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Impact of chronic ischemic heart disease on the health care costs of COPD patients – An analysis of German claims data

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ABSTRACT

Objectives: Chronic Obstructive Pulmonary Disease (COPD) has a substantial impact on health care systems worldwide. Particularly, cardiovascular diseases such as ischemic heart disease (IHD) are frequent in individuals with COPD, but the economic consequences of combined COPD and IHD are by large unknown. Therefore, our study has the objective to investigate excess costs of IHD in COPD patients.
Methods: Out of German Statutory Health Insurance claims data we identified 26,318 COPD patients with and 10,287 COPD patients without IHD based on ICD-10 codes (COPD J44; IHD I2[0,1,2,5]) of the year 2011 and matched 9986 of them in a 1:1 ratio based on age and gender. Then, we investigated health care service expenditures in 2012 via Generalized Linear Models. Moreover, we evaluated a potential non-linear association between health care expenditures and age in a gender-stratified Generalized Additive Model.
Results: The prevalence of IHD in individuals with COPD increases with rising age up to a share of 50%. COPD patients with IHD cause adjusted mean annual per capita health care service expenditures of ca. €7400 compared with ca. €5800 in COPD patients without IHD. Moreover, excess costs of IHD have an inverse u-shape, peaking in the early (men) respectively late seventies (women).
Conclusions: IHD in COPD patients is associated with excess costs of ca. € 1,500, with the exact amount varying age- and gender-dependently. Subgroups with high excess costs indicate medical need that calls for efficient care strategies, considering COPD and IHD together particularly between 70 and 80 years of age.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality worldwide and therefore an important contributor to healthcare cost [1].

Comorbid conditions are highly prevalent in patients with COPD [2] and have been shown to be associated with an additional reduction in health-related quality of life [3], worse prognosis [4], and excess costs [5,6].

Ischemic Heart Disease (IHD) is a very frequent comorbid condition in COPD [7,8] which is associated with worse health status [9] and represent a significant cause of mortality in individuals with COPD [10,11].

So far, no integrated guidance how to manage IHD in COPD patients exists. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends treatment of COPD patients with concomitant IHD according to usual IHD guidelines [1].

In Germany, treatment of IHD incurred direct medical costs of ca. €6.2 billion in 2008 and ca. €3.5 billion were dispensed on chronic bronchitis, emphysema and COPD [12]. These estimates take an isolated view on COPD and IHD and do not reflect to which extent IHD affects costs of care in individuals with COPD. In order to understand health care as it is actually being delivered, the impact

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of comorbidity has to be considered. This paper aims to detail the cost consequences of IHD in COPD patients. Adopting the payer perspective of Germany's Statutory Health Insurance (SHI), our study has the threefold objective to.

a) analyze the structure of health care expenditures in COPD patients with and without comorbid IHD.
b) assess the impact of comorbid IHD on SHI expenditures for COPD patients.
c) describe age- and gender-specific cost profiles for both groups.

In addition to these analyses, we compare the impact on results of using simple matched-pairs comparison versus multivariate regression for achieving comparability between patients with and without IHD.

2. Methods

2.1. Data set and sample selection

In Germany, health insurance is compulsory for the entire resident population. The SHI system covers all individuals up to a qualifying income limit which is the case for ca. 87% of the resident population. SHI is organized by the principles of a pay-as-you-go financing and income-dependent, but risk-independent contributions. It is designed as a full coverage insurance with access to a broad range of medical services for little copayment. With some minor exceptions, the remaining population is insured by private funds which raise risk-dependent fees. This is particularly the case for freelancers and employees with an income above the mentioned threshold.

For this study the research data base of arvato health analytics GmbH - which includes claims data of seven German SHI funds – was used. It contains information of about 7 million insurants from 2007 to 2014 including demographic, in- and outpatient as well as medication data. This population is representative for whole Germany, as confirmed by various tests concerning age, gender, morbidity, and mortality. For our analysis we restricted to a subsample of the database with more detailed information (so-called “feingranularer Datensatz”) and only considered insurants aged 40 years and older (in 2012) that were continuously enrolled from 2011 to 2013 or died in 2013 (n = ca. 748,600). We identified COPD patients by their respective ICD-10 WHO GM code (J44). To be included as COPD patient, a minimum of two in- or outpatient diagnoses of COPD in 2011 was required. The approach of multiple diagnoses is well-established in claims data analyses to reduce the likelihood of false-positive diagnoses. The same requirements had to be fulfilled for the identification of IHD patients, where the codes I2[0,1,2,5] were taken into account. In doing so, we identified 36,605 individuals with COPD of whom 10,287 had comorbid IHD.

For each patient the following set of attributes in 2011 was derived: age (reference point 2012), gender, time of death (if in 2013), member status (pensioner, family insured, regular member) presence of emphysema (ICD-code J43), bronchitis (ICD-Codes J41, J42), asthma (ICD-Code J45), lung cancer (ICD-Code C34), heart insufficiency (ICD-Code I50), diabetes (ICD-Codes E10-E14) as well as an acute (i.e. diagnosis in 2012) myocardial infarction (ICD-Codes I21, I22).

For the primary analysis, a matched-pairs design, we combined COPD patients with and without IHD based on age (in years) and gender. An exact age and gender matching was not feasible for 301 COPD patients with IHD (2.9%), thus 9986 pairs were included in the analyses.

In addition to the matched-pairs approach, we performed a regression approach within a sensitivity analysis (SA1) that included not only the matched-pairs but all individuals with COPD with (n = 10,287) and without IHD (n = 26,318) identified in the initial data set. As second sensitivity analysis (SA2) a matched-pairs approach based on a less restrictive definition of COPD was run. Here, the diagnoses J41, J42 and J43 were also considered to reflect “COPD” which led to 11,877 pairs.

2.2. Outcome parameter

Our main outcome parameter was mean per capita health care service expenditures in COPD patients with and without IHD in the year 2012. This per patient approach takes into account all expenditures incurred and is not restricted to COPD- respectively IHD-related spending. We considered inpatient hospital treatment, outpatient physician treatment (general practitioners and medical specialists), and outpatient drug prescriptions which together accounted for ca. 70% of 2012-SHI expenditures [13]. In addition, spending on non-physician services, medical aids and rehabilitation was considered collapsed under the heading “other health care services”.

Moreover, we estimated expenditures on COPD-related and IHD-related drug prescriptions and hospitalizations. In the case of COPD, we accounted for spending on drug prescriptions with ATC-Code “R03” (drugs for obstructive airway diseases) and for spending on hospital stays with COPD (ICD-code J44) as the principal diagnosis. In case of IHD, we looked at expenditures on antiplatelet drugs (ATC-Code “B01A”), ACE inhibitors (ATC-Code “C09A”, “C09B”), beta blockers (ATC-Code “C07”), and statins (ATC-Codes “C10”), and spending on hospital stays with IHD (ICD-codes I2[0,1,2,5]) as the principal diagnosis.

IHD-associated costs of care were assessed using an excess cost approach [14], which compares expenditures of COPD-patients with and without IHD. The difference in spending is assumed to be IHD-related.

2.3. Statistical analysis

In a descriptive analysis, we compared raw health care service expenditures on individuals with and without IHD within the distinct SHI service domains.

For our main analyses and SA2 we ran morbidity and mortality adjusted regression models. Mortality was operationalized as death in 2013, i.e. the year following the year of observation, in a dummy coded format. Comorbidity burden was addressed via the morbidity-oriented factors from the risk structure schemes between German sickness funds. These factors (“hierarchical morbidity groups (HMG)”) refer to chronic diseases and other severe cost-intensive health conditions and are routinely recorded in SHI data for each year. Within the HMGs cost-intense comorbidities are assigned to a distinct surcharge factor. All 301 HMG factors except those for COPD and IHD were summarized to a single continuous HMG-weight to best possibly also account for the impact of lifestyle-related and socio-economic status-related diseases on COPD. Since the HMG-weight was heavily skewed to the right, the corresponding variate was winsorized to the 99% percentile (p99), i.e. all individuals who had a HMG weight higher than p99 were assigned the HMG-weight at p99. Since health care expenditures, too, were heavily skewed to the right, we consequently used costs of care winsorized at p99 as the dependent variable. We also tested other operationalisations of comorbidity such as number of HMG conditions and number of chronic conditions in the elderly as suggested by Schaefer [15] which did not lead to a better model fit as measured by the information criteria AIC and BIC.

To estimate mean annual per capita expenditures in the group

with respectively without IHD we ran separate Generalized Linear Models (GLM) for each SHI service domain assuming a gamma distribution with log link. For the service categories "outpatient physician care", "outpatient drug prescriptions", and "entire SHI expenditures", which had a user quota of more than 90%, we applied a one-step GLM. Since gamma models are only defined for positive values we assigned the fictive amount of €10 to individuals with zero costs to keep them in the analysis sample.

For the remaining service domains with lower user quota we ran two-part regression models. The two-part approach consists of two conditionally linked parts: Part 1 applies logistic regression with the covariates described above to estimate the probability of positive expenditures. Part 2 represents a GLM with gamma distribution and log link to calculate expenditures for those who had positive spending in part 1 [16]. Part 1 and part 2 are finally linked multiplicatively to reach adjusted per capita costs.

Following, for both, the one and the two-part models, adjusted mean expenditures for both groups were investigated via recycled predictions. In this approach, two predictions are derived based on the regression estimates: first, assuming all subjects do not have IHD; second, assuming that all have IHD. The mean differences between these predictions are the excess costs of IHD adjusted for covariates [17,18].

Two-sided 95%-confidence intervals were constructed using 1000 non-parametric bootstrap replications, whereupon the bootstrapping algorithm ensured the drawing of both partners of the matched pair.

For SA1 the same statistical approach as described above was applied with gender, age and age^2 as additional covariates, since this combination showed the best model fit according to AIC. Here it was not necessary to account for dependent data within the bootstrapping algorithm.

Following, we investigated a supposable non-linear association between overall SHI expenditures and age in men and in women. To do so, we constructed a Generalized Additive Model (GAM) allowing a separate smooth function for COPD patients with and without IHD of both sexes. In this secondary analysis, smooth functions fitted via thin plate regression splines with smoothing parameters based on generalized cross-validation were applied [19]. A significance level of 5% was used for all analyses, which were performed with the software package SAS, version 9.3.

3. Results

3.1. Sample characteristics

Table 1 gives the characteristics of the matched pairs. The mean HMG-weight was 1.9 in COPD patients with IHD and 1.2 in COPD patients without IHD. The prevalence of other cardiac diseases and diabetes was substantially higher in the group with IHD, and so was the risk of death within the year following the year of observation. In most patients COPD stage was not documented. This effect was slightly more pronounced in individuals with COPD only. Regarding the presence of additional pulmonary diseases, COPD patients with and without IHD were by large comparable.

3.2. Raw mean per capita expenditures in COPD patients with and without IHD

As visualized in Fig. 1, raw mean annual per capita SHI expenditures for COPD patients with IHD (€7797) were by almost 50% higher than those on COPD patients without IHD (€5270). Within both groups, inpatient hospital treatment was the main contributor to costs of care followed by prescribed drugs and outpatient physician treatment.

3.3. Model-based excess costs of IHD

Table 2 describes the model-based cost estimates as well as the resulting excess costs in both groups with the corresponding 95% confidence intervals. After adjusting for comorbidity and mortality individuals with IHD incurred by 26% higher overall SHI

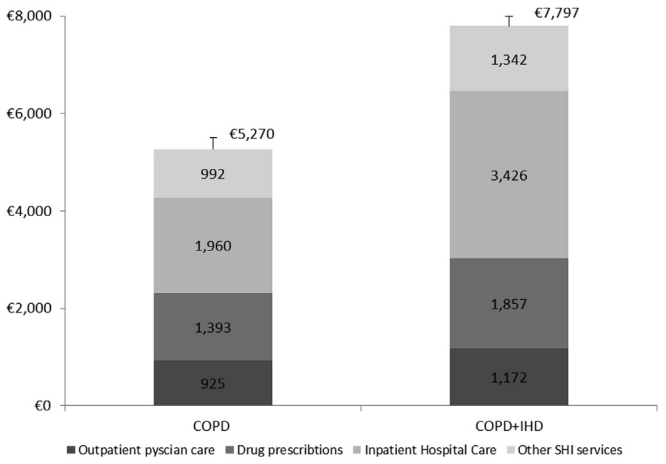

Fig. 1. Raw mean annual per capita costs of care for COPD patients with and without IHD.

Table 1
Characteristics of the study sample.

	COPD without IHD		COPD with IHD	
N	9986		9986	
Mean age [SD]	73.7	[10.0]	73.7	[10.0]
Female [as %]	4880	48.9	4880	48.9
Death within the following year [as a %]	671	[6.7]	809	[8.1]
Mean HMG weight [SD][a]	1.2	[2.0]	1.9	[2.6]
COPD stage unknown [as a %]	7091	[71.0]	6608	[66.2]
Emphysema (ICD-Code J43) [as a %]	970	[9.7]	989	[9.9]
Chronic bronchitis (ICD-Codes J41, J42) [as a %]	715	[7.1]	765	[7.7]
Asthma (ICD-Code J45) [as %]	2043	[20.5]	2068	[20.7]
Congestive heart failure (ICD-Code I50) [as a %]	1308	[13.1]	3101	[31.1]
Myocardial infarction (ICD-Codes I21, I22 in previous year [as %][b]	0	[0.0]	319	[3.2]
Myocardial infarction(ICD-Codes I21, I22) in observation period[b] [as a %]	0	[0.0]	167	[1.7]
Diabetes (ICD-Codes E10-E14) [as a %]	2748	[27.5]	4298	[43.0]

[a] Exclusive HMG-groups for COPD and IHD.
[b] Only inpatient diagnoses included.

Table 2
Adjusted mean costs per group and excess costs of IHD in SHI service domains.

	COPD without IHD	COPD with IHD	Excess Costs
Outpatient physician treatment	925 [906; 945]	1089 [1071; 1106]	164 [137; 184]
Outpatient drug prescriptions	1528 [1489; 1571]	1825 [1780; 1869]	297 [255; 335]
thereof COPD-related	377 [366; 388]	350 [340; 360]	−26 [−41; −13]
thereof IHD-related	92 [77; 95]	201 [196; 206]	120 [104; 130]
Inpatient Hospitaltreatment	2192 [2093; 2305]	3012 [2906; 3122]	819 [673; 959]
thereof COPD-related	116 [103; 115]	131 [119; 144]	15 [-2; 32]
thereof IHD-related	./.	65 [60; 72]	
Other SHI services	1139 [1091; 1188]	1240 [1195; 1283]	101 [45; 157]
Total SHI expenditures[a]	5846 [5682; 6020]	7366 [7199; 7536]	1520 [1317; 1689]

Adjustment for HMG-weight winsorized at p99 and death within year post observation.
[a] Results of model estimation, addition of distinct service domains yields slightly different figures.

expenditures. Spending on individuals with IHD was higher than spending on individuals without IHD in all SHI service domains, whereupon the relative effect was particularly pronounced in the hospital sector (+37%). Expenditures on COPD-related medication were significantly lower in individuals with comorbid IHD, whereas we observed no differences in spending on COPD-related hospital stays.

3.4. Age and gender-specific cost profiles

The results of the GAM, which investigated a non-linear association between age and costs of care, are presented in Fig. 2. Our analysis observed different age-dependent – and to lesser extent gender-specific - trends. In the group without IHD SHI expenditures increased in a linear way, with a steeper increase in women. The cost-curve in the group with IHD presented an inverse u-shape, which peaked at around 80 years of age in women and almost one decade earlier in men. In consequence, excess costs of IHD first increased with age, but after this turning point subsequently decreased and were eventually evened out in the oldest of the old.

Moreover, in females the cost difference was more pronounced than in men, particularly in younger age groups. This can be illustrated by following example: At 75 years of age excess costs for men with COPD and IHD were ca. €2700 [IHD: €8100; no IHD: €5400] and excess costs for women with COPD and IHD were ca. €2900 [IHD: €8300; no IHD: €5400]. Hence, the difference in excess costs was ca. €200. At 50 years of age however, men with COPD and IHD incurred excess costs of only €1000 [IHD: €5300; no IHD: €4300] compared to excess costs of ca. €1800 in women [IHD: €5300; no IHD: €3500], which led to a difference in excess costs of ca. €800.

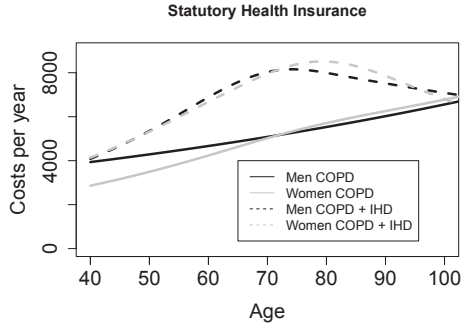

Fig. 2. Age-dependent cost profiles in COPD patients with and without IHD stratified by sex.

3.5. Results of the sensitivity analyses

As highlighted in Table 3, which includes all COPD patients identified in the data set before matching, the prevalence of IHD in individuals with COPD increased with rising age and finally stabilized at a share of ca. 50%.

As a consequence for SA1, individuals with IHD and COPD were remarkably older (mean age: 74.0 vs. 65.2) and less likely female (48% vs. 57%) than those with COPD only (Appendix Table 1). Moreover, the morbidity and mortality gap between individuals with COPD and IHD and those with COPD but without IHD was much higher than in the matched-pairs design.

Compared to the main analysis, the multivariate regression model applied for SA1 (Appendix Table 2) estimated SHI expenditures by ca. €1000 lower in individuals without IHD and by ca. €1300 lower in individuals with IHD. In consequence, the absolute amount of excess expenditures was by ca. €300 lower, whereas the relative difference (26%) was identical to the main analysis.

SA2 which based on a wider definition of COPD yielded comparable demographic characteristics as the main analysis, with a slightly higher share of individuals with an unknown COPD stage as the only exception (Appendix Table 3).

For both, the group with and the group without IHD adjusted mean annual per capita SHI expenditures were by ca. €200 lower than in the main analyses but excess costs (ca. €1500) and impact of IHD (26%) was identical (Appendix Table 4).

4. Discussion

According to the best of our knowledge, this is one of the first studies investigating the impact of IHD as a distinct comorbid condition on costs of care in individuals with COPD. The few pre-existing studies rely on COPD-cohorts [20,21] and might not be representative for COPD patients with IHD as a whole owing to self-selection processes. Moreover, the mentioned studies included fewer individuals and present less recent data.

Our analyses revealed that comorbid IHD is associated with a remarkable increase in expenditures for individuals with COPD in all SHI domains [ratio between 1.09 (other SHI services) and 1.37 (hospital treatment)]. Given the age and gender structure of our IHD group (mean age 74 years, 49% females), overall SHI expenditures on COPD patients with comorbid IHD were ca. € 7400 compared to ca. € 5800 in individuals with COPD only, which is a factor of ca. 1.28. The results were robust against shifting to a less strict definition of COPD as done in SA2. The found factor fits well with a previous study based on a large German COPD cohort reporting that healthcare cost in COPD patients with a history of myocardial infarction were increased by 27% [22], but is substantially lower than the 55% increase of costs in COPD patients with cardiovascular diseases reported by Mannino et al. [6].

Cost differences between individuals with and without IHD varied age-dependently. We observed increasing excess expenditures until the early (men) respectively late seventies (women) of age. Following excess expenditures decreased and eventually evened out among the oldest of the old. The economic relevance of the high excess burden of IHD between 65 and 85 years of age is underlined by increasing prevalence of the comorbidity in this time frame. However, it has to be assumed that the profiles are also

Table 3
Prevalence of IHD in COPD patients per 5 years of age.

	Age group												
	40–45	45–50	50–55	55–60	60–65	65–70	70–75	75–80	80–85	85–90	90–95	≥95	Total
COPD + IHD [as a %]	25	107	304	581	865	1083	1919	2142	1796	1051	364	50	10,287
	2.2	5.1	9.4	14.56	19.7	26.4	34.5	40.7	46.3	50.1	51.3	50.5	
COPD only [as a %]	1128	2007	2940	3401	3530	3024	3644	3122	2082	1045	346	49	26,318
	97.8	94.9	90.6	85.4	80.3	73.4	65.5	59.3	53.7	49.7	48.7	49.5	
Total	1153	2114	3244	3982	4395	4107	5563	5264	3878	2096	710	99	36,605

driven to some extent by survival bias since individuals with more severe IHD die before they reach an age of eighty years and older. A comprehensive adjustment for mortality in both groups might have partially addressed this issue, but survival information was only available for one year after the observation period (2013), even though incorporating mortality aspects at least in a medium timeframe of three years would have been desirable.

COPD medication accounted for ca. one fifth (group with IHD) respectively one quarter (group without IHD) of entire drug expenditures, whereupon per capita expenditures on COPD medication were lower for individuals with comorbid IHD. This suggests slightly less intense COPD treatment in this more vulnerable population. A possible explanation for this observation is that physicians decide against the prescription of therapeutic agents for COPD which have earlier been discussed to be contra-indicated in IHD patients [23,24]. Another - even more intuitive - explanation might be that physicians put higher emphasis on IHD treatment and consider COPD as the less crucial point of concern. COPD patients without IHD also incurred costs for IHD-related medication but on a substantially lower level than patients with IHD. This finding was expected and does not question our selection strategy. It can be explained by the fact that the recommended IHD guideline medication (antiplatelet drugs, ACE inhibitors, beta blockers, and statins) is not specific for IHD but also prescribed in cases of e.g. hypertension, heart failure or hypercholesterinemia – which might be prevalent in COPD patients without IHD as well.

The results of our analyses have to be interpreted under some caveats.

First, the accuracy of diagnoses remains unclear. There is a broad body of literature dealing with discrepancies between documented morbidity and prevalent morbidity (e.g. Refs. [25–27]). We best possibly addressed this issue by relying on multiple diagnoses of COPD to increase the true-positive rate. SA2 also allowed the ICD 10 codes of J41, J42 and J43 which might reflect “mis-coded” COPD patients in an early stage. Since SA2 confirmed the results of the main analyses, we are convinced that our cost-estimates for cost of care in COPD patients with and without IHD are accurate. However, it has to be considered that our results refer to diagnosed patients with COPD only. As COPD is known to be largely underdiagnosed [28, 29], the true cost difference between the groups considered is probably underestimated as most of undiagnosed patients have early grades of COPD.

Second, claims data do not provide information on clinical parameters such as FEV_1-values, socio-economic background such as household income and risk factors particularly smoking habits. The only means to account for these factors was an indirect way via comorbidity adjustment via HMG-weight as a comprehensive measure.

Third, despite COPD stage is an established cost driver regarding costs of care [22], we had no means to investigate a potential interaction between COPD severity and comorbid IHD on costs of care. An explicit inclusion of disease severity as adjustment or stratification variable failed because COPD stage was only documented for ca. 30% of the study population and among these patients the documented stages often did not show plausible patterns over time. This might be explained by the fact, that within the German ICD-10 coding system the digits for COPD severity (3,2,1,0) are inversely coded compared to the clinically established GOLD stages (1,2,3,4) and that FEV_1 percentage predicted thresholds differ. Due to the high degree of uncertainty regarding COPD stage we were not able to control for differences in the COPD severity distribution between the group with respectively without IHD directly but we think that the HMG-weight at least allowed an indirect reflection of disease severity since comorbidity is more prevalent in more advanced COPD stages.

Fourth, our analysis reflects a payer perspective and does hence not address cost components outside the health care system such as productivity losses (indirect costs) and out-of-pocket payments. Indirect costs in COPD are mainly driven by disease-related absenteeism, but owing to different methodological approaches, target populations and health care systems the estimated amount varies substantially [30,31]. For Germany, a recent comparison of COPD patients in different GOLD stages with lung healthy controls yielded an excess of indirect costs between €8600 (grade 1) and €27,700 (grade 4) [22]. Evidence whether indirect costs in COPD patients with and without IHD differ is lacking, but it seems justified to suppose higher productivity loss in those with IHD owing to a higher morbidity burden. Credible data on out-of-pocket payments in COPD are scarce [31,32], and sound conclusions on differences in out-of-pocket payments between COPD patients with and without IHD are hardly feasible. Altogether, excess expenditures from a payer perspective as reported in this paper most probably underestimate the full economic dimension of IHD in COPD patients and have to be seen as a kind of lower threshold.

As a fifth issue, we did not include a third cohort with IHD but no COPD. Consequently, we were not able to consider the effect of COPD on cost of care in IHD. As far as we are able to judge, COPD is not expected to substantially affect IHD treatment. This is because GOLD recommends to treat COPD in IHD patients according to current practice as there is no evidence for a possible modification of IHD treatment due to COPD [1]. This argumentation is based on speculation and the question whether COPD substantially affects cost of care in IHD patients can only be addressed within an additional study comparing IHD patients with and without COPD which is beyond the scope of this paper.

Despite these data-driven and methodological limitations, we are strongly convinced that a claims data-based approach is suited to provide a large unbiased insight into current costs structures of COPD care in Germany. First, previous analyses have shown that the data set of Arvato Health Analytics GmbH is representative for the entire SHI population in terms of morbidity and mortality structures, hence we feel confident that our sample is representative for German COPD patients.

A second advantage of our approach is detailing the structure of excess costs. In addition to reporting health care specific cost differences (c), we also assessed the share of directly COPD (b)

respectively IHD-related (a) spending, whenever possible. This itemization enables a more comprehensive judgement of different types of cost differences. a) Excess costs owing to IHD-treatment per se (IHD-related drug prescriptions and hospital treatment) are expected and are hence not considered a crucial issue; (b) in contrast, cost differences in COPD-treatment between patients with and without IHD indicate a different intensity in COPD care. Here the reasons beyond obvious differences need to be further investigated; c) overall cost differences at the service domain level help to quantify the consequential costs of IHD (which arise in addition to direct treatment costs) and provide as a third strength vital input for the design and parametrization of more realistic cost-effectiveness models in COPD [33] as existing COPD models often neglect the existence of comorbid conditions [34].

So far there is no scientific consensus how bias in non-randomized observational studies might be mitigated best, but basically multivariate regression and propensity score matching are considered equivalent strategies [35,36]. The fourth strength is that we explored several different methodological strategies (1:1 age and gender matching, multivariate regression, investigation of non-linear associations). The primary analysis (matched-pairs) and SA1 (multivariate regression) yielded similar results regarding the impact of IHD on costs of care and the structure of excess costs, whereas, the absolute amount was estimated by ca. 20% lower in the multivariate regression. This is because the SA1 includes more young individuals, resulting in a decreased mean age compared to the matched-pairs sample (67.2 vs.73.7) - and matches with the GAM, which found a turning point of excess costs in the decade between 70 and 80 years. Given the consistency of all three methods, we strongly believe in the robustness of our results.

5. Conclusions

For the German hospital system, admissions of COPD cases have been predicted to grow by more than 4% per year through to 2018 [37]. Our study identified IHD as a substantial cost driver in COPD with an age-dependent variation of excess costs. Adding to the continuing importance of COPD, the results of this study emphasize an increasing need for further health care planning to focus on comorbidity management as there will be a rising number of patients due to continued exposure to risk factors and an ageing population. In consequence there is high need to further investigate interactions between COPD and IHD and to convert the results of these research activities in combined guidelines and disease management programs which support clinicians to initiate patient-centered treatment strategies for the relevant target group of COPD patients with IHD. A corresponding integrated care approach will support a more efficient patient management, especially in the particularly well represented age group between 70 and 80, where excess costs are highest.

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All authors were involved in the conception of the research and decided on the research question and study design. LS designed analyses, programmed the statistical models, and wrote the manuscript. MW supported data analysis and designed the tables and figures. JE programmed the selection algorithm. JH provided continuous support regarding data management issues. KL was the main contact person for clinical questions. Together with RL she initiated the project. RL was the main contact person for health economic questions. All coauthors proofread the manuscript critically and approved its final version.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2016.08.001.

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