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Longitudinal analyses of economic, patient-reported, and clinical outcomes related to disease progression in patients with COPD: evidence from the German patient cohort COSYCONET

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Contents

List of abbreviations

BMI	Body mass index
BOLD	Burden of lung disease
CAT	COPD Assessment Test
COPD	Chronic obstructive pulmonary disease
COSYCONET	COPD and Systemic Consequences - Comorbidities Network
EQ-5D-3L	Euro-Qol 5 dimensions questionnaire, three levels
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Pulmonary Disease
HRQL	Health-related quality of life
IPW	Inverse probability weights
MCID	Minimal clinically important difference
mMRC	Modified Medical Research Council
SABD	Short acting bronchodilators
SGRQ	Saint George´s Respiratory Questionnaire
VAS	Visual Analog Scale

List of publications included in this thesis

Byng D*, **Lutter JI***, Wacker ME, Jörres RA, Liu X, Karrasch S, Schulz H, Vogelmeier C, Holle R: Determinants of healthcare utilization and costs in COPD patients: first longitudinal results from the German COPD cohort COSYCONET. Int J Chron Obstruct Pulmon Dis 2019, 14:1423-1439. *contributed equally

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Zusammenfassung

Die chronisch obstruktive Lungenerkrankung (COPD) ist aufgrund ihrer hohen Prävalenz und Mortalität ein großes Problem weltweit. Das heterogene Krankheitsbild stellt eine finanzielle Belastung für die Gesundheitssysteme dar und führt zudem zu erheblichen Belastungen bei betroffenen Patienten und der Gesellschaft. Patienten mit einer chronischen Erkrankung sind bis zu ihrem Tod auf Leistungen des Gesundheitssystems angewiesen. Aufgrund des demografischen Wandels – weniger Geburten bei höherer Lebenserwartung – verschiebt sich die Altersstruktur der Gesamtbevölkerung und folglich gewinnt die Finanzierung von Gesundheitsleistungen zusammen mit der Identifikation von Maßnahmen zur Verlangsamung des Verlaufs chronischer Erkrankungen zunehmend an Bedeutung. Die medikamentöse Therapie der COPD zielt primär auf die Linderung von Symptomen ab. Da COPD eine nicht heilbare jedoch behandelbare Erkrankung ist, kommt Selbstmanagementstrategien eine wichtige Bedeutung zu und nicht-pharmakologische Maßnahmen komplementieren die medikamentöse Therapie.

Ziel dieser Arbeit ist es, gesundheitsökonomische Aspekte im Zeitverlauf in einer geschlossenen COPD Kohorte zu untersuchen, um Trends und Veränderungen zu erkennen, die entweder für den Patienten, für Leistungserbringer im Gesundheitswesen oder für Entscheidungsträger von Bedeutung sind. Innerhalb von drei Artikeln werden verschiedene Facetten der Versorgung untersucht: Zu Beginn steht eine Analyse der Entwicklung der Inanspruchnahme von Gesundheitsressourcen und der direkten Kosten über einen Zeitraum von 18 Monaten. Der zweite Artikel untersucht Veränderungen der gesundheitsbezogenen Lebensqualität (LQ) innerhalb von drei Jahren und deren Zusammenhang mit physiologischen Veränderungen. Ein dritter Schwerpunkt liegt auf der Nutzung nicht-pharmakologischer Interventionen, sowie auf der Identifikation von Determinanten der Nutzung. Darüber hinaus werden in allen Artikeln Risikogruppen in Hinblick auf die steigende Nachfrage nach medizinischer Versorgung, die Verschlechterung der LQ und mögliche Versorgungslücken identifiziert.

Als Datenquelle wurde die prospektive Patientenkohorte COSYCONET genutzt, innerhalb derer zwischen 2010 und 2013 insgesamt 2741 Patienten in 31 Studienzentren in ganz Deutschland rekrutiert wurden. Nach 6, 18 und 36 Monaten fanden Folgeuntersuchungen derselben Patienten statt. Die Analyse von longitudinalen Daten bringt einige Besonderheiten mit sich, wie zum Beispiel die Berücksichtigung von Korrelationsstrukturen mehrerer Messungen pro Individuum, Überlegungen zum Phänomen „Regression zur Mitte“ und den methodischen Umgang mit Patienten, welche die Kohorte im Lauf der Zeit verlassen. In allen Artikeln wurden geeignete statistische Methoden ausgewählt und angewandt, um diese Besonderheiten angemessen zu berücksichtigen.

Die Untersuchung der Kostenentwicklung nach 18 Monaten ergab einen signifikanten Anstieg der Arzneimittelkosten um 12% und einen Anstieg der direkten Gesamtkosten um 5%. Obwohl der Anstieg der Gesamtkosten statistisch nicht signifikant war, zeigte sich bereits innerhalb des kurzen Beobachtungszeitraums ein Trend steigender Kosten. Prädiktoren für den Kostenanstieg waren Untergewicht, Atemnot und Indikatoren für die Schwere der Erkrankung. In die Analyse zur gesundheitsbezogenen LQ wurden die Daten einer weiteren Visite einbezogen und somit ein Zeitraum von drei Jahren untersucht. Innerhalb dieses Zeitraums wurde eine signifikante Verschlechterung der krankheitsspezifischen LQ beobachtet, welche vollständig durch den Teilbereich Aktivität – ein Maß der durch Atemnot verursachten Einschränkungen – bedingt war. Die Veränderungen der LQ und physiologische Veränderungen zeigten einen annähernd linearen Zusammenhang. Gleichzeitig ergab die Analyse, dass ein Anstieg der Lungenfunktion mit größeren LQ-Gewinnen assoziiert war als eine vergleichbare Abnahme mit Verlusten. Dies könnte eine Folge von Anpassungsprozessen an eine chronische Erkrankung durch den Patienten sein. Atemnot wurde als Schlüsseldeterminante für Kostenanstiege und LQ-Verschlechterung identifiziert. Daher befasst sich der dritte Aufsatz mit der Nutzung nicht-pharmakologischer Interventionen und deren Determinanten. Insgesamt wurden niedrige Nutzungsraten ermittelt. Eine Ausnahme war die Grippeimpfung, die von dreiviertel der Patienten im letzten Herbst/Winter genutzt wurde. Eine vorangegangene Empfehlung zur Nutzung durch einen Arzt war mit erhöhter Inanspruchnahme assoziiert, wobei Männer und Raucher insgesamt die niedrigste Nutzung aller Maßnahmen verzeichneten.

Zusammenfassend geben die Ergebnisse dieser Arbeit detaillierte Einblicke in die Entwicklung von direkten medizinischen Kosten und den Verlauf der patientenrelevanten LQ – zwei Indikatoren für den Krankheitsfortschritt von COPD – über den Zeitraum von bis zu drei Jahren bei Teilnehmern einer großen deutschen Patientenkohorte. Insbesondere die Ergebnisse zu den Prädiktoren des Krankheitsfortschritts, welcher sowohl aus Kosten- als auch Patientenperspektive untersucht wurde, sind auf den globalen Kontext übertragbar und können zur Identifikation von Patienten mit einem Risiko für zukünftige Kostensteigerungen und ungünstige LQ-Entwicklungen eingesetzt werden. Untergewichtige Patienten und Patienten, die eine hohe Einschränkung alltäglicher Aktivitäten durch Atemnot oder Kurzatmigkeit berichten, sollten genau überwacht und deren medikamentöse Therapie angepasst werden. Zusätzlich sollten alle Patienten mit COPD regelmäßig ermutigt werden, nicht-pharmakologische Interventionen zu nutzen.

Summary

Chronic obstructive pulmonary disease (COPD) is a major public health problem due to its high prevalence and associated mortality. The heterogeneous disease imposes a financial burden on healthcare systems and causes substantial burden on patients and the society as a whole. Patients with a chronic disease are dependent on treatment until their death and due to the demographic change leading to an overall older German population, the financing of health care services together with the detection of measures to slow down the progression of the disease are becoming increasingly important. Medical therapy is available, which mainly targets the relief of symptoms. As patients spend their entire lives with the disease, self-management strategies must be acquired, and non-pharmacological measures are available to supplement medication.

The aim of this thesis is to study health economic aspects of COPD longitudinally in a fixed cohort to investigate trends and changes, which are of relevance for either the patient, healthcare providers or decision makers. Three articles highlight three facets of care: First, an analysis of the development of healthcare resource utilization and direct healthcare costs over an 18 months' time span is presented. The second article analyzes changes in health-related quality of life (HRQL) over three years and their association with physiological changes. Within the third article, the utilization of non-pharmacological interventions for COPD and determinants of utilization are discussed. Furthermore, all three articles aim at identifying risk groups with regard to the increasing demand for medical care, HRQL deterioration, and possible gaps in care.

Data were taken from the prospective patient cohort COSYCONET. Between 2010 and 2013, 2741 patients were recruited in 31 study centers across Germany and follow-up visits were scheduled after 6, 18, and 36 months. In order to investigate the research questions, some unique challenges of longitudinal data analysis had to be taken into account in the statistical analysis: the consideration of correlation structures of multiple measurements per individual, the consideration of regression to the mean, and the methodical handling of patients leaving the cohort over time. Within all articles, appropriate statistical methods were chosen and applied to adequately consider these challenges.

With regard to cost developments after 18 months, the analysis showed a significant increase in medication costs by 12% and a 5% increase in total direct healthcare costs. Although the increase in total costs was not statistically significant, it indicated a trend of development already within the short observation period. Predictors of cost increases were low body weight, high dyspnea burden, and indicators of disease severity. For the analysis of HRQL developments, data of an additional follow-up visit were included, which enabled the investigation of a three years period. Within this period, a significant deterioration in disease-specific HRQL was observed, which was completely driven by

the activity subdomain – a measure of limitations due to breathlessness. The relationship between changes in HRQL and physiological changes was approximately linear meaning that changes in HRQL followed those in forced expiratory volume in one second (FEV_1). Importantly, increases in FEV_1 were associated with greater HRQL-gains than equal decreases with losses. This could be a consequence of adaptation processes to a chronic disease by the patient. Breathlessness was identified as a key determinant of cost increases and HRQL deterioration. Therefore, the third article dealt with non-pharmacological interventions for COPD, which prevent infections, alleviate symptoms, train the patient in the management of the chronic disease and especially teach techniques to facilitate breathing. The analyses showed low levels of use with the exception of influenza vaccination, which was reported by almost three quarters of patients. Overall, participation was higher in those who reported the recommendation by their physician, while utilization was lowest in males and smokers.

In conclusion, the results of this thesis give detailed insights into the treatment of patients with COPD in Germany, focusing on the development of health care costs and patient-relevant quality of life – two indicators of disease progression – over a period of up to three years. Especially the results regarding predictors of disease progression, which were investigated from both a cost and patient perspective, are applicable to the global context and help identify patients at risk for cost increases in the future and unfavourable HRQL developments. Underweight patients and patients with a high dyspnea burden should be closely monitored in order to reassess and adjust treatment if necessary. All patients with COPD should be frequently encouraged to utilize non-pharmacological interventions.

Chapter 1 General introduction

1.1 Chronic Obstructive Pulmonary Disease

1.1.1 Epidemiology, etiology, and diagnosis

Chronic obstructive pulmonary disease (COPD) is a major public health issue worldwide. The disease is highly prevalent affecting more than 200 million people [1]. In Europe, the prevalence is estimated between 5 and 10% in the adult population aged older than 40 years [2]. The incidence is expected to increase in upcoming years because of the ageing of the population, longevity, and the persistent exposure to risk factors. In 2016, COPD was globally the third leading cause of death and was accountable for 5.3% of all deaths [3]. COPD causes substantial economic, personal, and social costs. Among respiratory diseases, COPD is associated with the greatest loss of working days.

For Germany, the prevalence of COPD was estimated at 13.2% based on data of the Burden of Lung Disease (BOLD) study [4] and in 2012, COPD was accountable for excess annual direct healthcare costs between € 2595 and € 8924 depending on the severity of the disease. Indirect costs were even higher with € 8621 for the lowest and € 27,658 for the highest disease stage [5]. Beyond the financial burden, COPD is also associated with a significant impairment of the health-related quality of life (HRQL) of those affected [6].

COPD is characterized by persistent respiratory symptoms and airflow limitation caused by the non-reversible obstruction of airways and the accelerated decline of lung function [7, 8]. Chronic inflammation of the lung leads to a narrowing of small airways and destruction of the lung parenchyma [9]. Because healthy repair mechanisms no longer work, this results in loss of alveolar attachment to the small airways, which causes a reduction in the elastic recoil of the lung. Consequently, this leads to a restricted opening of the airways during expiration [7]. For the diagnosis of COPD, a post-bronchodilator Tiffenau index (forced expiratory volume in one second / forced vital capacity (FEV_1/FVC)) < 0.70 is required, which is determined in spirometry. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), the FEV_1 is also used to assign a patient one of four degrees of airflow limitation severity (GOLD 1 to GOLD 4).

The leading symptom of COPD is shortness of breath, also referred to as dyspnea. It is often accompanied by coughing and sputum production, which occur with varying intensity over the course of the disease [7]. The most important risk factor for the development of COPD is tobacco smoking. However, exposure to occupational [10, 11] or environmental [12] noxious particles or gases, low socioeconomic status [13] and respiratory tract infections in early childhood [14] have also been linked to the development of COPD. Furthermore, genetic abnormalities (alpha-1-antythrypsin deficiency), abnormal lung development and accelerated aging are congenital causes of COPD [15].

Comorbidities are frequent in patients with COPD and especially in mild-to-moderate COPD, cardiovascular diseases and lung cancer are the leading causes of mortality [16]. Besides, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, and depression are frequent concomitant chronic diseases in patients with COPD [17]. Screening for and treatment of these comorbidities is important due to their association with hospitalization, morbidity and mortality in patients with mild, moderate and severe airflow limitations [7].

1.1.2 Natural history of COPD and disease progression

Lung function is the central measure for the diagnosis of COPD and the decline of FEV_1 marks the progression of COPD over lifetime. Studies have shown that there are significant relations with COPD-related morbidity and mortality, which makes lung function a key predictor of outcome and the essential element in understanding the natural history of COPD [18, 19]. The mean annual decline of FEV_1 in healthy never-smoking adults is about -20 ml/per annum (p.a.) with a less steep lifetime curve for female never-smokers compared to male never-smokers [20]. The course of COPD is by no means identical in all patients and thus the heterogeneity of the disease becomes apparent in different trajectories through life. While in some individuals, the maximum level of lung function is significantly lower than the mean maximum, the rate of decline is steeper in others, and some experience a late accelerated decline of lung function [21]. Episodic accelerated decline, which is characterized by the alternating decrease and increase in FEV_1, has also frequently been observed in patients with COPD [22]. Exacerbations are a driver of accelerated lung function decline. These are episodes of acute worsening of symptoms and overall health status due to viral or bacterial infections, environmental pollutants or other unknown factors and require additional therapy. There are three levels depending on the additional treatment required: mild (handled by the patient itself and treated with short acting bronchodilators (SABDs)), moderate (treated with SABDs plus antibiotics and/or oral corticosteroids, which were prescribed by a primary care physician) and severe (leads to hospitalization) [7]. Besides their impact on lung function, COPD exacerbations have been linked to increased healthcare costs and mortality [23].

1.1.3 Pharmacological and non-pharmacological treatment

COPD is a treatable, however, not curable disease. Especially in the context of a chronic, lifelong disease, longitudinal analyses of patient relevant outcomes are important to evaluate whether treatment is appropriate or changes in therapy might be indicated. Furthermore, longitudinal investigations can help to identify characteristics that determine treatment decisions. International [7] and national [24] guidelines recommend pharmacologic therapy to relief symptoms, reduce the frequency of ex-

acerbations, improve overall health status and maintain exercise capacity. Since 2011, treatment decisions are guided by the GOLD ABCD-classification, which combines the patient's exacerbation risk and symptoms (based on either the modified Medical Research Council dyspnea scale (mMRC) [25] or the COPD Assessment Test (CAT) [26]). The multidimensional combination of symptoms and exacerbation risk culminates in four groups: GOLD A-D [7].

Based on this classification, different groups of active ingredients can be prescribed. Bronchodilators (anticholinergics, beta-2 agonists) are the primary drugs used to reduce the symptoms in stable COPD patients. They can be used according to need in acute respiratory distress or on a regular basis. If used regularly, long-acting bronchodilators are preferable to short-acting preparations. Inhaled or systemic corticosteroids and phosphodiesterase-4 inhibitors are also frequently used and combinations of different bronchodilators and / or corticosteroids are common [7, 24].

Although pharmacotherapy has beneficial effects on the current health status and future exacerbations, there is no evidence regarding a potential modification of long-term lung function decline. In contrast, a lasting effect on lung function has been shown for smoking cessation, which has the ability to slow down the progression of the disease [27, 28]. Other non-pharmacological interventions include vaccinations, physical training, physiotherapy, patient education and nutritional advice. Pulmonary rehabilitation (outpatient or inpatient) can include several of the above-mentioned measures and trains the patient in self-management and thus in dealing with his or her illness on a daily basis. Finally, oxygen therapy, ventilator support and surgical interventions such as lung volume reduction surgery or lung transplantation are available and are mostly used to treat patients in advanced stages of the disease [7, 24].

1.2 Health services research and health economics

1.2.1 Definitions and relevance in COPD

Health services research is a multidisciplinary field bringing together researchers from epidemiology, medicine, economics, social sciences, and others and combining their knowledge and methods [29]. Investigating the current health care landscape, researcher deal with questions regarding access to, demand and utilization of healthcare services, costs and quality of care, and patient relevant outcomes such as HRQL [30]. In the context of health services research, health economic research is of major importance. This discipline describes the application of economic theories and principles to the healthcare sector. Research mainly focuses on questions regarding efficient and cost-effective alternatives of action under the premises of resource scarcity [31]. Over- and under-provision of care is being investigated as well as who receives which treatment. Since the purpose of health services

research is to present health care under everyday conditions, certain data sources are particularly suitable for questions in this area. These are claims data and observational studies, such as prospective cohort studies.

Although there are a number of observational COPD cohorts worldwide, which monitor patients over several years, there is currently little literature on longitudinal health economic research, such as the development of healthcare resource utilization and associated costs in different sectors of healthcare provision. Since COPD is a costly disease and is associated with the presence of several comorbidities that require treatment and cause additional costs, such longitudinal investigations are of relevance for healthcare providers and decision makers due to their potential to identify predictors of unfavorable disease progression [32]. Furthermore, knowledge on cost developments related to chronic diseases will become even more important as the demand for health care services will increase in upcoming years while financial, personnel and material resources cannot grow in a proportional manner [33, 34].

Patient-reported outcomes, such as generic and disease-specific HRQL, play an important role in health economic research. They are used to evaluate interventions, estimate quality-adjusted life years (QALY), and to determine the impact and burden of a disease from the patient's perspective [35]. Especially in chronic diseases, there is a need for longitudinal studies of patient-reported outcomes to identify changes in patient's health status over time in conjunction with physiological markers of disease progression and to detect patients at risk for unfavourable HRQL developments [36]. This information is needed to coordinate care and improve treatment over the course of chronic diseases.

1.2.2 Healthcare costs

Cost of illness studies are an important tool to estimate the financial impact a disease imposes on healthcare systems, health insurances or individuals. Identifying and calculating the costs of a disease is also an important basis for allocation decisions [37]. Within these studies, direct and indirect costs, which are linked to a disease, are estimated by multiplying resources used with unit cost estimates for each resource. Indirect or direct measures are available to assess the healthcare resource utilization of patients. Indirect methods include the documentation in claims data or patient record files, while the direct assessment of healthcare utilization is frequently done by asking patients or relatives via standardized questionnaires or interviews [38].

1.2.3 Health-related quality of life

HRQL can be assessed by generic and disease-specific measures via self- or interviewer- administered questionnaires [39]. Generic instruments are designed to measure effects on several aspects of

health independent of a disease and therefore enable the comparison across different diseases and the contrast of healthy and sick individuals. The Euroqol 5-dimension 3 level (EQ-5D-3L) [40] is an example of a generic instruments and its second part, the Visual Analog Scale (VAS), was used and analyzed in Chapter 3. On the other hand, disease-specific instruments focus on symptom burden, functional impairments and the influence of one specific condition on daily activities. These measures are frequently used in clinical trials to measure changes in HRQL associated with medical interventions. The Saint George´s Respiratory Questionnaire (SGRQ) [41, 42] and the COPD Assessment Test (CAT) [26] represent disease-specific instruments (see Chapter 3). Both classes of instruments carry out two basic functions: the assessment of cross-sectional differences in HRQL between patients (discriminative ability), and the evaluation of longitudinal changes in HRQL within patients (evaluative ability) (see Chapter 3) [39]. To determine whether an observed change is significant or negligible, the concept of minimal clinically important difference (MCID) has been developed [43]. If the observed change exceeds the MCID, it can be assumed that the change is of clinical relevance for the patient.

1.3 Methodological aspects of longitudinal studies

The COSYCONET study "**CO**PD and **SY**stemic consequences-**CO**morbidities **NET**work" [44] provided the data for the three research articles. Within this prospective cohort study, 2741 patients were recruited in 31 study centers, distributed across Germany, between 2010 and 2013. Thereafter, patients were invited to attend follow-up visits, which were scheduled at 6, 18, and 36 months and are still ongoing. Due to data availability reasons, data up to the three-year follow up were analyzed in this thesis.

To investigate trends, characterize changes in parameters, and to examine factors that may influence changes, longitudinal data with multiple assessments per patient are necessary. At the same time, it is important to consider some specifics when conducting longitudinal research. Three aspects that have played an important role in addressing the research questions of this thesis will be explained in detail:

In longitudinal studies, measurements of the same individual are taken repeatedly over time [45]. Within an individual, the repeated measures are correlated; therefore, the central assumption of a linear regression model is no longer fulfilled. Still, measurements from different individuals are considered to be independent. Statistical models must therefore be applied that take the specific correlation structure of data into account. In an analysis with only two measurements per patient (Chapter 2 and Chapter 3), a change score model can be used to analyze the change between baseline and follow-up measurement [46]. Here, the dependent variable is calculated as the change by subtracting the

follow-up value from the baseline value for each patient. Using the calculated change, one can analyze the data set with a linear regression model. Advanced models are necessary for the analysis of data with more than two measurements per patient. One example are hierarchical linear models (Chapter 3), which can be applied on unbalanced data with missing values and unlimited assessments per patient [47]. A random intercept accounts for the positive correlation structure, and the model estimates a separate effect for the inter-individual difference (cross-sectional effect) and the intra-individual change (longitudinal effect), while adjusting for time-varying or time-constant covariates.

Regression toward the mean (Chapter 2 and Chapter 3) is a phenomenon, which occurs due to measurement error or random fluctuations within patients over time. When analyzing change between two repeated measurements, an individual who had an extreme measurement at the first visit is more likely to move to the overall mean with his/her second measurement [48]. It therefore directly affects the calculated change in that individuals with extremely low values at first measurement are likely to have a somewhat bigger overall positive change and vice versa. To account for regression toward the mean, one could include the baseline measurement as an independent covariate in statistical models. Some models, for example the hierarchical linear model, are designed to be robust against regression toward the mean [47]. Additionally, the phenomenon and possible influence on the results should be discussed in the article because the complete elimination of bias during measurement is not possible.

In an observational study that runs over several years, it is inevitable that individuals leave the cohort over time. In most cases, this is not random; hence, selective dropout could induce bias to the research findings and should therefore be considered in longitudinal analyses [49]. Reasons for the termination range from “not interested”, “too ill to participate” to “deceased” and in some cases, patients exit the cohort without indicating a reason or being available for a request. Within the COSYCONET study, a strong effort was put into collecting the reasons for the dropout, which allowed its consideration in the analyses. The dropout was addressed in three ways: characterization, adjustment, discussion. First, the numbers of participants at each study visits together with the proportions of dropouts by given reasons was displayed (see Flow Chart diagram in Chapter 3). Furthermore, the comparison between baseline characteristic of participants and dropouts showed differences between groups (see Table 5 Chapter 2, Table S1 Chapter 4). Second, Inverse Probability Weights (IPW) [50] were included in the regression analyses (Chapter 2 and Chapter 3). According to the characterization of dropouts, those patients were older and had a higher disease burden. However, follow-up measurements were only available for the reduced cohort. To imitate the cohort as recruited at baseline, weights were calculated for the complete cases based on the inverse probability of attending the follow-up assessment. This was modelled using demographic variables, disease characteristics and quality of life, all meas-

ured at baseline. The result was an artificially enlarged follow-up cohort, with similarities to the cohort recruited at baseline. Third, the potential bias through selective dropout and its influence on the findings has been discussed in each article.

1.4 Objectives and contents of this thesis

The overarching objective of this thesis is to study health economic aspects of COPD longitudinally to investigate trends and changes in parameters deemed to be important for the course of the disease. In detail, this included the analysis of short-term development of resource utilization and healthcare costs (Article 1) and the analysis of changes in HRQL and their association with physiological changes (Article 2). Building on the findings of the first two articles, a third focus was placed on the utilization of non-pharmacological interventions for COPD (Article 3), which are particularly important in the context of a chronic and lifelong disease. All three articles aimed at identifying risk groups with regard to the increasing demand for medical care, HRQL deterioration, and possible gaps in care.

In the following, the research questions of the three articles are outlined and a short summary of each chapter is given:

Within **Chapter 2**, the development of the healthcare resource utilization and associated costs of patients with COPD over an 18-month period is explored. Annual direct costs were calculated based on self-reported information on utilization, which was assessed at baseline and follow up. The two direct cost measurements per patient, separated by 18 months, were analyzed using change score models. Overall, an increase in inflation-adjusted mean annual direct costs of 5% was observed. Patients with baseline GOLD grade 4, underweight patients and patients with a high dyspnea burden were at high risk for cost increases after 18 months. Additionally, a history of moderate or severe exacerbations and the presence of more than three comorbidities were significant predictors of cost increases. To conclude, the analysis of intra-individual changes in utilization and direct healthcare costs identified clinically plausible and relevant cost-drivers. Assuming that higher utilization is linked to higher disease severity, the results might be used to guide therapy decisions according to characteristics, which determine the course of the disease.

Chapter 3 focuses on patient-reported HRQL in the progression of COPD, which was assessed by the lung function parameter FEV_1. HRQL was measured with the generic EQ-5D VAS and the disease-specific SGRQ. Since there is conflicting literature regarding the association between lung function development and change in HRQL, this article examines the longitudinal association between change in FEV_1 and change in disease-specific and generic HRQL based on up to three measurements per patient over a period of three years. Besides the descriptive analysis of change in HRQL and

FEV_1, three models, designed to analyse longitudinal data, were applied: change score models, generalized additive models, and hierarchical linear models. On the population level, a significant +1.3 unit deterioration in SGRQ was observed. The single most important driver of this change was the activity subdomain, which measures restricted activity caused by shortness of breath and activities that cause breathing difficulties. The mean value of the generic instrument EQ-VAS did not significantly change over three years. Regarding lung function, 58% of patients experienced a clinically relevant decrease in FEV_1. The relationship between HRQL and FEV_1 appeared to be approximately linear with decrease in FEV_1 being statistically significantly associated with a deterioration in HRQL and increase being associated with improvements. In conclusion, there was a strong correlation between change in the physiological measure and the patient-reported HRQL. The main driver of deterioration was the increasing restriction of everyday activities due to breathlessness. The physical status and lung function of patients with a high dyspnea burden should be carefully re-examined to induce reassessment of therapeutic regimes, and to initiate the utilization of non-pharmacological interventions.

Chapter 4 investigates the utilization of non-pharmacological interventions for COPD and aims at detecting specific characteristics of patients that determine utilization. At the 36-months follow-up, the use of smoking cessation programs, influenza vaccination, physiotherapy, sports programs, patient education programs, and pulmonary rehabilitation was assessed based on self-reports. Descriptive statistics were used to compare the cohort at baseline and the subpopulation. Utilization and determinants of utilization were analyzed using logistic regression models stratified by sex and severity of disease. In general, utilization was highest for influenza vaccination (73%), while therapy options that require the active involvement of the patient were used less often (physiotherapy 10%, smoking cessation program 24%). Regarding all interventions, utilization was lower in men and current smokers and furthermore, smokers reported less often that they had received a recommendation to utilize any intervention by a physician. This is especially important, since utilization was higher in those reporting that they received a recommendation to use by a physician. To conclude, use of non-pharmacological interventions for COPD in Germany was relatively low with the exception of influenza vaccination. However, smoking cessation has been shown to positively influence lung function development and other non-pharmacological interventions can lead to improvements in HRQL and symptom relief. These are all important markers associated with the progression of the chronic diseases. Therefore, a higher utilization should be aimed for, especially among men and smokers, and recommendations to use non-pharmacological interventions by the physician might help to increase uptake.

In summary, on the basis of longitudinal data over three years from the German COSYCONET patient cohort, the progression of COPD has been described in terms of increasing health services demand leading to increasing costs and a deterioration of HRQL, which was in parallel to the measured decline in FEV_1. As described in Chapters 2 and 3, dyspnea was found to be a critical predictor of these developments. Chapter 4 therefore addressed interventions, which were shown to relieve breathlessness, increase physical activity, and improve HRQL in patients with COPD. Especially the use of interventions, which require a high level of patient commitment, was found to be insufficient. An improvement in care could be achieved by increasing utilization.

1.5 Individual contribution of the author

The author of this thesis has contributed substantially to the concept of all three articles and the definition of the research questions. She prepared and analyzed the data and wrote the original manuscript of the articles 2 and 3. Article 1 was conducted as a shared first authorship. Within the preparation for the first submission, considerable methodological reconsiderations were made. Subsequently, the author carried out the necessary recalculations and wrote the corresponding methods and results section. The author also mainly contributed to the structure and text of the discussion. Furthermore, she accompanied the publication process as the corresponding author for all articles and was the main contributor to editing and reviewing the article. The author was not involved in the data collection of the COSYCONET study but contributed to the ongoing quality control of data.

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Chapter 2 Determinants of healthcare utilization and costs in COPD patients: first longitudinal results from the German COPD cohort COSYCONET

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ORIGINAL RESEARCH

Determinants of healthcare utilization and costs in COPD patients: first longitudinal results from the German COPD cohort COSYCONET

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Background: In light of overall increasing healthcare expenditures, it is mandatory to study determinants of future costs in chronic diseases. This study reports the first longitudinal results on healthcare utilization and associated costs from the German chronic obstructive pulmonary disease (COPD) cohort COSYCONET.

Material and methods: Based on self-reported data of 1904 patients with COPD who attended the baseline and 18-month follow-up visits, direct costs were calculated for the 12 months preceding both examinations. Direct costs at follow-up were regressed on baseline disease severity and other co-variables to identify determinants of future costs. Change score models were developed to identify predictors of cost increases over 18 months. As possible predictors, models included GOLD grade, age, sex, education, smoking status, body mass index, comorbidity, years since COPD diagnosis, presence of symptoms, and exacerbation history.

Results: Inflation-adjusted mean annual direct costs increased by 5% (n.s., €6,739 to €7,091) between the two visits. Annual future costs were significantly higher in baseline GOLD grades 2, 3, and 4 (factors 1.24, 95%-confidence interval [1.07–1.43], 1.27 [1.09–1.48], 1.57 [1.27–1.93]). A history of moderate or severe exacerbations within 12 months, a comorbidity count >3, and the presence of dyspnea and underweight were significant predictors of cost increase (estimates ranging between + €887 and + €3,679, all $p<0.05$).

Conclusions: Higher GOLD grade, comorbidity burden, dyspnea and moderate or severe exacerbations were determinants of elevated future costs and cost increases in COPD. In addition we identified underweight as independent risk factor for an increase in direct healthcare costs over time.

Keywords: direct costs, population-based, healthcare expenditures, outpatient costs, inpatient costs, change score

Background

Chronic obstructive pulmonary disease (COPD) is of major concern as a source of growing global burden of disease.[1,2] Globally, its prevalence is estimated at 174.5 million individuals[3] and expected to grow, in parallel with the aging of populations and the high frequency of smoking as the major risk factor.[4]

COPD is a progressive disease without effective cure, with symptoms and functional impairment closely linked to reductions in health-related quality of life (HRQoL),[5,6] and high costs for healthcare systems.[7] Opportunities to lower the costs of disease

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management point towards improving symptoms and reducing the frequency and severity of exacerbations that are known to be major drivers of disease progression and increased costs in COPD.[8–10]

The majority of available economic studies on healthcare utilization and costs in COPD are cross-sectional.[7,11] For a disease that is progressive with huge variation between patients, longitudinal studies are of particular interest, as they may identify predictors of future developments. We have already performed a number of cross-sectional analyses on direct and indirect costs in the large German COPD cohort COSYCONET,[12] thereby providing a sound empirical basis for longitudinal analyses. In the present study we aimed to evaluate whether healthcare utilization and costs over a period of 18 months already allow for the identification of cost predictors from easily available baseline information, such as disease severity, demographic data and COPD-related symptoms and exacerbations. Since healthcare costs reflect HRQoL, predicting future direct costs and cost increases over 18 months could also identify risk groups who would benefit from improved treatment even within this relatively short period of time.

Materials and methods

Study design and study cohort

The German COPD cohort COSYCONET (German COPD and Systemic Consequences – Comorbidities Network) is a prospective, observational, multicenter cohort study.[13] A total of 2,741 subjects were recruited in 31 study centers across Germany between September 2010 and December 2013. After the baseline visit, participants were evaluated in follow-up visits at 6 and 18 months, and further ongoing visits. Data for the present analysis were drawn from the baseline examination (visit 1) and the 18-month follow-up (visit 3). Patients fulfilling enrolment inclusion criteria into the cohort were aged 40 years and older with a physician diagnosis of COPD (according to the GOLD criteria) or chronic bronchitis. Additionally, patients must have had availability for repeated study visits over at least 18 months. Patients were excluded if they experienced any of the following: having undergone major lung surgery (eg, lung volume reduction, lung transplant); moderate or severe exacerbation within the last four weeks; having a lung tumor; physical or cognitive impairment resulting in an inability to walk or understand the intention of the project.

Healthcare utilization and cost measurement

Health insurance coverage in Germany is compulsory. Statutory German health insurance scheme based on income-oriented contributions cover 89% of the German population, whereas the remaining 11% receive coverage through a private health insurance scheme based on risk-oriented contributions. Under both schemes, the majority of health services are covered. Exceptions are co-payments for drugs and inpatient hospital days (€10 per outpatient prescription and €10 per inpatient hospital day), which likely minimally financially burden patients with COPD.

All-cause healthcare utilization was assessed from standardized interviews and questionnaires at baseline and after 18 months. The reason for accessing care was not specified, while different time frames for each type of care were used in order to minimize recall bias.[14] Outpatient care was defined by the number of outpatient physician visits in the previous three months. Inpatient care was captured as the number of hospital days in the previous 12 months. Medication use was assessed according to the number of prescription pharmaceuticals used in the previous week, based on defined daily doses and patient-reported information on drug code.[15]

In order to estimate the costs for the preceding year, outpatient physician visits and prescribed medication use were extrapolated to a 12-month period. In- and outpatient visits were multiplied by the corresponding 2012 German unit costs,[16] and medication costs per year were calculated from 2012 pharmacy retail prices.[17] The standardized unit costs derived from Bock et al's 2012 study[16] are based on a societal perspective and allow the comparison of healthcare utilization across Germany, regardless of location. There was no indication of clustering effects by geographic region and study center, and these factors are therefore not controlled for in this analysis.

Covariates: participant characteristics, disease status, lung function, symptoms, comorbidities, and quality of life

This study emphasizes four major characteristics of the disease: severity of airflow obstruction, presence of symptoms, exacerbation history/risk, and presence of

comorbidities. As further characteristics we included age, sex, highest attained level of school education, smoking status, body mass index (BMI, kg/m^2), and years since COPD diagnosis. Indices of HRQoL at baseline (Saint George's Respiratory Questionnaire [SGRQ] and COPD Assessment Test [CAT]) were used to compare participants lost to follow-up with those included in the present analysis. The SGRQ is a HRQoL variable measuring symptoms, functional impairment, and psycho-social impact.[18]

Lung function and COPD definition

COPD was defined according to the spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, requiring a ratio FEV_1/FVC below 70%,[9] as obtained in standardized post-bronchodilator spirometry. Based on the results, participants were assigned GOLD grades 1 to 4 according to FEV_1 values as percent predicted according to the Global Lung Function Initiative.[19] A total of 301 participants had $FEV_1/FVC \geq 0.7$ at baseline, despite reporting a diagnosis of COPD by a physician. These participants were included in this analysis as "grade unclassified", since they are patients receiving treatment for COPD within the healthcare system. Patients identified as having alpha 1-antitrypsin deficiency (A1ATD, n=170 at baseline), either through self-reports or according to their use of A1ATD substitution therapy, were excluded from the present analysis due to the known high costs of A1ATD substitution therapy, which may bias cost estimates. Cost and utilization data of this subgroup are reported elsewhere.[20]

Symptoms, exacerbation history, and comorbidities

Three binary variables were constructed from scores on self-assessed symptom severity and functional impairment questionnaires, indicating the presence of three important COPD-related symptoms: cough, sputum production, and dyspnea. Cough and sputum production variables were taken from responses to the CAT.[21] The symptom-related questions in the CAT utilize a scale of 0 to 5, with higher scores representing greater symptoms or impairment. The presence of cough was defined by a cut-off of >2 for responses to the question "I never cough/I cough all the time". A similar variable was defined for the presence of sputum production, with a cut-off of >2 in response to "I have no phlegm (mucus) in my chest at all/My chest is completely full of phlegm (mucus)". A variable representing dyspnea was adapted from responses on the British modified Medical Research Council (mMRC) Questionnaire,[22] which utilizes a scale of 0 to 4, with higher grades indicating more severe breathlessness. A cut-off of ≥2 was chosen for this variable to define groups with less/more breathlessness. Exacerbation history was captured using mutually exclusive categories ranked by severity (no exacerbation to severe exacerbation) during the 12 months preceding the examination. The different severity levels of exacerbations were defined according to GOLD (acute respiratory worsening for several days and the need for specific measures, mild: handled by the patient itself, moderate: visited their primary care physician, severe: led to a hospital admission).

The presence of 33 pre-defined comorbidities was assessed through the following question, "Has a physician ever diagnosed you with one of the following diseases?" This information was consolidated into one variable representing comorbidity count, which has been shown to be useful in quantifying comorbidity among COPD populations.[23] The regression models included a binary version of this variable, using the median value as the cut-off (>3 comorbidities at baseline) to define groups with low/high comorbidity burden. This was also done in accordance with previously published COSYCONET data.[6,24]

Statistical analyses

To quantify the changes in patient characteristics, healthcare utilization and costs between the two visits, descriptive analyses and statistical tests for paired data were used, specifically the McNemar test for categorical variables, and the Wilcoxon Signed Rank test for numeric variables.

The association of baseline characteristics with future costs and with cost increases, both after 18 months of follow-up, were analyzed using gamma regression and change score models, respectively. To prevent the influence of extreme cost outliers on the results of the regression models, cost data were winsorized at the 95% level. All regression models included the baseline variables GOLD grade, age, sex, education, smoking status, BMI, comorbidity count, years since COPD diagnosis, presence of symptoms (cough, sputum production, dyspnea), and exacerbation history in the previous 12 months.

First, the association of baseline COPD grades and other covariates with annual costs measured at the 18-month follow-up were estimated via generalized linear regression models (GLM) with separate models for outpatient, inpatient, medication, other (physiotherapy and

rehabilitation), and total annual direct costs. Given the highly skewed distribution of cost data, we used a GLM approach with a log-link function and gamma distribution. The exponentials of the regression coefficients can be interpreted as factors.

In a second step, change score models were used to explore the baseline determinants of direct cost changes within 18 months. Differences between costs measured at follow-up and baseline were calculated based on the winsorized data set. Calculated cost changes were then regressed on baseline characteristics using GLM models with normal distribution. Positive values can be interpreted as an increase in costs, whereas negative values refer to a reduction of costs from baseline to follow-up. In addition to the above named covariates, direct costs at baseline were considered as a potential predictor of cost changes in the change score models.

A significant proportion of participants from the baseline study cohort (667/2741, 24%) were lost to follow-up at 18 months due to various reasons, and were thus excluded from the main analyses. Descriptive analyses were therefore undertaken to compare the baseline characteristics of participants present at baseline and 18 months, and those lost to follow-up. For this purpose, independent samples *t*-tests for continuous variables, Chi^2-tests for categorical variables, and Mann-Whitney U tests for non-normally distributed continuous variables were applied.

All analyses were performed using the SAS software (SAS Institute Inc., Cary, NC, USA, Version 9.3) package. *P*-values of 0.05 or less were considered statistically significant.

Sensitivity analyses

A sensitivity analysis was performed to account for drop-out bias by implementing Inverse Probability Weighting (IPW) in the regression analyses. Weights were calculated for the complete cases based on the inverse probability of attending the follow-up assessment. This was modelled using demographic variables, disease characteristics and quality of life, all measured at baseline. Complete cases that were found to be similar to patients who dropped out, were assigned higher weights resulting in a weighted population imitating the cohort as recruited at baseline. Patients who died between baseline and follow-up were excluded from the IPW calculation. The sensitivity analysis was performed for the outcome total direct costs and both models: the gamma regression model and the change score model.

Additionally, all models were calculated with the non-winsorized cost data to ensure the replicability of the results based on the raw data.

Ethics statement

The COSYCONET study was approved by the Ethics Committees of the local study centers. This approval covered the subsequent data analyses as performed here. All participants gave their written informed consent.

Results

Study population

After excluding 667 participants without data for the 18-month follow-up visit and another 170 participants with A1ATD, data from a total of 1904 participants were available for the analyses of baseline and 18 month follow-up data (Table 1). The comparison between the two time points showed a statistically significant decrease in lung function, as demonstrated by an overall fall in FEV_1 (1.72 L vs 1.64 L, $p<0.0001$). This was accompanied by an increase in the proportion of underweight patients (2.6 vs 3.4%, $p=0.0053$), as well as those reporting the presence of dyspnea (41.3 vs 43.5%, $p=0.0268$). The mean comorbidity count was also significantly higher at the 18-month follow-up (3.9 vs 4.7, $p<0.0001$). In contrast, at the follow-up a lower proportion of patients reported a severe exacerbation in the previous 12 months (17.6 vs 12.9%, $p<0.0001$).

Healthcare utilization

Healthcare utilization is reported in Table 2. Among the 1904 patients, the proportion of users of outpatient care (general practitioner, specialist, and hospital) decreased (95.7 vs 92.9%, $p<0.0001$), as did the mean total number of visits (6.3 vs 5.8, $p<0.0001$), while there were no significant changes in inpatient hospital care during this time period. The proportion of participants using prescribed medication was high at both visits, with an increase in the mean number of prescribed medicines (5.7 vs 6.0, $p<0.0001$); this increase was consistent across all GOLD grades (Table 2).

Costs

Comparison of costs at baseline and follow-up

Mean annual direct costs per person are shown in Table 2. Consistent with changes observed in outpatient services utilization, mean outpatient costs slightly dropped over

Table 1 Characteristics of the study population

	GOLD classification					All Participants[a] (n=1904)		*p*-value
	Grade 1 (n=168)	Grade 2 (n=719)	Grade 3 (n=568)	Grade 4 (n=135)	Grade unclassified (n=301)			
	Baseline					Baseline	Visit 3	
Age (years)	65.8 (8.6)	65.5 (8.0)	64.9 (7.6)	62.3 (7.2)	65.5 (9.1)	65.1 (8.1)	66.8 (8.1)	<0.0001[c]
% Age <55 years	10.1	9.3	9.3	14.1	14.3	10.6	7.7	<0.0001[b]
% Age 55–64 years	28.0	33.0	37.3	49.6	28.6	34.1	28.8	<0.0001[b]
% Age 65–74 years	48.8	46.0	44.9	31.9	41.9	44.4	46.7	0.0085[b]
% Age >74 years	13.1	11.7	8.5	4.4	15.3	10.9	16.6	<0.0001[b]
% Males	62.5	60.5	60.2	63.7	52.5	59.5		
Lung Function								
FEV_1 (liter)	2.62 (0.6)	1.85 (0.5)	1.20 (0.3)	0.76 (0.2)	2.30 (0.7)	1.72 (0.7)	1.64 (0.7)	<0.0001[c]
FVC (liter)	4.12 (0.9)	3.31 (0.8)	2.68 (0.8)	2.07 (0.6)	2.99 (0.9)	3.05 (1.0)	2.95 (1.0)	<0.0001[c]
FEV_1/FVC	64.0 (4.1)	56.6 (7.9)	46.3 (8.8)	38.9 (9.6)	76.8 (5.1)	56.1 (13.5)	55.2 (13.8)	<0.0001[c]
Smoking Status								
% Never smoker	6.6	6.0	6.0	6.7	11.6	7.0	7.0	.
% Former smoker	66.1	64.8	73.4	75.6	64.8	68.3	71.6	<0.0001[b]
% Current smoker	27.4	29.2	20.6	17.8	23.6	24.7	21.4	<0.0001[b]
BMI (kg/m^2)	26.8 (4.8)	27.5 (4.9)	26.5 (5.2)	24.5 (4.9)	29.5 (5.6)	27.2 (5.2)	27.1 (5.4)	0.0044[c]
% Underweight (BMI <18.5)	1.8	1.8	3.9	6.7	1.0	2.6	3.4	0.0053[b]
% Normal weight (18.5≤ BMI <25)	36.3	31.7	38.3	54.8	21.3	34.1	35.1	0.1670[b]
% Overweight (25≤ BMI <30)	41.1	38.3	36.0	27.4	34.9	36.5	35.8	0.4347[b]
% Obese (BMI ≥30)	20.8	28.2	21.9	11.1	42.9	26.8	25.8	0.0563[b]
Exacerbation[d]								
% No exacerbation	66.7	52.0	37.4	30.4	55.8	48.2	54.2	<0.0001[b]
% Mild exacerbation	3.0	6.8	3.0	4.4	4.7	4.8	3.5	0.0366[b]
% Moderate exacerbation	22.6	29.2	33.5	26.7	27.6	29.4	29.4	0.9381[b]
% Severe exacerbation	7.7	12.0	26.1	38.5	12.0	17.6	12.9	<0.0001[b]
Symptoms								
% with presence of cough	43.7	42.4	43.7	43.3	51.8	44.5	43.1	0.2323[b]
% with presence of sputum production	44.6	43.1	46.5	46.3	50.7	45.8	45.9	0.8930[b]
% with presence of dyspnea	19.3	30.4	58.4	78.2	30.7	41.3	43.5	0.0268[b]
Comorbidity count	4.1 (2.6)	3.9 (2.6)	3.8 (2.5)	3.1 (2.2)	4.6 (3.0)	3.9 (2.6)	4.7 (2.9)	<0.0001[c]
% Comorbidity count >3	51.8	49.0	48.4	38.5	59.1	49.9	70.5	<0.0001[b]

Notes: Data are mean (standard deviation) or percentage. Means and percentages relate to participants with valid data for that particular variable. [a]13 participants have missing GOLD grades at baseline, but are included under "All participants". [b]p-value based on McNemar test. [c]p-value based on Wilcoxon Signed Rank test.[d]Exacerbation history in previous 12 months.

Table 2 Unadjusted healthcare utilization and resulting mean annual direct costs (€), at baseline and 18 month follow-up visit (Visit 3)

	GOLD grade 1 (n=168)		GOLD grade 2 (n=719)		GOLD grade 3 (n=568)		GOLD grade 4 (n=135)		grade unclassified (n=301)		All participants[a] (n=1,904)		*p-value*
	Baseline	**Visit 3**	**Baseline**	**Visit 3**	**Baseline**	**Visit 3**	**Baseline**	**Visit 3**	**Baseline**	**Visit 3**	**Baseline**	**Visit 3**	
Healthcare utilization													
Outpatient services[d] (3 months)													
% User	95.2	92.2	94.3	92.5	97.5	93.2	97.0	96.2	95.7	92.9	95.7	92.9	<0.0001[b]
Total number of visits	6.6 (6.5)	5.8 (6.3)	6.1 (5.4)	5.5 (5.1)	6.5 (5.6)	5.9 (7.3)	5.9 (4.5)	5.2 (5.4)	6.5 (5.2)	6.6 (7.6)	6.3 (5.5)	5.8 (6.4)	<0.0001[c]
Inpatient services (12 months)													
% User	28.1	27.3	32.6	32.0	41.6	36.6	50.8	51.5	35.1	31.3	36.6	34.1	0.0645[b]
Number of hospital days	2.9 (6.2)	2.7 (6.5)	3.6 (8.9)	4.8 (13.0)	6.7 (13.3)	6.5 (14.2)	9.4 (17.3)	9.5 (13.6)	4.0 (13.1)	4.5 (12.2)	4.9 (11.7)	5.4 (12.9)	0.6211[c]
Prescribed medication (7 days)													
% User	95.8	96.4	96.9	97.8	99.5	98.2	98.5	100.0	93.0	93.4	97.1	97.2	0.6961[b]
Number of prescribed drugs	4.8 (3.2)	5.0 (3.3)	5.3 (3.0)	5.7 (3.3)	6.6 (3.2)	6.8 (3.4)	6.7 (3.3)	7.2 (3.8)	5.3 (3.8)	5.6 (4.1)	5.7 (3.3)	6.0 (3.6)	<0.0001[c]
Direct costs (12 months), Euro (2012 values)													
Outpatient costs	832 (809)	771 (952)	828 (773)	732 (712)	897 (769)	809 (1133)	829 (646)	724 (667)	840 (728)	840 (981)	850 (758)	776 (918)	<0.0001[c]
Inpatient costs	1,689 (3,638)	1,589 (3,826)	2,113 (5,235)	2,842 (7,633)	3,923 (7,862)	3,827 (8,372)	5,559 (10,198)	5,576 (8,018)	2,379 (7,694)	2,633 (7,185)	2,895 (6,916)	3,169 (7,595)	0.5746[c]
Medication costs	2,241 (5,097)	1,974 (2,304)	2,057 (2,133)	2,539 (5,090)	2,793 (3,450)	2,901 (3,454)	2,901 (3,550)	2,844 (2,016)	1,836 (2,203)	2,355 (4,725)	2,311 (3,060)	2,580 (4,207)	0.0458[c]
Other costs[e]	376 (1,022)	384 (1,318)	443 (1,074)	507 (1,318)	681 (1,246)	525 (1,138)	738 (1,375)	747 (1,226)	465 (1,092)	535 (1,079)	533 (1,153)	520 (1,220)	0.0885[c]
Total direct costs	5,362 (7,724)	4,841 (6,258)	5,553 (6,394)	6,573 (10,322)	8,300 (9,677)	8,091 (11,012)	10,172 (11,846)	9,734 (9,032)	5,821 (9,170)	6,616 (10,834)	6,739 (8,629)	7,091 (10,274)	0.1016[c]

Notes: Numbers represent participants in each GOLD grade category assigned at baseline. Data are mean (standard deviation) or percentage. Means and percentages relate to participants with valid data for that particular variable. [a]13 participants have missing GOLD grades at baseline, but are included under "All participants". [b]p-value based on McNemar test. [c]p-value based on Wilcoxon Signed Rank test. [d]Includes general practitioner, specialist, and outpatient hospital care.

18 months, whereas costs for inpatient services and medication utilization increased, however statistically significantly only for medication. Inpatient costs, followed by medication costs constituted the largest proportions of total direct costs at both time points. Total annual direct costs also showed a 5.2% increase (€6,739 vs €7,091 per patient), though this was not statistically significant due to large interindividual variation.

Determinants of future annual costs

Table 3 displays the results of the regression analysis for future annual costs. The factors for COPD grades 2 to 4 relative to grade 1 (reference) ranged from 1.24 to 1.57. Higher education was associated with lower costs (OR 0.90; 95%CI 0.80–1.00). The key drivers of future annual costs were underweight (OR 1.65; 95%CI 1.28–2.13) and the occurrence of a severe exacerbation in the 12 months before baseline (OR 1.73; 95%CI 1.55–1.93). Other variables with a significant impact on future annual costs included age 65–74 years (OR 1.24; 95%CI 1.07–1.42), age >74 years (OR 1.20; 95%CI 1.01–1.43), being a current smoker (OR 1.19; 95%CI 1.00–1.42), comorbidity count >3 (OR 1.49; 95%CI 1.37–1.61), presence of dyspnea (OR 1.30; 95%CI 1.19–1.41), and moderate exacerbation in the 12 months before baseline (OR 1.22; 95%CI 1.11–1.34). The majority of associations for inpatient and medication costs were similar to those for the total costs, whereas few variables were associated with future outpatient and other costs (see Table 3).

Predictors of cost increases over 18 months of follow-up

Table 4 shows the results of the five change score models, describing the predictive value for baseline variables on the increases in annual direct costs at follow-up. COPD grade 4 was significantly associated with increases in total annual costs (€2,346; 95%CI €960–€3,732), as was age 65–74 years (€1,018; 95%CI: €66–€1,969), a history of moderate (€887; 95%CI: €258–€1,516) or severe (€1,425; 95%CI €577–€2,273) exacerbations, a comorbidity count of >3 (€1,579; 95%CI €1,029–€2,129), and the presence of dyspnea (€1,131; 95%CI €538–€1,724). Being underweight also contributed to an increase in total direct costs at follow-up (€3,679, 95%CI €1,978–€5,380). Baseline costs, which were included to account for a possible regression to the mean effect, were highly significant for all cost categories. Sex, smoking status, years since diagnosis and symptoms (excluding dyspnea) did not have a statistically significant impact on the increases in total direct costs at the 18-month follow-up visit.

Sensitivity analyses

The models including the inverse probability weights identified similar determinants for future costs and cost increases compared to the complete case analysis. However, in comparison with the estimates derived from the complete case analysis (Table 4), the IPW estimated larger cost increases, ranging from +€38 (GOLD grade 4) to +€326 (underweight), indicating an underestimation of cost increases, when excluding participants lost to follow-up. The effect estimates of the Gamma regression model remained nearly unchanged (See Table 6).

When analyzing the association of baseline patient characteristics with future total direct costs (GLM model) based on the non-winsorized cost data set, the category "COPD grade unclassified" also reached statistical significance, with 1.26 times higher future costs compared to grade 1. No further changes in terms of statistical significance or direction of estimates were observed, although due to the broader distribution of cost data, all confidence intervals were considerably wider. Moreover, applying the change score model to the non-winsorized annual total direct costs had a limited impact on the results. Whereas COPD grade 4 and exacerbation history were no longer significantly associated with an increase in costs, estimates for underweight, comorbidity burden and dyspnea remained unchanged and were still predictors of annual direct cost increases.

Participants lost to follow-up

The comparison of baseline data between participants present for both visits with those of patients lost to follow-up indicated significant differences between the groups (Table 5). On average, participants lost to follow-up were older, had poorer lung function, experienced at least one severe exacerbation, reported the presence of symptoms and had worse HRQoL at baseline. There were also obvious differences regarding utilization and costs, whereby patients lost to follow-up showed significantly higher direct costs at baseline.

Discussion

In this study, we analyzed longitudinal data on the utilization of healthcare services and associated costs among COPD patients, and identified determinants of future annual direct costs and increases. On average, there was

Table 3 Effect of COPD and baseline characteristics on future annual direct costs

Covariate		Outpatient costs[a]	Inpatient costs	Medication costs	Other costs[b]	Total Direct costs
		n=1,819	n=1,813	n=1,804	n=1,782	n=1,731
Intercept		**433.29 [302.40–620.85]**	**457.74 [194.46–1,077.47]**	**1,203.80 [987.53–1,467.44]**	**189.71 [89.72–401.16]**	**2,301.23 [1,758.09–3,012.17]**
COPD GOLD	grade 1	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	grade 2	0.99 [0.82–1.20]	1.48 [0.93–2.36]	1.08 [0.97–1.20]	1.37 [0.90–2.08]	**1.24 [1.07–1.43]**
	grade 3	1.00 [0.81–1.22]	1.49 [0.89–2.47]	**1.23 [1.10–1.38]**	1.23 [0.79–1.93]	**1.27 [1.09–1.48]**
	grade 4	0.94 [0.71 1.24]	**2.39 [1.22–4.69]**	**1.23 [1.05–1.43]**	1.74 [0.97–3.14]	**1.57 [1.27–1.93]**
	grade unclassified	1.03 [0.83–1.29]	1.17 [0.69–1.97]	0.96 [0.84–1.08]	**1.61 [1.00–2.58]**	1.14 [0.96–1.34]
Age (years)	<55	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	55–64	1.04 [0.86–1.25]	1.30 [0.83–2.02]	1.02 [0.92–1.14]	1.00 [0.67–1.48]	1.09 [0.95–1.26]
	65–74	1.04 [0.86–1.26]	**1.90 [1.22–2.95]**	1.09 [0.98–1.21]	1.02 [0.68–1.51]	**1.24 [1.07–1.42]**
	>74	1.11 [0.87–1.40]	1.52 [0.87–2.65]	1.13 [0.99–1.30]	0.90 [0.54–1.49]	**1.20 [1.01–1.43]**
Sex	male	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	female	1.03 [0.92–1.15]	0.83 [0.63–1.08]	0.99 [0.93–1.05]	1.17 [0.92–1.49]	0.95 [0.87–1.03]
Education	basic	ref.	ref.	ref.	ref.	ref.
	secondary	1.10 [0.98–1.24]	1.05 [0.79–1.41]	0.98 [0.92–1.05]	1.06 [0.82–1.38]	1.03 [0.94–1.13]
	higher	0.96 [0.83–1.11]	0.78 [0.55–1.10]	0.94 [0.87–1.02]	1.01 [0.74–1.37]	**0.90 [0.80–1.00]**
Smoking status	never smoker	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*

(*Continued*)

Table 3 (Continued).

Covariate		Outpatient costs[a]	Inpatient costs	Medication costs	Other costs[b]	Total Direct costs
		n=1,819	**n=1,813**	**n=1,804**	**n=1,782**	**n=1,731**
	smoker	1.06 [0.83–1.34]	1.62 [0.92–2.85]	1.03 [0.91–1.17]	0.90 [0.55–1.48]	**1.19 [1.00–1.42]**
	former smoker	1.07 [0.87–1.33]	1.11 [0.66–1.85]	1.11 [0.99–1.25]	0.94 [0.59–1.49]	1.08 [0.92–1.27]
Weight (BMI)	normal	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	overweight	1.01 [0.89–1.14]	1.02 [0.76–1.39]	1.07 [0.99–1.14]	1.10 [0.84–1.45]	1.04 [0.95–1.15]
	obese	1.05 [0.91–1.21]	1.08 [0.77–1.51]	**1.13 [1.05–1.23]**	0.89 [0.66–1.21]	1.05 [0.94–1.17]
	underweight	1.16 [0.83–1.62]	1.93 [0.88–4.25]	**1.24 [1.03–1.49]**	1.57 [0.78–3.19]	**1.65 [1.28–2.13]**
Comorbidity count >3		**1.29 [1.16–1.43]**	**1.76 [1.37–2.26]**	**1.29 [1.22–1.37]**	**1.43 [1.13–1.80]**	**1.49 [1.37–1.61]**
Years since COPD diagnosis		1.00 [1.00–1.01]	0.99 [0.97–1.01]	1.00 [1.00–1.01]	1.00 [0.98–1.02]	1.00 [0.99–1.00]
Presence of cough		1.01 [0.88–1.15]	0.94 [0.69–1.27]	0.98 [0.91–1.06]	0.88 [0.66–1.16]	0.99 [0.89–1.09]
Presence of sputum production		1.12 [0.98–1.28]	0.97 [0.72–1.31]	1.04 [0.97–1.13]	1.23 [0.93–1.63]	1.02 [0.92–1.12]
Presence of dyspnea		1.11 [0.99–1.24]	**1.50 [1.14–1.98]**	**1.24 [1.16–1.32]**	**1.33 [1.05–1.69]**	**1.30 [1.19–1.41]**
Exacerbation history	no exacerbations	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	mild exacerbations	1.14 [0.89–1.46]	0.89 [0.50–1.59]	1.14 [1.00–1.31]	0.84 [0.49–1.43]	1.08 [0.89–1.30]
	moderate exacerbations	1.13 [1.00–1.28]	**1.42 [1.05–1.91]**	**1.09 [1.01–1.16]**	1.23 [0.93–1.62]	**1.22 [1.11–1.34]**
	severe exacerbations	**1.19 [1.03–1.38]**	**2.57 [1.81–3.64]**	**1.26 [1.16–1.37]**	**1.56 [1.13–2.16]**	**1.73 [1.55–1.93]**
Goodness of fit	Scaled Deviance	1.1997	1.5600	1.0765	1.5102	1.1218

Notes: Estimates with $p<0.05$ are printed in bold. [a]Includes general practitioner, specialist, and outpatient hospital care. [b]Includes rehabilitation and physiotherapy costs.

Table 4 Predictors of changes in annual direct costs after 18 months (in €)

Covariate		Outpatient costs[a]	Inpatient costs	Medication costs	Other costs[b]	Total direct costs
Intercept		**229 [55 to 403]**	−677 [−2,043 to 688]	175 [−167 to 516]	105 [−183 to 392]	515 [−1,236 to 2,267]
COPD GOLD	grade 1	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	grade 2	−6 [−100 to 89]	602 [−149 to 1,353]	42 [−144 to 228]	138 [−22 to 297]	930 [−40 to 1,899]
	grade 3	−19 [−120 to 82]	584 [−214 to 1382]	33 [−165 to 231]	54 [−116 to 224]	813 [−213 to 1,838]
	grade 4	−65 [−201 to 71]	**2031 [948 to 3,114]**	37 [−229 to 302]	**264 [34 to 494]**	**2346 [960 to 3,732]**
	grade unclassified	34 [−73 to 141]	503 [−348 to 1,354]	54 [−159 to 267]	166 [−15 to 348]	689 [−420 to 1,797]
Age (years)	<55	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	55–64	34 [−58 to 126]	692 [−33 to 1,416]	−48 [−230 to 134]	3 [−151 to 157]	468 [−4,845 to 1421]
	65–74	33 [−59 to 125]	**1,188** [461 to 1,915]	1 [−181 to 184]	51 [−104 to 205]	**1,018 [66 to 1,969]**
	>74	55 [−61 to 171]	902 [−17 to 1820]	36 [−192 to 265]	−15 [−209 to 180]	791 [−402 to 1,983]
Sex	male	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	female	8 [−47 to 62]	−335 [−771 to 100]	−39 [−146 to 68]	**121 [29–214]**	−153 [−714 to 408]
Education	basic	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	secondary	**80** [20 to 140]	81 [−395 to 556]	−11 [−128 to 105]	−14 [−115 to 88]	150 [−461 to 762]
	higher	−10 [−82 to 61]	−528 [−1,094 to 38]	−37 [−177 to 103]	14 [−106 to 134]	−608 [−1,336 to 120]
Smoking status	never smoker	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*

(*Continued*)

Table 4 (Continued).

Covariate		Outpatient costs[a]	Inpatient costs	Medication costs	Other costs[b]	Total direct costs
	smoker	6 [−110 to 122]	**942** **[20 to 1,863]**	112 [−113 to 337]	−47 [−240 to 147]	937 [−237 to 2,110]
	former smoker	26 [−80 to 132]	222 [−623 to 1,068]	118 [−87 to 323]	−53 [−230 to 123]	312 [−757 to 1,380]
Weight (BMI)	normal	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	overweight	15 [−47 to 77]	99 [−392 to 591]	11 [−111 to 132]	42 [−62 to 147]	176 [−458 to 811]
	obese	19 [−51 to 89]	−91 [−645 to 463]	70 [−66 to 206]	−63 [−181 to 56]	−54 [−768 to 660]
	underweight	74 [−89 to 237]	**1978** **[691 to 3266]**	294 [−27 to 615]	137 [−138 to 412]	**3679** **[1,978 to 5,380]**
Comorbidity count >3		**107** **[53 to 161]**	**835** **[412 to 1,257]**	**187** **[82 to 292]**	**136** **[47 to 225]**	**1,579** **[1,029 to 2,129]**
Years since COPD diagnosis		2 [−2 to 6]	−9 [−40 to 23]	−3 [−11 to 4]	1 [−6 to 8]	−8 [−48 to 32]
Presence of cough		17 [−51 to 84]	−192 [−724 to 340]	−30 [−161 to 101]	−77 [−190 to 36]	−217 [−901 to 467]
Presence of sputum production		58 [−9 to 125]	−118 [−644 to 408]	35 [−94 to 165]	82 [−30 to 194]	2 [−676 to 679]
Presence of dyspnea		48 [−10 to 106]	**839** **[380 to 1,299]**	**174** **[60 to 287]**	**100** **[3 to 198]**	**1,131** **[538 to 1,724]**
Exacerbation history	no exacerbation mild exacerbation moderate exacerbation severe exacerbation	*ref.* 33 [−89 to 155] **83** **[21 to 144]** **76** **[2 to 150]**	*ref.* 51 [−923 to 1,025] **595** **[107 to 1,082]** **1,779** **[1,098 to 2,460]**	*ref.* −12 [−250 to 226] −54 [−174 to 67] 61 [−84 to 206]	*ref.* −139 [−348 to 70] 75 [−29 to 179] **214** **[88 to 339]**	*ref.* 171 [−1,100 to 1,441] **887** **[258 to 1,516]** **1,425** **[577 to 2273]**
Direct costs at baseline[c]		**−704** **[−747 to −661]**	**−821** **[−884 to −757]**	**−126** **[−175 to −78]**	**−920** **[−965 to −876]**	**−669** **[−727 to −611]**
Goodness of fit	Scaled Deviance	1.0140	1.0141	1.0143	1.0146	1.0153

Notes: Estimates with $p<0.05$ are printed in bold. [a]Includes general practitioner, specialist, and outpatient hospital care. [b]Includes rehabilitation and physiotherapy costs. [c]Direct costs at baseline per €1,000.

Table 5 Baseline comparison of demographics and disease status, patients present for both visits (study participants) vs patients lost to follow-up (baseline only)

	Study participants with follow-up (n=1904)	Baseline only (n=667)	*p-value*
% grade unclassified	15.9	17.1	<0.0001[a]
% GOLD grade 1	8.9	4.4	
% GOLD grade 2	38.0	28.5	
% GOLD grade 3	30.0	36.4	
% GOLD grade 4	7.1	13.5	
Age (years)	65.1 (8.1)	66.0 (9.2)	0.0262[b]
% Males	59.5	58.9	0.8094[a]
% Basic school education	55.7	59.1	0.1492[a]
% Secondary school education	27.2	23.4	
% Higher school education	17.1	17.5	
FEV_1/FVC	56.1 (13.5)	54.5 (14.5)	0.0130[b]
% Never smoker	7.0	6.0	0.0818[a]
% Former smoker	68.3	65.1	
% Current smoker	24.7	28.9	
BMI (kg/m^2)	27.2 (5.2)	27.1 (6.0)	0.5464[b]
% Underweight (BMI <18.5)	2.6	5.1	0.0198[a]
% Normal weight (18.5≤ BMI <25)	34.1	33.4	
% Overweight (25≤ BMI <30)	36.5	36.4	
% Obese (BMI ≥30)	26.8	25.0	
% No exacerbation	48.2	42.7	0.0012[a]
% Mild exacerbation	4.8	5.4	
% Moderate exacerbation	29.4	27.5	
% Severe exacerbation	17.6	24.4	
% with presence of cough	44.5	50.6	0.0065[a]
% with presence of sputum production	45.8	51.4	0.0137[a]
% with presence of dyspnea	41.2	59.3	<0.0001[a]
Number of comorbidities	3.9 (2.6)	3.8 (2.8)	0.3424[c]
SGRQ[d]	40.7 (19.4)	48.3 (21.1)	0.0001[b]
Total direct costs[e]	6,739 (8,628)	8,657 (12,789)	0.0002

Notes: Data are mean (standard deviation) or percentage. Means and percentages relate to participants with valid data for that particular variable. [a]p-value based on Chi^2 test. [b]p-value based on *t*-test. [c]p-value based on Mann-Whitney U test. [d]Scoring ranges from 0 to 100, with higher scores indicating worse HRQoL. [e]Includes rehabilitation and physiotherapy costs, in addition to outpatient, inpatient and medication costs.

a non-significant 5% increase in direct costs over a period of 18 months. Statistically significant baseline determinants of increases in costs included a history of moderate or severe exacerbations in the previous 12 months, a comorbidity count >3, being underweight, and the presence of dyspnea.

Of the small number of published longitudinal studies on costs and utilization in COPD, few have reported developments of costs over time from a cohort perspective. For example, a claims database study by Jansson et al followed a relatively small sample of patients with COPD (n=244) for more than 10 years, and compared the costs in 1999 with those in 2010. However, the authors did neither report an overall change in costs for the total sample nor did they identify baseline characteristics associated with individual cost changes.[25] Medication has consistently been identified as one of the most important contributors to direct costs in COPD.[12,26,27] Our study confirms the role of medication by the observed 11.6% increase in unadjusted all-cause medication costs even after just 18 months. These increases were seen in GOLD grades 2 and 3 and in physician diagnosed COPD patients without airflow obstruction at visit 1 (GOLD unclassified).

Table 6 Determinants of future costs and cost increases calculated with Inverse Probability Weighting to adjust for dropout bias

		Future costs (Table 3) – Gamma regression model	Cost increases (Table 4) – Change Score model
		Total Direct costs	**Total Direct costs**
Intercept		**2,400 [1,829 to 3,150]**	660 [−1,131 to 2,451]
COPD GOLD	grade 1	ref.	*ref.*
	grade 2	**1.23 [1.05 to 1.43]**	923 [−116 to 1,961]
	grade 3	**1.25 [1.07 to 1.47]**	788 [−298 to 1,873]
	grade 4	**1.57 [1.28 to 1.93]**	**2,384 [986 to 3,781]**
	grade unclassified	1.13 [0.95 to 1.34]	753 [−409 to 1,914]
Age (years)	<55	ref.	*ref.*
	55–64	1.08 [0.94 to 1.24]	424 [−522 to 1,370]
	65–74	**1.22 [1.06 to 1.40]**	929 [−14 to 1,873]
	>74	1.16 [0.98 to 1.38]	621 [−545 to 1,786]
Sex	male	ref.	*ref.*
	female	0.95 [0.87 to 1.03]	−161 [−728 to 407]
Education	basic	ref.	*ref.*
	secondary	1.03 [0.94 to 1.13]	147 [−478 to 772]
	higher	**0.89 [0.80 to 0.99]**	−638 [−1,373 to 96]
Smoking status	never smoker	ref.	*ref.*
	smoker	1.17 [0.98 to 1.39]	810 [−374 to 1,993]
	former smoker	1.08 [0.92 to 1.26]	283 [−799 to 1,365]
Weight (BMI)	normal	ref.	*ref.*
	overweight	1.05 [0.95 to 1.15]	237 [−408 to 881]
	obese	1.05 [0.94 to 1.17]	−35 [−762 to 692]
	underweight	**1.69 [1.33 to 2.15]**	**4005 [2,365 to 5,645]**
Comorbidity count >3		**1.48 [1.36 to 1.60]**	**1589 [1,031 to 2,147]**
Years since COPD diagnosis		1.00 [0.99 to 1.00]	−7 [−48 to 34]
Presence of cough		0.98 [0.89 to 1.09]	−290 [−984 to 403]
Presence of sputum production		1.02 [0.92 to 1.12]	39 [−648 to 726]
Presence of dyspnea		**1.30 [1.19 to 1.42]**	**1,174 [572 to 1776]**
Exacerbation history	no exacerbation	ref.	*ref.*
	mild exacerbation	1.08 [0.90 to 1.29]	142 [−1,126 to 1,411]
	moderate exacerbation	**1.23 [1.12 to 1.35]**	**941 [299 to 1583]**

(*Continued*)

Table 6 (Continued).

		Future costs (Table 3) – Gamma regression model	Cost increases (Table 4) – Change Score model
		Total Direct costs	**Total Direct costs**
	severe exacerbation	**1.73 [1.55 to 1.93]**	**1,531 [685 to 2377]**
Direct costs at baseline[a]		-	**−681 [−740 to −623]**
Goodness of fit	Scaled Deviance	1.1230	1.0154

Notes: Estimates with $p<0.05$ are printed in bold. [a]Direct costs at baseline per €1,000. Inverse Probability Weights were calculated based on the probability of participating in the follow-up. Weights ranged between 1.07 and 2.52 and the sum of weights was 2408, imitating the cohort at baseline.

The increase in healthcare utilization and direct costs over 18 months was accompanied by a small but statistically significant mean decline in lung function, and increases in the proportion of patients reporting dyspnea, underweight, and with a higher number of comorbidities. Over this period, the proportion of current smokers in our study population decreased. We also observed a decrease in the proportion of patients reporting a severe exacerbation within the previous 12 months. This might be due to the recruitment process of the baseline cohort. Although having had a severe exacerbation within the last four weeks was defined as an exclusion criterion of study participation, those who were admitted to the hospital had a higher change of being recruited into the study as soon as their disease status stabilized.

With our first set of regression models (Table 3), we amended the direct cost model published by Wacker et al,[12] based on cross-sectional baseline data of the COSYCONET cohort. Cross-sectional analyses of cost determinants can be criticized, because cost estimates are usually based on healthcare utilization in the time period of up to 12 months before assessment and thus causality remains unclear. By using data collected at a follow-up visit, we were able to separate the assessment of baseline characteristics (possible predictors) and the self-reported healthcare utilization and related costs (future costs). In doing so, we could identify determinants of future direct costs, which were not included in the previous analyses[12] as they would simultaneously count as patient characteristics and resource utilization; eg, severe exacerbations are, by definition, connected with a hospital stay and therefore contribute to inpatient costs. In the present analysis a history of moderate and severe exacerbations was not only associated with direct costs but also predicted future direct costs.

The results of the change score models shown in Table 4 further emphasize the role played by exacerbations, symptoms, and comorbidities, this time in predicting cost increases over a period of 18 months. The comorbidity count, as well as dyspnea and a history of exacerbations were associated with increased costs in outpatient and inpatient care, medication, rehabilitation, and physiotherapy as reported at the follow-up visit. Previous studies have already identified underweight as a risk factor for mortality and higher healthcare costs in COPD.[28,29] In our study, underweight was not only a major predictor of future costs and increases in costs, but the effect estimates were similar to or even greater than those of GOLD grade 4, compared to grade 1. In accordance with the cross-sectional findings, higher COPD grades and higher age were important predictors of increasing costs.

Of additional interest are results concerning the unclassified GOLD grade participants, who had not been included in the baseline study,[12] but clearly demonstrated high healthcare costs. Remarkably, all analyses showed effect estimates closer to those for GOLD grade 2 than GOLD grade 1. However, these remained non-significant. These findings underline that patients with physician diagnosed COPD with an unclassified GOLD grade do carry a significant disease burden and should be studied further.

When analyzing unadjusted costs, standardized to 2012 unit costs, only medication costs significantly increased between the two time points. However, there are different potential biases to these analyses. For one, although there were different recruitment paths for the COSYCONET study and ongoing exacerbations were an exclusion criterion, it can still be expected that patients had a higher likelihood to be recruited if they had received inpatient or outpatient health care within the last 12 months before baseline. In addition, participants still alive but lost to follow-up can be expected to be in worse health and therefore receiving increased health care in the follow-up period. The sensitivity analysis, which included IPW, indicated that the complete case analysis

slightly underestimated the impact of various predictors on increases in direct costs at follow-up, but identified the same baseline variables as predictors of costs. However, the exclusion of patients lost to follow up from the longitudinal analysis may also have induced an underestimation of the overall mean change in costs over time. Nevertheless, this limitation is inevitable within prospective cohort studies of a broad spectrum of patients, some of whom can show deteriorations preventing them from participation in follow-up visits.

Besides non-participation bias, there are further limitations in this study, particularly the potential for recall bias in the self-reported healthcare utilization. While the follow-up period of 18 months may be considered a limitation, it is important to note that we were interested in revealing whether changes would occur even over a short period of time. As a further limitation, costs beyond inpatient and outpatient care, medication, rehabilitation and physiotherapy were not captured within this study, and thus 'real' total direct costs may be higher due to the exclusion of important healthcare-related costs, eg, for nursing care and medical devices such as oxygen therapy at home. Finally, due to the design of the questionnaire which was used to assess healthcare utilization, it was not possible to disentangle disease-related costs from overall healthcare costs. However, in practice this differentiation is very difficult, because COPD is recognized as a systemic disease with extrapulmonary manifestations.

Conversely, one of the strengths of our analyses is that in contrast to previously published longitudinal studies of costs based on administrative data in COPD, they are based on data from a prospective, multicenter cohort study that collected detailed, standardized clinical and demographics characteristics.[13] This enables us to identify predictors of future costs and cost changes over time, favored by a large sample size.

In conclusion, through analysis of intra-individual changes in the utilization of healthcare services and the associated costs, we identified cost-drivers that were clinically plausible and relevant even within the short time period of 18 months. Taking costs as an overall indicator of health status, this may help in guiding therapy decisions based on those characteristics deemed to be most important for the course of the disease.

Data Availability

The full dataset supporting the conclusions of this article is available upon request and application from the Competence Network Asthma and COPD (ASCONET, http://www.asconet.net/html/cosyconet/projects).

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Disclosure

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Chapter 3 Health-related quality of life associates with change in FEV1 in COPD: results from the COSYCONET cohort

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RESEARCH ARTICLE Open Access

Health-related quality of life associates with change in FEV_1 in COPD: results from the COSYCONET cohort

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Abstract

Background: Forced expiratory volume in one second (FEV_1) characterizes the pathophysiology of COPD and different trajectories of FEV_1 decline have been observed in patients with COPD (e.g. gradual or episodic). There is limited information about the development of patient-reported health-related quality of life (HRQL) over the full range of the natural history of COPD. We examined the longitudinal association between change in FEV_1 and change in disease-specific and generic HRQL.

Methods: We analysed data of 1734 patients with COPD participating in the COSYCONET cohort with up to 3 years of follow-up. Patients completed the Saint George's Respiratory Questionnaire (SGRQ) and the EQ-5D Visual Analog Scale (EQ VAS). Change score models were used to investigate the relationship between HRQL and FEV_1 and to calculate mean changes in HRQL per FEV_1 change categories [decrease (≤ − 100 ml), no change, increase (≥ 100 ml)] after 3 years. Applying hierarchical linear models (HLM), we estimated the cross-sectional between-subject difference and the longitudinal within-subject change of HRQL as related to a FEV_1 difference or change.

Results: We observed a statistically significant deterioration in SGRQ (total score + 1.3 units) after 3 years, which was completely driven by the activity component (+ 4 units). No significant change was found for the generic EQ VAS. Over the same period, 58% of patients experienced a decrease in FEV_1, 28% were recorded as no change in FEV_1, and 13% experienced an increase. The relationship between HRQL and FEV_1 was found to be approximately linear with decrease in FEV_1 being statistically significantly associated with a deterioration in SGRQ (+ 3.20 units). Increase in FEV_1 was associated with improvements in SGRQ (− 3.81 units). The associations between change in FEV_1 and the EQ VAS were similar. Results of the HLMs were consistent and highly statistically significant, indicating cross-sectional and longitudinal associations. The largest estimates were found for the association between FEV_1 and the SGRQ activity domain.

(Continued on next page)

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Conclusions: Difference and change in FEV_1 over time correlate with difference and change in disease-specific and generic HRQL. We conclude, that deterioration of HRQL should induce timely re-examination of physical status and lung function and possibly reassessment of therapeutic regimes.

Trial registration: NCT01245933. Date of registration: 18 November 2010.

Keywords: COPD, Cohort, Longitudinal, Patient reported outcome, Health status, Physical activity

Background

Chronic obstructive pulmonary disease (COPD) is defined by the presence of post-bronchodilator airways obstruction, respiratory symptoms such as breathlessness, cough, and sputum production and a history of exposure to inhalational injury [1]. Patients with COPD experience an accelerated decline in FEV_1 compared to healthy never smoking individuals, where a decline of about 20 ml per years was shown [2]. However, the natural history of COPD is not always characterized by a gradual accelerate decline but can also present as episodic accelerated decline of FEV_1. Here, episodes of deteriorated and improved lung function mark the overall downward trajectory of lung function over time [3]. Accordingly, patients with declining or rapidly declining FEV_1 but also patients with stable or even improved FEV_1 over time have been identified in large COPD cohorts [4–6].

While measures like FEV_1 and blood gases reflect the pathophysiology of COPD, measures of health-related quality of life (HRQL) reflect the patient's perspective of his/her disease. They are meaningful instruments to monitor the course of COPD as they cover the severity of symptoms, the impact of the disease on daily life and have also been found to predict mortality [7–9]. The longitudinal association between change in FEV_1 and change in HRQL is not fully understood. Estimates based on RCTs and only few observational studies range from only a weak correlation [10] to strong correlations [11–13] and often focus on one direction of FEV_1 change– i.e. decrease only [14] or increase only [11, 13]. Furthermore, the transferability of findings from RCTs to routine care is limited, because of highly selected patient samples.

In summary, there is limited information about the development of HRQL over the full range of the natural history of COPD, which includes FEV_1 decrease in the context of exacerbations, FEV_1 increase as a consequence of treatment, as well as unchanged FEV_1. We therefore analysed data from a large, real-world observational cohort of COPD patients followed for 3 years, with the aim to analyse and possibly quantify the association between longitudinal FEV_1 change and change in generic and disease-specific HRQL.

Methods

Study design and study population

Between September 2010 and December 2013, the prospective, multicentre COSYCONET ("German COPD and Systemic Consequences – Comorbidities Network") study recruited 2741 participants in 31 study centres across Germany and re-examinations took place after 18- and 36-months. Briefly, baseline inclusion criteria of COSYCONET were age ≥ 40 years and a physician's diagnosis of COPD. Detailed information about the inclusion and exclusion criteria and the recruitment process are available elsewhere [15].

For the present analysis, we excluded patients with (a) missing FEV_1 values at baseline, (b) $FEV_1/FVC \geq 0.7$ at baseline, and (c) no further study participation after baseline. Patients with alpha-1-antiythrypsin deficiency were not excluded, since their HRQL was found to be comparable to patients without the immune deficiency in a cross-sectional analysis [16]. An overview of the study population is given in Fig. 1.

COPD definition and HRQL assessment

Participants underwent standardized post-bronchodilator spirometry at each visit. GOLD grades 1–4 were assigned at baseline based on FEV_1 predicted, whereby reference values were taken from the Global Lung Initiative [17]. For the stratified analysis, GOLD grades were further aggregated in two groups (GOLD 1/2 and 3/4) because of limited numbers of patients in GOLD grades 1 and 4 (each less than 10% of the total sample).

At each visit, HRQL was assessed using two self-administered questionnaires: the generic 3-level version of Euro-Qol 5D (EQ-5D-3 L) and the disease-specific Saint George's Respiratory Questionnaire for COPD (SGRQ) [18, 19]. The generic instrument EQ-5D is designed to assess HRQL regardless of a specific disease and consists of two parts, the descriptive section and the valuation section. For the present analysis, we used the descriptive section only, i.e. the Visual Analogue Scale (EQ VAS), since this descriptive section was found to better discriminate between COPD grades compared to the EQ-5D valuation section. Furthermore, the VAS was preferred as a simple measure of generic HRQL since the EQ-5D utility index requires a country-dependent tariff and is less sensitive due to its skewed distribution [20]. When using the EQ VAS, participants value their current health status on a scale between 0 (worst possible) and 100 (best imaginable) and a 6.9 units change

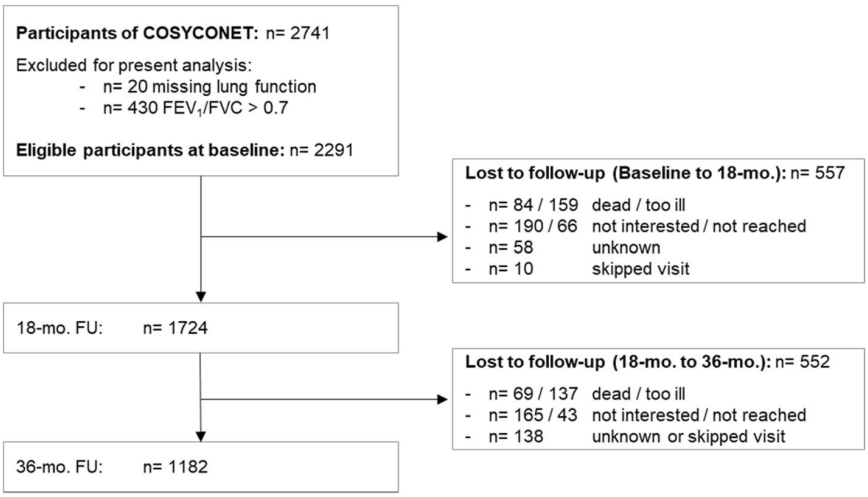

Fig. 1 Overview of the study population. Abbreviations: mo. = months; FU = follow-up

has been proposed as the minimal clinically important difference [21]. To assess disease-specific HRQL, we used the SGRQ in its COPD specific version. This questionnaire consists of 40 questions related to three components of HRQL (symptoms, activity, and impacts). The total score ranges between 0 and 100 with higher values indicating worse HRQL. Its reliability, validity and responsiveness has been demonstrated in patients with COPD and a 4 units change is considered to indicate the minimal clinical important difference [22].

Assessment of covariates

Age, sex, education, and smoking status were assessed in standardized interviews complemented by self-administered questionnaires. Body mass index (BMI) was calculated based on measured height and weight. Information on 33 comorbid conditions was obtained by asking "Has a physician ever diagnosed one of the following diseases?". This information was summarised into a single count indicating the number of comorbidities (range 0–33) at each visit. This approach has been previously proven to be a sufficient proxy for total comorbidity burden [23]. Again based on self-reports the history of exacerbations was defined according to GOLD guidelines as no exacerbation, mild, moderate, or severe exacerbation. For each patient, only the most severe exacerbation that occurred in the 12 months preceding the respective study visit was coded. In this way, we attempted to minimize a potential recall bias especially with regard to an underestimation of lighter events. In case of missing values, we imputed the most frequent category or the mean value for continuous data. Considering all three visits and > 4500 observations, a total of only 25 values were imputed for the covariates.

Statistical analysis

Since loss of lung function and HRQL are both dependent on disease severity, patient characteristics including FEV_1 and measures of HRQL at baseline and all analyses are reported stratified by GOLD grade (1/2 vs. 3/4) [4, 24]. For 1182 patients with participation in the 3 year follow-up, change in FEV_1 and HRQL over 3 years was evaluated based on t-tests for paired data. To investigate the association between FEV_1 and HRQL over time, two statistical approaches were employed: change score analysis and hierarchical linear models. All models were adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history.

Change score analyses

First, using ordinary least squares linear regression models, we regressed the change in HRQL between baseline and 36 months follow-up on three categories of FEV_1 change and covariates to calculate mean changes in HRQL. The within-subject change in FEV_1 after 36 months was defined as either decrease in absolute $FEV_1 \geq 100$ ml, increase in absolute $FEV_1 \geq 100$ ml, and no change (in between). The 100 ml cut-off in FEV_1 was chosen in accordance with the previously published minimal important difference for COPD [25]. As we considered the change in FEV_1 to be dependent on baseline lung function, an interaction term to account for the relation between the FEV_1 change category and baseline FEV_1 was incorporated.

Second, generalized additive models (GAM) were conducted, to investigate the relationship between HRQL and a continuous measure of FEV_1. This nonparametric regression models the association between the dependent variable change in HRQL and

the independent variable change in FEV_1 using a smoothing function while adjusting for covariates. Further details have been published elsewhere [26].

Hierarchical linear model

We applied hierarchical linear models (HLM), which enable the inclusion of time-variant and time-invariant covariates and can be applied on datasets with missing variables at different time points (i.e. patient dropped out after second follow-up). These models were designed to provide information regarding mean population trends and individual change over time. Considering time points as time nested in individuals, the model divides the original independent variable into the mean over time (between-subject differences) and the deviation from the mean over time (within-subject change) [27]. In our specific case, the model distinguished between the cross-sectional between-subject and the longitudinal within-subject association of FEV_1 (included as a continuous variable with the unit 100 ml difference or change) and HRQL.

Sensitivity analysis

To account for selective dropout bias, we performed a sensitivity analysis including Inverse Probability Weights (IPW) in the change score- and hierarchical linear models. We first modelled the probability of follow-up based on baseline characteristics (demographics, disease characteristics and quality of life). Weights were then assigned to all patients, who were included in the present analysis, by calculating the inverse of the estimated probability of follow-up. Using this approach, patients, who were found to be similar to those who dropped out, were given greater weights resulting in a weighted population simulating a population without dropout.

All analyses were carried out using the SAS software (SAS Institute Inc., Cary, NC, USA, Version 9.4) package.

Results

Of the 2741 patients recruited into the COSYCONET cohort, 450 had to be excluded because of missing or non-obstructive spirometry at baseline. Of those entering the cohort ($n = 2291$), 1724 were seen at the second, and 1182 at third follow-up visit. Another 10 participants skipped the first follow-up, but were re-examined in the second follow-up and thus included for the present analysis, resulting in a sample size of $n = 1734$ at baseline.

Table 1 displays the baseline characteristics of the study sample, stratified by GOLD grade 1/2 versus 3/4. Patients with COPD GOLD 1/2 were found slightly older and reported a greater number of comorbidities. The proportion of patients reporting at least one severe exacerbation in the 12 months before the baseline examination was greater for GOLD grade 3/4, as was the proportion of underweight patients. Similarly, mean baseline SGRQ total score and EQ VAS indicated worse HRQL for GOLD 3/4 compared to GOLD 1/2.

Change in FEV_1 and HRQL over three years

For 1182 COPD patients with participation at baseline and at the 36 months follow-up visit, mean change in FEV_1 and HRQL was calculated (Table 2). Baseline characteristics of this subpopulation are available in Additional file 1. For the 3 years time period, a 150 ml FEV_1 decrease was observed for all patients, while this decrease was 180 ml for those with GOLD 1/2 and 90 ml for those with GOLD 3/4 at baseline. Over the same period, we also observed a statistically significant deterioration in disease-specific HRQL (SGRQ total score + 1.3 units) on the population level. This overall change in SGRQ was fully driven by a + 4 units change in the activity component, which was present for both baseline GOLD strata. On an individual level, 73% of patients experienced a clinically relevant change in SGRQ after 3 years (40% deterioration, 33% improvement) (Additional file 1 Table A2).

Analysing the change of the generic EQ VAS in the same way, no significant change was observed on the population level. However, 66% of patients experienced a clinically relevant change in EQ VAS (34% deterioration, 32% improvement).

Relationship between FEV_1 and HRQL over time

Change score analysis

We then analysed all pairs of repeated FEV_1 and HRQL measurements stemming from 1173 patients who completed the follow-up after 36 months. Altogether, COPD patients with GOLD 1/2 at baseline contributed 695 pairs of observations, while those with GOLD 3/4 contributed 478 pairs. We observed a ≥ 100 ml FEV_1 decrease in 58% of the total sample, 28% were recorded as no change in FEV_1, and the remaining 13% experienced a ≥ 100 ml FEV_1 increase over the 3 years period (Table 3).

Figure 2 displays the adjusted mean change in SGRQ and EQ VAS as associated with FEV_1 change (decrease, no change, increase) for all participants and stratified by baseline GOLD grade of severity. Overall, a decrease in FEV_1 was associated with a deterioration in disease-specific and generic HRQL (mean change [95% CI] SGRQ + 3.20 [1.43 to 4.97], EQ VAS -1.05 [− 3.32 to 1.22]), although this was not significant for EQ VAS. On the other hand, we observed statistically significant improvement in generic and disease-specific HRQL for all patients with increased FEV_1 (SGRQ -3.81 [− 6.28 to −

Table 1 Characteristics of the study population at baseline

		Total sample	GOLD 1/2	GOLD 3/4	
n		1734	943	791	*p*-value[1]
Male		1054 (60.8)	570 (60.5)	484 (61.2)	0.7523
Age, yrs		64.6 ± 8.2	65.5 ± 8.3	63.6 ± 8.0	<.0001
Age category	< 55	203 (11.7)	96 (10.2)	107 (13.5)	<.0001
	55–64	610 (35.2)	300 (31.8)	310 (39.2)	
	65–74	750 (43.3)	432 (45.8)	318 (40.2)	
	> = 75	171 (9.9)	115 (12.2)	56 (7.1)	
BMI category[2]	Normal	648 (37.4)	319 (33.8)	329 (41.6)	<.0001
	Overweight	642 (37.0)	366 (38.8)	276 (34.9)	
	Obese	392 (22.6)	242 (25.7)	150 (19.0)	
	Underweight	52 (3.0)	16 (1.7)	36 (4.6)	
FEV_1 (liters)		1.61 ± 0.64	2.00 ± 0.56	1.13 ± 0.33	<.0001
FEV_1% predicted		54.1 ± 18.4	69.6 ± 12.8	38.0 ± 8.2	<.0001
Education	Primary	939 (54.2)	480 (50.9)	459 (58.0)	0.0017
	Secondary	487 (28.1)	270 (28.6)	217 (27.4)	
	Higher	308 (17.8)	193 (20.5)	115 (14.5)	
Smoking status	Never smoker	124 (7.2)	73 (7.7)	51 (6.5)	<.0001
	Current smoker	403 (23.2)	258 (27.4)	145 (18.3)	
	Former smoker	1207 (69.6)	612 (64.9)	595 (75.2)	
Comorbidities	Mean number	3.8 (2.6)	3.9 ± 2.6	3.6 ± 2.5	0.0171
Exacerbation history[3]	none	806 (46.5)	519 (55.0)	287 (36.3)	<.0001
	mild	86 (5.0)	57 (6.0)	29 (3.7)	
	moderate	529 (30.5)	266 (28.2)	263 (33.3)	
	severe	313 (18.1)	101 (10.7)	212 (26.8)	
HRQL measures	SGRQ total score	41.6 ± 19.3	35.5 ± 18.5	48.8 ± 17.7	<.0001
	Activity component	56.2 ± 25.5	46.6 ± 24.3	67.6 ± 21.9	<.0001
	Symptoms component	54.4 ± 21.1	50.4 ± 21.6	59.1 ± 19.6	<.0001
	Impacts component	28.6 ± 19.8	23.8 ± 18.7	34.2 ± 19.4	<.0001
	EQ VAS	57.7 ± 19.6	62.9 ± 18.6	51.6 ± 19.0	<.0001

Data are presented as mean ± SD or n (%)
[1]*p*-values based on Chi-square-Tests and ANOVA
[2]BMI groups were defined as normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), obese (BMI ≥ 30), and underweight (BMI < 18.5)
[3]previous 12 months before examination
BMI Body mass index; *FEV_1* forced expiratory volume in 1 s; *HRQL* Health-related quality of life; *SGRQ* Saint George's Respiratory Questionnaire; *EQ VAS* Visual Analog Scale

1.34], EQ VAS + 5.38 [3.34 to 7.86]). Regarding the category no change in FEV_1, we found non-significant improvements in EQ VAS while the SGRQ remained unchanged. Both GOLD strata mirrored the results of the total sample. Our data indicated an approximately linear relationship between change in HRQL and FEV_1 (Fig. 3). However, the graph was found to be shifted to the left side of the x-axis meaning that a zero change in FEV_1 did not correspond to a zero change in HRQL but was associated with slight improvements in HRQL. Consequently, a clinical relevant deterioration in SGRQ was associated with a decrease in FEV_1 of more than − 600 ml, while an increase of more than 200 ml FEV_1 was associated with a clinical relevant improvement in SGRQ.

Hierarchical linear model

The results of the HLM analysis detailing the cross-sectional (between-subject) and longitudinal (within-subject) estimates for HRQL and FEV_1 are presented in Tables 4 and 5. Regarding the SGRQ total score (Table 4) and according to the cross-sectional estimate, higher FEV_1 was associated with better HRQL with 100 ml more (difference) FEV_1 corresponding to a mean improvement by − 1.42 units in SGRQ. Corresponding estimates for the

Table 2 Change in FEV_1 and HRQL for 1182 COPD patients who complete the 36-month follow-up

		Baseline	18-month	36-month	3 year change[1]	
FEV_1% predicted	Total sample *[missing values]*	56.1 (18.2) *[–]*	54.4 (18.5) [17]	53.0 (19.2) [9]	−3.0	<.0001
	GOLD 1/2	68.0 (12.8)	65.3 (14.7)	64.1 (15.5)	−3.9	<.0001
	GOLD 3/4	38.8 (8.1)	38.3 (9.8)	37.0 (11.0)	−1.8	<.0001
FEV_1 (liters)	Total sample	1.68 (0.65) *[–]*	1.60 (0.63) [17]	1.53 (0.64) [9]	−0.15	<.0001
	GOLD 1/2	2.02 (0.57)	1.90 (0.58)	1.84 (0.58)	−0.18	<.0001
	GOLD 3/4	1.17 (0.34)	1.14 (0.38)	1.08 (0.41)	−0.09	<.0001
SGRQ total score	Total sample	40.2 (19.1) [6]	39.7 (20.4) [22]	41.5 (20.4) [17]	1.3	0.0015
	GOLD 1/2	35.0 (18.3)	34.3 (19.3)	35.9 (19.6)	0.9	0.1201
	GOLD 3/4	47.9 (17.7)	47.9 (19.2)	49.8 (18.8)	1.9	0.0019
Activity component	Total sample	54.2 (25.3) [4]	54.8 (26.7) [17]	58.2 (26.9) [16]	4.0	<.0001
	GOLD 1/2	45.9 (24.1)	46.6 (26.0)	49.6 (26.1)	3.7	<.0001
	GOLD 3/4	66.2 (22.0)	67.1 (22.9)	71.0 (22.7)	4.8	<.0001
Symptoms component	Total sample	54.1 (21.3) [3]	52.2 (22.6) [18]	53.4 (22.0) [16]	− 0.7	0.2494
	GOLD 1/2	50.5 (21.6)	48.4 (22.4)	49.4 (22.5)	−1.1	0.1403
	GOLD 3/4	59.4 (19.7)	57.8 (21.6)	59.3 (19.8)	−0.1	0.9660
Impacts component	Total sample	27.2 (19.6) [3]	26.5 (20.3) [19]	27.5 (20.6) [15]	0.3	0.6627
	GOLD 1/2	23.2 (18.6)	22.1 (18.7)	23.0 (19.3)	−0.2	0.5685
	GOLD 3/4	33.1 (19.5)	33.1 (20.9)	34.0 (20.8)	0.9	0.1990
EQ VAS	Total sample	59.1 (19.4) [9]	59.9 (19.5) [22]	58.6 (19.5) [10]	−0.5	0.2830
	GOLD 1/2	63.5 (18.2)	64.1 (18.6)	62.4 (18.7)	−1.1	0.0899
	GOLD 3/4	52.7 (19.4)	53.7 (19.1)	52.9 (19.3)	0.2	0.8051

Data are presented as mean (SD), *[number of missing values]*
Patient numbers in each GOLD group: Total sample $n = 1182$; GOLD1/2 $n = 702$; GOLD 3/4 $n = 480$
[1]p-values based on paired t-test statistics

single GOLD strata were – 1.00 for GOLD 1/2, and – 1.57 for GOLD 3/4. Conversely, the longitudinal within-subject estimate indicated the effect of a 100 ml FEV_1 decrease within a patient. Overall, a 100 ml decrease in FEV_1 resulted in a deterioration in disease-specific HRQL, indicated as a 0.83 units change in SGRQ ($p < 0.0001$).

Regarding the three component scores of the SGRQ, we observe statistically significant longitudinal associations between a 100 ml decrease in FEV_1 and all domains (activity, symptoms, and impacts). The biggest impact of FEV_1 decrease was found on the activity domain, followed by the symptoms- and impacts components (data not shown).

Table 3 Change in FEV_1 over 36 months stratified by baseline GOLD grades

	Change in FEV_1		
	decrease ≥ 100 ml	no change	increase ≥ 100 ml
GOLD 1/2 (*n* = 695)	63,6%	24,6%	11,8%
GOLD 3/4 (*n* = 478)	50,4%	33,7%	15,9%
Total sample (*n* = 1173)	58,2%	28,3%	13,5%
Mean FEV_1 change	− 311 ml	−11 ml	269 ml
Responder[1] SGRQ	29,1%	35,5%	48,4%
Responder[1] VAS	26,5%	37,2%	43,9%

[1]Indicates the percentage of patients who experienced a clinically relevant improvement in HRQL

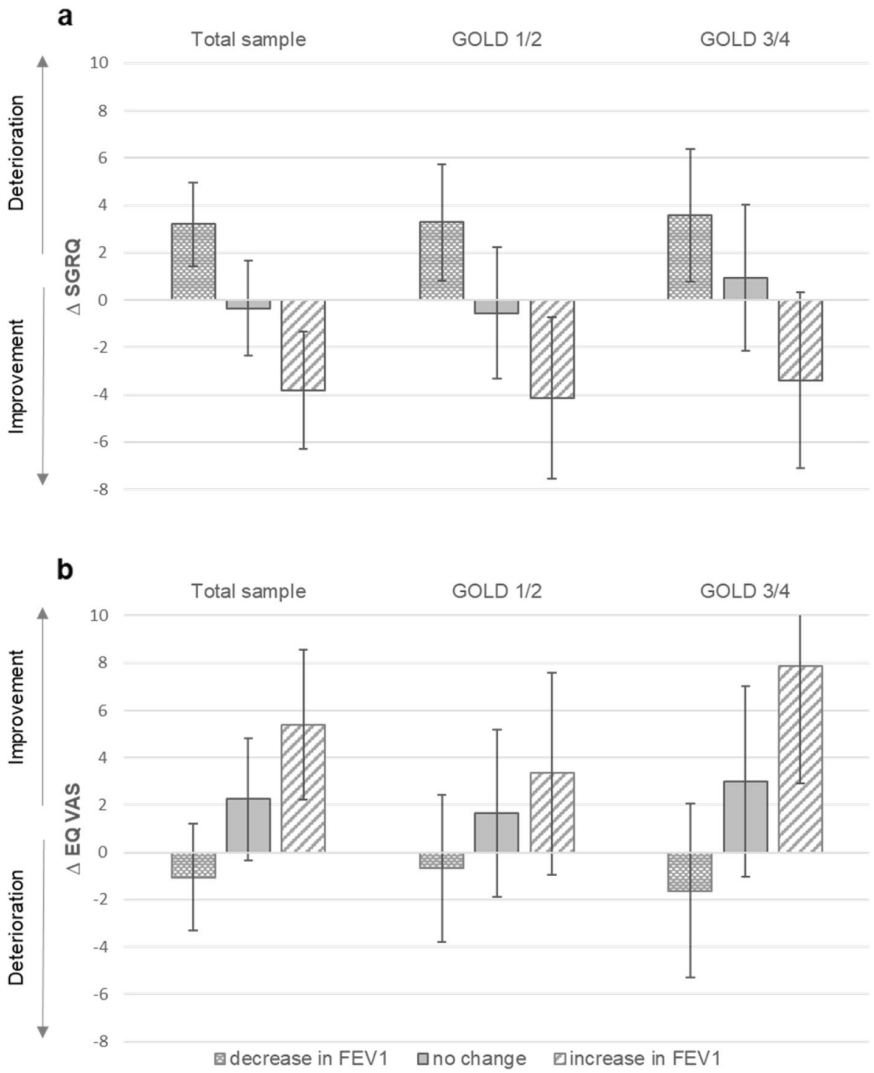

Fig. 2 Absolute adjusted mean change in SGRQ (a) and EQ VAS (b) after 36 months. Ordinary least square regression models were adjusted for age, sex, BMI, education, smoking status, number of comorbidities, exacerbation history, and FEV_1 change*baseline FEV_1. Error bars indicate 95% confidence intervals. Change categories in FEV_1 were defined as decrease in absolute $FEV_1 \geq 100$ ml, increase in absolute $FEV_1 \geq 100$ ml, and no change (in between) after 36 months

Regarding the generic EQ VAS (Table 5), we observed estimates of the same direction, but overall estimates were smaller regarding both the between- and within-subjects analysis in relation to a 100 ml FEV_1 difference or change, respectively.

Sensitivity analysis

The results of the sensitivity analysis are displayed in Additional file 2 (Change Score model) and Additional file 3 (HLM). Overall, the inclusion of IPW confirmed our results since all estimates and *p*-values were nearly identical. However, it also indicated a slight underestimation of the effect of change in FEV_1 on HRQL particularly in patients with GOLD 3/4 at baseline when excluding dropouts. For example, in patients with baseline GOLD 3/4, the deterioration in SGRQ associated with decrease in FEV_1 was more pronounced when considering participants who dropped out through IPW (SGRQ mean change + 4.11 [1.37 to 6.84] including IPW vs. + 3.59 [0.79 to 6.38] without IPW (see Additional file 2).

Discussion

We analysed the change in HRQL over 3 years associated with change in FEV_1 and investigated both the cross-sectional and the longitudinal association of FEV_1

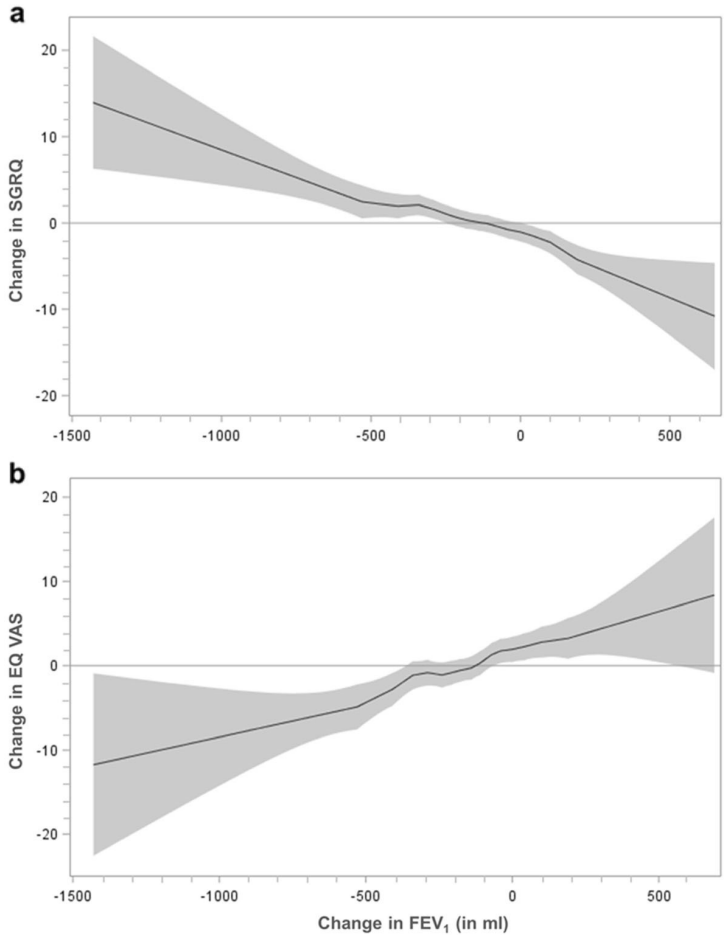

Fig. 3 Relationship between change in FEV_1 and SGRQ (a), EQ VAS (b). Generalized additive models were adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history. The solid curves represent the estimated smooth functions of the association between FEV_1 and HRQL. The shaded areas indicate 95% confidence intervals

and HRQL. On the population level, the overall decline in SGRQ total score was small but statistically significant and was completely driven by a significant deterioration of + 4 units in the activity domain. On the individual patient level, more than one-third of patients experienced a clinically relevant deterioration in SGRQ. We found a linear relationship between change in FEV_1 and change in HRQL meaning that decrease in FEV_1 was associated with a deterioration in HRQL whereas an increase in FEV_1 was similarly found associated with improved

Table 4 Cross-sectional and longitudinal estimates for the association between FEV_1 and disease-specific HRQL as measured with the SGRQ

Outcome: SGRQ	Total sample	GOLD 1/2	GOLD 3/4
	estimate [95% CI]	*estimate [95% CI]*	*estimate [95% CI]*
FEV_1 between-subjects	−1.42* [− 1.55 to − 1.29]	−1.00* [− 1.23 to −0.78]	−1.57* [− 1.95 to − 1.19]
FEV_1 within-subjects	0.83* [0.65 to 1.01]	0.86* [0.63 to 1.09]	0.92* [0.60 to 1.23]

*$p < 0.001$

Hierarchical linear models (HLM) adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history

Interpretation: Positive estimates indicate deterioration in HRQL. FEV_1 between-subjects: cross-sectional difference in HRQL per 100 ml difference in FEV_1 between subjects. FEV_1 within-subjects: longitudinal change in HRQL per 100 ml decrease in FEV_1 within subjects over time

Table 5 Cross-sectional and longitudinal estimates for the association between FEV_1 and generic HRQL as measured with the EQ VAS

Outcome: EQ VAS	Total sample	GOLD 1/2	GOLD 3/4
	estimate [95% CI]	*estimate [95% CI]*	*estimate [95% CI]*
FEV_1 between-subjects	1.08* [0.95 to 1.21]	0.71* [0.49 to 0.93]	1.20* [0.83 to 1.58]
FEV_1 within-subjects	−0.87* [− 1.13 to − 0.62]	−0.67* [− 0.98 to − 0.35]	−1.20* [− 1.64 to − 0.76]

*$p < 0.001$

Hierarchical linear models (HLM) adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history

Interpretation: Positive estimates indicate improvement in HRQL. FEV_1 between-subjects: cross-sectional difference in HRQL per 100 ml difference in FEV_1 between subjects. FEV_1 within-subjects: longitudinal change in HRQL per 100 ml decrease in FEV_1 within subjects over time

HRQL. Remarkably, a no change in FEV_1 was also associated with slight improvements in HRQL. We found a highly significant relation between a 100 ml within-subject FEV_1 decrease and generic and disease-specific HRQL, with the largest estimate for the activity domain of the SGRQ.

The overall decline in the disease-specific HRQL in COPD is in line with the literature [12, 28, 29]. Noteworthy enough, the decline was not steady over time, as we found small reductions in the SGRQ total score (i.e. improvement in HRQL) and symptoms component as well as in the EQ VAS for the first 18-months of follow-up, similar to what has been previously observed by Yoo and co-workers [30].

The deterioration in SGRQ was completely driven by the activity component. This aligns with Waschki et al. who reported a substantial decrease in physical activity over 3 years in a COPD cohort [31]. The finding, that the symptoms and impact component remained unchanged or even improved, would be compatible with the assumption that these factors can be managed through adequate medical or non-medical therapy [14]. Our data underline that maintenance of physical activity should play a much greater role in the treatment of COPD.

The mean changes in HRQL as related to the three FEV_1 change categories did not exceed the MCID. However, a mean deterioration in HRQL on the population level, which is significantly different from zero, indicates an important development, given that a relevant proportion of patients experienced a clinical relevant change in HRQL after 3 years. Furthermore, our results are in line with a systematic review by Westwood and co-workers, who summarized the information of 22 randomized controlled trials on the effects of long-acting bronchodilator therapy and analysed the relationship between increase in FEV_1 and patient-reported outcomes, including HRQL as measured using the SGRQ [13]. According to this analysis, a mean 2.5 units decrease in SGRQ total score (i.e. improvement) was estimated for a 100 ml increase in FEV_1.

Our results partly concur with Westwood et al., finding that even no change in FEV_1 is associated with improved HRQL. While the GAM indicated slight improvements in HRQL for a zero change in FEV_1, the stratified analysis confirmed this only for patients with baseline GOLD grades 1/2, but indicated a trend for deteriorations in SGRQ for the more severe grades GOLD 3/4. Westwood et al. discuss a potential Hawthorne effect – a phenomenon whereby patients modify their behaviour because of their active participation in science and their awareness of being observed [32]. However, in our study, this effect might be small because the intensity of supervision is rather low with more than a year between study visits. Adaptation processes or changes in treatment after recruitment into the cohort might rather play a role and additional research is needed to further explore this.

The observational Japanese COPD cohort HOKKAIDO evaluated the relationship between FEV_1 decline and change in SGRQ and its component scores. Based on the degree of the annual decline in FEV_1, the cohort was split into three categories: rapid decliner (− 63 ± 2 ml/year), slow decliner (− 31 ± 1 ml/year) and sustainers (including improvements in FEV_1 (− 2 ± 1 ml/year)). The authors report deterioration in HRQL for the rapid decliners indicated by a change of 5 units of the SGRQ total score after 5 years, zero change for slow decliners and an improvement in HRQL (− 4 units SGRQ) for the sustainers [14]. Calculation of the change in SGRQ per 100 ml FEV_1 decrease based on the data given for the rapid decliner, results in a mean deterioration in HRQL by a 1.59 units change in SGRQ total score. The within-subject estimate of our HLM indicated a deterioration in HRQL of half the size (+ 0.83 units SGRQ per 100 ml FEV_1 decrease), which is not surprising, considering that our population was not stratified by categories of FEV_1 decline.

Both HRQL measures differentiated between GOLD strata at baseline and the longitudinal within-subject association between FEV_1 and HRQL showed a similar relationship. However, the overall change in EQ VAS after 3 years (− 0.5 units, n.s.) might have been too small to detect significant mean changes in EQ VAS as related to the FEV_1 change category decrease. Methodological

aspects could explain part of the observed differences. Whereas the SGRQ covers history and current health status, the EQ VAS refers to the patients' current short-term health status, which might show more variation than a sort of averaging as implemented in the SGRQ. Moreover, the EQ VAS as a generic measure of HRQL includes aspects of the patients' life that are not related to his/her COPD all. We conclude that disease-specific instruments are more suitable for the longitudinal assessment of HRQL in patients with COPD.

Selective dropout of patients is an issue in long-term observational cohort studies. Regarding our data set of 2291 eligible patients recruited at baseline of the COSYCONET cohort study, 557 and 552 patients were not re-examined at the 18-month and 36-month follow-up visit, respectively. Of those 1109 patients, 153 (14%) died and 296 (27%) terminated their participation due to worsening of their health status. However, we do not think that dropout severely affected our findings and the sensitivity analysis including the IPW confirmed this hypothesis. One reason might be that our aim was to analyse the association of change in FEV_1 and HRQL and not to predict HRQL development. The latter would indeed be influenced by dropout as one would expect those with deteriorating COPD to also experience worse HRQL. Second, the hierarchical linear model also included patients who were available for only two examinations, therefore minimizing the number of patients not considered.

With regard to the observational and longitudinal design of our study, some limitations need to be addressed. First, regression to the mean might have occurred in the repeated measurement of lung function and HRQL values [33]. This bias seems, however, unlikely since we were interested in the association between the change in FEV_1 and the change in HRQL, which was independent from FEV_1 group assignment. Furthermore, longitudinal results were also confirmed by the HLMs, which are thought to be robust against a bias from regression to the mean. Second, our analyses do not allow drawing conclusions regarding treatment effects on lung function. All patients were under their usual therapy, but medication-specific variables were not considered in the models. This aspect might, however, be less important, as in general the treatment in the COSYCONET cohort is very intense and broad [34].

Conclusions

To conclude, our study provides estimates for both the cross-sectional and longitudinal association between FEV_1 and HRQL and these were highly statistically significant regarding both outcomes: disease-specific and generic HRQL. Overall, change in HRQL followed change in FEV_1, however, increases in FEV_1 were associated with greater HRQL gains than equal decreases in FEV_1 with HRQL losses. To monitor the progression of COPD from the patient's perspective, the disease-specific SGRQ was found superior to the generic EQ-VAS. As quality of life is an important aspect in patients' life, determining the course of the disease and therapeutic requirements, the findings suggest that optimal treatment of lung function and a minimization of its deterioration over time has an impact beyond the patients' functional status. Furthermore, deterioration of HRQL should induce timely re-examination of physical status and lung function and possibly reassessment of therapeutic regimes, particularly in patients with severe airflow obstruction.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12890-020-1147-5.

Additional file 1. Table A1 Baseline characteristics of COPD patients who completed the 36-month follow-up and Table A2 Clinically important change in HRQL after 36-month.

Additional file 2. Inverse Probability Weighting: Absolute adjusted mean change in SGRQ (a) and EQ VAS (b) after 36 months

Additional file 3. Table A3 Inverse Probability Weighting: Cross-sectional and longitudinal estimates for the association between FEV1 and disease-specific HRQL as measured with the SGRQ.

Abbreviations

BMI: Body mass index; COPD: Chronic obstructive pulmonary disease; COSYCONET: COPD and systemic consequences - comorbidities network; EQVAS: Euro-qol visual analog scale; EQ-5D: Euro-qol 5 dimensions questionnaire; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; GAM: Generalized additive model; GOLD: Global Initiative for chronic obstructive pulmonary disease; HLM: Hierarchical linear model; HRQL: Health-related quality of life; IPW: Inverse probability weights; RCT: Randomized controlled trial; SGRQ: Saint George's respiratory questionnaire

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Authors' contributions
JL and RH conceptualized the paper and performed the statistical analysis. JL, RJ, HS, LS, MS, and RH interpreted the data. JL and RH drafted the manuscript. RJ, SK, KK, HS, and CV were involved in the coordination and the data acquisition of the COSYCONET study. All authors took part in the discussion and critical revision of this manuscript. All authors read and approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Availability of data and materials
Data may be obtained from a third party and are not publicly available. The full dataset supporting the conclusions of this article is available upon request and application from the Competence Network Asthma and COPD (ASCONET, http://www.asconet.net/html/cosyconet/projects).

Ethics approval and consent to participate
The COSYCONET study complies with the Declaration of Helsinki and Good Clinical Practice Guidelines and has been approved by the ethics committee of the medical faculty of the Philipps-Universität Marburg, the local ethics committees of the participating centers (a list of all participating study centers can be found here: http://www.asconet.net/html/cosyconet/studzent) and by the concerned data security authority (data security agency of the federal states of Hesse, Baden-Württemberg, Lower-Saxony, and Saarland). This approval covered the subsequent data analyses as performed here. All cohort participants gave their written informed consent.

Consent for publication
Not applicable.

Competing interests
CV reports grants and personal fees outside the submitted work from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Mundipharma, Novartis, and personal fees from Cipla, Berlin Chemie/Menarini, CSL Behring, Teva, Bayer Schering Pharma AG, MSD, and Pfizer. All other authors declare no conflicts of interest.

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Publisher's Note

Appendix

Additional file 1

Table A1 Baseline characteristics of COPD patients who completed the 36-month follow-up

		Total sample	GOLD 1/2	GOLD 3/4	
n		1182	702	480	p-value[1]
Male		719 (60.8)	424 (60.4)	295 (61.5)	0.7140
Age, yrs		64.4 ± 8.2	65.5 ± 8.3	63.6 ± 8.0	<.0001
Age category	< 55	144 (12.2)	73 (10.4)	71 (14.8)	<.0001
	55 - 64	427 (36.1)	227 (32.3)	200 (41.7)	
	65-74	503 (42.6)	323 (46.0)	180 (37.5)	
	>= 75	108 (9.1)	79 (11.3)	29 (6.0)	
BMI category[2]	Normal	421 (35.6)	224 (31.9)	197 (41.0)	0.0002
	Overweight	462 (39.1)	284 (40.5)	178 (37.1)	
	Obese	269 (22.8)	182 (25.9)	87 (18.1)	
	Underweight	30 (2.5)	12 (1.7)	18 (3.8)	
FEV_1 (liters)		1.68 ± 0.65	2.02 ± 0.57	1.17 ± 0.34	<.0001
FEV_1% predicted		56.1 ± 18.2	68.0 ± 12.8	38.8 ± 8.1	<.0001
Education	Primary	619 (52.4)	345 (49.2)	274 (57.1)	0.0156
	Secondary	336 (28.4)	207 (29.5)	129 (26.9)	
	Higher	227 (19.2)	150 (21.4)	77 (16.0)	
Smoking status	Never smoker	86 (7.3)	52 (7.4)	34 (7.1)	0.0003
	Current smoker	273 (23.1)	190 (27.1)	83 (17.3)	
	Former smoker	823 (69.6)	460 (65.5)	363 (75.6)	
Comorbidities	Mean number	3.8 ± 2.6	3.9 ± 2.6	3.6 ± 2.6	0.0494
Exacerbation history[3]	none	557 (47.1)	388 (55.3)	169 (35.2)	<.0001
	mild	60 (5.1)	39 (5.6)	21 (4.4)	
	moderate	369 (31.2)	201 (28.6)	168 (35.0)	
	severe	196 (16.6)	74 (10.5)	122 (25.4)	
HRQL measures	SGRQ total score	40.2 ± 19.1	35.0 ± 18.3	47.9 ± 17.7	<.0001
	Activity	54.2 ± 25.3	45.9 ± 24.1	66.2 ± 22.0	<.0001
	Symptoms	54.1 ± 21.3	50.5 ± 21.6	59.4 ± 19.7	<.0001
	Impacts	27.2 ± 19.6	23.2 ± 18.6	33.1 ± 19.5	<.0001
	EQ VAS	59.1 ± 19.4	63.5 ± 18.2	52.7 ± 19.4	<.0001

Data are presented as mean ± SD or n (%)
[1] p-values based on Chi-square-Tests and ANOVA
[2] BMI groups were defined as normal weight (18.5 ≤ BMI <25), overweight (25 ≤ BMI < 30), obese (BMI ≥ 30), and underweight (BMI < 18.5).
[3] previous 12 months before examination

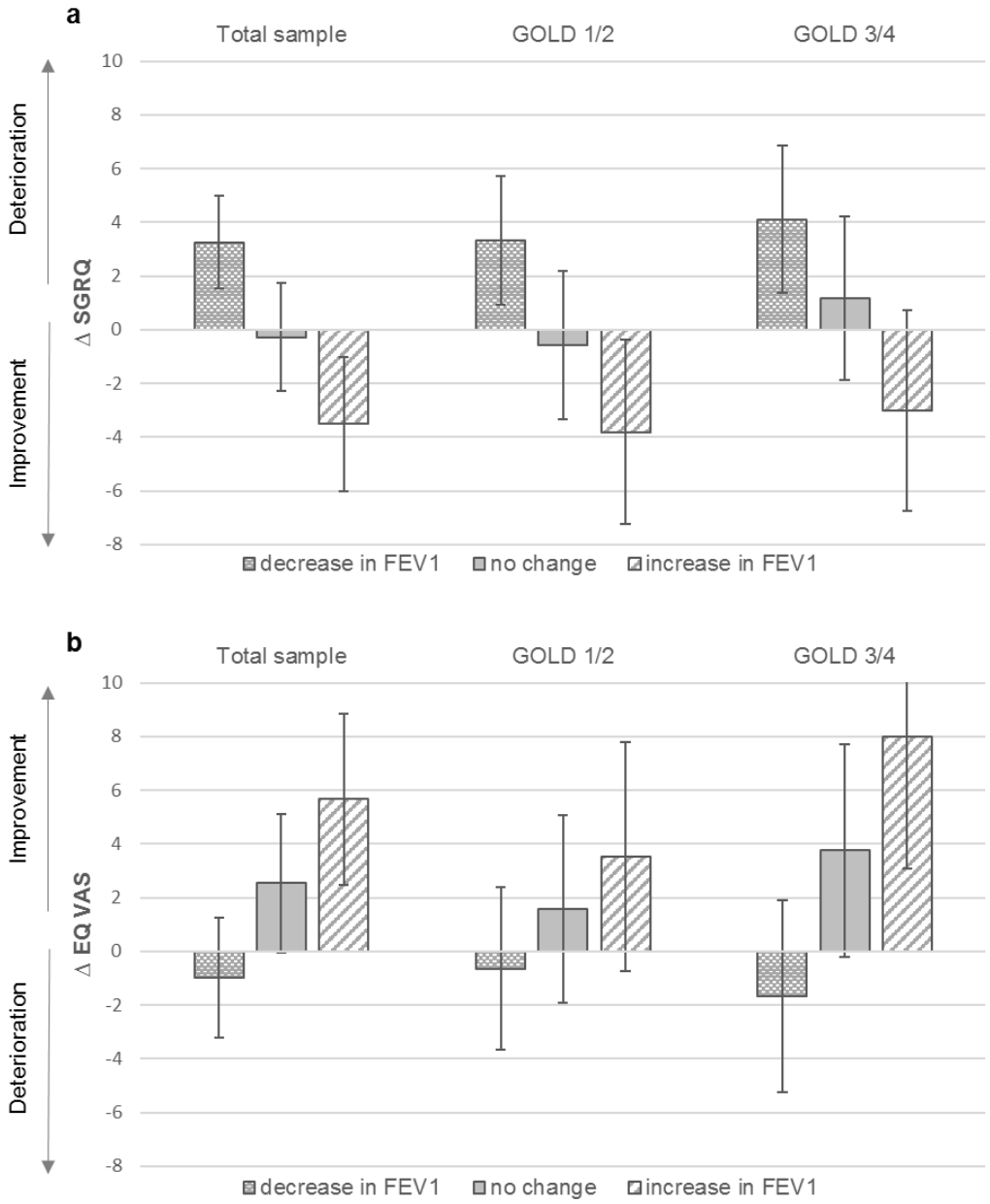
Table A2 Clinically important change in HRQL after 36-month

SGRQ	**Total sample**	**GOLD 1/2**	**GOLD 3/4**
n	1159[1]	690	469
clinically important deterioration	458 (39,5)	260 (37,7)	198 (42,2)
No change	314 (27,1)	191 (27,7)	123 (26,2)
clinically important improvement	387 (33,4)	239 (34,6)	148 (31,6)
VAS	**Total sample**	**GOLD 1/2**	**GOLD 3/4**
n	1163[2]	692	471
clinically important deterioration	398 (34,2)	230 (33,2)	168 (35,7)
No change	399 (34,3)	258 (37,3)	141 (29,9)
clinically important improvement	366 (31,5)	204 (29,5)	162 (34,4)

Data are presented as n (%)

Additional file 2

Inverse Probability Weighting: Absolute adjusted mean change in SGRQ (a) and EQ VAS (b) after 36 months



Ordinary least square regression models were adjusted for age, sex, BMI, education, smoking status, comorbidity burden, exacerbation history, and FEV_1 change*baseline FEV_1. Error bars indicate 95% confidence intervals. Models include inverse probability weights to account for dropout. Change categories in FEV_1 were defined as decrease in absolute FEV_1 ≥ 100 ml increase in absolute FEV_1 ≥ 100 ml, and no change (in between) after 36 months.

Additional file 3

Table A3

Inverse Probability Weighting: Cross-sectional and longitudinal estimates for the association between FEV_1 and disease-specific HRQL

Outcome: SGRQ	**Total sample**	**GOLD 1/2**	**GOLD 3/4**
	estimate [95 % CI]	*estimate [95 % CI]*	*estimate [95 % CI]*
FEV_1 between-subjects	-1.41*** [-1.54 to -1.27]	-0.99*** [-1.21 to -0.76]	-1.57*** [-1.95 to -1.19]
FEV_1 within-subjects	0.85*** [0.66 to 1.04]	0.87*** [0.64 to 1.10]	0.96*** [0.63 to 1.29]

*** $p < 0.001$

Hierarchical linear models (HLM) adjusted for age, sex, BMI, education, smoking status, number of comorbidities, and exacerbation history. Models include inverse probability weights to account for dropout.

Interpretation: Positive estimates indicate deterioration in SGRQ. FEV_1 between-subjects: cross-sectional difference in HRQL per 100 ml difference in FEV_1 between subjects. FEV_1 within-subjects: longitudinal change in HRQL per 100 ml decrease in FEV_1 within subjects over time.

Chapter 4 Utilization and determinants of use of non-pharmacological interventions in COPD: Results of the COSYCONET cohort

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Utilization and determinants of use of non-pharmacological interventions in COPD: Results of the COSYCONET cohort

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ABSTRACT

Background: Guidelines for chronic obstructive pulmonary disease (COPD) recommend supplementing pharmacotherapy with non-pharmacological interventions. Little is known about the use of such interventions by patients. We analyzed the utilization of a number of non-pharmacological interventions and identified potential determinants of use.

Methods: Based on self-reports, use of interventions (smoking cessation, influenza vaccination, physiotherapy, sports program, patient education, pulmonary rehabilitation) and recommendation to use were assessed in 1410 patients with COPD. The utilization was analyzed according to sex and severity of disease. Potential determinants of utilization included demographic variables and disease characteristics and were analyzed using logistic regression models.

Results: Influenza vaccination in the previous autumn/winter was reported by 73% of patients. About 19% were currently participating in a reimbursed sports program, 10% received physiotherapy, 38% were ever enrolled in an educational program, and 34% had ever participated in an outpatient or inpatient pulmonary rehabilitation program. Out of 553 current or former smokers, 24% had participated in a smoking cessation program. While reports of having received a recommendation to use mainly did not differ according to sex, women showed significantly ($p < 0.05$) higher utilization rates than men for all interventions except influenza vaccination. Smoking was a predictor for not having received a recommendation for utilization and also significantly associated with a reduced odds of utilization. We found a correlation between recommendation to use and utilization.

Conclusions: Utilization of non-pharmacological interventions was lower in men and smokers. A recommendation or offer to use by the physician could help to increase uptake.

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1. Introduction

Chronic obstructive pulmonary disease (COPD) carries a high burden and is currently the third leading cause of death worldwide [1,2]. The prevalence of COPD in Germany is estimated at 13% in the adult population aged 40 years and older [3]. Current international and national COPD guidelines recommend non-pharmacological interventions – with different levels of evidence – to improve symptoms (cough, sputum production, and dyspnea), prevent exacerbations, enhance self-management behavior and optimize daily activity levels [1,4]. These include preventive measures, such as smoking cessation and vaccination, interventions to promote physical activity and self-management (i.e. pulmonary rehabilitation, lung sports programs, patient education), together with oxygen therapy, ventilator support, and surgical interventions. Smoking cessation is the most effective intervention in the management of COPD, with positive effects on survival and the deceleration of lung function decline [5].

There is evidence for sex-specific differences in the diagnosis, phenotype and therapeutic response of COPD [6,7]. With regard to non-pharmacological interventions, a Swedish register study found that women had higher utilization rates for education programs and contact with a physiotherapist or dietician [8]. Furthermore, Watson et al. reported, that women were more likely to receive smoking cessation advice [9].

In Germany, data on the pharmacological treatment of COPD [10] as well on the utilization of general healthcare services independent from COPD (e.g. doctor visits, hospital stays, rehabilitation measures) has been investigated [11,12]. However, data on the uptake of specific guideline-recommended non-pharmacological interventions is lacking. The present analysis aimed to provide data on the use of recommended, COPD-specific, non-pharmacological interventions according to sex and GOLD groups A–D. A secondary aim was to identify determinants of utilization and to explore the association between recommendation by a physician and utilization of interventions.

2. Material and methods

2.1. Study population and assessment of non-pharmacological interventions

We used data from the baseline visit and 36-month follow-up of the COSYCONET cohort (German COPD and Systemic Consequences – Comorbidities Network). In this prospective, observational, multicenter cohort study, 2741 patients were included at baseline between 2010 and 2013 across Germany and re-examined after 6, 18, and 36 months, with ongoing follow-up visits. Subjects were included if they were ≥40 years and had physician-diagnosed COPD. A standard operating procedure (SOP) was developed to ensure comparability of the scheduled assessments and tests between all study centers. Furthermore, instruments including devices for lung function testing were homogeneous across study sites and clinical investigators participated in regular training. Detailed information on the recruitment process, the standardized data collection, and quality control measures is available elsewhere [13].

The flow-diagram (Fig. 1) shows the inclusion criteria and study sample of the present analysis.

At the 36-month follow-up, 1427 patients (47.9% of baseline participants) were re-examined, with questions designed to assess the utilization of non-pharmacological interventions incorporated into the assessments for the first time. Questions were binary (yes/no) and covered different time frames. In detail, this included the following specifically for COPD ("[…] we ask you a number of questions about medical treatment and care for your COPD. However, they refer explicitly only to your COPD."): influenza vaccination (previous autumn or winter), physiotherapy (currently), sports program that is reimbursed by your health insurance company (currently), patient educational program (ever), inpatient or outpatient pulmonary rehabilitation (ever), and smoking cessation (ever; only for current smokers or patients who quit smoking within the previous 10 years). Oxygen therapy, ventilator support and surgical intervention were not included in the present analysis. Additionally, we assessed whether patients reported to have ever received a recommendation for the use of influenza vaccination and educational program, or an offer to participate in a smoking cessation program expressed by their physician or insurance company.

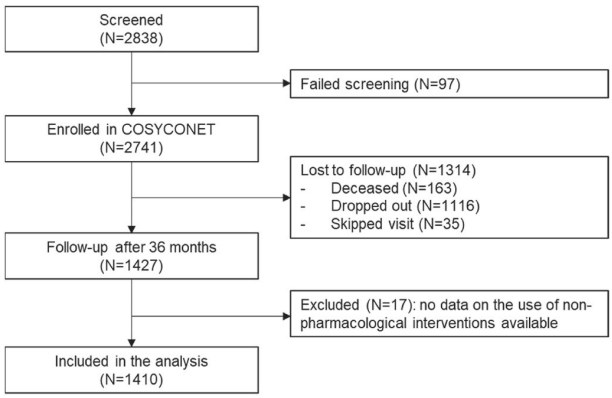

Fig. 1. Overview of the study population.

2.2. Assessment of covariables

Assessment of covariables was based on data of the baseline visit of the study. GOLD groups were defined according to ABCD scheme. Low/no symptom patients were classified as groups A/C (modified Medical Research Council dyspnea scale [mMRC] 0–1). Highly symptomatic patients were assigned to groups B/D (mMRC ≥2). Based on exacerbations of all severities within the previous 12 months, patients were classified as group A/B (0–1 exacerbation), and as group C/D (≥1 inpatient (severe) or ≥ 2 non-hospitalized exacerbations) [4].

Lung function was characterized by FEV_1 expressed as percent predicted according to the Global Lung Function Initiative (FEV_1%pred). The values were determined in a standardized post-bronchodilator spirometry following the standard operating procedures of COSYCONET, which align with established guidelines [13]. Information on age, sex, smoking status, body mass index, and level of education (basic education duration ≤9 years, secondary education 10–11 years, higher education >11 years) was assessed via standardized interviews, questionnaires, and examinations. Exacerbation history was assessed as the highest severity level of exacerbation that occurred in the 12 months prior to the examination. The severity levels were defined according to GOLD (acute respiratory worsening for several days and the need for specific measures; mild: self-managed, moderate: patient visited primary care physician, severe: led to hospital admission).

Information about the specialization of the patients' main attending physician was collected at the 36-month follow-up by asking "What is the specialty of the physician who has treated you for the most part for your COPD in the last 12 months?".

2.3. Statistical analysis

Baseline characteristics of participants were summarized using unadjusted means and standard deviations (SD) for continuous variables and percentages for categorical variables. Analysis of variance (ANOVA) for continuous variables and chi^2-tests for categorical variables were used to compare characteristics between participant groups. Descriptive measures were used to present utilization rates of non-pharmacological interventions. Results were stratified by sex and by GOLD groups A–D, and differences were assessed by chi^2-tests. To identify determinants of

Table 1
Baseline characteristics of the study population, stratified by sex.

		Male (n = 833)	Female (n = 577)	Total (n = 1410)	p-value
Age (years)	Mean age	65.3 (8.2)	63.4 (8.5)	64.5 (8.4)	<0.0001[a]
Spirometry	FEV_1%pred	60.0 (20.3)	61.1 (20.5)	60.5 (20.3)	0.3100[a]
	FVC%pred	81.8 (18.4)	81.8 (17.2)	81.8 (17.9)	0.9943[a]
GOLD group (mMRC)	A	405 (48.9)	242 (42.1)	647 (46.1)	0.0896[b]
	B	173 (20.9)	133 (23.1)	306 (21.8)	
	C	118 (14.2)	90 (15.7)	208 (14.8)	
	D	133 (16.0)	110 (19.1)	243 (17.3)	
Smoking status	Current smoker	170 (20.4)	147 (25.5)	317 (22.5)	<0.0001[b]
	Former smoker	614 (73.7)	361 (62.6)	975 (69.2)	
	Never smoker	49 (5.9)	69 (12.0)	118 (8.4)	
BMI (kg/m^2)	Mean BMI	27.7 (4.7)	26.5 (5.6)	27.3 (5.1)	<0.0001[a]
	Normal weight (18.5 ≤ BMI < 25)	237 (28.5)	232 (40.2)	469 (33.3)	<0.0001[b]
	Overweight (25 ≤ BMI < 30)	358 (43.0)	189 (32.8)	547 (38.8)	
	Obese (BMI ≥ 30)	230 (27.6)	135 (23.4)	365 (25.9)	
	Underweight (BMI < 18.5)	8 (1.0)	21 (3.6)	29 (2.1)	
Education	Basic education	439 (52.7)	301 (52.2)	740 (52.5)	<0.0001[b]
	Secondary education	203 (24.4)	195 (33.8)	398 (28.2)	
	Higher education	191 (22.9)	81 (14.0)	272 (19.3)	
Exacerbation history[c]	None/Mild	484 (58.1)	277 (48.0)	761 (54.0)	0.0002[b]
	Moderate/Severe	349 (41.9)	300 (52.0)	649 (46.0)	
mMRC	mMRC ≥2	306 (36.9)	243 (42.3)	549 (39.1)	0.0434[b]
Years since COPD diagnosis		8.1 (7.3)	7.2 (6.4)	7.7 (6.9)	0.0152[a]

Notes: Data are mean (SD) or n (percentage).
[a] p-value based on ANOVA.
[b] p-value based on Chi2-Test.
[c] Previous 12 months before study visit.

recommendation and utilization of non-pharmacological interventions, multiple logistic regression models were used to generate odds ratios (OR) and 95% confidence intervals (CI). The models included FEV_1% pred, age, sex, education, smoking status, BMI, exacerbation history, presence of dyspnea, time since COPD diagnosis, all assessed at the baseline visit of the study. The specialty of the attending physician was included only for the interventions with current use.

Since we analyzed data from a follow-up visit of COSYCONET, a substantial proportion of patients had already left the cohort. To assess differences between the cohort at baseline and at the 36-month follow-up, descriptive analyses were undertaken to compare the baseline characteristics of participants included and those lost to follow-up.

Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA, version 9.4), and p-values of 0.05 or less were considered to be statistically significant.

3. Results

The baseline characteristics of the study population are given in Table 1. The majority of participants was male (59%), with a mean age of 64.5 years at baseline. Current smoking was reported by 20% of male and 26% of female participants. Whereas lung function values and GOLD groups did not differ between sexes, females reported significantly higher levels of dyspnea (mMRC ≥2) and were more likely to have experienced an exacerbation in the preceding 12 months.

3.1. Utilization of non-pharmacological interventions

Fig. 2 displays the percentages of unadjusted utilization of non-pharmacological interventions. Overall, utilization rates of >50% were found only for influenza vaccination in the previous autumn or winter. Females showed significantly higher utilization rates for every

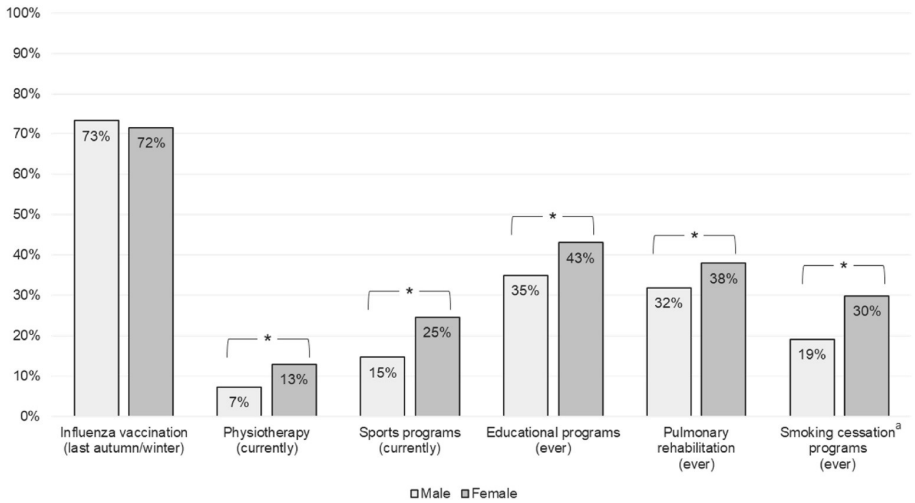

Fig. 2. Utilization of non-pharmacological interventions, stratified by sex. *Significantly different according to Chi2-tests ($p < 0.01$). [a] Only for n = 553 current smokers or patients who quit smoking ≤10 years ago.

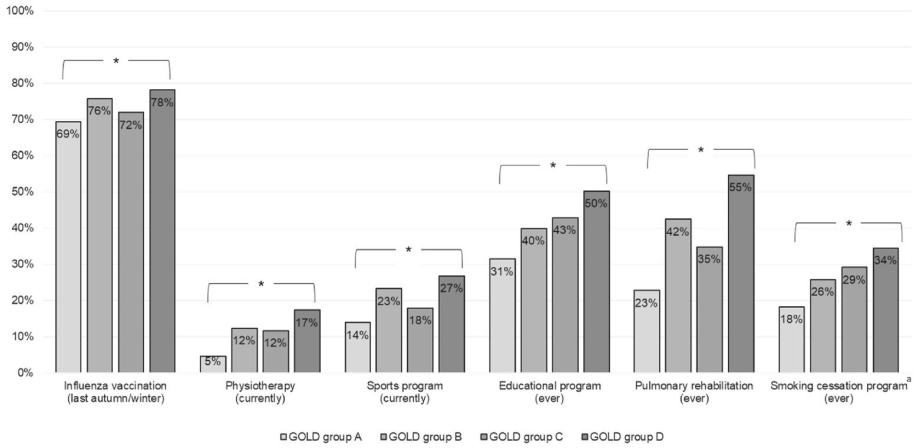

Fig. 3. Utilization of non-pharmacological interventions, stratified by GOLD groups A–D (mMRC). *Significantly different according to Chi2-tests ($p < 0.01$). [a] Only for n = 553 current smokers or patients who quit smoking ≤10 years ago.

intervention compared to males with the exception of influenza vaccination (male 73.3% vs female 71.6%, p = 0.48). The biggest difference with regard to proportions was found for smoking cessation programs (19.0% vs. 30.0%, p = 0.0025).

The utilization of non-pharmacological interventions across GOLD groups A–D can be found in Fig. 3. Patients in GOLD group A were the least likely to have received all interventions while utilization was found highest for GOLD D.

3.2. Association between healthcare resource utilization and recommendation to use

Fig. 4 shows the utilization rates of non-pharmacological interventions for patients who had been given a recommendation to use by their physician or insurance company compared to patients who had not received a recommendation. For all three interventions, a recommendation to use or offer to participate (smoking cessation) was associated with higher utilization rates. For example, 89% of patients who indicated that a doctor recommended taking part in an educational program, reported utilization of such a program, while 13% reported utilization without a previous recommendation.

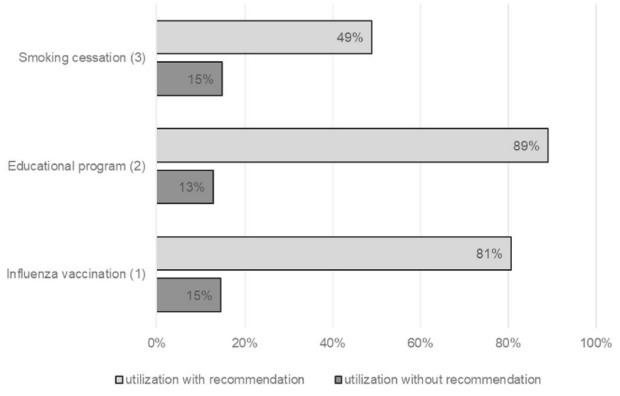

Fig. 4. Association between utilization of non-pharmacological interventions and recommendation of use. (1) Has your doctor ever recommended you to be vaccinated against influenza? (Yes: 88%). (2) Has your doctor ever recommended taking part in a patient educational program for your COPD? (Yes: 33%). (3) Has your doctor or health insurance company ever offered you to take part in a smoking cessation program? (Yes: 25%).

3.3. Determinants of utilization and recommendation to use

Determinants of utilization of non-pharmacological interventions are shown in Table 2. Values of FEV_1%pred ≤50% (vs >80%) were a significant predictor of utilization regarding all interventions except smoking cessation. Moreover, patients aged ≥65 years (vs < 55 years) were more likely to have received influenza vaccination, while on the other hand older age was associated with a lower probability of currently seeing a physiotherapist or having had pulmonary rehabilitation.

Consistent with the unadjusted results, females had significantly higher odds of utilization for every intervention except influenza vaccination and pulmonary rehabilitation.

Regarding the patient's smoking status, being a current smoker (vs never smoker) was associated with a significantly reduced probability of utilization of influenza vaccination, sports program, educational program, and pulmonary rehabilitation. Obesity was also significantly associated with a reduced probability of utilization of some interventions.

A history of moderate or severe exacerbations in the 12 months before the baseline study visit and mMRC ≥2 was significantly associated with higher probabilities of utilization for the majority of outcomes.

With regard to determinants of previous recommendations by physicians, current smoking was significantly associated with a reduced odds of having received a recommendation for influenza vaccination or participation in an educational program. Female sex, on the other hand, was associated with a higher probability of having received a recommendation for influence vaccination (see Table 3).

Comparison between the study sample and the cohort at baseline

At the 36-month follow-up, 1116 patients were still alive but no longer available. Compared to our study sample (n = 1410 participants), these patients were older, had poorer lung function and reported higher levels of dyspnea (mMRC) at baseline. This was also reflected in greater proportions of patients in GOLD groups B and D (Table S1).

4. Discussion

In this study, we analyzed the utilization of non-pharmacological interventions for COPD and identified its determinants based on data from the established German COPD cohort COSYCONET. First, with the exception of influenza vaccination, fewer than half of the patients participated in the recommended panel of non-pharmacological

Table 2
Determinants of healthcare resource utilization of non-pharmacological interventions in COPD.

		Influenza vaccination	Physiotherapy	Sports program	Educational program	Pulmonary rehabilitation	Smoking cessation
Covariate		*OR [95% CI]*	*OR [95% CI]*	*OR [95% CI]*	*OR [95% CI]*	*OR [95% CI]*	*OR [95% CI]*
FEV_1%pred	>80%	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	50–80%	1.02 [0.74–1.41]	1.77 [0.86–3.65]	1.17 [0.76–1.81]	1.30 [0.95–1.79]	1.43 [1.00–2.04]	0.67 [0.38–1.18]
	30–50%	**1.57 [1.06–2.32]**	**2.83 [2.36–5.89]**	**2.09 [1.31–3.32]**	**1.96 [1.37–2.81]**	**2.60 [1.77–3.84]**	1.13 [0.60–2.13]
	<30%	**2.87 [1.29–6.36]**	**2.64 [1.03–6.73]**	1.53 [0.74–3.15]	**3.35 [1.85–6.05]**	**3.04 [1.63–5.64]**	1.18 [0.37–3.79]
Age (years)	<55	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	55–64	1.40 [0.94-2.07]	0.70 [0.40–1.25]	1.63 [0.96–2.77]	1.32 [0.90–1.93]	0.97 [0.65–1.46]	0.65 [0.38–1.14]
	65–74	**1.94 [1.30–2.90]**	**0.47 [0.26–0.87]**	**1.77 [1.04–3.02]**	1.31 [0.89–1.92]	0.67 [0.44–1.00]	0.94 [0.52–1.72]
	>74	**1.91 [1.11–3.30]**	0.44 [0.18–1.07]	1.55 [0.79–3.06]	1.01 [0.61–1.68]	**0.50 [0.29–0.86]**	1.56 [0.45–5.37]
Sex	Male	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	Female	1.08 [0.83–1.40]	**1.84 [1.24–2.75]**	**1.99 [1.47–2.68]**	**1.36 [1.07–1.73]**	1.28 [0.99–1.66]	**1.75 [1.13–2.71]**
Education	Basic	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	Secondary	1.14 [0.84–1.53]	0.96 [0.61–1.52]	0.96 [0.69–1.35]	**1.49 [1.14–1.94]**	0.88 [0.66–1.18]	0.99 [0.62–1.59]
	Higher	1.12 [0.80–1.57]	1.28 [0.77–2.14]	0.81 [0.54–1.21]	0.94 [0.69–1.29]	1.09 [0.78–1.51]	0.81 [0.44–1.50]
Smoking status	Never smoker	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	
	Current smoker	**0.54 [0.32–0.90]**	0.48 [0.20–1.16]	**0.40 [0.22–0.74]**	**0.44 [0.28–0.71]**	**0.31 [0.18–0.52]**	0.65 [0.42–1.01]
	Former smoker	1.01 [0.62–1.64]	1.32 [0.67–2.60]	0.89 [0.55–1.46]	**0.64 [0.42–0.97]**	0.91 [0.59–1.42]	*ref.*
Weight (BMI)	Normal	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	Overweight	0.94 [0.69–1.26]	0.89 [0.58–1.37]	1.14 [0.82–1.58]	0.93 [0.71–1.22]	1.03 [0.77–1.38]	0.97 [0.59–1.61]
	Obese	1.12 [0.80–1.58]	**0.39 [0.21–0.72]**	**0.61 [0.40–0.93]**	0.99 [0.73–1.34]	**0.70 [0.50–0.98]**	1.03 [0.59–1.80]
	Underweight	0.46 [0.20–1.06]	1.98 [0.74–5.34]	0.72 [0.25–2.06]	0.63 [0.28–1.44]	1.33 [0.56–3.19]	1.23 [0.39–3.86]
Exacerbation history	None/mild	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*	*ref.*
	Moderate/severe	1.22 [0.94–1.59]	**1.75 [1.15–2.65]**	1.19 [0.88–1.61]	**1.35 [1.07–1.70]**	**1.64 [1.28–2.11]**	**1.60 [1.04–2.48]**
mMRC $\geq$ 2		1.10 [0.83–1.46]	**1.91 [1.26–2.90]**	**1.46 [1.07–1.99]**	1.11 [0.86–1.42]	**1.94 [1.49–2.52]**	1.44 [0.91–2.27]
Years since COPD diagnosis	Per 5 years	1.03 [0.93–1.13]	**1.17 [1.02–1.33]**	0.98 [0.88–1.09]	1.07 [0.98–1.16]	1.06 [0.97–1.16]	**1.33 [1.10–1.59]**
Attending physician	General practitioner	*ref.*	*ref.*	*ref.*			
	Internal specialist	0.77 [0.45–1.31]	1.00 [0.38–2.67]	1.03 [0.50–2.12]			
	Pulmonologist	1.29 [0.95–1.75]	1.52 [0.86–2.67]	**1.52 [1.01–2.28]**			

Numbers of patients with missing information for the independent variables: influenza vaccination (n = 4), physiotherapy (n = 10), sports programs (n = 9), educational programs (n = 3), pulmonary rehabilitation (n = 12), and smoking cessation programs (n = 4).

interventions. Second, utilization was higher with increasing severity of COPD as determined by GOLD groups, and for female patients, while current smoking was associated with a reduced utilization. Third, current smoking was also significantly associated with a reduced probability of having received a recommendation to use non-pharmacological interventions by a physician.

When stratified by sex, our analysis demonstrated that female patients participated to a higher degree in all non-pharmacological interventions, except influenza vaccination, which showed already high levels for men and women. Similar results have been published in previous reports, which showed that women tend to communicate more frequently with healthcare providers and utilize more healthcare resources than men [14–16]. This was also found in other chronic diseases such as diabetes [17,18]. Similarly, Henoch et al. found higher participation rates for educational programs and physiotherapy for women compared to men and also higher vaccination rates [8]. Logistic regression models confirmed that female sex was a significant determinant of utilization by increasing the odds of participation in non-pharmacological interventions. Interestingly, female sex was not significantly associated with having received a recommendation for smoking cessation or educational program. This is in contrast to Watson et al., who found women to be more likely to get smoking cessation advice [9].

Smoking cessation is the most effective and cost-effective intervention in the management of COPD. In our study, not even a quarter of current or previous smokers had ever participated in a smoking cessation program. This is a concern, as smoking cessation fundamentally influences the course of COPD by attenuating the decline of lung function and improving survival [1,19,20]. Even within COPD, non-smoking patients tend to have less airflow limitation and gas exchange abnormalities and fewer symptoms than current smokers [21,22]. In comparison, a Swiss study by Kaufmann et al. reported participaton rates of 52% for smoking cessation programs in 50 smokers with COPD in the outpatient setting [23] and according to a Swedish register study, 34% of patients participated in a smoking cessation program [8]. Our data indicated, that smoking was also associated with reduced probabilities

Table 3
Determinants of recommendations for the use of non-pharmacological interventions in COPD.

		Recommendation for influenza vaccination	Recommendation to participate in an educational program	Offer to participate in a smoking cessation program
Covariate		*OR [95% CI]*	*OR [95% CI]*	*OR [95% CI]*
FEV_1%pred	>80%	*ref.*	*ref.*	*ref.*
	50–80%	**1.62 [1.08–2.42]**	1.36 [0.98–1.88]	1.25 [0.71–2.19]
	30–50%	**2.80 [1.65–4.75]**	**1.61 [1.11–2.31]**	1.37 [0.72–2.61]
	<30%	**3.41 [1.23–9.47]**	**2.85 [1.59–5.10]**	1.07 [0.35–3.29]
Age (years)	<55	*ref.*	*ref.*	*ref.*
	55–64	1.01 [0.61–1.68]	1.08 [0.74–1.57]	0.85 [0.50–1.43]
	65–74	1.54 [0.90–2.63]	0.99 [0.68–1.45]	0.67 [0.37–1.21]
	>74	1.32 [0.64–2.72]	0.94 [0.57–1.57]	2.02 [0.67–6.13]
Sex	Male	*ref.*	*ref.*	*ref.*
	Female	**1.48 [1.03–2.13]**	1.26 [0.99–1.60]	1.11 [0.73–1.68]
Education	Basic	*ref.*	*ref.*	*ref.*
	Secondary	1.04 [0.70–1.53]	1.23 [0.94–1.61]	0.81 [0.51–1.28]
	Higher	1.38 [0.86–2.21]	0.80 [0.58–1.11]	0.77 [0.43–1.38]
Smoking status	Never smoker	*ref.*	*ref.*	
	Current smoker	**0.45 [0.22–0.94]**	**0.51 [0.32–0.81]**	–
	Former smoker	0.95 [0.47–1.92]	**0.57 [0.38–0.86]**	–
Weight (BMI)	Normal	*ref.*	*ref.*	*ref.*
	Overweight	0.88 [0.59–1.32]	1.06 [0.80–1.40]	1.19 [0.73–1.93]
	Obese	1.26 [0.78–2.02]	1.16 [0.85–1.58]	1.25 [0.73–2.13]
	Underweight	0.49 [0.18–1.31]	1.05 [0.47–2.32]	1.02 [0.31–3.37]
Exacerbation history	None/mild	*ref.*	*ref.*	*ref.*
	Moderate/ severe	1.16 [0.82–1.65]	1.16 [0.92–1.47]	**1.57 [1.04–2.39]**
mMRC ≥ 2		0.87 [0.59–1.26]	1.00 [0.78–1.29]	0.97 [0.62–1.52]
Years since COPD diagnosis	Per 5 years	1.04 [0.91–1.18]	1.02 [0.94–1.12]	1.17 [0.98–1.39]

Numbers of patients with missing information for the independent variables: Recommendation for influenza vaccination (n = 4), Recommendation to participate in an educational program (n = 1), Offer to participate in a smoking cessation program (n = 7).

of participation in all other non-pharmacological interventions, which could lead to two different considerations: smokers with COPD in the cohort refuse to utilize the non-pharmacological therapy options as a somewhat non-compliant behavior. However, the participation in the cohort over several years might be an argument against a general rejection and non-adherence. On the other hand, smoking was also a predictor for not having received a recommendation for two interventions. This could indicate that a physician might be less likely to offer other non-pharmacological options if a patient continues smoking. An alternative explanation could also be that smokers forget about or pay less attention to recommendations they had been given. However, recall bias among smokers seems unlikely, as 98% of all current smokers report that they had ever been advised by a physician to quit smoking.

Nearly three quarters of patients had received influenza vaccination in the previous autumn or winter. This is an important achievement, as influenza vaccination lowers the likelihood of respiratory infections and can reduce exacerbation rates [1,24,25]. Thus, the result obtained for Germany can be considered acceptable, especially when compared to other reported vaccination rates in patients with COPD, such as 49% in Swiss patients, or 34% in population-based and 71% in hospital-based patients in Norway [23,26].

Structured education programs for outpatients include information on risk factors and their reduction or elimination, and in particular emphasize the importance of smoking cessation and have shown to improve inhalation technique, increase self-control of disease, reduce the frequency of acute exacerbations, and reduce costs while improving quality of life [4,27,28]. Consistent with this, use of other non-pharmacological interventions, especially smoking cessation, could be improved by higher participation rates in educational programs. In particular, participation in a patient education program is considered an important step towards behavioral change and improved self-management [1,4,29,30]. According to a Swedish register study, the utilization rate of any patient education program was 22%. In our study, 40% of all patients had participated in an educational program while a third reported utilization of pulmonary rehabilitation. There might be an overlap between these two interventions, since pulmonary rehabilitation often includes aspects of patient education [31]. Progression of the disease, indicated by lower FEV_1%pred, worse dyspnea, and severe exacerbations, was associated with utilization.

Convincing evidence is available for measures promoting physical activity and its benefits for patients with COPD including improving strength, endurance, agility and coordination [1,4]. Utilization rates of physiotherapy (9.5%) and participation in sports programs (18.5%) were rather low and might be explained by the shorter time horizon in the respective question compared to those referring to the other interventions ("currently" vs "ever"). Furthermore, it is important to note that the questionnaire specifically assessed participation in a reimbursed sports program and therefore, conclusions regarding daily activity levels of patient are not supported by our data.

Our results are consistent with previous publications, in that therapy options requiring a high degree of behavioral change (such as smoking cessation or physical activity) are recognized as difficult for patients to adopt [32,33]. Physician's advice or offer to utilize non-pharmacological options was found to be significantly associated with utilization. One should also keep in mind, that a physician's recommendation could be an indicator for access to certain interventions, especially with regard to smoking cessation and educational programs, which could explain part of the positive correlation.

We found a trend towards higher participation in guideline-recommended non-pharmacological interventions, if patients reported pulmonologists vs GPs as attending physicians. This was adjusted for pulmonary function and symptoms. Our finding is consistent with that reported by Garcia-Aymerich et al., showing that COPD patients treated by a pulmonologist were more likely to receive pharmacological and non-pharmacological treatments and were more likely to perform inhalation maneuvers correctly [34]. Pothirat et al. [35] compared the management of patients with COPD by pulmonologists vs internists and also found higher guideline adherence by pulmonologists as well as significantly lower rates and frequencies of severe adverse events in patients managed by them. Other studies, however, did not observe differences in resource utilization intensity or patient survival [36,37]. Nevertheless, the overall results suggest that in order to maximize

treatment efficiency it might be beneficial to integrate specialists early into the treatment process [38].

Potential limitations of our study should be kept in mind when interpreting the findings. First, selection bias is likely as there was a substantial dropout of nearly 50% between baseline and the 36-month follow-up visit. Patients who did not attend the follow-up visit were older and more severely ill, thus the study population demonstrates healthy participation bias during follow-up. This was also confirmed in previous longitudinal analyses [12,39]. We might therefore underestimate the utilization in the general population of patients with COPD. On the other hand, patients who continuously participate in a cohort study over four visits might be more interested in the management of their chronic condition and the available treatment options, leading to higher utilization compared to the general COPD population. Second, the utilization data was collected at the 36-month follow-up visit with different monitoring periods. Although we temporally separated the assessment of outcomes from the independent variables by using baseline variables for the characterization of patients, causal relationships cannot be drawn based on the analyzed dataset, especially, when referring to the time frame "ever". Third, there is a chance for recall bias when surveying self-reported information on healthcare utilization tending towards underestimation of utilization [40]. However, it is unlikely that binary questions (yes/no) about whether patients participated in interventions are markedly susceptible to recall bias. Finally, there is a lack of standardization of non-pharmacological interventions within our study and in comparison to other studies. To avoid different interpretations within the data assessment, additional descriptions were included in the questionnaire.

The main strength of our study is the large and well-characterized patient sample, which included a panel of determinants and subgroups of different severity. The high number of female patients provided enough power to investigate differences from men regarding the utilization of non-pharmacological interventions.

5. Conclusions

With the exception of influenza vaccination, our findings indicate relatively low levels of use of guideline-recommended, non-pharmacological interventions for COPD in Germany. Women demonstrated higher participation rates than men, while active smoking was associated with reduced utilization. Recommendations or offers to use non-pharmacological interventions by the physician might help to increase uptake, especially in men and smokers. Future efforts could explore cost-efficient ways to inform and encourage patients to undertake guideline-recommended, non-pharmacological interventions for COPD.

Ethics approval and consent to participate

The COSYCONET study complies with the Declaration of Helsinki and Good Clinical Practice Guidelines and has been approved by the ethics committee of the medical faculty of the Philipps-Universität Marburg, the local ethics committees of the participating centers (a list of all participating study centers can be found here: http://www.asconet.net/html/cosyconet/studzent) and by the concerned data security authority (data security agency of the federal states of Hesse, Baden-Württemberg, Lower-Saxony, and Saarland). This approval covered the subsequent data analyses as performed here. All cohort participants gave their written informed consent.

Availability of data and materials

Data may be obtained from a third party and are not publicly available. The full dataset supporting the conclusions of this article is available upon request and application from the Competence Network Asthma and COPD (ASCONET, http://www.asconet.net/html/cosyconet/projects).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CV reports grants and personal fees outside the submitted work from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Grifols, Mundipharma, Novartis, and personal fees from Cipla, Berlin Chemie/Menarini, CSL Behring, Teva, Bayer Schering Pharma AG, MSD, Pfizer, and Nuvaira. SK, BB, CV, RH, JL report grants from German Federal Ministry of Education and Research (BMBF), during the conduct of the study. All other authors declare no conflicts of interest.

CRediT authorship contribution statement

Johanna I. Lutter: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Investigation. **Marco Lukas:** Formal analysis, Writing - original draft, Writing - review & editing, Investigation. **Larissa Schwarzkopf:** Conceptualization, Writing - review & editing, Investigation. **Rudolf A. Jörres:** Data curation, Writing - review & editing, Project administration, Investigation. **Michael Studnicka:** Writing - review & editing, Investigation. **Kathrin Kahnert:** Methodology, Writing - review & editing, Investigation. **Stefan Karrasch:** Data curation, Writing - review & editing, Investigation. **Burkhard Bewig:** Writing - review & editing, Investigation. **Claus F. Vogelmeier:** Project administration, Funding acquisition, Writing - review & editing. **Rolf Holle:** Supervision, Conceptualization, Writing - review & editing, Investigation.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106087.

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Appendix

Table S1: Baseline comparison of patients present for both visits (Study participants) vs patients lost to follow-up excluding deceased patients (Dropouts)

		Study participants (n=1410)	Dropouts (n=1116)	*p-value*
Age (years)		64.5 (8.4)	65.2 (8.9)	0.0453 [a]
Spirometry	FEV_1%pred	60.5 (20.3)	54.2 (21.6)	< 0.0001 [a]
	FVC%pred	81.8 (17.9)	75.7 (19.4)	< 0.0001 [a]
% GOLD groups (mMRC)	A	46.1	35.4	<0.0001 [b]
	B	21.8	26.6	
	C	14.8	13.0	
	D	17.3	25.0	
% Smoking status	Current smoker	22.5	26.9	0.0376 [b]
	Former smoker	69.2	65.4	
	Never smoker	8.4	7.7	
BMI (kg/m^2)		27.3 (5.1)	26.9 (5.7)	0.1018 [a]
% Education	Basic education	52.5	58.2	0.0138 [b]
	Secondary education	28.2	25.7	
	Higher education	19.3	16.1	
% Exacerbation history[c]	None/ Mild	54.0	49.4	0.0531 [b]
	Moderate/ Severe	46.0	50.6	
% mMRC	mMRC ≥2	39.1	51.6	<0.0001 [b]
Years since COPD diagnosis		7.7 (6.9)	7.7 (7.0)	0.7984 [a]

Notes: Data are mean (SD) or %.

[a] p-value based on ANOVA
[b] p-value based on Chi^2-Test
[c] Previous 12 months before study visit

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