Direct and indirect costs of COPD and its comorbidities: results from the German COSYCONET study

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Abstract

Background

Reliable up-to-date estimates regarding the economic impact of chronic obstructive pulmonary disease (COPD) are lacking. This study investigates COPD excess healthcare utilization, work absenteeism, and resulting costs within the German COPD cohort COSYCONET.

Methods

Data from 2,139 COPD patients in GOLD grade 1-4 from COSYCONET were compared with 1,537 lung-healthy control subjects from the population-based KORA platform. Multiple generalized linear models analyzed the association of COPD grades with healthcare utilization, work absence, and costs from a societal perspective while adjusting for sex, age, education, smoking status, body mass index (BMI), and several comorbidities.

Results

COPD was significantly associated with excess healthcare utilization, work absence, and premature retirement. Adjusted annual excess cost of COPD in 2012 for GOLD grade 1-4 amounted to €2,595 [1,770 – 3,678], €3,475 [2,966 – 4,102], €5,955 [5,191 – 6,843], and €8,924 [7,190 – 10,853] for direct costs, and €8,621 [4,104 – 13,857], €9,871 [7,692 – 12,777], €16,550 [13,743 – 20,457], and €27,658 [22,275 – 35,777] for indirect costs respectively. Comorbidities contributed to the primary effect of COPD on direct costs only. An additional history of cancer or stroke had the largest effect on direct costs, but the effects were smaller than those of COPD grade 3/4.

Conclusions

COPD is associated with substantially higher costs than previously reported.

Keywords

COPD – healthcare – cost – comorbidity

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of morbidity and mortality. Tobacco smoking and other inhaled noxious particles are the main risk factors for this progressive disease, which is preventable and treatable [1]. With aging of the global population, the public health challenge of COPD is expected to increase in the coming years [2].

A diagnosis of COPD is associated with impaired health-related quality of life: exacerbations and comorbidities, in particular, which have gained increased interest in recent years in COPD research, contribute to the overall severity of disease [3-7]. Simultaneously, COPD is responsible for a high economic burden on society in terms of disability, production loss, and premature mortality, but also on healthcare systems as a result of medical treatment for patients. Acknowledging the probable underestimation, the European Lung White Book reports direct costs of COPD of €23.3 billion and indirect costs of €25.1 billion in the EU countries in 2011 [8]. Previous estimates for Germany gave a range of costs per COPD case from €1,212 to €3,492 for the price year 2010 [9]. Comorbidities have been identified as a major driver of excess costs of COPD patients [10-14]. Recent, comprehensive, consistent, and representative evidence on the economic impact of COPD is scarce. However, actual and reliable cost estimates are needed to raise COPD awareness and to provide a rational basis for decision makers.

Therefore, the aim of this cross-sectional and observational study was to investigate excess healthcare utilization, work absenteeism, and resulting costs of COPD from a societal perspective by comparing COPD patients from a large national cohort with lung-healthy control subjects and to quantify the contribution of comorbidities to costs.

Methods

Data and study design

This analysis is based on data from the baseline examination (visit 1) of the German COPD cohort COSYCONET (*German **CO**PD and **Sy**stemic Consequences - **Co**morbidities **Net**work*), which is a prospective, observational, multicenter study that included 2,741 patients aged 40 years or older with physician-diagnosed COPD between September 2010 and December 2013. Patients were recruited by outpatient and inpatient healthcare providers, patient groups, and media campaigns and examined in 31 study centers covering all major regions of Germany. Exclusion criteria were previous lung transplantation or lung volume reduction surgery and lung malignancies. Furthermore, all participants had to be clinically stable, defined as having had no moderate or severe exacerbations for at least 4 weeks at the time of enrollment. Details of the cohort have been reported elsewhere [15, 16].

In order to build a control group without COPD, data from two studies within the KORA research platform ("Cooperative Health Research in the Augsburg Region") were used. KORA comprises population-based health surveys with subsequent follow-up studies in Southern Germany. Details on the KORA platform have been published elsewhere [17]. In brief, the KORA F4L study examined lung function in 1,051 participants aged 44-65 years in 2010. The KORA-Age cohort (2008) recruited participants from former KORA studies aged 65-89 years and examined a randomly selected sample of 1,079 participants [18]. Pooled data from the KORA-Age 1 and the F4L studies covered the age range of 44-89 years, which is comparable to the COPD cohort.

Lung function test and COPD definition

Standardized spirometry [19] was performed after bronchodilation in the COPD cohort and without bronchodilation in the KORA studies.

COPD was defined in both the patient and the population cohorts according to the GOLD criteria via spirometric parameters requiring a ratio of $FEV_1/FVC < 0.7$ [1]. In the KORA group, participants with COPD according to this definition were excluded from the control group. Furthermore, 92 KORA participants with a self-reported history of asthma were excluded in order to form a lung-healthy control group.

For the grading of COPD in the patient cohort, percentage predicted values were calculated based on reference values from the Global Lung Function Initiative [20]. COPD patients were classified as grade

1 with FEV_1 % pred. ≥ 80, grade 2 with 50 ≤ FEV_1 % pred. < 80, grade 3 with 30 ≤ FEV_1 % pred. < 50 and grade 4 with FEV_1 % pred. < 30.

Some 430 participants from the patient cohort reporting a physician diagnosis of COPD but not showing an airflow limitation in spirometry (former GOLD 0) were excluded from this analysis as well as 20 participants with missing GOLD grades. COPD patients with alpha 1-antitrypsin deficiency (A1ATD) defined by self-reports or A1ATD substitution therapy were overrepresented in the remaining COSYCONET cohort due to specific recruitment (n=152, 6.6% in COPD grade 1-4). This group was excluded from the main analyses because of the very high costs of A1ATD substitution therapy which may bias cost estimates.

Healthcare utilization, work absenteeism and calculation of costs

In all studies analyzed, healthcare utilization (irrespective of cause) was assessed by standardized interviews and questionnaires. The number of outpatient physician visits in the last 3 months, subdivided for 13 specializations, the number of hospital days in the last 12 months, and the use of prescribed pharmaceuticals in the last week were assessed. Furthermore, participants gave information on retirement, employment, and work absence in the last 12 months.

Annual costs were calculated from a societal perspective. Healthcare costs were derived by extrapolating physician visits to 12 months and by multiplying in- and outpatient utilization frequencies with German unit costs, which were updated to the price year 2012 [21]. Unit costs are listed in ***Table 1***. Utilization of prescription-only pharmaceuticals was estimated using participants' information about name and national drug code and information on defined daily doses [22]. Costs per year were calculated from 2012 pharmacy retail prices [23]. Over-the-counter pharmaceuticals, non-pharmacy medicines, dietary supplements, and vitamins were excluded.

Indirect costs as a consequence of production losses were considered for participants under the age of 65 years. Costs of sick days were calculated for participants reporting a regular full- or part-time employment. If participants stated more sick days than the maximum number of 210 working days in 2012 in Germany, their reports were restricted to 210 (n=6). Costs per day of work loss were calculated by dividing annual labor costs (€37,126) by 210 working days in 2012, yielding costs of €177 per working day [24, 25]. Premature retirement before the regular retirement age of 65 years was valued by mean annual German labor costs.

The human capital approach was applied to calculate productivity losses in paid work for society, following current guidelines [26]. In sensitivity analyses the friction cost approach was also used as the methodological discussion about the most appropriate valuation is still on-going [27]. According to the human capital approach, costs for sick days and retirement were fully considered, whereas the friction cost approach charged only 80% of the cost for a maximum of 50 sick days and neglected the costs of retirement [27].

Table 1: Unit costs[1] (all costs expressed as Euros (€) at 2012 values)

	Unit costs (€) per day / visit
Direct cost categories	
Physician visits in total (3 months)[a]	
General practitioner or GP for internal medicine	20.22
Specialist for internal medicine (incl. pneumologist)	64.65
Gynecologist	30.53
Ophthalmologist	35.09
Orthopedist	25.27
Otorhinolaryngologist	27.55
Surgeon	44.11
Dermatologist	19.10
Radiologist	43.97
Urologist	24.97
Neurologist / psychiatrist / psychotherapist	45.58
Specialist in occupational medicine	20.22
Other physician	43.97
Hospital treatment (12 months) [b]	
Inpatient hospital day	589.32
Prescribed pharmaceuticals (7 days)	AOK Institute
Indirect cost categories[a]	
Work absence[b] (number of days, 12 months)	177.21 per day
Premature retirement pension	37,126 per year

[a] indirect costs only for subjects of employable age < 65 years

[b] work absence only for full-time and regular part-time employees

[1] German unit costs by Bock et al. [21] were calculated based on regularly published sources from different players in the German healthcare system (mainly accounting data and official statistics; differences between statutory and private health insurance were considered) and represent an approximation of societal opportunity cost. An annual update is provided by Bock et al. Details on utilization frequencies of the total study sample can be found in the Online Appendix Table A1.

Comorbidities and covariables

In standardized interviews and questionnaires, participants' characteristics, socio-economic variables, and data on comorbid conditions were assessed in all studies.

Participants' age and sex were considered as well as their level of school education, smoking status, and body mass index (BMI, kg/m^2). The presence of comorbidities was assessed by asking participants the question: "Has a physician ever diagnosed you with one of the following diseases?". Information on diabetes, cancer, stroke, myocardial infarction, and arthritis as frequent comorbid conditions was assessed in all studies in a comparable way and considered as comorbidities. Five observations with missing information on diabetes and arthritis and two participants with missing weight were excluded from extended regression models.

Statistical analysis

Characteristics of COPD patients in different grades and of control subjects were compared using analysis of variance (ANOVA) for continuous variables and Chi^2-tests for categorical variables. Unadjusted means of healthcare utilization and costs were compared between the five groups by non-parametric Kruskal-Wallis tests.

Generalized linear regression models were conducted to quantify the association between COPD in grades 1-4 and healthcare utilization, work absence, and costs while adjusting for possible confounders. As the distribution of both utilization and cost data is typically highly skewed, a negative binomial distribution with log-link was assumed for utilization data and sick days, and a gamma model with log-link was used for cost data. The exponents of the regression coefficients in both models can be interpreted as factors.

In order to quantify the impact of comorbidities, all analyses were performed with and without regression adjustment for comorbidities. This approach allows division of the estimated excess costs of COPD into a part related to COPD itself and a part related to associated comorbidity. In the first step, the basic models included age group, sex, and level of school education as covariates. Extended models considered smoking status, BMI, and the selected comorbidities as additional covariables. Recycled predictions were used to estimate absolute cost differences between groups and adjusted excess costs of COPD [28] based on the basic models. 95% confidence intervals (CI) for the adjusted cost differences were estimated from 1,000 bootstrap replications using the percentile method.

In addition, interactions between COPD and comorbidities were analyzed by variable selection methods (PROC GLMSELECT with backward selection method) in order to examine non-additive effects of comorbidities on direct and indirect cost. Cost regression models were performed separately for COPD cases and control subjects to investigate the different effects of comorbidities in each group. Furthermore, regression models for direct costs were performed stratified for a younger (<65 years) and an older (≥ 65 years) age group with the median age as a cut-off point.

Statistical analyses were performed using SAS software (SAS Institute Inc., Cary, NC, USA, version 9.3), and p-values of 0.05 or less were considered to be statistically significant.

Ethics statement

The COSYCONET study was approved by the Ethics Committees of the local study centers. All cohort participants gave their written informed consent. The KORA studies were approved by the Ethics Committee of the Bavarian Medical Association, and written informed consent was obtained from the study participants.

Results

Patients and control subjects

Data from 2,139 COPD patients in grades 1- 4 and from 1,537 lung-healthy control subjects were available for this analysis. ***Table 2*** gives the characteristics of the study population. Direct comparison of cases and control subjects shows that the mean age was 65.4 years in the COPD cohort and 63.5 years in the control group ($p<0.0001$). There was a higher proportion of males in the COPD cohort (61.1 vs. 47.8% in the control group, $p<0.0001$). The proportion of never smokers was lower in the COPD group compared with the control subjects (5.4 vs. 49.6%, $p<0.0001$) as well as the proportion with higher education (17.0 vs. 20.8%, $p=0.004$) and mean BMI (26.8 vs. 28.2 kg/m^2, $p<0.0001$).

Regarding comorbidities, 37% of COPD patients and 33% of control subjects ($p=0.02$) reported at least one of the selected comorbidities. Mean number of comorbidities was 0.5 in COPD patients and 0.4 in control subjects ($p=0.05$). Diabetes and myocardial infarction were reported more frequently in the COPD group (13.1 vs. 10.4% and 8.9 vs. 5.0%), whereas arthritis was described more often in the control group (8.3 vs. 12.6%).

Table 2: **Characteristics of the study population**

	KORA lung-healthy control subjects	COPD grade 1	COPD grade 2	COPD grade 3	COPD grade 4	*p-value*
n	1,537	197	908	810	224	
age (years)	63.5 (11.8)	66.2 (8.6)	65.8 (8.4)	65.4 (7.9)	62.9 (7.5)	*< 0.0001* [a]
% age > 74 years	22.8	14.7	13.3	11.2	7.6	*< 0.0001* [b]
% age 65-74 years	21.5	48.7	45.2	45.3	33.0	
% age 55-64 years	28.2	26.9	31.8	34.3	45.5	
% age < 55 years	27.5	9.6	9.7	9.1	13.8	
% males	47.8	60.4	60.9	60.7	63.8	*< 0.0001* [b]
FEV_1 (liter)	3.05 (0.9)	2.61 (0.6)	1.85 (0.5)	1.18 (0.3)	0.74 (0.2)	*< 0.0001* [a]
FVC (liter)	3.91 (1.1)	4.09 (0.9)	3.29 (0.8)	2.63 (0.8)	2.02 (0.6)	*< 0.0001* [a]
FEV_1/FVC	78.2 (4.7)	64.2 (4.1)	56.8 (7.8)	46.3 (8.8)	38.6 (8.9)	*< 0.0001* [a]
% basic school education	56.5	49.2	53.7	61.5	60.7	*< 0.0001* [b]
% secondary school education	22.7	25.9	27.5	24.1	27.2	
% higher school education	20.8	24.9	18.7	14.4	12.1	
% smokers	11.5	31.5	30.3	23.3	16.1	*< 0.0001* [b]
% former smokers	39.0	61.4	64.1	71.9	78.6	
% never smokers	49.6	7.1	5.6	4.8	5.4	
BMI (kg/m^2) (nmiss=2)	28.2 (4.7)	26.8 (4.7)	27.6 (5.1)	26.5 (5.5)	24.4 (5.1)	*< 0.0001* [a]
% normal weight (18.5 ≤ BMI < 25)	24.3	36.6	31.1	38.0	50.5	*< 0.0001* [b]
% overweight (25 ≤ BMI < 30)	45.9	41.1	39.1	36.1	27.2	
% obese (BMI ≥ 30)	29.7	20.8	28.2	21.5	12.5	
% underweight (BMI < 18.5)	0.2	1.5	1.7	4.5	9.8	
% diabetes (nmiss=1)	10.4	9.6	13.7	13.6	12.1	*0.05* [b]
% stroke	4.0	4.1	4.3	5.1	2.7	*0.56* [b]
% myocardial infarction	5.0	6.6	9.0	10.3	5.8	*< 0.0001* [b]
% cancer	9.4	10.7	12.0	10.6	8.0	*0.24* [b]
% arthritis (nmiss=4)	12.6	10.2	8.3	8.8	4.9	*< 0.0002* [b]

Data are mean (standard deviation) or percentage
[a] p-value based on ANOVA [b] p-value based on Chi^2-test

Healthcare utilization, work absence and retirement

Table 3 shows unadjusted frequencies of healthcare utilization, work absence, and retirement. Compared with control subjects, physician visits in the last 3 months were increased by a factor of 2 in COPD patients independent of disease grade. The number of hospital days in the last 12 months and the number of prescribed pharmaceuticals was significantly higher in COPD patients and increased with disease grade. 35-72% of COPD patients in grades 1-4 were retired before the age of 65 years, whereas premature retirement was only reported by 15% of control subjects. The number of sick days reported by COPD patients for the last 12 months was increased by a factor of 3.7 to 5.6 compared with control subjects.

Appendix Table A2 shows the results of the negative binomial models. After adjusting for age, sex, and education in the basic model, all COPD grades were still associated with an increase in physician visits by approximately a factor of 2 compared with control subjects. Regarding hospitalization, the number of hospital days was increased by a factor of 1.8 in COPD grade 1 and increased monotonously to a factor of 7.6 in grade 4. Furthermore, COPD was associated with a higher intake of prescribed pharmaceuticals (factor of 2.2- 2.5 in early grades, 3.1-3.5 in higher grades). Factors for the number of sick days in the last year ranged from 3.6 in grade 2 to 6.0 in grade 4. All estimates were highly significant.

Table 3: **Unadjusted healthcare utilization, work absenteeism and resulting costs**

	KORA lung-healthy control subjects (n=1,537)	COPD grade 1 (n=197)	COPD grade 2 (n=908)	COPD grade 3 (n=810)	COPD grade 4 (n=224)	*p-value*
Healthcare utilization						
outpatient services (3 months)						
% user	66.4	92.9	94.6	95.8	96.0	*< 0.0001* [b]
total number of visits	3.0 (4.4)	5.9 (5.4)	6.0 (5.3)	6.1 (5.5)	5.4 (4.3)	*< 0.0001* [a]
general practitioner	1.4 (2.5)	1.9 (1.8)	2.3 (2.5)	2.4 (2.8)	2.2 (2.0)	*< 0.0001* [a]
specialist	1.6 (3.1)	4.0 (4.5)	3.8 (4.1)	3.7 (4.0)	3.3 (3.3)	*< 0.0001* [a]
inpatient services (12 months)						
% user (nmiss=24)	15.1	26.5	33.5	41.9	54.3	*< 0.0001* [b]
number of hospital days	1.5 (6.9)	2.7 (6.4)	3.9 (10.9)	7.0 (15.9)	11.4 (20.1)	*< 0.0001* [a]
prescribed medication (7 days)						
% user	68.3	95.4	97.4	99.5	99.1	*< 0.0001* [b]
number of prescribed drugs	2.1 (2.4)	4.7 (3.2)	5.4 (3.1)	6.6 (3.2)	7.0 (3.3)	*< 0.0001* [a]
Direct costs (12 months)						
outpatient costs	334 (547)	794 (772)	832 (756)	868 (802)	803 (683)	*< 0.0001* [a]
inpatient costs (nmiss=24)	882 (4,044)	1,589 (3,787)	2,322 (6,444)	4,139 (9,356)	6,699 (11,869)	*< 0.0001* [a]
medication costs	622 (2,032)	2,145 (4,747)	2,214 (3,130)	2,731 (2,998)	2,900 (2,959)	*< 0.0001* [a]
total direct costs (nmiss=24)	1,839 (4,793)	4,539 (7,002)	5,374 (7,534)	7,747 (10,336)	10,409 (12,662)	*< 0.0001* [a]

Work absenteeism (participants < 65 years)

	KORA control subjects (n=856)	COPD grade 1 (n=72)	COPD grade 2 (n=377)	COPD grade 3 (n=352)	COPD grade 4 (n=133)	
% retired	14.7	34.7	36.6	51.4	72.2	*< 0.0001* [b]
% employed	74.8	50.0	47.5	31.8	15.8	*< 0.0001* [b]

% with sick days (12 months) (nmiss=9)	44.1	75.0	71.1	70.6	76.2	*< 0.0001* [b]
number of sick days (12 months) (nmiss=10)	7.1 (22.0)	31.3 (54.6)	26.3 (44.3)	34.1 (53.9)	40.1 (71.0)	*< 0.0001* [a]
Indirect costs (12 months, participants < 65 years)						
sick days (nmiss=10)	936 (3,416)	2,774 (7,350)	2,170 (5,835)	1,889 (6,019)	1,123 (5,548)	*< 0.0001* [a]
premature retirement	5,465 (13,161)	12,891 (17,799)	13,590 (17,908)	19,090 (18,582)	26,798 (16,699)	*< 0.0001* [a]
total indirect costs (nmiss=10)	6,407 (13,222)	15,665 (17,272)	15,979 (17,229)	21,144 (17,560)	27,921 (15,779)	*< 0.0001* [a]

Data are mean (standard deviation) or percentage.

[a] p-value based on Kruskal-Wallis test [b] p-value based on Chi^2-test

Costs

Unadjusted annual healthcare costs were increased by a factor of 2.5 in COPD grade 1 as shown in ***Table 3***. This factor increased up to 5.7 in grade 4, with inpatient costs representing the largest driver of direct costs in all disease grades except grade 1. Indirect costs in participants aged <65 years were increased by a factor of 2.4 in early disease grades and by a factor of 4.4 in grade 4 with premature retirement as the major cost driver.

Table 4 shows the results of the regression analyses for costs. Adjusted factors of excess costs of COPD grades 1-4 range from 2.4 to 5.8 for direct costs and from 2.4 to 5.5 for indirect costs.

Adjusted mean annual costs for COPD grades 1-4 and for control subjects resulting from the basic model are illustrated in ***Table 5***. Corresponding direct excess costs compared with control subjects were €2,595 [1,770 – 3,678] for COPD grade 1, €3,475 [2,966 – 4,102] for grade 2, €5,955 [5,191 – 6,843] for grade 3, and €8,924 [7,190 – 10,853] for grade 4. For indirect costs, excess cost amounted to €8,621 [4,104 – 13,857] in COPD grade 1, €9,871 [7,692 – 12,777] in grade 2, €16,550 [13,743 – 20,457] in grade 3, and €27,658 [22,275 – 35,777] in grade 4. When following the friction cost approach for indirect costs in a sensitivity analysis, excess costs of COPD grades were highest in grade 1 (€707 [281 – 1,219]) and decreased with more advanced disease grades and an increasing share of premature retirement, as shown in ***Appendix Table A3***.

Table 4: **Effect of COPD on annual direct and indirect costs – basic and extended models**

		direct costs		*indirect costs*[1]	
Covariate		*basic model*	*extended model*	*basic model*	*extended model*
intercept		**1,135.15** [989-1,303]	**902.09** [750-1,085]	**2,264.97** [1,721-2,981]	**1,739.67** [1,167-2,592]
COPD	no COPD	**1.00**	**1.00**	**1.00**	**1.00**
	grade 1	**2.41** [1.96-2.95]	**2.60** [2.11-3.20]	**2.40** [1.39-4.16]	**2.62** [1.47-4.66]
	grade 2	**2.88** [2.57-3.23]	**3.10** [2.73-3.52]	**2.61** [1.97-3.45]	**2.72** [1.99-3.72]
	grade 3	**4.23** [3.75-4.76]	**4.61** [4.03-5.26]	**3.70** [2.78-4.92]	**3.58** [2.63-4.87]
	grade 4	**5.83** [4.81-7.08]	**6.60** [5.38-8.10]	**5.51** [3.61-8.41]	**5.61** [3.56-8.85]
age (years)	< 55	1.00	1.00	1.00	1.00
	55-64	**1.50** [1.31-1.72]	**1.32** [1.13-1.52]	**4.02** [3.02-5.05]	**3.88** [3.08-4.90]
	65-74	**1.81** [1.58-2.06]	**1.50** [1.30-1.73]	-	-
	> 74	**2.03** [1.74-2.37]	**1.62** [1.38-1.91]	-	-
sex	male	1.00	1.00	1.00	1.00
	female	1.00 [0.92-1.10]	**1.10** [1.00-1.21]	1.05 [0.85-1.30]	1.09 [0.87-1.36]
education	basic	1.00	1.00	1.00	1.00
	secondary	**1.15** [1.03-1.28]	**1.13** [1.02-1.26]	0.86 [0.66-1.11]	0.89 [0.68-1.15]
	higher	**0.87** [0.77-0.98]	0.92 [0.82-1.03]	**0.65** [0.49-0.86]	**0.66** [0.50-0.88]
smoking status	never smoker		1.00		1.00
	smoker		0.93 [0.79-1.09]		0.96 [0.68-1.36]
	former smoker		1.04 [0.91-1.18]		1.24 [0.93-1.67]
weight	normal weight		1.00		1.00
	underweight		1.01 [0.74-1.38]		1.18 [0.58-2.38]
	overweight		0.99 [0.89-1.10]		0.98 [0.75-1.28]
	obese		**1.19** [1.05-1.34]		1.31 [0.98-1.76]
comorbidities	diabetes		**1.43** [1.24-1.64]		1.08 [0.72-1.63]
	stroke		**1.74** [1.39-2.16]		1.46 [0.73-2.93]
	infarction		**1.44** [1.21-1.71]		1.20 [0.69-2.08]
	cancer		**1.77** [1.53-2.05]		1.42 [0.91-2.21]
	arthritis		**1.31** [1.13-1.51]		1.20 [0.82-1.75]

[1] for participants aged < 65 years only

Estimates with $p<0.05$ are printed in bold

Table 5: Adjusted mean annual direct and indirect costs and excess costs of COPD grades

	mean annual costs (€)	excess costs (€)
direct cost		
KORA control subjects	1,846 [1,614 – 2,088]	
COPD grade 1	4,441 [3,633 – 5,468]	2,595 [1,770 – 3,678]
COPD grade 2	5,321 [4,872 – 5,897]	3,475 [2,966 – 4,102]
COPD grade 3	7,801 [7,058 – 8,653]	5,955 [5,191 – 6,843]
COPD grade 4	10,770 [8,973 – 12,694]	8,924 [7,190 – 10,853]
indirect cost (human capital approach)[1]		
KORA control subjects	6,137 [5,261 – 7,029]	
COPD grade 1	14,758 [10,307 – 19,766]	8,621 [4,104 – 13,857]
COPD grade 2	16,008 [14,095 – 18,732]	9,871 [7,692 – 12,777]
COPD grade 3	22,687 [19,927 – 26,494]	16,550 [13,743 – 20,457]
COPD grade 4	33,795 [28,561 – 41,870]	27,658 [22,275 – 35,777]

[1] for participants aged < 65 years only

Contribution of comorbidities and interactions

When considering differences between groups regarding smoking status, BMI, and the five comorbidities in the extended models, the effects of COPD grades hardly changed or even increased slightly, as shown in ***Table 4 and Appendix Table A2***. The comorbid conditions had additional effects on direct and indirect costs, but these effects were much smaller than the effects of COPD. Statistically significant interactions between COPD grades and comorbidities were not observed. Effect estimates of COPD grades were virtually unchanged when considering interactions between COPD and comorbidities.

Table 6 shows the effects of comorbid conditions on direct and indirect cost stratified for COPD patients and control subjects. For direct costs, effect estimates for all comorbidities considered were slightly higher for control subjects, except for stroke. As to indirect costs, comorbidities in COPD patients do not seem to have additional effects. In all, the strengths and significance of association only differed slightly between cases and control subjects.

When stratifying the analyses for direct costs according to age, both the effects of COPD grades on direct cost as well as the effects of comorbidities except diabetes were stronger in the younger age group, as shown in ***Appendix Table A4***. Estimates for comorbidities in the younger age group were still considerably smaller than the estimates of COPD grades.

Table 6: Association of selected comorbidities with annual direct and indirect cost in COPD cases and control subjects

	direct costs		***indirect costs***[1]	
Covariate	*COPD cases*	*KORA control subjects*	*COPD cases*	*KORA control subjects*
diabetes	**1.45** [1.28-1.64]	**1.40** [1.05-1.87]	0.99 [0.63-1.54]	1.42 [0.62-3.23]
stroke	**1.67** [1.37-2.04]	**1.59** [1.01-2.50]	1.18 [0.57-2.41]	1.64 [0.38-7.04]
infarction	**1.27** [1.09-1.46]	**1.83** [1.22-2.76]	1.09 [0.63-1.90]	1.72 [0.46-6.45]
cancer	**1.31** [1.15-1.49]	**2.45** [1.81-3.31]	1.08 [0.63-1.86]	1.53 [0.75-3.10]
arthritis	0.97 [0.84-1.12]	**1.63** [1.25-2.12]	1.04 [0.63-1.73]	1.29 [0.73-2.31]
obesity	1.06 [0.95-1.19]	1.17 [0.92-1.49]	0.96 [0.67-1.36]	**1.61** [1.01-2.56]

[1] for participants aged < 65 years only

Estimates with p<0.05 are printed in bold

Discussion

This study estimated the actual costs of COPD patients in different grades compared with population-based, lung-healthy control subjects. Even in mild disease grades, COPD was associated with significantly higher direct and indirect costs. Adjusting for major comorbid conditions did not decrease the effect of COPD and the difference between COPD patients and control subjects, but comorbidities added to the effect of COPD on costs. Indirect costs were shown to be substantial, exceeding direct excess costs by up to a factor of 3.

When comparing our results with previously published work, a high variation in COPD cost estimates is apparent. A systematic literature review on German cost of COPD studies found a range of €1,212 to €3,492 per COPD case and year (price year 2010). Medication was identified as the most important component of direct costs [9]. This was also confirmed in our study for mild COPD grades, whereas hospitalization was the main cost driver in higher grades. One of the studies included in this review compared population-based COPD cases with mild-to-moderate disease and control subjects without COPD and found much lower direct costs than our study [29]. Direct annual costs of COPD cases in grade 1 and control subjects did not differ, but increased by 54% in COPD grade 2+, resulting in €990 annual excess costs of grade 2+ (price year 2008). Taking into account cost differences between COPD patients with and without physician diagnosis [30], the fact that no excess costs of mild COPD grades were found in this study may be because 75% of COPD cases considered were previously undiagnosed [29].

Regarding the effect of comorbidities, our study found an association between comorbid conditions and direct costs, but excess costs of COPD were mainly due to the lung disease and its severity.

In a population-based setting in Sweden, Jansson et al. investigated direct healthcare costs resulting from respiratory and non-respiratory conditions in COPD patients and control subjects. Adjusted annual total costs were increased by 33% in COPD patients compared with control subjects [31]. Non-respiratory diseases and especially hospitalization for non-respiratory conditions were identified as the main cost drivers, with the latter accounting for 46% of the total costs of COPD patients.

Previous studies reported larger effects of COPD comorbidities on healthcare costs, e.g. a recent systematic literature review on the excess cost of COPD comorbidities reports on average a doubling in healthcare costs in the comorbid case [13]. Based on administrative data from a large health insurance provider in Canada, Gershon et al. found that COPD patients had adjusted rates of hospital and ambulatory care visits that were 63% or 48% higher than those without COPD [32]. Most of the excess utilization of in- and outpatient services was attributed to comorbidities, which could not be shown in our study. Ford et al. [33] estimated national US COPD-attributable direct and indirect costs in 2010 based on survey data. Direct excess costs per COPD case were about $4,000 when adjusting for demographic factors only and decreased to $3,100 when considering a number of medical conditions in addition and to $520 when also controlling for COPD-associated medical conditions. Although comorbidities added to direct cost in our study, the excess costs of COPD grades did not decrease when considering comorbidities as possible confounders. This finding might be explained by the survey method used for comorbidities that did not consider the severity of disease: a history of stroke or cancer in the past might be less associated with healthcare utilization than an actual COPD diagnosis that has led to participation in a COPD study. As to indirect cost, the restriction to the age group aged < 65 years might explain the non-significant contribution of comorbidities.

In relation to indirect cost, previous studies have reported divergent results depending on the population under study. Erdal et al. compared hospital-recruited COPD patients, population-based COPD cases and control subjects without COPD in Norway and reported employment rates of 31%, 55%, and 87% respectively [34]. Excess days of productivity losses were 5.8 in population-based patients and 331 for hospital-recruited COPD patients compared with control subjects. Exacerbations of respiratory symptoms and comorbidities explained most of the productivity losses of populations-based COPD cases and a large part of the losses of hospital-recruited COPD cases. For the US, a review by Patel et al. reported a workforce participation rate of 56-69% in subjects with COPD and 65-77% in individuals without COPD, depending on the population considered [35].

In general, observed cost differences between studies are large. In addition to varying underlying populations under consideration, the comparison and transferability of cost results between countries is hindered by different national treatment patterns, labor markets, social security systems, and price structures.

The strength of this study is based on its large sample size and the availability of a control group. As the COSYCONET cohort also comprises more advanced COPD grades in sufficient number, we had enough power to detect differences between all COPD grades. Previous population-based studies often suffered from a lack of severe or very severe COPD cases and could not perform separate analyses for these groups. Besides a comprehensive spectrum of COPD grades, detailed clinical information, which is often lacking in claims data, enabled us to provide grade-dependent cost data. Furthermore, as a result of the broad inclusion criteria of COSYCONET, our results may be more generalizable than those from clinical COPD trials. Therefore, we think that our study provides recent and comprehensive evidence of the economic impact of COPD needed for rational decision making.

However, our analysis is subject to several limitations. Besides regional restriction of the control group, possible selection bias in all studies considered might have led to an under- or overestimation of excess costs of COPD and limits the potential for external validation. It has to be kept in mind that our results refer to a diagnosed COPD population only. Therefore, results cannot be transferred to previously undiagnosed COPD cases that are often found in population-based studies.

Furthermore, self-reported information on healthcare utilization and work absence is prone to recall bias. The study design tried to minimize the possibility of recall bias by considering different recall periods for different health services. This has been shown to be a valid approach [36]. Although estimates of healthcare utilization in surveys tend to underestimate the true utilization [37], it is reasonable to assume that excess costs should not be affected as recall bias might have occurred in an equivalent magnitude in the COPD and control groups.

Additional healthcare services such as nursing, medical aids and appliances, as well as costs of premature death could not be considered. This has probably led to an underestimation of the real cost of COPD to society. Medication use was assessed for the last week and extrapolated to 12 months. As participants in the COPD cohort had to be free of moderate or severe exacerbations within the last 4 weeks before participation, exacerbation-related medication costs might have been underestimated. Importantly, very high excess costs of COPD could be explained in part by the occurrence of further comorbidities, which could not be compared between COPD cases and control subjects because of data limitations. This restriction could have led to an overestimation of COPD-attributable costs. However, the comorbid conditions considered in this analysis have been shown to be important in terms of prevalence and clinical relevance [38]. Comorbidities considered in our study might be less acute and more a history of conditions. The effects of recent comorbid events on costs might be more significant. Furthermore, the definition of the control group was based on pre-bronchodilator spirometry. This might have resulted in a slightly healthier control group than one based on post-bronchodilator spirometry. However, as we aimed to compare the COPD cohort with a lung-healthy control group, this approach might be reasonable because we expect that we have excluded mainly additional KORA participants suffering from asthma.

COPD patients with A1ATD were excluded from this cost analysis as they were overrepresented in the COSYCONET cohort. Both direct medical costs as well as indirect costs were considerably higher in this patient group, as shown in ***Appendix Table A5***. Excess direct costs of A1ATD patients exceeded excess direct costs of COPD patients without A1ATD by a factor of 3.8 to 8.0.

Nevertheless, our study provides real-world and up-to-date cost estimates of COPD in Germany that are needed to raise COPD awareness. Furthermore, health economic models for cost-effectiveness analyses of preventive or therapeutic interventions rely on valid cost parameters. Previous population-based studies included mainly early grades of COPD and did not have a sufficient number of cases from the higher COPD grades. Therefore, statistical power was often not sufficient to find differences for costs in advanced disease.

Conclusions

In conclusion, our results demonstrate that COPD is associated with higher direct and indirect cost than previously estimated for Germany, even in mild disease grades. From a societal perspective, besides COPD prevention efforts, interventions focusing on improving the ability to work in younger COPD patients would be beneficial in order to reduce the significant costs of COPD.

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Conflict of interest

CV reports personal fees from the pharmaceutical companies Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Janssen, Mundipharma, Novartis, Takeda, Cipla, and grants and personal fees from Grifols outside the submitted work.

All other authors declare no conflicts of interest.

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