thesis. High indirect costs highlight the great impact of asthma on individuals and families, because these costs also reflect the functioning and quality of life of patients in the presence of the disease [101]. Since indirect costs only occur when the disease has become sufficiently intrusive to interfere with a patient's lifestyle [102], the results of this thesis provide further evidence that asthma is a substantial burden for both the individual and society in Europe.

In agreement with other economic evaluations [46,58,103], medications costs were the largest driver of the direct medical expenditures, in particular among the persistent controlled/partially controlled asthmatics. It is known that out-patient and in-patient care are the largest component of direct costs in developing regions, while therapy costs are the main drivers in richer countries where there is a higher access to control medications. Good control achieved by adequate therapy could prevent encounters with the health care system and could reduce indirect costs. Accordingly, we found that the persistent/uncontrolled patients were characterized by a lower expenditure for medication and by higher costs due to hospital services and loss of productivity than better controlled patients.

Higher costs were reported by the asthmatics with coexisting chronic cough or phlegm. This result is consistent with the findings of previous COI studies and suggests that these subjects could have a poorer level of disease control [104] and/or a more severe form of asthma [105]. Indeed, since it is known

that chronic cough or phlegm significantly increases the risk of developing COPD in adult subjects regardless of smoking habits [68], the asthmatic patients with this symptom could have higher costs because of the coexistence of asthma and chronic obstructive pulmonary disease [106].

In the asthmatic patients, the mean annual cost significantly increased or decreased over a 10-year period when the disease status worsened or improved, respectively. This positive association was also confirmed after adjusting for a set of potential confounding variables, such as the socio-economic status. Most studies in literature reported a simple difference in the costs of asthma across the control levels completely ignoring the effect of confounding factors. Compared to the patients who reported a worsened disease status, those who had an improvement showed a significant increase in drug costs and a substantial decrease in the indirect non-medical costs and in the hospital services burden. The achievement of a proper asthma management can permit to control the disease in the majority of patients with substantial cost savings from both the individual and societal perspectives, since the costs of uncontrolled asthma far outweigh the additional costs of the control measures. This relationship might reflect the fact that patients whose asthma is controlled require less medication and incur fewer costs, and it is consistent with the results from prospective trials and initiatives aimed at increasing the use of controller treatment to achieve higher levels of control and to avoid exacerbations [107-110]. Indeed, while some patients might be relatively refractory to controllers and require costly maintenance treatment without reaching satisfactory levels of control [53], the majority of asthmatic subjects can achieve control with doses of treatment that are affordable in most health systems. Therefore, the potential reduction in the costs of asthma when an individual moves from the uncontrolled to the con-

trolled state can be considered a preventable source of burden for both the society and individuals.

The main strength of this thesis was to consider general population samples rather than clinically selected groups. While this approach made it possible to provide a real-world assessment of the economic impact of asthma, COPD and chronic bronchitis among adults in Europe, on the other hand it allowed to obtain very limited data on the cost of severe COPD. In spite of this, these findings showed that the mean annual cost per COPD patient was not negligible even in subjects with a mild/moderate form of the disease.

Overall, the prevalence of mild and moderate COPD is greater than the prevalence of severe and very severe COPD, but a not appropriate therapy in this group of patients could increase the total socioeconomic burden of this population [14]. Accordingly, the results of this thesis showed that patients with mild/moderate COPD were characterized by a relatively low expenditure for medication and very high indirect costs. Therefore, a more appropriate use of medications to treat COPD, particularly in the early stages of the disease, may reduce COPD-related complications and the overall burden of the disease. In addition, due to the fact that COPD is a heterogeneous disease, more research is required to understand the characteristics of each patient to provide the best individualised intervention.

So far, this is the first study that evaluated the cost of chronic bronchitis in patients who did not have either asthma or COPD, taking into account the impact of coexisting comorbidities on the total cost. In patients with chronic bronchitis, the total cost was mainly driven by the indirect non-medical costs and the distribution of the other cost components differed according to the presence of comorbidities. After adjusting for the effect of the other potential predictors, the individual total cost was more than 3-fold higher among pa-

tients with comorbidities compared with those with only chronic bronchitis and it was characterized by a four-fold increase in hospital costs. In subjects with chronic bronchitis, these results highlighted the important contribution of comorbidities to the total cost. Therefore, strategies for the prevention, diagnosis, and effective management of comorbidities would also decrease the overall financial burden associated with chronic bronchitis and should be promoted in future health economic evaluations of the disease.

Due to complexity and heterogeneity of human diseases, it may be very difficult to transform their possible interconnectedness with multimorbidities into economic models. However, as stated by Barabasi et al. [111], it would be difficult if not counter-intuitive to consider human diseases as invariably independent. Therefore, the pressure for including comorbidities in the evaluation of economic interventions seems to mount. Both systems biology and network medicine (linking disease phenotypic features with known disease genes or with protein interactions) are currently giving rise to new ways for understanding the interconnectedness of multimorbidities that may also enable more accurate health economic evaluations in the future.

In conclusion, the economic cost of asthma, COPD and chronic bronchitis is high in Europe also among patients from the general population. The cost of asthma significantly increases with the lack of disease control in patients with a persistent disease and with the coexistence of chronic cough or phlegm. The individual total cost is high in subjects with COPD and chronic bronchitis according to the presence of chronic cough or phlegm and comorbidities, respectively.

In the challenging context of health care systems, which are dynamically influenced by many factors (e.g. the emergence of new treatments, the update of disease guidelines, the change in demographics and in environmen-

tal/behavioral risk factors), decision makers need to make sound decisions on how to spend constrained resources to maximise population health. Therefore, up-to-date estimates of the socio-economic burden of diseases can help in informing resource allocations. COl studies can provide such estimates that are policy-relevant and can be used in combination with other information for developing a strategic perspective on health care.

Chapter 10

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Chapter 11

Appendix

SOURCE OF THE MONETARY UNIT VALUES

Estonia

Ministry of Social Affairs; Estonian Health Insurance Health Services List `https://www.riigiteataja.ee/akt/123022013001` [doctor visits, clinical and laboratory tests, ED visits, hospital admissions]. Estonian State Agency of medicines `http://www.sam.ee/` [pharmacological treatment, antibiotics, vaccinations, other vaccinations]. Statistical Office of Estonia `http://www.stat.ee/67065` [productivity losses, leisure time forgone].

France

Vidal drug compendium. 99th edition. OVP Edition, Paris [pharmacological treatment, antibiotics, vaccinations, other vaccinations]. Nomenclature Generale des Actes Professionnels, Union Nationale des Caisses de Securite Sociale, Paris [doctor visits]. Nomenclature des Actes de Biologie Medicale, site de l'Assurance Maladie `http://www.ameli.fr` [clinical and laboratory tests]. Assistance Publique des Hopitaux de Paris (APHP), Direction des Finances; Groupes homogenes de sejours (GHS) (diagnosis-related stays) [ED visits, hospital admissions]. Institut national de la statistique et des etudes

economiques (INSEE), France, http://www.insee.fr; Action Medicale et Sociale e Domicilie (AMSD) Paris [productivity losses, leisure time forgone].

Germany

Betriebskrankenkasse, Landesvertretung Bayern; Krauth C et al. Empirical standard costs for health economic evaluation in Germany - a proposal by the working group methods in health economic evaluation. Gesundheitswesen. 2005;67(10):736-46. Updated to 2012 using the rate of change in physician reimbursement per case according to the KBV (National Association of Statutory Health Insurance Physicians) [clinical and laboratory tests, doctor visits, ED visits]. Betriebskrankenkasse-Bavaria http://www.bkk-lv-bayern.de; http://www.krankenhaus-aok.de; German diagnose-related groups http://www.g-drg.de [hospital admissions]. Wissenschaftliches Institut der Allgemeine Ortskrankenkasse http://www.wido.de [pharmacological treatment, antibiotics, vaccinations, other vaccinations]. Federal Statistical Office of Germany https://www.destatis.de/DE/Startseite.html [productivity losses, leisure time forgone].

Iceland

Agreement between Medical Association in Iceland and The State Social Security Institute and cost figures from Reykjavik Primary Health Care Services, Department of Administration [doctor visits]. Agreement between Medical Association in Iceland and The State Social Security Institute [clinical and laboratory tests]. Icelandic Medicines Agency https://www.ima.is [pharmacological treatment]. Landspitali University Hospital, Department of Information and Finance [ED visits, hospital admissions]. Hagstofa Islands (Institute of Icelandic Economy). Reykjavik homeservice. Institute of Labour Market Research, Reykjavik [productivity losses, leisure time forgone].

Italy

Prontuario Servizio Sanitario Nazionale [pharmacological treatment, antibiotics, vaccinations, other vaccinations]. Tariffario regionale Regione Lombardia [clinical and laboratory tests, doctor visits, ED visits]. Ministero della salute - Tariffario Unico Nazionale 2009 [hospital admissions]. Istituto Nazionale di Statistica `http://www.istat.it`; Federazione Italiana Lavoratori Commercio Alberghi Mense e Servizi - Confederazione Generale Italiana del Lavoro (FILCAMS-CGIL) `http://www.filcams.cgil.it` [productivity losses, leisure time forgone]

Norway

Costs supplied by the Norwegian Pharmacy Association by a list of maximum prices set by the Norwegian Medicines Agency [pharmacological treatment]. Vegard HÃěvik Senior Advisor at the The Norwegian Directorate of Health [doctor visits, ED visits]. Haukeland University Hospital, Bergen, Norway [clinical and laboratory tests, hospital admissions]. Statistics Norway, Oslo [productivity losses, leisure time forgone].

Sweden

FASS, Swedish Association of the Pharmaceutical Industry `http://www.fass.se` and Uppsala County Council [pharmacological treatment, antibiotics, vaccinations, other vaccinations]. Uppsala County Council [doctor visits, clinical and laboratory tests, ED visits, hospital admissions]. Statistics Sweden, Stockholm `http://www.scb.se` [productivity losses, leisure time forgone].

Switzerland

Swiss Compendium of Medication [pharmacological treatment]. Swiss Medical Tariff (TARMED) [doctor visits, clinical laboratory tests, ED visits, hospital admissions]. Swiss Federal Office of Statistics and International

Labour Organization - Database of Conditions of Work and Employment Laws [productivity losses, leisure time forgone].

The United Kingdom

NHS Electronic Drug Tariff [pharmacological treatment, antibiotics]. National Institute for Health and Care Excellence [vaccinations]. Flu immunization programme of the Department of Health and National Institute for Health and Care Excellence on the basis of the information reported in the British National Formulary [other vaccinations]. Department of Health [ED visits]. Department of Health - National Schedule of Reference Costs (Year: 2013-14) [hospital admissions]. Personal Social Services Research Unit (PSSRU) [doctor visits]. NHS Foundation Trust [clinical and laboratory tests]. Office for National Statistics - Annual Survey of Hours and Earnings 2013, `http://www.ons.gov.uk/ons/index.html` [productivity losses, leisure time forgone].

Chapter 12

Tables

Table 12.1: Monetary unit value of each cost component (reference year: 2013).

	Monetary unit value (Euro)[1]
Doctor visits	24.397 (general practitioner) 40.561 (chest physician, allergy/internal medicine specialist or ENT doctor)
Clinical and laboratory tests	46.411 (spirometry) 48.380 (skin test for allergy) 113.704 (blood test for allergy-specific IgE) 20.565 (chest X-rays) 83.755 (thorax CT)
Pharmacological treatment	Market price of a single dose of each active principle[2]
Desensitisation for allergy	421.735 (desentisation to grass) 421.735 (desentisation to house dust mite 428.698 (desentisation to some other agent)
Injections	19.234 (long acting or depot steroid injections) Omalizumab: 179.393 (Xolair 75mg); 390.958 (Xolair 150mg)
Vaccinations	9.931 (vaccination against flu) 30.425 (vaccination against pneumonia)
ED visits	165.669
Hospital admissions	General ward: 783.587 (Asthma); 569.020 (COPD); 734.674 (Chronic bronchitis) Chest medicine: 799.496 (Asthma); 592.059 (COPD); 734.674 (Chronic bronchitis) Intensive care unit: 1,708.743 (Asthma); 1,986.688 (COPD); 1,708.743 (Chronic bronchitis) Rehabilitation ward: 321.850 (Asthma); 321.850 (COPD); 321.850 (Chronic bronchitis)
Productivity losses	159.843[3] 45.385 (housewives)[4]
Leisure time forgone	27.231[5]

ENT: Ear, Nose and Throat. 1. Purchasing Power Parity (PPP) adjusted median; reference year: 2013. 2. Obtained by averaging the market price of a single dose of the most prescribed medicines. 3. Average daily wage. 4. Hourly wage of part-time help (EUR 9.077), five working hours per day assumed. 5. Hourly wage of part-time help (EUR 9.077) as replacement value, three hours of limited, not work-related activities per day assumed.

Table 12.2: Main characteristics of the asthmatic subjects according to disease severity and control.

	Intermittent (n=356)	Persistent controlled/ partially controlled (n=244)	Persistent uncontrolled (n=181)	p-value[1]
Females (%)	58.7	61.5	60.2	0.790
Age (years), mean (sd)	53.0 (7.1)	54.8 (7.2)	54.8 (7.1)	0.002
BMI (Kg/m^2), median (IQR)	26.0 (23.1-29.1)	26.7 (24.1-31.4)	28.4 (24.2-32.8)	0.0002
Smoking habits (%)[2]				0.693
past/current smokers	52.3	50.0	54.1	
nonsmokers	47.7	50.0	45.9	
Age at onset (years) (%)				0.191
0-9	29.8	20.9	26.6	
10-19	21.7	22.7	24.3	
>=20	48.6	56.4	49.1	
Chronic cough or phlegm (%)[3]	19.5	32.6	48.9	<0.0001
Allergic rhinitis (%)[4]	62.9	63.1	66.7	0.667

sd: standard deviation; BMI: body mass index; IQR: interquartile range. 1. P-values obtained by using the chi-square test, or parametric or non parametric ANOVA. 2. Subjects were considered smokers -current or past- if they had reported having smoked at least 20 packs of cigarettes or 360 grams of tobacco in their lifetime, or at least one cigarette per day or one cigar a week for one year. 3. Having reported cough and/or phlegm from the chest, usually in winter and on most days for as long as 3 months each year. 4. Having reported any nasal allergies, including hay fever.

Table 12.3: Main characteristics of the subjects with COPD.

	COPD (n=181)
Females (%)	45.3
Age (years), mean (sd)	55.3 (6.8)
Severity status (%)	
Mild/moderate COPD	95.6
Severe COPD	4.4
BMI (Kg/m^2), median (IQR)	26.1 (23.1-29.6)
Smoking habits (%)[1]	
past/current smokers	81.8
nonsmokers	18.2
Chronic cough or phlegm (%)[2]	25.6
Allergic rhinitis (%)[3]	17.1

sd: standard deviation; BMI: body mass index; IQR: interquartile range. 1. Subjects were considered smokers - current or past- if they had reported having smoked at least 20 packs of cigarettes or 360 grams of tobacco in their lifetime, or at least one cigarette per day or one cigar a week for one year. 2. Having reported cough and/or phlegm from the chest, usually in winter and on most days for as long as 3 months each year. 3. Having reported any nasal allergies, including hay fever.

Table 12.4: Main characteristics of the subjects with chronic bronchitis with and without comorbidities.

	Chronic bronchitis without comorbidities (n=201)	Chronic bronchitis with comorbidities (n=326)	p-value[1]
Females (%)	48.3	46.6	0.715
Age (years), mean (sd)	52.6 (6.7)	55.7 (6.9)	<0.0001
BMI (Kg/m^2), median (IQR)	25.9 (23.4-29.3)	27.6 (24.6-31.2)	<0.001
Smoking habits (%)[2]			0.491
past/current smokers	62.7	65.6	
nonsmokers	37.3	34.4	
Allergic rhinitis[3] (%)	32.0	31.8	0.960

sd: standard deviation; BMI: body mass index; IQR: interquartile range. 1. P-values obtained by using the chi-square test or the Student's t-test. 2. Subjects were considered smokers -current or past- if they had reported having smoked at least 20 packs of cigarettes or 360 grams of tobacco in their lifetime, or at least one cigarette per day or one cigar a week for one year. 3. Having reported any nasal allergies, including hay fever.

Table 12.5: Components of the mean annual cost per patient with intermittent asthma (n=356).

	N° of users (%)	Mean N° of interventions/user	Mean N° of interventions/patient	Mean individual annual cost in 2013 (EUR)
Doctor visits	81 (23.0%)	2.1	0.5	14
General practitioner	72 (20.2%)	1.7	0.3	
Specialist	24 (6.7%)	2.3	0.2	
Clinical and laboratory tests	17 (4.8%)	2.1	0.1	5
Spirometry	12 (3.4%)	1.3	0.8	
Skin tests for allergy	3 (0.8%)	1.3	0.2	
Blood tests for allergy	5 (1.4%)	1.0	0.2	
Chest X-rays	7 (2.0%)	1.3	0.4	
Thorax CT	1 (0.3%)	1.0	0.1	
Pharmacological treatment	130 (36.5%)	-	-	39
Antibiotics	49 (13.8%)	1.3	0.2	2
Vaccinations	5 (1.4%)	-	-	5
Other vaccinations	81 (22.8%)	-	-	2
ED visits	0	0	0	0
Nights spent in hospital	0	0	0	0
	N° of patients who lost days (%)	Mean N° of days/ patient who lost days	Mean N° of days/ patient who lost days	Mean individual annual cost in 2013 (EUR)
Working days lost	16 (4.5%)	5.7	0.3	41
Leisure time forgone	9 (2.6%)	62.7	1.6	44
Premature retirement	0	0	0	0
Total cost				143 [95% CI: 94-204]

Table 12.6: Components of the mean annual cost per patient with persistent controlled asthma (n=244).

	N° of users (%)	Mean N° of interventions/user	Mean N° of interventions/patient	Mean individual annual cost in 2013 (EUR)
Doctor visits	107 (43.9%)	2.8	1.2	37
General practitioner	81 (33.2%)	2.3	0.8	
Specialist	55 (22.5%)	2.3	0.2	
Clinical and laboratory tests	28 (11.5%)	2.8	0.3	15
Spirometry	25 (10.3%)	1.7	1.4	
Skin tests for allergy	5 (2.1%)	1.0	0.2	
Blood tests for allergy	5 (2.1%)	1.2	0.2	
Chest X-rays	15 (6.2%)	1.4	0.7	
Thorax CT	4 (1.6%)	1.3	0.2	
Pharmacological treatment	192 (78.7%)	-	-	328
Antibiotics	42 (17.4%)	1.6	0.3	3
Vaccinations	5 (2.1%)	-	-	7
Other vaccinations	108 (44.3%)	-	-	5
ED visits	0	0	0	0
Nights spent in hospital	0	0	0	0
	N° of patients who lost days (%)	Mean N° of days/ patient who lost days	Mean N° of days/ patient who lost days	Mean individual annual cost in 2013 (EUR)
Working days lost	6 (2.5%)	4.7	0.1	18
Leisure time forgone	0	0	0	0
Premature retirement	0	0	0	0
Total cost				398 [95% CI: 345-457]

Table 12.7: Components of the mean annual cost per patient with a persistent uncontrolled asthma (n=181).

	N° of users (%)	Mean N° of interventions/user	Mean N° of interventions/patient	Mean individual annual cost in 2013 (EUR)
Doctor visits	127 (70.2%)	4.1	2.9	82
General practitioner	114 (63.0%)	3.5	2.2	
Specialist	54 (29.8%)	2.4	0.7	
Clinical and laboratory tests	54 (29.8%)	3.8	1.1	55
Spirometry	43 (23.8%)	2.0	1.5	
Skin tests for allergy	12 (6.6%)	1.3	0.3	
Blood tests for allergy	21 (11.6%)	1.1	0.4	
Chest X-rays	36 (19.9%)	1.9	1.2	
Thorax CT	11 (6.1%)	1.2	0.2	
Pharmacological treatment	160 (88.4%)	-	-	425
Antibiotics	88 (48.6%)	2.2	1.1	13
Vaccinations	7 (3.9%)	-	-	14
Other vaccinations	87 (48.1%)	-	-	5
ED visits	46 (25.6%)	1.9	0.5	79
Nights spent in hospital	15 (8.3%)	4.1	0.3	351
	N° of patients who lost days (%)	Mean N° of days/ patient who lost days	Mean N° of days/ patient who lost days	Mean individual annual cost in 2013 (EUR)
Working days lost	44 (24.4%)	16.6	4.1	647
Leisure time forgone	44 (24.4%)	70.3	17.2	468
Premature retirement	15 (9.0%)	203.8	18.4	2,943
Total cost				5,050 [95% CI: 3,296-6,275]

Table 12.8: Two-level negative binomial regression: asthma

	IRR	95% CI	p-value
Asthma status vs intermittent asthma (%)			
Persistent controlled	2.75	1.83-4.14	<0.0001
Persistent uncontrolled	26.80	16.82-42.69	<0.0001
Female	1.33	0.94-1.89	0.110
Age (5-year increase)	1.18	1.04-1.34	0.012
BMI (1-unit increase)	1.03	0.99-1.06	0.110
Past smokers/smokers vs nonsmokers	0.95	0.68-1.31	0.740
Age at onset, vs 0-9 years			
10-19 years	0.86	0.52-1.42	0.560
>= 20 years	1.31	0.86-1.97	0.200
Chronic cough or phlegm	1.56	1.07-2.28	0.020

Table 12.9: Components of the mean annual cost per patient with COPD (n=181).

	N° of users (%)	Mean N° of interventions/user	Mean N° of interventions/patient	Mean individual annual cost in 2013 (EUR)
Doctor visits	30 (16.6%)	2.6	0.4	12
General practitioner	25 (13.8%)	2.4	0.3	
Specialist	12 (6.6%)	1.5	0.1	
Clinical and laboratory tests	10 (5.5%)	3.6	0.2	9
Spirometry	8 (4.4%)	1.9	1.4	
Skin tests for allergy	2 (1.1%)	1.0	0.2	
Blood tests for allergy	2 (1.1%)	1.0	0.2	
Chest X-rays	7 (3.9%)	2.0	1.3	
Thorax CT	3 (1.7%)	1.0	0.3	
Pharmacological treatment	18 (9.9%)	-	-	67
Antibiotics	15 (8.3%)	1.2	0.1	1
Vaccinations	2 (1.1%)	-	-	0.1
Other vaccinations	43 (23.8%)	-	-	2
ED visits	4 (2.2%)	1.3	0.03	5
Nights spent in hospital	3 (1.7%)	4.7	0.1	46
	N° of patients who lost days (%)	Mean N° of days/ patient who lost days	Mean N° of days/ patient who lost days	Mean individual annual cost in 2013 (EUR)
Working days lost	10 (5.5%)	28.0	1.5	115
Leisure time forgone	6 (3.4%)	30.0	1.0	27
Premature retirement	2 (1.2%)	209.0	2.5	413
Total cost				694 [95% CI: 198-1,253]

Table 12.10: Two-level negative binomial regression: COPD

	IRR	95% CI	p-value
COPD with chronic bronchitis vs COPD without chronic bronchitis	17.10	3.04-96.22	0.001
Female	3.48	0.60-20.11	0.160
Age (5-year increase)	1.31	0.71-2.43	0.380
BMI (1-unit increase)	1.02	0.92-1.13	0.680
Past smokers/smokers vs nonsmokers	0.56	0.06-4.83	0.060

Table 12.11: Components of the mean annual cost per patient with chronic bronchitis without comorbidities (n=201).

	N° of users (%)	Mean N° of interventions/user	Mean N° of interventions/patient	Mean individual annual cost in 2013 (EUR)
Doctor visits	31 (15.4%)	2.4	0.4	11
General practitioner	27 (13.4%)	1.9	0.2	
Specialist	10 (5.0%)	2.3	0.1	
Clinical and laboratory tests	5 (2.5%)	3.0	0.1	4
Spirometry	3 (1.5%)	1.3	0.6	
Skin tests for allergy	1 (0.5%)	1.0	0.1	
Blood tests for allergy	1 (0.5%)	2.0	0.3	
Chest X-rays	3 (1.5%)	2.0	1.0	
Thorax CT	2 (1.0%)	1.0	0.3	
Pharmacological treatment	12 (6.0%)	-	-	12
Antibiotics	21 (10.5%)	1.7	0.2	2
Vaccinations	3 (1.5%)	-	-	4
Other vaccinations	26 (12.9%)	-	-	1
ED visits	1 (0.5%)	2.0	0.0	2
Nights spent in hospital	2 (1.0%)	2.0	0.0	15
	N° of patients who lost days (%)	Mean N° of days/ patient who lost days	Mean N° of days/ patient who lost days	Mean individual annual cost in 2013 (EUR)
Working days lost	6 (3.0%)	8.7	0.3	42
Leisure time forgone	3 (1.5%)	20.0	0.3	8
Premature retirement	0	0	0	0
Total cost				94 [95% CI: 38-166]

Table 12.12: Components of the mean total cost per patient with chronic bronchitis with comorbidities (n=326).

	N° of users (%)	Mean N° of interventions/user	Mean N° of interventions/patient	Mean individual annual cost in 2013 (EUR)
Doctor visits	71 (21.8%)	2.5	0.5	16
General practitioner	62 (19.0%)	2.1	0.4	
Specialist	25 (7.7%)	1.9	0.1	
Clinical and laboratory tests	19 (5.8%)	2.9	0.2	8
spirometry	11 (3.4%)	1.5	0.7	
skin tests for allergy	3 (0.9%)	1.0	0.1	
blood tests for allergy	8 (2.5%)	1.1	0.4	
chest X-rays	15 (4.6%)	1.6	1.0	
thorax CT	3 (0.9%)	1.0	0.1	
Pharmacological treatment	29 (8.9%)	-	-	34
Antibiotics	49 (15.0%)	1.5	0.2	3
Vaccinations	2 (0.6%)	-	-	1
Other vaccinations	72 (22.1%)	-	-	2
ED visits	6 (1.9%)	1.0	0.0	3
Nights spent in hospital	6 (1.8%)	14.2	0.3	199
	N° of patients who lost days (%)	Mean N° of days/ patient who lost days	Mean N° of days/ patient who lost days	Mean individual annual cost in 2013 (EUR)
Working days lost	13 (4.0%)	9.2	0.4	59
Leisure time forgone	16 (4.9%)	75.3	3.7	101
Premature retirement	2 (0.7%)	209.0	1.4	222
Total cost				642 [95% CI: 249-1,131]

Table 12.13: Two-level negative binomial regression: chronic bronchitis

	IRR	95% CI	p-value
Chronic bronchitis with comorbidities vs without comorbidities	2.88	1.10-7.55	0.031
Female	0.55	0.22-1.38	0.201
Age (5-year increase)	1.70	1.20-2.39	0.003
BMI (1-unit increase)	0.94	0.87-1.01	0.113
Past smokers/smokers vs nonsmokers	0.58	0.23-1.45	0.242
Allergic rhinitis	3.50	1.37-8.91	0.009

Table 12.14: Monetary unit value of each cost component used in the Study 2 (reference year: 2013).

	Monetary unit value (Euro)[1]
Doctor visits	24.397 (general practitioner) 40.561 (chest physician, allergy/internal medicine specialist or ENT doctor)
Clinical and laboratory tests	46.411 (spirometry) 48.380 (skin test for allergy) 113.704 (blood test for allergy-specific IgE) 20.565 (chest X-rays)
Pharmacological treatment	Market price of a single dose of each active principle[2]
ED visits	165.669
Hospital admissions	General ward: 783.587 Chest medicine: 799.496 Intensive care unit: 1,708.743 Rehabilitation ward: 321.850
Productivity losses	159.843[3] 45.385 (housewives)[4]
Leisure time forgone	27.231[5]

ENT: Ear, Nose and Throat. 1. Purchasing Power Parity (PPP) adjusted median; reference year: 2013. 2. Obtained by averaging the market price of a single dose of the most prescribed medicines. 3. Average daily wage. 4. Hourly wage of part-time help (EUR 9.077), five working hours per day assumed. 5. Hourly wage of part-time help (EUR 9.077) as replacement value, three hours of limited, not work-related activities per day assumed.

Table 12.15: Main characteristics of the asthmatic subjects according to the change of their disease status.

	Intermittent (n=128)	Improved (n=136)	Worsened (n=146)	p-value[1]
Females (%)	54.7	57.4	62.3	0.425
Age (years), mean (sd)	40.8 (6.9)	43.4 (7.3)	43.3 (7.1)	0.003
Disease status at the ECRHS II (%)				
Intermittent	100.0		47.9	
Persistent controlled/partially controlled		49.3	13.7	
Persistent uncontrolled		50.7	38.4	
BMI (Kg/m^2), median (IQR)	24.3 (22.0-26.8)	26.1 (23.1-29.8)	26.0 (23.7-29.5)	<0.0001
Low socio-economic class (%)[2]	11.7	30.2	22.9	0.001
Ever smoking (%)	48.4	52.2	52.7	0.747
Age at onset (years) (%)				0.145
0-9	35.8	24.6	31.5	
>=10	64.2	75.4	68.5	
Chronic cough or phlegm (%)[3]	15.9	21.8	37.3	<0.0001
Allergic rhinitis (%)[4]	68.8	61.0	68.5	0.311

sd: standard deviation; BMI: body mass index; IQR: interquartile range. 1. P-values obtained by using the chi-square test ot the parametric or non parametric ANOVA. 2. Having completed full-time education before the age of 16. 3. Having reported cough and/or phlegm from the chest, usually in winter and on most days for as long as 3 months each year. 4. Having reported any nasal allergies, including hay fever.

Table 12.16: Components of the mean annual cost per patient with intermittent asthma at the ECRHS II and ECRHS III.

	ECRHS II			ECRHS III		
	N° of users (%)	Mean N° of interventions per user	Mean annual cost/patient in 2013 (EUR)	N° of users (%)	Mean N° of interventions per user	Mean annual cost/patient in 2013 (EUR)
Doctor visits	39 (30.5%)	2.1	19	31 (24.2%)	1.6	11
General practitioner	33 (25.8%)	1.6		27 (21.1%)	1.3	
Specialist	11 (8.6%)	2.5		10 (7.8%)	1.4	
Clinical and laboratory tests	10 (7.8%)	2.3	10	5 (3.9%)	1.4	3
spirometry	6 (4.5%)	1.3		2 (1.6%)	1.0	
skin tests for allergy	5 (3.9%)	1.0		0	0	
blood tests for allergy	5 (3.9%)	1.0		2 (1.6%)	1.5	
chest X-rays	4 (3.1%)	1.3		2 (1.6%)	1.5	
Pharmacological treatment	60 (46.9%)		15	50 (39.1%)		26
ED visits	0	0	0	0	0	0
Nights spent in hospital	0	0	0	0	0	0
	N° of patients (%)	Mean N° of days/patient who lost days	Mean annual cost/patient in 2013 (EUR)	N° of patients (%)	Mean N° of days/patient who lost days	Mean annual cost/patient in 2013 (EUR)
Working days lost	12 (9.7%)	5.5	63	9 (7.0%)	5.1	57
Leisure time forgone	10 (7.9%)	27.6	59	4 (3.2%)	69.0	60
Premature retirement	0	0	0	0	0	0
Total cost			166 [95% CI: 107-227]			157 [95% CI: 70-292]

Table 12.17: Components of the mean annual cost per patient with an improved disease status from the ECRHS II to the ECRHS III.

	ECRHS II			ECRHS III		
	N° of users (%)	Mean N° of interventions per user	Mean annual cost/patient in 2013 (EUR)	N° of users (%)	Mean N° of interventions per user	Mean annual cost/patient in 2013 (EUR)
Doctor visits	78 (57.4%)	3.2	56	46 (33.8%)	2.5	26
General practitioner	58 (42.7%)	2.9		35 (25.7%)	1.9	
Specialist	39 (28.7%)	2.2		21 (15.4%)	2.3	
Clinical and laboratory tests	37 (27.2%)	3.2	48	10 (7.4%)	2.9	9
spirometry	35 (25.7%)	2.1		9 (6.6%)	2.0	
skin tests for allergy	11 (8.1%)	1.0		1 (0.7%)	1.0	
blood tests for allergy	12 (8.8%)	1.7		1 (0.7%)	2.0	
chest X-rays	14 (10.3%)	1.1		5 (3.7%)	1.6	
Pharmacological treatment	122 (89.7%)		253	97 (71.3%)		205
ED visits	18 (13.2%)	1.6	34	0	0	0
Nights spent in hospital	7 (5.2%)	3.0	136	0	0	0
	N° of patients (%)	Mean N° of days/patient who lost days	Mean annual cost/patient in 2013 (EUR)	N° of patients (%)	Mean N° of days/patient who lost days	Mean annual cost/patient in 2013 (EUR)
Working days lost	32 (24.2%)	13.3	422	5 (3.7%)	5.6	33
Leisure time forgone	18 (13.3%)	30.0	109	1 (0.7%)	168.0	34
Premature retirement	0	0	0	0	0	0
Total cost			1,058 [95% CI: 752-1,423]			308 [95% CI: 227-405]

Table 12.18: Components of the mean annual cost per patient with a worsened disease status from the ECRHS II to the ECRHS III.

	ECRHS II			ECRHS III		
	N° of users (%)	Mean N° of interventions per user	Mean annual cost/patient in 2013 (EUR)	N° of users (%)	Mean N° of interventions per user	Mean annual cost/patient in 2013 (EUR)
Doctor visits	75 (51.7%)	3.7	57	83 (56.9%)	4.0	65
General practitioner	62 (42.8%)	3.0		73 (50.0%)	3.4	
Specialist	36 (24.8%)	2.6		35 (24.0%)	2.5	
Clinical and laboratory tests	33 (22.6%)	3.0	34	36 (24.7%)	3.5	40
spirometry	28 (19.2%)	1.8		28 (19.2%)	2.1	
skin tests for allergy	8 (5.5%)	1.1		10 (6.9%)	1.2	
blood tests for allergy	11 (7.5%)	1.3		13 (8.9%)	1.1	
chest X-rays	19 (13.0%)	1.4		20 (13.7%)	2.1	
Pharmacological treatment	104 (71.2%)		200	130 (89.0%)		342
ED visits	14 (9.7%)	2.1	34	24 (16.7%)	2.2	59
Nights spent in hospital	5 (3.5%)	16.2	446	8 (5.5%)	2.4	104
	N° of patients (%)	Mean N° of days/patient who lost days	Mean annual cost/patient in 2013 (EUR)	N° of patients (%)	Mean N° of days/patient who lost days	Mean annual cost/patient in 2013 (EUR)
Working days lost	30 (21.6%)	10.7	270	25 (17.2%)	19.6	539
Leisure time forgone	26 (17.8%)	37.4	181	25 (17.1%)	75.0	350
Premature retirement	4 (2.7%)	209.0	915	11 (8.0%)	198.1	2,524
Total cost			2,137 [95% CI: 935-3,753]			4,023 [95% CI: 2,419-5,530]

Table 12.19: Two-level random-intercept Laplace quantile regression model.

	Cost variation (EUR)	95% CI	p-value
Disease status variation, vs intermittent (%)			
Improved	-144.8	-274.6; -15.0	0.029
Worsened	184.8	58.5; 311.2	0.005
Female	-7.9	-89.3; 73.6	0.847
Age, vs 28-37 years			
38-46 years	27.1	-134.0; 188.2	0.737
47-56 years	31.0	-131.7; 193.6	0.704
Ever smoker, vs nonsmoker	-3.1	-68.8; 62.6	0.924
Low socioeconomic class	-3.7	-103.1; 95.6	0.940

Chapter 13

Figures

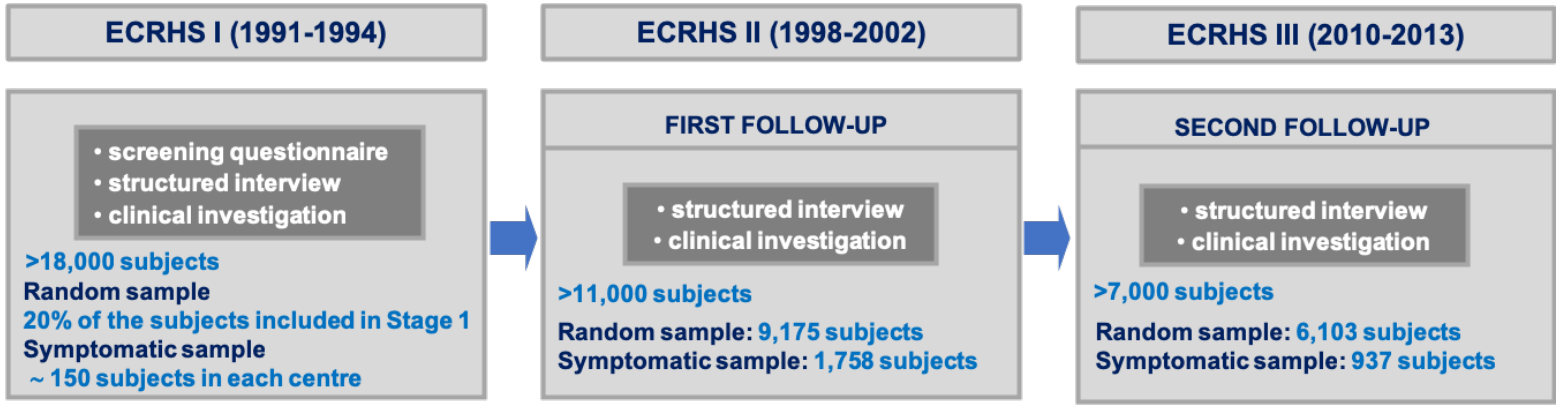
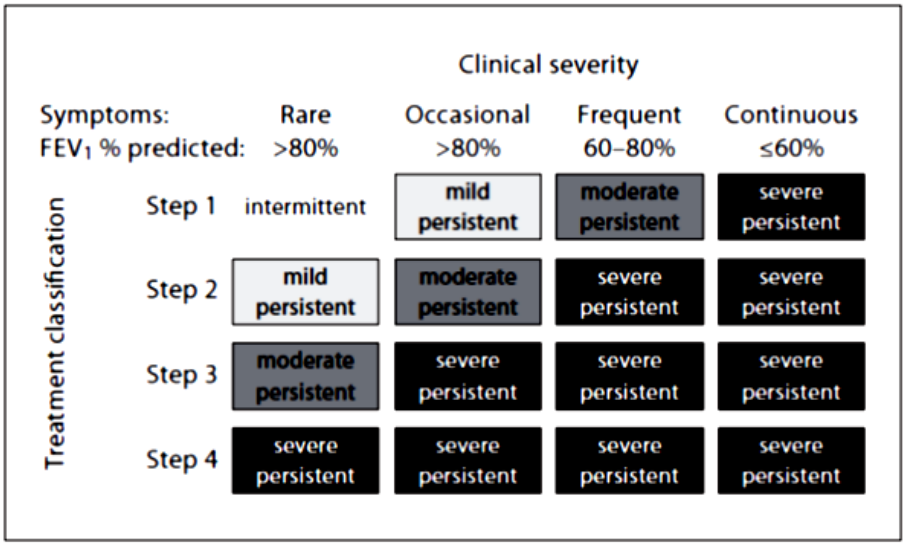


Figure 13.1: ECRHS study design.

Figure 13.2: Classification of asthma severity according to the GINA guidelines.



Composite classification of asthma severity over the last 3 months based on the clinical severity on current treatment and on the treatment classification according to the GINA. Step 1 = No daily controller; Step 2 = low-dose inhaled corticosteroid (ICS), leukotriene modifier, theophylline or cromones; Step 3 = low/medium-dose ICS combined with long-acting beta2-agonists (LABA), or medium dose ICS combined with leukotriene modifier or theophylline, or high-dose ICS alone; Step 4 = high-dose ICS combined with LABA or with leukotriene modifier. The subjects who reported they had used oral steroids either in short courses or continuously in the last 12 months were classified as Step 4. Symptoms refers to the frequency of diurnal/nocturnal symptoms.

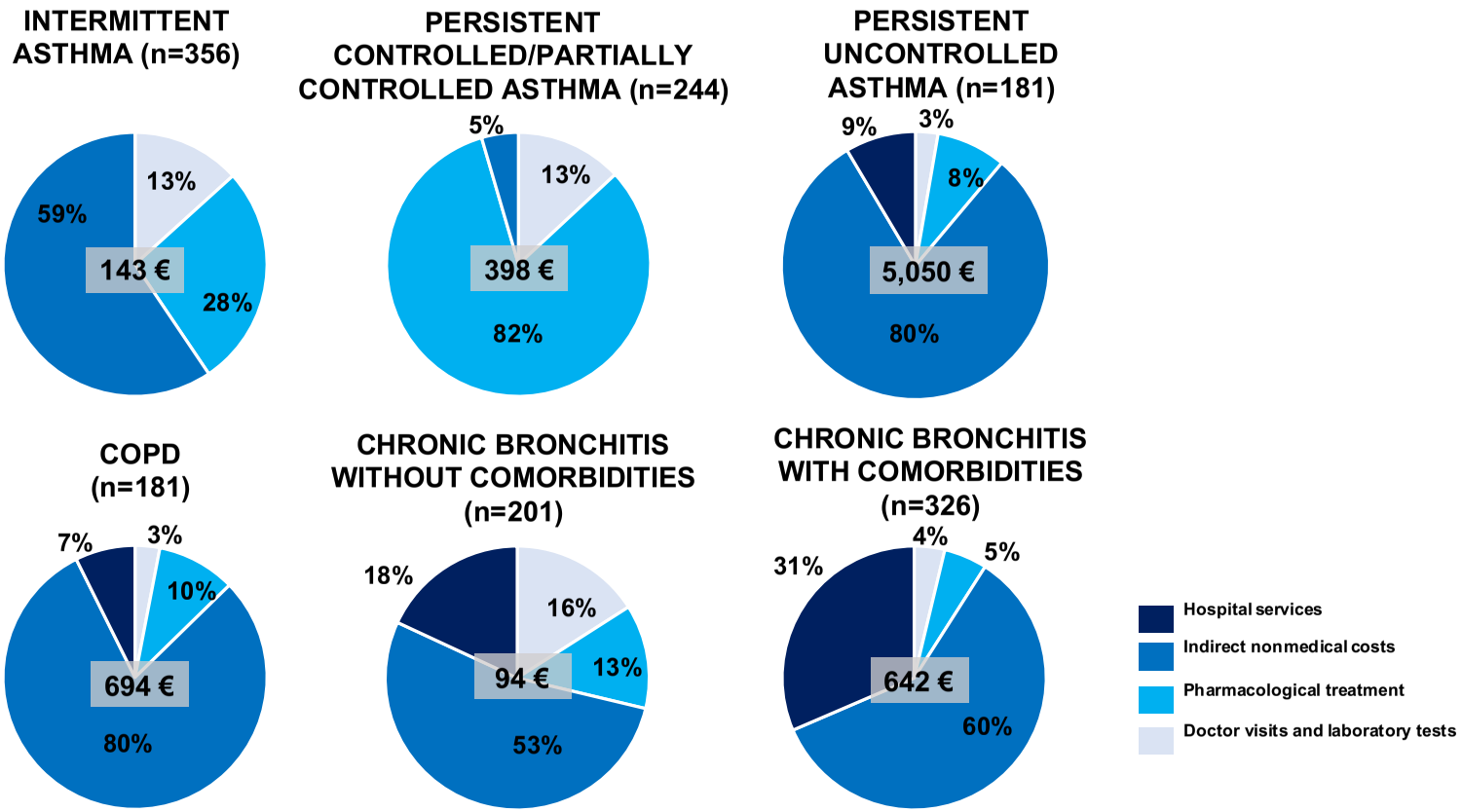
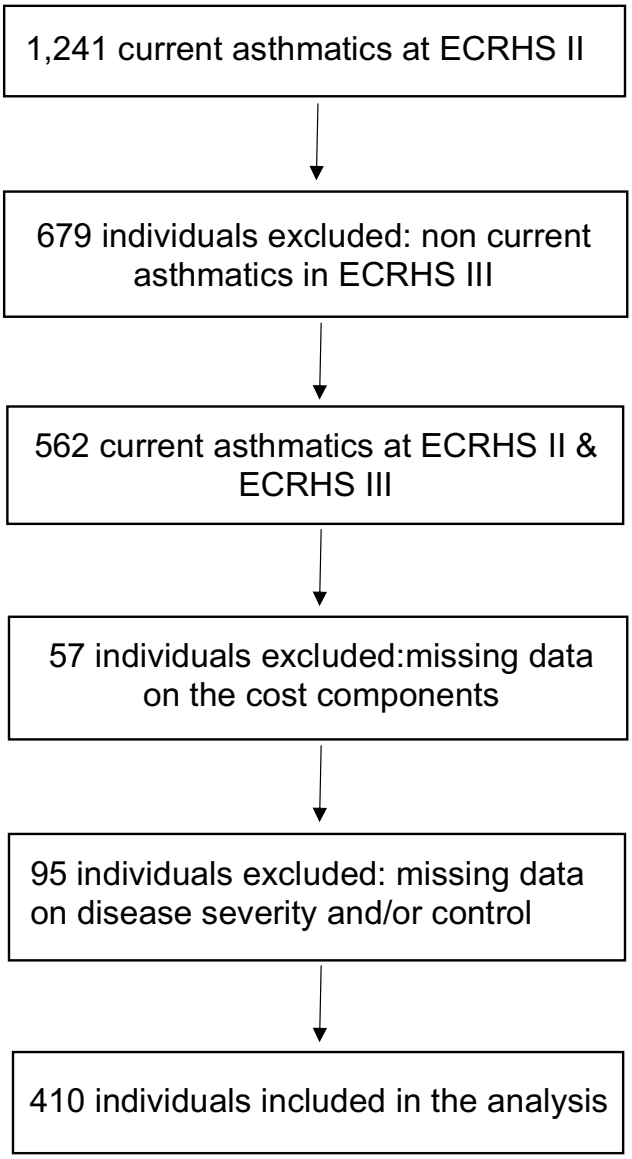


Figure 13.3: Distribution of the cost components according to the disease.

Figure 13.4: Flow-chart of the subjects included in Study 2.



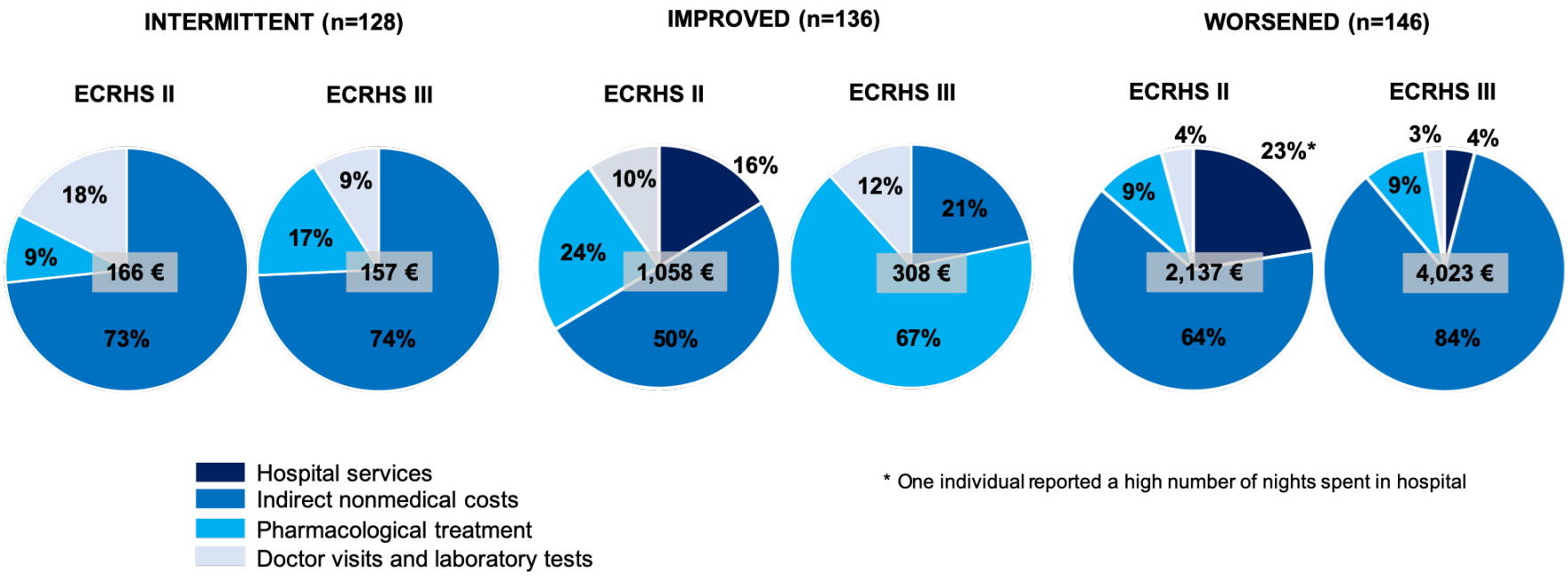


Figure 13.5: Distribution of the cost components according to the change of disease status. The mean annual cost per patient (in 2013 values) at the ECRHS II and ECRHS III is reported.