



Economic burden of incident interstitial lung disease (ILD) and the impact of comorbidity on costs of care

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ABSTRACT

Introduction: Evidence about the economic burden related to interstitial lung diseases (ILDs) and the cost-driving factors is sparse. In the knowledge that distinct comorbidities affect the clinical course of ILDs, our study investigates their impact on costs of care within first year after diagnosis.

Methods: Using claims data of individuals diagnosed with Idiopathic Interstitial Pneumonia (IIP) (n = 14 453) or sarcoidosis (n = 9106) between 2010 and 2013, we calculated total and ILD-associated mean annual per capita costs adjusted by age, sex and comorbidity burden via Generalized Linear Gamma models. Then, we assessed the cost impact of chronic obstructive pulmonary disease (COPD), diabetes, coronary artery disease, depression, gastro-esophageal reflux disease, pulmonary hypertension (PH), obstructive sleep apnoea syndrome (OSAS) and lung cancer using the model-based parameter estimates.

Results: Total mean annual per capita costs were €11 131 in the pooled cohort, €12 111 in IIP and €8793 in sarcoidosis, each with a 1/3 share of ILD-associated cost. Most comorbidities had a significant cost-driving effect, which was most pronounced for lung cancer in total (1.989 pooled, 2.491 sarcoidosis, 1.696 IIP) and for PH in ILD-associated costs (2.606 pooled, 2.347 IIP, 3.648 sarcoidosis). The lung-associated comorbidities COPD, PH, OSAS more strongly affected ILD-associated than total costs.

Conclusion: Comorbidities increase the already substantial costs of care in ILDs. To support patient-centred ILD care, not only highly cost-driving conditions that are inherent with high mortality themselves require systematic management. Moreover, conditions that are more rather restricting the patient's activities of daily living should be addressed – despite a low-cost impact.

1. Introduction

Interstitial lung diseases (ILDs) is an umbrella term for more than 300 rare lung diseases with various aetiology and clinical course. The most frequently diagnosed ILD subtypes are IIP (idiopathic pulmonary fibrosis (IPF)) and sarcoidosis, which together comprise about 50% of ILDs [1]. According to the American Thoracic Society/European Respiratory Society statement, sarcoidosis reflects a subtype with potential for absolute regression, whereas the course of IPF is irreversible and progressive [2].

IPF and sarcoidosis are associated with a large number of comorbidities, including chronic obstructive pulmonary disease (COPD) [3–8], depression [4,9–11], coronary artery disease (CAD) [4,6,8,12], gas-

tro-esophageal reflux disease (GERD) [4,7,12–14], obstructive sleep apnoea syndrome (OSAS) [4,8,15–18], lung cancer [4,10,19,20], pulmonary hypertension (PH) [4,7,12,21,22] and diabetes [3,4,8,19]. Previous studies have substantiated the negative impact of comorbidities on disease progression and mortality in IPF and sarcoidosis [8,10,19], but their impact on economic burden has not yet been examined. To close this knowledge gap, our study investigates (a) the per capita costs of care during the first-year post diagnosis in individuals with IIP and sarcoidosis, (b) the ILD-associated per capita costs in the first-year post diagnosis and (c) the impact of relevant comorbid conditions on (ILD-associated) costs of care. To emphasize subtype-specific peculiarities in cost compilation, all analyses are presented for the total cohort as well as stratified by IIP and sarcoidosis.

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2. Methods

2.1. Dataset

We used 2009 to 2014 patient-individual health insurance claims data provided by the Scientific Institute of the AOK Statutory Health Insurance Funds (WIdO) – which have a market share of about 30% of the German resident population [23]. Consultation with an ethics committee was not necessary for this retrospective analysis because secondary and anonymized data were utilized [24].

Our dataset reflects the IIP (J84.1; n = 14 453) and sarcoidosis patients (D86.0-D86.9; n = 9106) of the study by Schwarzkopf et al. [25] who applied following inclusion criteria: a) confirmed outpatient diagnosis from a pulmonologist, or an internal specialist respectively an inpatient diagnosis; b) at least one relevant diagnostic procedure (bronchoscopy, computerized tomography of the lungs (CT), pulmonary function testing, and assessment of autoantibodies) during the visit of the diagnosis; and c) plausible longitudinal diagnostic patterns (e.g. exclusion of ILD after confirmed diagnosis). This selection algorithm stemmed from an ICD-10 transferred version of the IPF-validation algorithm by Esposito et al. [26], which had a positive predictive value of 83.3% in IPF patients but its validity for sarcoidosis is not yet verified.

2.2. Assessment of comorbidities

To assess relevant comorbidities, a systematic literature review was implemented in PubMed using the search terms ‘idiopathic pulmonary fibrosis’ and ‘comorbidities’ or rather ‘sarcoidosis’ and ‘comorbidities’ (See Supplementary Fig. S1). We considered the eight most frequent comorbidities, which were: COPD (J44), depression (F32–F34), CAD (I25.0, I25.1), GERD (K21.0, K21.9), OSAS (G47.31), lung cancer (C34), PH (I27.0, I27.8, I27.9) and diabetes (E10, E11). Comorbidity prevalence at baseline was defined via at least one inpatient or one confirmed outpatient diagnosis in the quarter of the incident ILD diagnosis.

2.3. Assessment of health care costs

To reflect patient-individual costs in the first-year post diagnosis, expenditures from the quarter of diagnosis until three quarters afterwards were added to ‘costs per year’. Costs covered outpatient physician care, medication, in- and outpatient hospital treatment and in- and outpatient rehabilitation and were split into total and ILD-associated costs. The latter were operationalized as follows: for outpatient physician care, all cases from a pulmonologist as well as cases with confirmed ILD diagnosis from a non-specialist were considered to be ILD associated. ILD-associated medication consisted of antifibrotic drugs (nintedanib, pirfenidone), immunosuppressants, acetylcysteine, pulmonary arterial hypertension drugs and systemic steroids. Hospital care was counted as ILD associated if the primary diagnosis was ILD. Moreover, primary diagnoses of respiratory infection, pneumothorax, pulmonary embolism, PH and right heart disease, respiratory insufficiency and other chronic and acute lung diseases were counted as ILD related. For rehabilitation, all stays with ILD as the reason for admission were classified as ILD-associated expenditures.

We did not inflate health care spending to a distinct base year but reported full € amounts as documented in the year of occurrence.

2.4. Statistical analyses

All analyses were performed for the total cohort as well as stratified by subtype.

First, we descriptively analysed baseline characteristics and comorbidity burden. For our primary analyses, costs and ILD-associated costs were estimated adjusted for age (in years), sex (reference: male), subtype (total cohort only), presence of the pre-specified comorbidities in a dummy-coded format (reference: no) and the overall number of comorbid conditions. To prevent overestimation of mean costs in patients with a short survival time, all analyses were weighted with survival.

For total costs as well as for outpatient physician and medication costs a one-part generalized linear gamma model with log link was used [27] because at least 90% of patients incurred any costs. As gamma models are defined for positive values only, we assigned the fictitious amount of €10 to the few patients with zero costs to keep them in the analyses. In case of more than 10% of patients incurring zero costs (hospital costs, ILD-associated hospital costs, rehabilitation costs, ILD-associated rehabilitation costs, ILD-associated outpatient physician costs and ILD-associated medication costs), we applied two-part models. In these models, the first part contains a logistic regression model, which predicts the probability of positive health care expenditures. In the second part, a gamma model, as described above, is used for estimating costs, conditional for non-zero costs. To derive unconditional predicted costs per patient, the probabilities from the first part of the model are multiplied by the predicted conditional costs of the second part of the model [28].

Recycled predictions were used to estimate surcharge factors for the comorbid conditions of interest. 95% confidence intervals (CIs) were calculated for surcharge factors and mean costs via 1000 non-parametric bootstrap replications [29].

To test the robustness of the results, we performed two sensitivity analyses (SA) within the total cohort. In SA1, the observation period was extended to three quarters after the incident ILD diagnosis to account for incident comorbidity. For SA2, patients dying within the first year after ILD diagnosis were excluded, because of extremely high health care expenditures at the end of life.

Statistical analyses were performed using the software package SAS (SAS Institute Inc., Cary, NC, USA, version 9.4). A significance threshold of 0.05 was used for all analyses.

3. Results

3.1. Population characteristics

According to Table 1, 51.1% of the total cohort were male. The mean age at diagnosis was 65.3 years and the death rate within the first year was 30.1%. IIP patients accounted for 61.3% (n = 14 453) of the sample. Compared to sarcoidosis (n = 9106; thereof were 16.4% of patients with an extrapulmonary manifestation) the IIP group presented a higher share of males (60.1% vs. 47.1%), a higher mean age at diagnosis (71.6 years vs. 55.4 years) and a higher death rate (30.1% vs. 9.5%).

Within SA2 including the 18 830 (79.9%) survivors, the proportion of IIP patients was reduced (56.5%) and so was the share of male patients (53.1%) and the mean age at diagnosis (63.4 years) (see Supplementary Table S1).

3.2. Comorbidities

Within the total cohort, COPD (54.2%; n = 12 763), diabetes (31.4%; n = 7393) and CAD (31.0%; n = 7299) were the most prevalent conditions. As illustrated by Fig. 1 this ranking also applied to IIP whereas depression instead of CAD ranked in position three in sarcoidosis.

In SA1, comorbidity prevalence was increased for each condition with a particular strong increase in PH. In SA2, all conditions except

Table 1
Baseline characteristics of the study sample.

n (%)	Total		Idiopathic interstitial pneumonia		Sarcoidosis	
	n	%	n	%	n	%
	23559	100.0	14453	61.4	9106	38.7
Male	12980	51.1	8692	60.1	4288	47.1
Ø age (years) at diagnosis (SD)	65.3	(15.3)	71.6	(11.4)	55.4	(15.5)
Dead at end of observation period	7091	30.1	6225	43.1	866	9.5
Comorbidities						
COPD	12763	54.2	9091	62.9	3672	40.3
Diabetes	7393	31.4	5167	35.8	2226	24.5
CAD	7299	31.0	5777	40.0	1522	16.7
Depression	4635	19.7	2858	19.8	1777	19.5
GERD	3472	14.7	2285	15.8	1187	13.0
PH	1871	7.9	1617	11.2	254	2.8
OSAS	1464	6.2	912	6.3	552	6.1
Lung cancer	1106	4.7	883	6.1	223	2.5
Patients without comorbidity	4343	18.4	1466	10.1	2877	31.6
Ø number of comorbidities (SD)	1.7	(1.3)	2.0	(1.2)	1.3	(1.2)

for OSAS presented a lower prevalence. Here, the most substantial decrease was observed for lung cancer (See Supplementary Fig. S2).

3.3. Costs

3.3.1. Total costs and ILD-associated costs

Fig. 2 depicts the results from the covariate adjusted main analysis. For the total cohort, we observed mean annual per capita costs of €11 131, of which €3707 (33.3%) were ILD associated. Hospital costs were the crucial driver for both, total costs (69.1%, €7687) and ILD-associated costs (80.4%, €2982). Expenditures for rehabilitation were negligible.

On the subtype level ILD-associated costs again accounted for around one third of total costs in IIP (€4036 of € 12 111) and sarcoidosis (€2938 of € 8793). For both subtypes, the share of hospital costs in total and ILD-associated costs reflected the proportions observed for

the total cohort. However, in sarcoidosis only, expenditures for ILD-associated physician care exceeded corresponding medication costs. The detailed values on domain-specific costs are presented in Supplementary Table S2.

3.3.2. Comorbidity impact on costs of care

For the total cohort as well as for the subtype strata, increasing age, male gender and comorbidity burden had a significantly cost driving effect.

Table 2 presents the cost impact of the distinct comorbid conditions on total respectively ILD-associated costs for the pooled cohort. The surcharge factors for the different SHI domains are shown in the supplementary Table S3.

As highlighted in Table 2, all comorbid conditions had a significant, in general cost-driving impact on total costs. Only COPD was associated with cost-savings. The highest cost increase was observed for lung cancer (surcharge factor: 1.979) and PH (surcharge factor: 1.710) followed after a large gap by diabetes (surcharge factor: 1.318).

Referring to ILD-associated costs, all conditions except for lung cancer had a significantly cost-driving effect. Now PH presented the highest surcharge factor (2.606), followed by diabetes (surcharge factor: 1.203) and depression (surcharge factor: 1.179).

Referring to IIP respectively sarcoidosis as done in Table 3, all conditions had a significant impact on total and ILD-associated costs. Again, COPD turned out to save total costs with in parallel increasing ILD-associated costs. Moreover, the effect of OSAS pointed in different directions for IIP (cost-driving) and sarcoidosis (cost-saving) for both total and ILD-associated costs. As a further inconsistency lung cancer turned out to decrease ILD-associated costs in IIP, whereas it increased ILD-associated costs in the case of sarcoidosis.

Altogether, lung-related comorbidities (COPD, PH and OSAS) had a stronger impact on ILD-associated costs, whereas age-associated comorbidities (diabetes, CAD) more strongly affected total costs. This finding was consistent for the pooled cohort as well as for IIP and sarcoidosis.

SA1 yielded the same crucial cost drivers as the main analysis, but the comorbidity-specific surcharge factors were generally higher (except for OSAS). The most important difference was that COPD was now cost-driving as well (see Supplementary Table S4). SA2 confirmed the results of the main analysis, with however slightly increased surcharge factors.

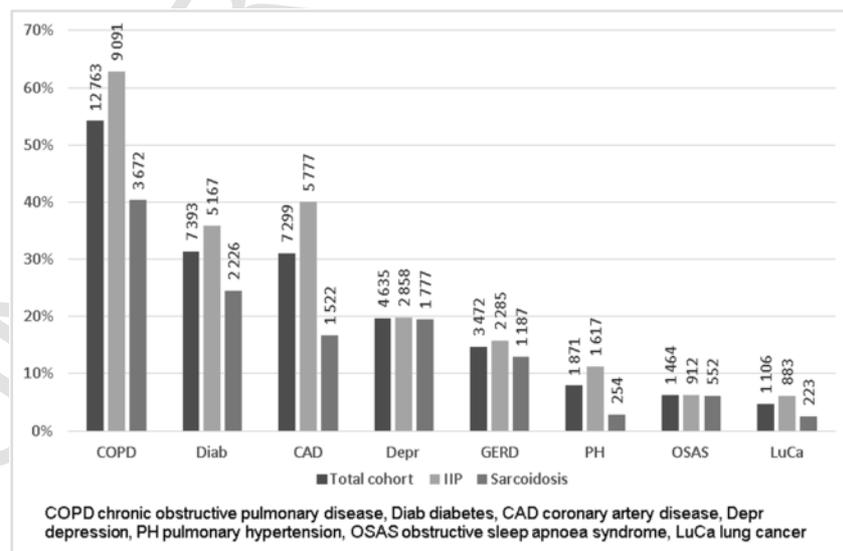


Fig. 1. Share of IIP/sarcoidosis patients within the different comorbidities compared with the total cohort.

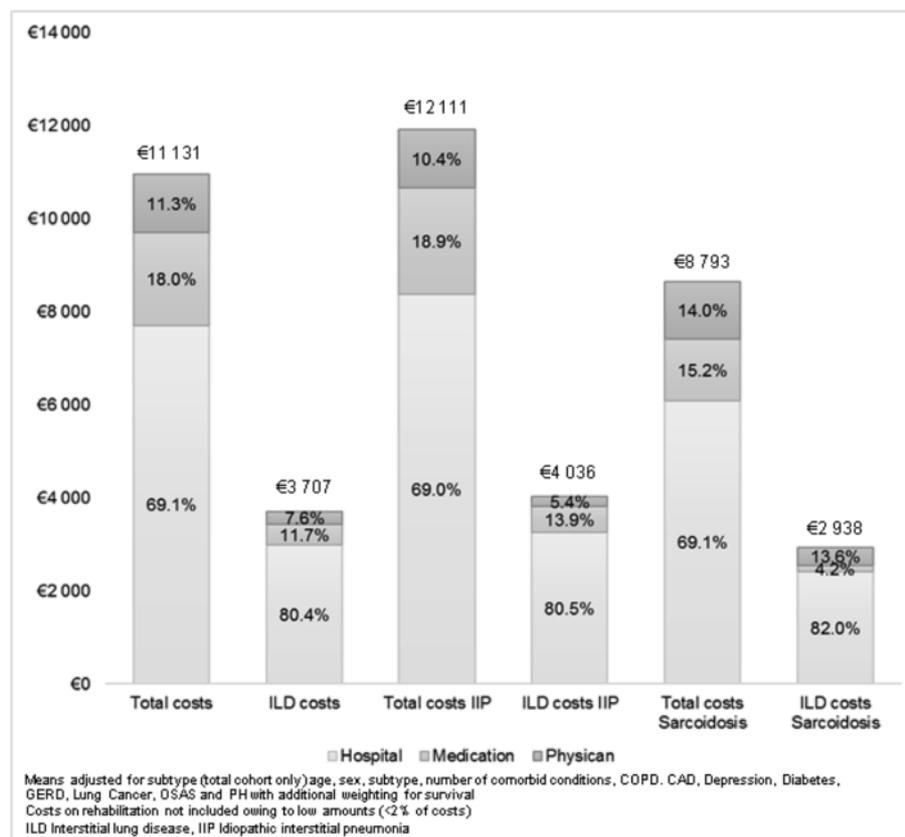


Fig. 2. Model-estimated mean annual per capita costs at the cohort and subtype level.

Table 2

Cost impact of comorbidities – parameter estimates calculated by recycled predictions.

	Total costs		ILD-associated costs				
	Surcharge factor [CI]	Euro (€) [CI]	Surcharge factor [CI]	Euro (€) [CI]			
Total sample							
Intercept	4934		2054				
Comorbidities							
COPD	0.966	[0.953; 0.979]	-168	[-238; -98]	1.148	[1.135; 1.161]	304 [264; 344]
Diab	1.318	[1.305; 1.331]	1568	[1492; 1645]	1.203	[1.190; 1.216]	417 [373; 460]
CAD	1.280	[1.267; 1.293]	1380	[1299; 1461]	1.161	[1.148; 1.174]	331 [285; 377]
Depr	1.261	[1.248; 1.274]	1287	[1200; 1374]	1.179	[1.166; 1.192]	368 [319; 418]
GERD	1.074	[1.061; 1.087]	364	[268; 460]	1.044	[1.031; 1.057]	91 [36; 145]
PH	1.710	[1.697; 1.723]	3504	[3368; 3640]	2.606	[2.593; 2.619]	3299 [3222; 3376]
OSAS	1.033	[1.020; 1.046]	163	[23; 303]	1.052	[1.039; 1.065]	107 [28; 186]
LuCa	1.979	[1.966; 1.992]	4830	[4650; 5010]	1.011	[0.997; 1.024]	22 [-80; 124]

All models additionally adjusted for age, gender and number of comorbid conditions.

Estimates with $p < 0.05$ are printed in bold.

CI 95% confidence interval, ILD interstitial lung disease, COPD chronic obstructive pulmonary disease, Diab diabetes, CAD coronary artery disease, Depr depression, GERD gastro-esophageal reflux disease, PH pulmonary hypertension, OSAS obstructive sleep apnoea syndrome, LuCa lung cancer.

4. Discussion

Our study identified that comorbid conditions are closely correlated with intensified costs in IIP and sarcoidosis. In particular, we were able to determine PH as an imperative factor for total and ILD-associated costs for both subtypes. Moreover, we substantiated evidence that lung-associated comorbidities have a more pronounced impact on ILD-associated costs, whereas age-associated comorbidities have a stronger impact on total costs.

IIP was associated with substantially higher costs of care than sarcoidosis even when differences in mortality – which are associated with increased expenditures in the terminal phase – are accounted (SA2). Despite a direct comparison of both groups is a sensitive issue

owing to the stratified analyses, the differences in amount and structure might be related to different clinical care pathways in both subtypes. Here, the higher relevance of medication expenditures in IIP (13.9% vs. 4.3%) is most probably related to treatment with more cost-intensive drugs (pirfenidone, nintedanib etc.) in IIP patients, whereas sarcoidosis patients are more likely to be treated with comparatively corticosteroids. The higher cost expenditures of outpatient care in sarcoidosis patients (13.6% vs. 5.4%) might be associated with a more complex care process in sarcoidosis, which require the involvement of different medical specialists (e.g. dermatologists, ophthalmologists, cardiologists), particularly in case of extrapulmonary manifestations. In contrast the heterogeneous manifestations of IIP, might be predominately handled by pulmonologists.

Table 3
Cost impact of comorbidities differed by entity.

		Total costs				ILD-associated total costs				
Entity		Surcharge factor [CI]		Euro (€) [CI]		Surcharge factor [CI]		Euro (€) [CI]		
Intercept	IIP	20 959				4795				
	Sarcoidosis	2492				1642				
Comorbidities										
COPD	IIP	0.954	[0.938; 0.971]	-959	[-1328; -589]	1.102	[1.085; 1.119]	490	[367; 613]	
	Sarcoidosis	0.930	[0.909; 0.951]	-174	[-233; -115]	1.088	[1.067; 1.109]	144	[96; 192]	
Diab	IIP	1.250	[1.233; 1.266]	5236	[4858; 5613]	1.153	[1.135; 1.170]	733	[607; 858]	
	Sarcoidosis	1.337	[1.316; 1.358]	840	[769; 910]	1.268	[1.247; 1.290]	441	[382; 499]	
CAD	IIP	1.281	[1.264; 1.297]	5883	[5499; 6267]	1.176	[1.158; 1.193]	842	[713; 970]	
	Sarcoidosis	1.352	[1.331; 1.373]	876	[793; 960]	1.206	[1.185; 1.228]	339	[271; 407]	
Depr	IIP	1.184	[1.167; 1.201]	3858	[3406; 4310]	1.171	[1.154; 1.189]	821	[672; 970]	
	Sarcoidosis	1.332	[1.311; 1.353]	827	[754; 900]	1.172	[1.151; 1.193]	283	[223; 343]	
GERD	IIP	1.025	[1.009; 1.042]	533	[50; 1016]	1.020	[1.003; 1.038]	97	[-62; 256]	
	Sarcoidosis	1.107	[1.086; 1.128]	267	[181; 353]	1.048	[1.027; 1.070]	79	[10; 149]	
PH	IIP	1.599	[1.582; 1.615]	12551	[11 958; 13 144]	2.347	[2.330; 2.365]	6459	[6265; 6654]	
	Sarcoidosis	2.315	[2.293; 2.337]	3277	[3089; 3465]	3.658	[3.635; 3.680]	4363	[4208; 4518]	
OSAS	IIP	0.948	[0.931; 0.964]	-1100	[-1813; -388]	0.963	[0.945; 0.981]	-177	[-410; 55]	
	Sarcoidosis	1.094	[1.072; 1.115]	233	[112; 355]	1.093	[1.071; 1.115]	153	[53; 253]	
LuCa	IIP	1.696	[1.679; 1.713]	14 592	[13 762; 15 421]	0.942	[0.925; 0.960]	-276	[-559; 7]	
	Sarcoidosis	2.491	[2.469; 2.513]	3715	[3517; 3912]	1.261	[1.239; 1.284]	429	[268; 589]	

All models additionally adjusted for age, gender and number of comorbid conditions.

Estimates with $p < 0.05$ are printed in bold.

CI 95% confidence interval, ILD interstitial lung disease, COPD chronic obstructive pulmonary disease, Diab diabetes, CAD coronary artery disease, Depr depression, GERD gastro-esophageal reflux disease, PH pulmonary hypertension, OSAS obstructive sleep apnoea syndrome, LuCa lung cancer, IIP idiopathic interstitial pneumonia.

In this context, it should be mentioned that we decided not to split our analysis in pulmonary and extrapulmonary sarcoidosis manifestations to support the comparability with the few sarcoidosis studies, which not made this distinction. Since our selection algorithm mainly addressed lung-associated diagnostic procedures, sarcoidosis patients without documented pulmonary involvement represent a minority of our sample (16.4%). Thus, the particularly cost-driving effect of cardiac, neuronal and ocular manifestations cannot be fully captured, and cost of sarcoidosis might be slightly underestimated.

An unexpected result was the detection of a cost-saving effect of COPD in total costs, whereas its effect on ILD-associated costs was positive. Our initial hypothesis, that this effect was driven by a survival bias (those with combined COPD and ILD are at increased risk of dying [30] and therefore have a reduced time span to incur costs of care) was falsified by SA2 (survivors only), which yielded the same direction of effects. We now consider some kind of synergetic treatment effect to be the most probable explanation. There might be some spill over of treatment with inhalative corticosteroids, which may have a beneficial impact on both conditions (COPD and IIP) [31]. Moreover, individuals with known COPD might be under closer medical control by pulmonologists. This increases the chance that the incident ILD is diagnosed at an earlier stage of the disease, at which the patients concerned have not yet had to deal with cost-driving complications and sequelae of the index disease ILD. This explanatory approach is supported by our SA1, which also accounted for incident comorbidity. Here, the assumed beneficial impact of already implemented routine medical control of the lung (reflected by prevalent COPD) no longer applies and indeed (newly diagnosed) COPD was now associated with increased total costs of care.

Even more complex to explain is the effect of OSAS pointing in the opposite direction for sarcoidosis in the total cohort (cost driving) and IIP (cost saving). We think this might be related to continuous positive airway pressure (CPAP) treatment of OSAS, which has been shown to improve activities of daily living (i.e. indirect association with all-cause health care utilization) and health status [32]. Moreover, decreased oxygen saturation was identified as a contributor to IPF progression [33], and thus increasing oxygen saturation in the context of CPAP might have a reverse effect (i.e. indirect association with ILD-related health care utilization). A corresponding effect might also exist for sar-

coidosis, but here it has to be kept in mind that sarcoidosis patients are commonly treated with corticosteroids, which tend to worsen the symptoms of OSAS [34]. This per se cost-driving effect might overlay the potential benefits of CPAP treatment of OSAS in sarcoidosis patients and contribute to an in the end cost-driving effect of OSAS for the sarcoidosis cohort.

Interestingly, we also observed a negative effect of lung cancer on IIP-associated costs, whereas the effect was consistently cost-driving for sarcoidosis and for total costs. We think this observation is more likely to be a reimbursement-related artefact than a true saving in the costs of care. A primary diagnosis of lung cancer in the inpatient setting generally results in a higher Diagnosis Related Groups (DRG) reimbursement than a primary diagnosis of IIP, which in turn establishes an incentive to classify IIP-related inpatient stays as lung cancer related.

Counterintuitively, rehabilitation expenditures played only a minor role within our study sample. This effect is most probably explained by the fact that inpatient rehabilitation for the working population (generally those below 65 years of age) are contained within the scope of the statutory pension insurance, whereas the SHI is only responsible for rehabilitation in people outside of the workforce (generally those above 65 years of age). Therefore, rehabilitation expenditures on behalf of the SHI do only partially reflect the rehabilitation-related economic burden, particularly in case of populations as sarcoidosis patients.

Previous studies analysed the Charlson index-based comorbidity burden [7,35,36] in IPF and sarcoidosis, and assessed the impact of distinct comorbidities on mortality [8,10,19]. However, information on comorbidity impact on costs of care is lacking so far, and even basic information on economic burden is sparse. Even in pieces of research targeting the costs of ILD, a comprehensive comparison of reported cost figures remains a sensitive issue. Each country has its peculiar cultural and health care system-related framework conditions, which substantially affect health care service utilization and the resulting costs.

Collard et al. [3] examined health care utilization and costs (1 year before and 1 year after the initial diagnosis) of patients aged 65 years and older. Their analyses yielded higher average total medical costs than our study \$22 452 (€18 552 vs. €11 131) but, in contrast to our analyses, their calculation also included (cost-intensive) skilled nursing facility costs and home health/durable medical equipment costs. About €9100 (49%) in the Collard et al. study were hospital related costs,

whereas our study reported circa €8300. This spending seems per se comparable taking into consideration that the population in the Collard study was restricted to individuals older than 65 years of age combined with the observed age-associated increase in costs of care. Another US-based study used claims data to investigate total health care costs and respiratory-related health care costs in patients with IPF [35]. The mean annual total cost was \$59 379 (€44 361) per patient in 2011. Some 36.6% of this amount was spent on respiratory-related care. In our study, the proportion of ILD-related costs is almost the same at 33.3%, but the absolute amount of total costs in IIP is much lower (€12 111). This might be due to some extent to the highly competitive health care system in the US, which among other things results in substantially higher costs for inpatient care than in the German system. When it comes to inpatient care, Cottin et al. [37] estimated median costs of €4510 for the first hospital admission of IPF patients. Our study revealed mean annual hospitalization costs of €8359 in the first year after the initial IIP diagnosis. Keeping in mind that, within this 12-month timeframe, the individuals within our sample had on average two inpatient stays (2.3 stays for IIP, 1.6 stays for sarcoidosis), calculating almost twice the costs of Cottin et al. is very reasonable.

The economic burden of sarcoidosis in the US is described by Baughman et al. [38]. They analysed annual health care costs, including pharmacy, inpatient and outpatient care, office, laboratory, emergency, home health, durable medical equipment and other for sarcoidosis patients. Comparing the sectors that were investigated in our study, Baughman et al. reported \$38 574 (€31 874) for sarcoidosis patients. Some 62.7% (\$24 177 (€19 978)) of this amount was sarcoidosis-related costs. In our study, the absolute amount of costs (€8793) and the percentage of 33.4 ILD-associated costs are much lower. The great difference in costs might be explained by their study sample consisting of patients who were part of a specific health care plan, whereas we looked at incident sarcoidosis patients in the routine care setting. Baughman et al. did not differentiate between incident and prevalent cases. However, it seems justified to assume that the specific health care plan is more likely to target patients with a more severe form of sarcoidosis, which are more likely to be prevalent cases. Finally, a special health care plan incorporates services that are not available to the population in routine settings. All these aspects presumably contribute to higher costs of care.

The findings of our study have to be interpreted under some caveats: The codes for IIP (J84.1) and sarcoidosis (D86.0–D86.9) can be utilized for other ILDs with fibrosis or not only for sarcoidosis of the lung. To prevent misclassification outpatient diagnosis had to be confirmed by a pulmonologist and at least one relevant diagnostic procedure had to be made; nevertheless, a misclassification of the ILD subtype cannot be fully excluded. Here particularly the transfer of an IPF-based validation on sarcoidosis might have resulted in a disregard of sarcoidosis patient with extrapulmonary manifestations. These restrictions seem however defensible since sarcoidosis is most often manifesting in the lung or the lymphatic system [39]. Another limitation is the lack of information concerning the severity of the underlying ILD and its comorbidities. Detailed clinical data (i.e. data including severity grade, quality of life data or documentation of prescribed doses) were not available in our study. As shown by Rice et al. [11], the more severe the disease or the comorbidity, the higher the cost. It is expected that the combination of comorbidities, for example COPD and diabetes, has a mutually reinforcing effect on costs of care. Therefore, the observed effect that each additional comorbidity yields a significant increase in the costs of care underestimates the full effect of disease combinations. However, taking the multiple possible interactions into account goes beyond the scope of this study because the variety of combinations is almost unlimited. In addition, we have to mention that we included only incident cases to mirror the impact of comorbidities on

costs of care. This might have resulted in comparatively high expenditures because the cost-intense phase of diagnosis [40] is included into the observation period. Concerning the methodical limitations, we must note that we did not inflate health care costs to a distinct base year. Health insurance expenditures are mainly derived from a fixed schedule of fees and are not the result of a market-driven negotiation. Therefore, issues of inflation do not substantially affect SHI. With inflation, annual per capita costs would have been slightly higher because a substantial share of patients were diagnosed in the early phase (2010: 29.0%, 2011: 26.3%) of our observation period. This patient distribution also contributes to low ILD-associated medication costs, because only the first year after diagnosis was looked at. In the last five years, the prescription of costly antifibrotic drugs (nintedanib, pirfenidone) has increased substantially, and therefore ILD-associated medication costs will be on the rise in the coming years.

Finally, the large sample size can be considered as an advantage. IIP and sarcoidosis are rare diseases, and our claims data-based approach allows the examination of special groups and the incorporation of rare events that are difficult to observe in clinical trials [41]. A further strength of our study is the representativeness of our data for Germany. One third of all German residents are insured by the AOK [23] and, thus, we deem our results to be generalizable to the German population. Another advantage is that our data source supplies a comprehensive picture of ILD- and non-ILD-associated costs in different cost sectors (outpatient physician care, medication, hospital care and rehabilitation), whereas most previous research has only focused on one aspect of health care service provision (e.g. cost of the first hospitalization). Our results create a link between the different sectors of health care service provision and allow the identification of sector transitions that require enhanced patient management. Furthermore, it is the first research considering the impact of distinct comorbidities in IIP and sarcoidosis that enables priority setting in comorbidity management for ILD patients.

5. Conclusion

In conclusion, comorbidity is a crucial cost driver in ILDs. Moreover, it must not be forgotten that individual cost impact and population-based cost impact do not necessarily match each other. From a population-based view, highly prevalent conditions with a small cost impact will in sum be more challenging for health care financing than rare conditions with a high cost impact. Therefore, not only highly cost-driving conditions that are inherent with substantial mortality themselves require systematic management. Indeed, conditions with low cost impact that are more restricting to the patient's activities of daily living should also be addressed to reduce patient-individual burden.

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List of abbreviations

CAD	Coronary artery disease
CCI	Charlson Comorbidity Index
COPD	Chronic obstructive pulmonary disease
DRG	Diagnosis Related Groups
GERD	Gastro-esophageal reflux disease
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPF	Idiopathic pulmonary fibrosis
OSAS	Obstructive sleep apnoea syndrome
PH	Pulmonary hypertension
SA1	Sensitivity analysis 1
SA2	Sensitivity analysis 2
SARC	Sarcoidosis
SD	Standard deviation
SHI	Statutory Health Insurance
WiDO	Scientific Institute of AOK (Wissenschaftliches Institut der AOK)

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmed.2019.04.009>.

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