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The impact of clinical indicators and type of physician on health-related quality of life (HRQoL) in COPD patients: a real-world study

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Alisa Stöber

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Dedicated to my “Oma”

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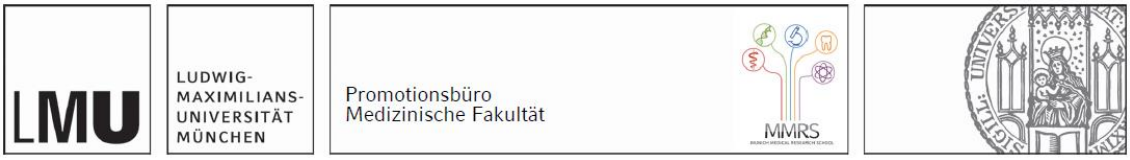

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List of abbreviations

BMI	Body mass index
BOLD	Burden of obstructive lung diseases
COPD	Chronic obstructive pulmonary disease
CAT	COPD assessment test
CCQ	Clinical COPD questionnaire
CRQ	Chronic respiratory disease questionnaire
DALYs	Disability-adjusted life years
DiD	Difference-in-difference
DMP	Disease management program
EQ-5D	Euro-Qol 5-dimension questionnaire
FVC	Forced vital capacity
FEV_1	Forced expiratory volume in 1 second
FEV_1%pred	FEV_1 percent predicted
GAM	Generalized additive model
GOLD	Global initiative for chronic obstructive lung disease
HRQoL	Health-related quality of life
ICD-10	International classification of diseases, tenth revision
MID	Minimal important difference
mMRC	Modified British medical research council questionnaire
PSM	Propensity score matching
PROM	Patient-reported outcome measure
SGRQ	St. George's respiratory questionnaire
SHI	Statutory health insurance
VAS	Visual analog scale of the Euro-Qol questionnaire

List of publications

Paper I

Title:

Impact of lung function and exacerbations on health-related quality of life in COPD patients within one year: real-world analysis based on claims data

Authors:

Alisa Stöber, Johanna I. Lutter, Larissa Schwarzkopf, Florian Kirsch, Anja Schramm, Claus F. Vogelmeier, Reiner Leidl

Journal:

International Journal of Chronic Obstructive Pulmonary Disease

Paper II

Title:

Does uptake of specialty care affect HRQoL development in COPD patients beneficially? A difference-in-difference analysis linking claims and survey data

Authors:

Alisa Stöber, Pavo Marijic, Christoph Kurz, Larissa Schwarzkopf, Florian Kirsch, Anja Schramm, Reiner Leidl

Journal:

The European Journal of Health Economics

1. Contribution to the publications

Both papers were written within a project funded by the Innovation Fund of the Federal Joint Committee (Gemeinsamer Bundesausschuss) of Germany. The project title was “LQ-DMP – Lebensqualität im Disease Management Programm COPD” (support code 01VSF16025). The aim of the "LQ-DMP" project was to identify potential impact factors on health-related quality of life (HRQoL) in COPD patients, in order to foster the stabilization or improvement of HRQoL, which is in turn an important and central objective of the COPD Disease Management Programs (DMP) in Germany. The “LQ-DMP” project was conceptualized and initiated by Reiner Leidl, Larissa Schwarzkopf, and Anja Schramm. Claims data for this project were provided by Anja Schramm (AOK Bayern). The data acquisition was done by Florian Kirsch and Reiner Leidl.

1.1 Contribution to paper I

Focusing on the first publication contributing to this dissertation, the PhD student, Alisa Stöber, was responsible for the data management in context of the specific research question. She developed the research concept, research question, and research design in coordination with Johanna Lutter, Florian Kirsch, and Reiner Leidl. She programmed the related algorithms in SAS and performed the statistical analysis. During this entire process she thoroughly checked both plausibility of her empirical data and scientific rigor of her analytical approach. She interpreted the data and decided on the design of research paper in coordination with Johanna Lutter and Reiner Leidl. She wrote and edited the manuscript, coordinated the internal review process with the co-authors until the final paper version was agreed upon and acted as corresponding author within the publication process. All co-authors contributed by reviewing and editing the manuscript. Claus F. Vogelmeier provided clinical support.

1.2 Contribution to paper II

Regarding the second publication within this dissertation, the PhD student, Alisa Stöber, was responsible for the data management in context of the specific research question. The research concept, research question, and research design were developed by her in coordination with Pavo Marijic, Christoph Kurz, and Reiner Leidl. She programmed the related algorithms in R and performed the statistical analysis in consultation with Pavo Marijic and Christoph Kurz. Throughout this process, she conscientiously checked the plausibility of the empirical data and the scientific rigor of the analytical approach. The decision on the design of research paper was made by her together with Pavo Marijic and Reiner Leidl. She interpreted the data in coordination with Pavo Marijic, Christoph Kurz, Larissa Schwarzkopf, and Reiner Leidl. The manuscript was written and edited by her. She coordinated the internal review process with all coauthors until the final paper version was completed and operated as corresponding author within the publication process. All co-authors contributed by reviewing and editing the manuscript.

2. Introductory summary

2.1 Brief overview of this thesis

Health-related quality of life (HRQoL) reflects an individual's subjective perception of general or topic-related well-being: contrasting HRQoL of healthy individuals with that of patients with distinct diseases enables conclusions on how disease symptoms impact on daily life [1]. Especially in chronical, non-reversible diseases, it is an important aim to stabilize or improve patients' HRQoL as cure cannot be achieved. One example for a corresponding disease is Chronic Obstructive Pulmonary Disease (COPD). In COPD patients, HRQoL is affected not only by clinical factors, such as lung function, exacerbations, body mass index (BMI) or disease severity [2–11], but also by non-clinical factors. Non-clinical factors could include social support, mental conditions, self-management and lifestyle (e.g., sleep, physical activity, and most important smoking habit), socio-oeconomic or -demographic factors, and the setting of care [5,10,12–14]. Broadly, the setting of care addresses distinct combinations of specialization level (primary care, secondary care, tertiary care), orientation (prevention, acute treatment, rehabilitation) and mode of delivery (inpatient, outpatient). COPD management care settings vary among continents and countries. Regarding outpatient care, especially area of specialization and degree of involvement of different medical disciplines differs [15,16]. In this thesis, the management care setting is thus considered as type of physician providing COPD care, i.e., whether a pulmonologist is included into care or not. To enhance a comprehensive view of possible impact factors on HRQoL in COPD patients, an integrative approach, that considers both non-clinical and clinical factors, is needed.

In the following sections, a comprehensive summary about COPD (2.2) is given, followed by a chapter about HRQoL (2.3). For COPD, firstly the definition, etiology, and clinical picture (2.2.1), and afterwards the Global initiative for chronic Obstructive Lung Disease (GOLD) disease classification system (2.2.2) as well as its prevalence, mortality, and burden (2.2.3) are described. Additionally, a brief description of the German health care system (2.2.4) follows. For HRQoL the conceptual approach (2.3.1), and clinical and non-clinical impact factors (2.3.2) are presented thereafter. In the following fourth section the methodology is described, including the study population (2.4.1) and the statistical evaluation (2.4.2). Section five (2.5) provides a summary of results and a final conclusion.

2.2 Introduction into COPD and COPD care

2.2.1 Definition, etiology, and clinical picture of COPD

COPD is a common but heterogeneous respiratory health condition with a commonly progressive and persistent path of airflow obstruction and characteristic clinical symptoms like cough, dyspnea, sputum production, and exacerbations [17,18]. Known risk factors are an interaction of genes (among others, mutations in SERPINA1 gene) and environment (commonly tobacco smoking, inhalation of toxic particles or polluted air over a person's lifetime) [19–21]. Especially in low- and middle-income countries the inhalation of polluted air (e.g., particulate matter, oxides of sulfur or nitrogen, heavy metals, ozone, and other greenhouse gases) causes half of the attributable risk for COPD [18,22]. While tobacco smoking remains the major attributable risk factor of COPD in high income countries [18,22,23].

Regarding the clinical picture of COPD, airflow obstruction in terms of lung function and exacerbations are described in the following.

Presence of COPD is usually determined by a substantial limitation of lung function. Lung function can be operationalized by various parameters measured by spirometry. One key parameter of lung function is forced expiratory volume in one second (FEV_1), which describes how much air in liters a person can forcefully exhale in the first second after maximal inhalation [24]. Furthermore, forced vital capacity (FVC) describes the volume of air in liters that a person can forcefully exhale at all [24]. A post-bronchodilation ratio of $FEV_1/FVC < 0.7$ is used to set a COPD diagnosis [18]. An additional lung function parameter, FEV_1 percent predicted (FEV_1%pred), serves for determining disease severity (described in the next chapter 2.2.2). It is calculated by dividing a person's measured FEV_1 value by a predicted FEV_1 value for similar persons, times 100 (while the predicted value is usually based on sex, age, height, and ethnicity) [25]. The lung function in healthy never-smoking persons generally develops from birth on and matures until the age of 20-25 years, reaches then a plateau and mildly declines with lung aging (annualized mean decline rate in FEV_1 of 17.6 ml in females and 19.6 ml in males) [26]. In COPD patients, the lung function declines with probably 23-79 ml per year much steeper than in healthy persons, depending on disease severity [27]. However, this does not imply an perpetual annual decline but rather episodes with a declining, stable or even improving FEV_1, on an overall downward pathway of lung function in COPD patients over time [28].

In the underlying research exacerbations were defined as an acute worsening in respiratory symptoms that demanded additional therapy [29]. Exacerbations were furthermore classified as moderate and severe, depending on the type of additional therapy required, e.g., a worsening in symptomatic that required a doctor's visit determined moderate exacerbations, and emergency room visits or hospitalizations determined severe exacerbations [30]. Meanwhile the conceptual approach of defining exacerbations has further evolved and an updated version was included in the GOLD 2023 report: in accordance with the Rome proposal exacerbations are defined as an event, inducing a worsening of dyspnea, sputum, and cough within 14 days, often accompanied by tachypnea/tachycardia and increased systemic/local inflammations [29]. For assessing the exacerbation's severity, a dyspnea intensity scale, the respiratory and heart rate, as well as an oxygen saturation level are recommended now [29,30].

2.2.2 COPD classification of diseases severity

The classification of COPD has continued to develop over the past few years. Initially, a simple spirometry classification system relying on airflow obstruction, measured by FEV_1%pred, grouped the patients into GOLD grades I to IV [18]. Figure 1 shows this classification on its lefthand side.

This disease severity assessment was extended in 2011 to a second classification system with GOLD groups A to D and combined lung function (GOLD I-IV), exacerbation history and symptomatic as one multidimensional assessment of COPD [18]. The symptomatic was based on either the modified Medical Research Council scale (mMRC), a breathlessness measure scaling up from 0 to 4, or the COPD Assessment Test (CAT), a health status measure further described in 2.3.1 [31,32]. The lung function was subsequently removed from the ABCD classification system, as FEV_1 values can differ on the individual patient level, and thus cause lower assessment precision while complexifying the classification [30,33–36]. Hence, the GOLD ABCD classification, which was used in the included studies of this thesis, classifies the more severe GOLD groups B and D by a mMRC >=2, and the more severe GOLD groups C and D by an occurrence of at least

2 moderate or one severe exacerbation [30,33]. An illustration of the GOLD ABCD classification is given in figure 1 on the righthand side. Within the GOLD 2023 report, this classification has been revised and a new definition, the GOLD ABE system, has been promoted. In GOLD ABE the groups A and B remain unchanged, while groups C and D are merged to one new group E, which credits the clinical importance of exacerbations, independent of the symptomatic [18]. Even if validation of the new system by clinical research is still pending [18], the results of both papers included in this thesis already combined GOLD groups C and D, and can thus also be interpreted in the new classification method.

GOLD grades I-IV

GOLD grade	FEV_1%pred
I	≥ 80%
II	< 80%
III	< 50%
IV	< 30%

GOLD groups A-D

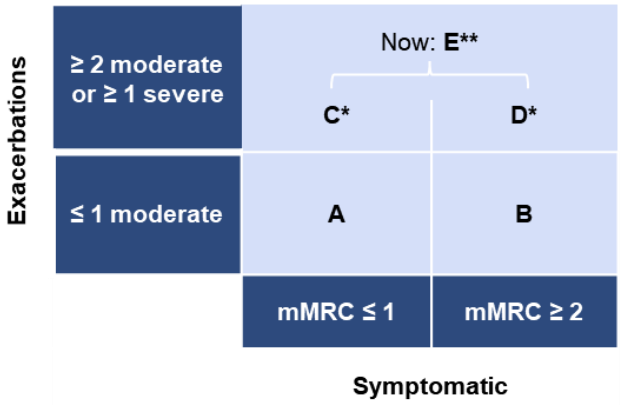

Figure 1: COPD severity assessment: GOLD grades I-IV and GOLD groups ABCD
Note: The figure demonstrates GOLD groups ABCD or ABE on mMRC basis, as this classification method was used for the analyses in the underlying papers. The figure is based on illustrations in GOLD reports 2017(*) and 2023(**) [18,33].

2.2.3 COPD prevalence, mortality, and burden

Prevalence

Globally, over 212 million COPD cases were reported in 2019 with an age standardized point prevalence of 2,638/100,000 [37]. Particularly high prevalence rates were found in North America, South Asia, Australasia, and western Europe in 2019 [37]. Depending on included age ranges, diagnostic criteria applied, and analytical approaches prevalence estimates vary to some extent. For example, other estimations for a global COPD prevalence were 9-10% (in 2004, age 40+), 11.7% (in 2014, age 30+) [38,39], or 3.9% (in 2017, all age groups) [40], while the Burden of Obstructive Lung Diseases (BOLD) study estimated a prevalence of 10.3% (≈392 million people, aged 30-79) in 2019 [41]. Further, the overall prevalence was found to be higher in men, higher in high income countries and in urban areas [38,42].

Within Europe the COPD prevalence is particularly high [37] and it is forecasted to further increase substantially (+40 %) over the next three decades [43]. However, prevalence rates differ between distinct European regions. In western Europe (which includes Germany) COPD accounts approximately for 26.3 of 36.8 million cases in the European region (point prevalence of 3,018/100,000), while central Europe accounts for 4.8 million (2,427/100,000) and Eastern Europe for 5.7 million

cases (1,822/100,000) [37]. Consequently, 70% of all 37 million European COPD cases occur in western Europe.

The actual prevalence in Germany is not exactly known but probably ranges between 5.8% (2014/2015, age 18+) [44], 6.4% (2017, age 40+) [45], and 7.1% (2021, age 40+) [46], indicating that around 3.4 million people in Germany over 40 are affected with COPD.

Mortality

All in all, the prevalence estimations in Germany and globally are assumed to be prone to a substantial under-diagnosis of COPD [47,48]. This under-diagnosis of COPD also leads to an underestimation of COPD-related mortality. The age standardized COPD-attributable mortality rate is estimated to be 42 per 100.000 population (almost 6% of all-cause deaths) [37,40,49]. Globally, COPD approximately accounts 3 million deaths per year [37,49,50] and is the third leading cause of death [49]. Considering population growth and ageing, combined with ongoing exposures to risk factors (e.g., air pollution and smoking [51]), it is estimated that the annual total number of deaths due to COPD will rise up to almost 5.5 million by 2045 [52,53]. Regarding relative death rates, previous reports indicated that COPD mortality worldwide and in the EU has been falling since 1990, however, this decrease is not universal in gender or countries [37,40,54,55]. In Germany, 28,341 people died due to COPD in 2021 [56]. Whilst COPD-related mortality increased over the last decades [56], a turning point might have been reached in 2019 with a decline thereafter (compare Figure 2).

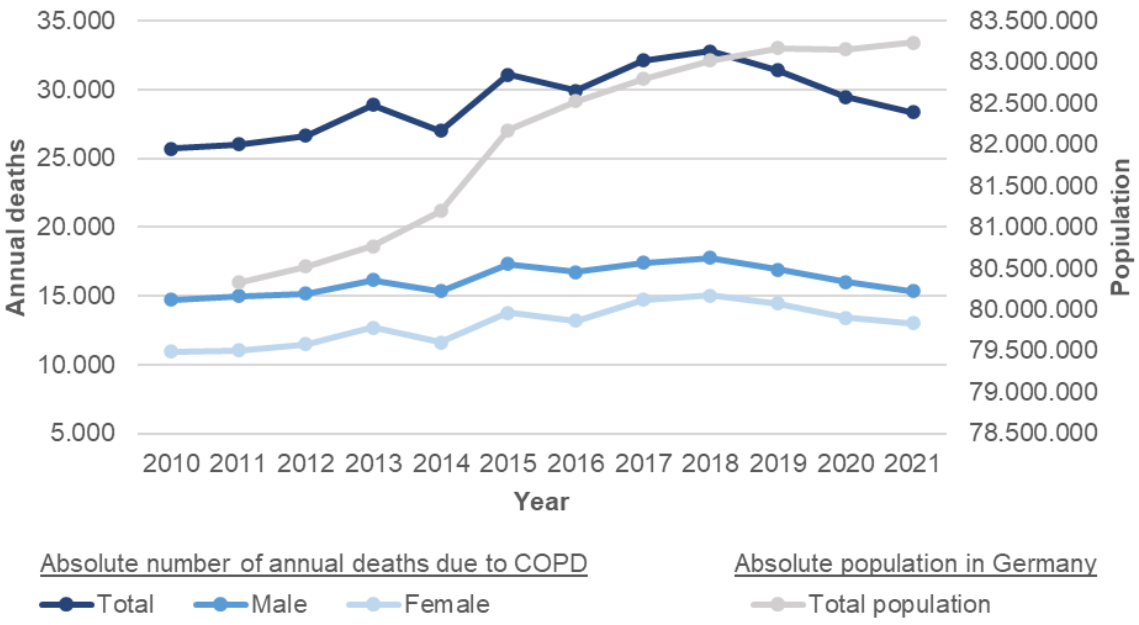

Figure 2: Absolute number of annual deaths due to COPD in Germany according to German Federal Health Monitoring [56,57]

Note: The population level relies on the census of 2011. The census usually takes place every 10 years and determinates the number of inhabitants in Germany. The population level in the years in-between is continuously determined based on the last census.

Burden

Overall, COPD is associated with an increasing and substantial economic but also social burden [37,58,59]. Regarding economic burden, total annual costs in the United States are expected to be $49.9 billion (2009) [58,60], while they are estimated to amount up to €48.4 billion in Europe (2011) [59]. Within Europe, annual direct cost per COPD patient range from €1,715 (Spain) to €10,701 (Norway), with Germany facing the second highest cost €9,580 [59]. Social burden can be described, among others, by Disability-Adjusted Life Years (DALYs) [61], which summarize years lost by early mortality and years lived with disabilities, adjusted for the disabilities' severity. Globally, COPD was found to be the seventh leading cause of reduced DALYs in 2019 [62].

2.2.4 Brief description of the German health care system and COPD management

Health care systems and COPD management vary from country to country. While COPD is primarily managed by general practitioners (GPs) with a gate-keeper role in many western European countries, it is commonly managed by pulmonologists in central and eastern European countries [15,16]. Within Germany, there is a mixed picture with GP care and pulmonologist care side by side. According to the National Medical Association (Bundesärztekammer), there were 2,807 pulmonologists and 44,451 GPs in Germany in 2021 [63]. Assuming a total of 3.4 million COPD patients in Germany [46], each pulmonologist would come up to 1,211 patients if every COPD patient would choose to include specialty care into their disease management.

In Germany, there is a legal obligation for health insurance, and every citizen is either ensured with a statutory health insurance (SHI) fund (88,1% of the resident population), with a private health insurance fund (10,5%) or covered else (1,4%), e.g., social welfare recipients, police, and armed forces [64,65]. SHI is designed as a comprehensive pay-as-you-use insurance system with only little copayment, financed via income-dependent but risk-independent contributions [66]. Insurants can freely choose their treating primary and secondary care physicians, thus decision for a gatekeeper or GP referral to a medical specialist are not mandatory [66,67]. Nevertheless, especially for elderly individuals or patients with chronic diseases some kind of voluntary gatekeeping (i.e. choice of one distinct GP who initiates second and third level care) is quite common [68]. Even though the usual path of care starts at GPs with referrals to specialists, the inclusion of specialists in care does not necessarily follow a coordinated way [69].

For COPD management global and national guidelines exist, while in Germany especially the global GOLD 2023 [18] recommendations and the German national S2k-guideline [70] are used.

Moreover, certain disease management programs (DMPs) exist in Germany. These DMPs are structured programs for chronically ill people, that were nationwide implemented in the German SHI landscape on a legal framework in order to strengthen solidarity and to foster continuity and quality of care, especially for high-risk patients [71]. DMPs are offered for type 1 diabetes mellitus, type 2 diabetes mellitus, coronary artery disease, chronic heart failure, breast cancer, depressions, chronic back pain, osteoporosis, rheumatoid arthritis, asthma bronchial, and COPD [72,73]. As they underly high-quality requirements, a strict central-accreditation process, and regular evaluations, the respective programs vary only marginal between different SHIs [72].

2.3 Health-related quality of life and its importance for COPD

2.3.1 Conceptual approach of HRQoL

COPD significantly impairs the HRQoL of COPD patients [74]. HRQoL mirrors a person-individual valuation of the own physical, mental, and social health status. By contrasting reported HRQoL in patients with distinct diseases with theoretically achievable HRQoL it is hence feasible to delineate their subjectively felt disease-related health impairment [1]. Thus, HRQoL is an import patient-reported outcome measure (PROM). PROMs are tools to measure the patients' view on how distinct diseases impair their health-related status or capabilities, e.g., for social participation [75,76], and they are argued to support patient-centered decision making by incorporating the patients perspective in addition to bare clinical parameters. This includes determining the cost-utility of clinical interventions, capturing patients' perception of the efficacy and impact of a clinical intervention or helping patients to compare quality of care between different services or service providers [75,77]. In Germany PROMS are not yet assessed routinely, but the quality of life is listed in the GOLD COPD guideline [18] and HRQoL is one important key outcome of the COPD DMP [78].

HRQoL can be measured with generic or disease-specific instruments. Disease-specific instruments capture the health status of specific diagnostic groups, often with the aim to measure clinical important changes of, e.g., an intervention [79]. Generic instruments, on the other hand, capture a more general perspective on health status and are broadly applicable to several diverse impairments, diseases or populations [79]. A collection of both measurements is recommended in order to adequately measure functional, physiological, and psychosocial aspects and to cover not only the disease-specific impact of COPD, but also the overall health-related burden [80].

Generic instruments

Generic HRQoL can be assessed, among others, by the generic 5-level Euro-Qol 5D (EQ-5D-5L) [54-55], which is a validated scale consisting of a valuation section with five dimensions and 5 answer levels each, as well as a visual analog scale (VAS) [81]. The VAS scales from the worst possible state (=0) to the best possible state (=100) of subjective perceived general health-related quality of life. Several estimates for its minimum important difference (MID) exist, thus a 6.9-point change in VAS was considered as MID [81,82]. The papers included in this thesis use VAS as generic HRQoL measure.

Disease-specific instruments

For disease-specific HRQoL assessment, common questionnaires are Chronic Respiratory Disease Questionnaire (CRQ), St. George's Respiratory Questionnaire (SGRQ), Clinical COPD Questionnaire (CCQ), and COPD Assessment Test (CAT). The first version of the CRQ was developed in 1987 [83] and subsequently modified to a self-report version [84], while both versions cover 20 items in four separately scored categories, specifically dyspnea (with 5 items), fatigue (with 4 items), emotional function (with 7 items), and perceived control (with 4 items), with higher scores indicating better HRQoL (ranging from 20 up to 140). The SGRQ covers HRQoL assessment in three components of symptoms, activity, and impact on daily life within 50 items and 76 responses [85]. A COPD specific version (SGRQ-C) consists of 40 items and ranges retrograde between 0 and 100, with 100 representing the worst possible HRQoL [86]. The CCQ includes 10 items in the domains of symptoms, mental, and functional state, retrogradely scaling from 0 (=best possible HRQoL) to 6 (= worst possible HRQoL) [87]. The CAT asses HRQoL also on a retrograde scale from the best possible state (=0) to the worst possible state (=40) on the basis of eight

dimensions (e.g. symptoms, breathlessness, activity, and sleep) and six answer levels each [32]. For CAT, a 2.0-point change reflects the established MID [88,89]. Based on a pre-project pilot study, CAT was used in the respective papers as disease-specific HRQoL measure [90].

2.3.2 Clinical and non-clinical impact factors on HRQoL in COPD

Stabilization or improvement of HRQoL is a key element in COPD management, as with diseases progression the HRQoL deteriorates [2,91–93]. Besides this overall downwards trend, HRQoL is affected by clinical and non-clinical factors.

Clinical impact factors

Regarding clinical factors, an association between HRQoL and lung function [2–5], dyspnea/mMRC [9,10], exacerbations [5–8], and BMI [11,94] has been demonstrated. More precisely, an increase in lung function (FEV_1), for example, was shown to significantly improve disease-specific and generic HRQoL [2]. A higher dyspnea scale is associated with a lower HRQoL [9,10]. Exacerbations, especially severe ones, significantly decrease HRQoL [5–8]. Regarding BMI, HRQoL was found to be the highest in patients with a BMI around 25, while for GOLD IV patients HRQoL was the highest in obesity [11]. Within obese patients an further BMI increase led to a decreasing HRQoL [94].

Non-clinical impact factors

But also non-clinical factors are significantly associated with HRQoL, such as patients' self-management [14] and socioeconomic status [13], or the setting of care. Moreover, patient's health-related behavior and concerns might also be considered as non-clinical factors [95], e.g. in terms of patients' physical activity [5], smoking habit [5], anxiety [12], and sleep [10]. Specifically, patients with a lower socio-economic status, sleep disorders or anxiety were found to have a lower HRQoL [10,12,13]. Smoking is significantly associated with a reduced HRQoL [5]. On the other hand, better adherence to pharmacological COPD management was found to be associated with a higher HRQoL [96]. Moreover, self-management and physical activity improve HRQoL in COPD patients [5,14]. Nonetheless, literature on non-clinical impact factors is still rare. No other study has evaluated the impact of "setting of care", with regard to the involvement of specialty care in COPD management as a potential key management aspect and its benefit on patients' health outcome, yet.

2.4 Aims of this thesis

The overall aim of this thesis is to demonstrate approaches for patient-oriented COPD management by identifying selected clinical and non-clinical factors and their impact on HRQoL. Within two papers, both types of impact factors are examined separately and their effect on generic and disease-specific HRQoL is discussed.

In Paper 1, the impact of two selected clinical factors, specifically, lung function (measured by FEV_1) and exacerbations, on HRQoL in COPD patients was evaluated. Therefore, change score models were applied, with the aim to identify the effect of changes in the clinical factors on changes in HRQoL within one year.

The second paper focused on the utilization of specialty care as a non-clinical impact factor on HRQoL in COPD patients. Linear Difference-in-Difference (DiD) models were used, with the aim

to identify the effect of newly initiated pulmonologist care on generic and disease-specific HRQoL over a one-year period.

2.5 Methods

2.5.1 Data and definition of the study population

The analyses for both papers are based on data from the LQ-DMP project, which examined how information on HRQoL can support COPD management and the potential that arises with routinely collected HRQoL data. In the context of this project, two selected HRQoL questionnaires (CAT and EQ-5D-5L, including VAS) plus additional questions on sociodemographic and mMRC were sent to 49,664 participants of the COPD DMP, who were insured at AOK Bavaria, a large regional but state-wide operating SHI. AOK Bavaria had a share of approximately 40% of the Bavarian SHI market (≈4.5 million policyholders) during the projects study period [97]. A follow-up survey was conducted after one year. This survey-based primary data was then linked to secondary SHI claims data and secondary data from the COPD DMP routine documentation. By combining both routine data sources, information on exacerbations, hospitalizations, outpatient treatments as well as clinical factors such as BMI and lung function (FEV_1) were accessible. Further details on the project methodology can be found in the project report [98].

Paper 1 included COPD DMP participants, who 1) participated at the baseline and the follow-up survey, 2) had complete data on both clinical factors, lung function and exacerbations, as well as 3) sufficient information (i.e., scores within their possible range) on HRQoL and covariates. Lung function was operationalized based on the DMP data as annual average of FEV_1%pred and presence of exacerbations was delineated from the claims data via the documented international classification of diseases (ICD-10) code “J441”.

For Paper 2, also 1) only responders of both survey parts, 2) with sufficient information on HRQoL and covariates were included, but with the addition that 3) solely patients without pulmonologists’ care before the first survey were considered, in order to assess the effect of newly initiated specialty care on HRQoL as a non-clinical impact factor. Specialty care was identified by pulmonologists’ practitioner identification codes in the claims data. Depending on the care patients received, they were separated into a treatment group (with specialty care) and a control group (without).

2.5.2 Statistical evaluation

To consider a comprehensive view on impact factors of HRQoL in COPD patients, both non-clinical and clinical factors need to be considered. Therefore, the first paper focused on clinical factors, while the second paper focused on a non-clinical factor.

In Paper 1, the role of FEV_1 and exacerbations, two key clinical factors, was evaluated. First, generalized additive models (GAM) were used to capture the non-linear relationship between HRQoL and FEV_1 [99]. To assess the impact of changes in both clinical impact factors (FEV_1 and exacerbations) on changes in HRQoL over one year, change score models were performed. These are linear regressions based on ordinary least squares (OLS). Changes in clinical factors were incorporated as absolute changes in FEV_1 and as occurrence of new severe exacerbations in individuals without prior severe exacerbations in the year before baseline. While most prior

studies on clinical impact factors stratified their analyses by GOLD I-IV classes or did not stratify by disease severity at all, the first paper stratified by GOLD AB and CD (=E). As COPD management evolves, so does GOLD classification, in terms of GOLD ABCD or ABE groups, respectively. Thus, a certain focus should also lie on the new groups as strata.

In Paper 2, specialty care as a non-clinical factor was evaluated. Linear Difference-in-Difference models were used to estimate the causal effect of pulmonologist care, as an “intervention”, on changes in HRQoL over one year. The applied control group covered non-specialty care treatment, while the treatment group covered newly initiated pulmonologist care. In DiD models, changes in the outcome, here HRQoL, from a pre-treatment assessment point to a post-treatment assessment point are contrasted between the newly treated group and control group without treatment [100]. As baseline characteristics between control and treatment group were imbalanced, a 1(intervention):3(control) propensity score matching (PSM) was used to balance both groups in advance [101,102]. This combination of PSM and DiD enables robust inferences, as both methods are considered to powerfully control for confounding in non-randomized studies [103,104]. The second paper analyzed the longitudinal association between specialty care and HRQoL also stratified by GOLD AB and CD (=E).

Both papers further include descriptive analyses with information on fundamental baseline and follow-up patient characteristics, their comparison, and the unadjusted change in HRQoL. Further details on methods are described in the papers.

2.6 Results summary and conclusion

This thesis focuses on the impact of clinical and non-clinical factors on HRQoL in COPD patients as an integrative approach, in order to examine possibilities to stabilize or improve HRQoL in a comprehensive view. Both, clinical factors, in terms of lung function and exacerbations, and non-clinical factors, in terms of specialty care, had a significant impact on the development of HRQoL within one year.

Paper 1 confirmed an overall deterioration in disease-specific and generic HRQoL in COPD patients, which was also previously observed in other studies [2,91,92]. By focusing on ABCD GOLD groups instead of commonly GOLD I-IV classifications as strata, the paper adds important new insights to previous studies, that described correlations between FEV_1 [2,3,105] or severe exacerbations [6–8,106,107] and COPD patients’ HRQoL. For the first clinical factor, lung function, a significant association between a decline in FEV_1 and a deterioration in disease-specific HRQoL (CAT) was observed. This association was however not significant for generic HRQoL, comparable to results of a similar study [2]. Noteworthily, within our study, stable or increased lung function were not able to counteract the overall downwards trend of HRQoL nor led to a reduced HRQoL decline, despite the other study clearly emphasized that preventing a deterioration of lung function, in terms of a stable or increased FEV_1, led to an improved HRQoL [2]. The analysis of exacerbations as second clinical factor also revealed a significant association between the new occurrence of at least one severe exacerbation and deterioration in disease-specific HRQoL (CAT), whereupon the average deterioration was considered clinically relevant in GOLD groups AB. This highlights the importance to avert severe exacerbations in patients with initially low (severe) exacerbation risk, in order to prevent a decrease in disease-specific HRQoL.

As a previous piece of evidence already indicated that pulmonologist-managed COPD patients experience fewer severe exacerbations than COPD patients managed by general-internal specialists [108] and exacerbations are a crucial trigger for HRQoL development, as observed in paper 1, a beneficial impact of pulmonologist involvement into COPD care on HRQoL was presumed. Paper 2 identified specialty care as a significant non-clinical impact factor on HRQoL: an uptake of pulmonologist care had a small but beneficial impact on the development of both generic (VAS) and disease-specific HRQoL (CAT) by slowing down the overall deterioration. This positive effect on COPD patients' health outcome was particularly evident in COPD GOLD groups AB, which represent the subgroup with a lower baseline risk for (severe) exacerbations. These results might indicate that early inclusion of specialist care in the patient management process could be able to enhance the patient's subjective wellbeing. Nonetheless, no clear recommendations on the ideal time point for a referral to a pulmonologist is given, yet [109] and should thus be also studied further, to provide more appropriate information about the inclusion of specialty care. In an international perspective, this could be particularly relevant for countries where COPD patients receive their care mainly from GPs. The German care system with GPs and outpatient specialists caring for COPD patients differs from countries with specialists in polyclinics. Thus, the generalization is limited, but also leaves space for further research in other health care systems and a subsequent international comparison.

The analyses in both papers are stratified by GOLD groups AB and CD and might thus be also interpretable in the new GOLD ABE system, as respective CD groups can be interpreted as E. Detailed results on the impact of the respective clinical and non-clinical factors on HRQoL are provided in the corresponding papers.

The study design involves limitations, e.g., only German non-deceased COPD patients who were enrolled to the COPD DMP at the respective regional SHI fund were included, pointing up that not all COPD patients in Germany from other regional or nationwide funds are represented, nor patients not enrolled in the DMP. Moreover, the enrollment in the DMP is voluntary for COPD patients, which infers a bias towards "good risk" patients. This might lead to more conservative results and an underestimation of the impact of clinical and non-clinical factors on HRQoL. Notably, the observation period comprised only one year, which might limit the possibility to capture the full effect of clinical and non-clinical factors on HRQoL. Further details on general and analysis-specific limitations can be found in the respective papers.
In context of the new GOLD ABE classification system, it must be considered, that the analyses used in this thesis rely on the previous exacerbation assessment and differentiate between patients with low exacerbation risk (pooling of GOLD groups A and B) and those with high exacerbation risk (pooling of GOLD groups C and D). With the newly introduced definition of exacerbations, exacerbations could possibly be classified differently between moderate, and severe, what, in turn, would lead to a different classification to GOLD groups in the new system.

The major contribution of this thesis is shading light on potentials for HRQoL-based COPD management. Despite claimed as a major goal of German DMPs, HRQoL is not yet routinely measured with in the DMP context. Thus, disease management targeted at enhancing HRQoL is not feasible. This thesis partially closes this flagrant gap by focusing on manageable clinical and non-clinical factors that are suited to enhance or to stabilize HRQoL of participants of COPD DMP. Indeed, certain care strategies that ought to be considered for an integrated COPD management have an obvious potential to enhance the HRQoL of COPD patients. These strategies include specialist involvement as well as preservation of lung function and the avoidance of severe exacerbations, which corresponds to currently valid guidelines [18].

Concludingly, HRQoL-targeted care strategies are supposed to be widely accepted, as they match the physicians' clinical interests (guideline conform treatment) with the patients seek for wellbeing (perseverance of HRQoL). Thus, a discussion if COPD management should be more strongly geared towards HRQoL as a target indicator is highly warranted as HRQoL-targeted management implicitly addresses state of the art management of central clinical factors. Further research should thus also focus on the conjoint influence of clinical and non-clinical factors, to find possibilities to improve or maintain patient-relevant outcomes. Furthermore, future research on transfer potentials to other DMPs e.g., asthma bronchial or diabetes seems paramount to answer the question whether HRQoL-centered patient management is an approach with generic potential or if its operability is limited to distinct conditions with COPD being one of them.

3. Paper I

Impact of Lung Function and Exacerbations on Health-Related Quality of Life in COPD Patients Within One Year: Real-World Analysis Based on Claims Data.

Reference: Stöber A, Lutter JI, Schwarzkopf L, Kirsch F, Schramm A, Vogelmeier CF, Leidl R. Impact of Lung Function and Exacerbations on Health-Related Quality of Life in COPD Patients Within One Year: Real-World Analysis Based on Claims Data. Int J Chron Obstruct Pulmon Dis. 2021; 16: 2637-2651

DOI: 10.2147/COPD.S313711

4. Paper II

Does uptake of specialty care affect HRQoL development in COPD patients beneficially? A difference-in-difference analysis linking claims and survey data.

Reference: Stöber A, Marijic P, Kurz C, Schwarzkopf L, Kirsch F, Schramm A, Leidl R. Does uptake of specialty care affect HRQoL development in COPD patients beneficially? A difference-in-difference analysis linking claims and survey data. Eur J Health Econ. 2023

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