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Effect of BMI on health care expenditures stratified by COPD GOLD severity grades: Results from the LQ-DMP study

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is characterized by persistent respiratory symptoms and airflow limitation, which is progressive and not fully reversible. In patients with COPD, body mass index (BMI) is an important parameter associated with health outcomes, e.g. mortality and health-related quality of life. However, so far no study evaluated the association of BMI and health care expenditures across different COPD severity grades.We used claims data and documentation data of a Disease Management Program (DMP) from a statutory health insurance fund (AOK Bayern). Patients were excluded if they had less than 4 observations in the 8 years observational period. Generalized additive mixed models with smooth functions were used to evaluate the association between BMI and health care expenditures, stratified by severity of COPD, indicated by GOLD grades 1–4.We included 30,682 patients with overall 188,725 observations. In GOLD grades 1–3 we found an u-shaped relation of BMI and expenditures, where patients with a BMI of 30 or slightly above had the lowest and underweight and obese patients had the highest health care expenditures. Contrarily, in GOLD grade 4 we found an almost linear decline of health care expenditures with increasing BMI.In terms of expenditures, the often reported obesity paradox in patients with COPD was clearly reflected in GOLD grade 4, while in all other severity grades underweight as well as severely obese patients caused the highest health care expenditures. Reduction of obesity may thus reduce health care expenditures in GOLD grades 1–3.

1. Background

Chronic Obstructive Pulmonary Disease (COPD) is globally a major cause of chronic morbidity and mortality [1]. The public health challenge of COPD is projected to increase in coming decades because of continued exposure to risk factors and aging of the population [2]. More than 50% of patients with COPD have at least one comorbidity rendering multi-morbidity an important management issue [3]. Obesity is a common comorbidity of COPD, which contributes to patients respiratory symptoms and reduces exercise capacity [4–6]. The propensity of obesity cause unfavourable outcomes in survival [7,8], health-related quality of life [9,10], and health care expenditures [11,12] in the general population. Paradoxically, cohort studies in patients with COPD have found that compared to normal weight ($18.5 \leq$ BMI < 25) - overweight ($25 \leq$ BMI < 30) and obesity ($30 \leq$ BMI < 35) are associated with reduced mortality [13–19], higher health-related quality of life [4,20–24] and fewer exacerbations [25–29]. This association was not consistently observed in extremely obese (BMI ≥ 35).

Furthermore, COPD is also associated with substantial expenditures. In the European Union, the direct health care expenditures of COPD are about 3% (€38.6 billion) of the total health care budget [30]. Mean annual health care expenditures per patient with COPD increase with disease severity, from €3809 in Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 1 to €8309 in grade 4 [31]. In contrast the BMI decreases constantly with increasing GOLD grades [31–33]. So far there is only a limited amount of studies measuring the effect of BMI on health care expenditures in patients with COPD [26,31–40]. This previous evidence was, not stratified for GOLD grades. Neglecting the opposing effects of health care expenditures and BMI in GOLD grades may overlay the effects of BMI on health care expenditures. Therefore,

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the aim of this study was to estimate the impact of BMI on health care expenditures in patients with COPD stratified by GOLD grades.

2. Methods

2.1. Data

The analysis was based on pseudonymized claims data routinely documented for participants of the structured German Disease Management Program (DMP) for COPD, offered by AOK Bayern, covering the years 2009–2018. The AOK Bayern is a large regional health insurance fund, which is the fourth biggest statutory health insurance in Germany with 4.5 Million insured persons reflecting a market share of more approximately 6% in Germany and 40% in Bavaria. The ethics committee of the Ludwig-Maximilians-Universität München approved the study (vote-no. 17–358). Participants provided written informed consent at the time of inclusion in the DMP.

2.2. Disease Management Programs

DMPs, through the implementation of evidence-based clinical practice, appears an intuitively appealing way to improve quality, and reduce health care expenditures in patients with chronic conditions [41,42]. The enrollment in the DMP is conducted by physicians. Physicians need to fulfill certain requirements (e.g. training sessions) to be entitled to conduct a DMP. In the DMP COPD physicians were only allowed to enroll patients if the Tiffeneau-Index (forced expiratory pressure in 1 s (FEV_1)/forced vital capacity (FVC)) was <70% post-bronchodilator airway obstruction spirometry and.

a) the FEV_1 was <80% of the reference value or
b) an increase in FEV_1 by less than 15% and/or by less than 200 ml in 10 min after inhalation of a short-acting beta-2-sympathomimetic or 30 min after inhalation of a short-acting anticholinergic or
c) an increase in FEV_1 by less than 15% and/or by less than 200 ml after at least 14 days of systematic glucocorticosteroids or at least 28 days of inhaled glucocorticosteroids in a stable disease episode and evidence of airway resistance elevation or pulmonary hyperinflation or gas exchange disorder in patients with FEV_1/FVC > 70% and a radiographic examination of the thoracic organs that has ruled out another symptom-explaining disease.

2.3. Study population

The statutory health insurance data include the years 2009–2018. All individuals enrolled in the DMP COPD (AOK Curaplan) on December 31, 2016 were the basis for our analysis. The calculation of FEV_1 percentage predicted [43] was based on FEV_1 measurements till December 31, 2018. The routinely FEV_1 measurements in the DMP COPD are conducted pre-bronchodilator airway obstruction. The last FEV_1 measurement of each patient was the end of the observation period. Annual periods were defined backwards from the last FEV_1 measurement. For each patient, annual periods were excluded if there were any missing values or implausible measures in covariates, e.g. height (< 90 cm), weight (< 20 kg), BMI (BMI < 10 or BMI > 50), FEV_1 (FEV_1 < 0.2l or FEV_1 > 6.5l), or FEV_1 percentage predicted (FEV_1 percentage predicted < 10% or FEV_1 percentage predicted > 150%). Observation years were also excluded if the persons were not insured the complete year. Finally, only patients with at least four observation years in the last 8 years were included in the present analysis. For the classification of GOLD grades, FEV_1 percentage predicted values were calculated based on reference values from the Global Lung Function Initiative (grade 1: $FEV_1 \geq 80\%$; grade 2: $50\% \leq FEV_1 < 80\%$; grade 3: $30\% \leq FEV_1 < 50\%$; grade 4: $FEV_1 < 30\%$) [43].

2.4. Health care expenditures

Overall health care expenditures from the perspective of a statutory health insurance fund (third party payer) included inpatient- and outpatient services, medication, rehabilitation, aids and remedies, and travel expenses. Health care expenditures for inpatient services were based on Diagnoses Related Groups. Billing of outpatient services were based on EBM, family doctor-centered health care, and integrated care. Lump-sum payments for physicians were considered in the period they were paid, even when they partially covered the period before or after. Medication expenditures were based on pharmacy sales prices (including discount agreements). Rehabilitation were based on rehabilitation invoices. If the ability to work is to be restored by the rehabilitation, the pension insurance is usually the funding agency, these cases are not included in our analysis. Aids and remedies were based on invoices of health care supply stores, and travel expenses were based on public transport tickets, invoices of taxis and a fixed fee per kilometer (by usage of private car). All health care expenditures were inflated to the year 2018, using the inflation rate as reported for Germany by the Organisation for Economic Co-operation and Development.

2.5. Covariates and comorbidities

Patients' characteristics, socio-economic variables, and comorbidities were assessed based on claims data and DMP documentation forms. Characteristics were patients' age group (<55; 55–64; 65–74; >74), sex, smoking status (smoker or non-smoker), body mass index (BMI = kg/m^2), FEV_1 percentage predicted [43], DMP interruption, and the year of observation (0 to −7). The socio-economic variable annual income was based on annual gross pay, retirement income, and pensions. For comorbidities we used the Charlson comorbidity index [44] including COPD. Additionally, pulmonary emphysema (International Statistical Classification of Disease and Related Health Problems (ICD-10): J43 and J684) were considered [45,46]. For each comorbidity a minimum of one inpatient or two secured outpatient diagnoses in different quarters were required. These requirements were derived from the German morbidity-based risk adjustment scheme [47]. Further we included the accumulated number of defined daily doses (DDDs) for corticosteroids as they tend to increase the BMI [48]. The accumulated number of DDDs were calculated by multiplying the number of corticosteroid prescriptions (the anatomical therapeutic chemical (ATC) classification system code (H02) with the DDDs per prescription. DDDs were supplied by the scientific institute of the AOK ('WIdO') based on a German adaption of the WHO database. The proportion of days covered (PDC) rates, provided as additional information in the descriptive statistics (Table 1), for LABA (ATC: R03AC12, R03AC13, R03AC18, R03AC19), LABA + ICS (ATC: R03AK06, R03AK07, R03AK08, R03AK10, R03AL11), ICS (ATC: R03BA01, R03BA02, R03BA04, R03BA05, R03BA08), LAMA (R03BB04, R03BB05, R03BB06, R03BB07), short acting bronchodilators (ATC: R03AC02, R03AC03, R03AC04, R03AC06, R03BB01, R03AK03, R03AK04), long acting bronchodilators (ATC: R03AC12, R03AC13, R03AC16, R03AC18, R03BB04, R03AK06, R03AK07) and oral bronchodilators (ATC: R03CC02, R03CC03, R03CC04, R03CC05, R03CC08, R03CC09, R03CC12, R03CC91, R03DA04, R03DA05) are based on the total number of DDDs per prescription, divided by the number of days under observation. In case of hospitalizations, it was assumed that drugs were supplied by the hospital and thus the number of days that needed to be covered was reduced by the length of hospital stays.

Table 1
Characteristics of study population.

	GOLD grade 1	GOLD grade 2	GOLD grade 3	GOLD grade 4	p-value
No. of observations	58,067 (30.77%)	88,807 (47.06%)	35,178 (18.64%)	6,673 (3.54%)	
Age (years)	68.28 [68.18–68.37]	67.90 [67.83–67.97]	67.69 [67.59–67.79]	64.86 [64.65–65.08]	< 0.0001
Age > 74 years	19,518 (33.61%)	27,033 (30.44%)	9228 (26.23%)	1037 (15.54%)	< 0.0001
Age 65–74 years	18,251 (31.43%)	29,213 (32.89%)	12,701 (36.10%)	2342 (35.10%)	
Age 55–64 years	12,997 (22.38%)	22,223 (25.02%)	10,117 (28.76%)	2464 (36.92%)	
Age < 55	7301 (12.57%)	10,338 (11.64%)	3132 (8.90%)	830 (12.44%)	
Female	30,470 (52.47%)	40,141 (45.20%)	13,024 (37.02%)	2128 (31.89%)	< 0.0001
Income < €5.000	15,645 (26.94%)	23,628 (26.61%)	8706 (24.75%)	1671 (25.04%)	< 0.0001
Income€5,000 < €10,000	19,002 (32.72%)	29,554 (33.28%)	12,827 (36.46%)	2564 (38.42%)	
Income €10,000 <€15,000	9773 (16.83%)	15,349 (17.28%)	6140 (17.45%)	1073 (16.08%)	
Income €15,000 < €20,000	4127 (7.11%)	5956 (6.71%)	2273 (6.46%)	383 (5.74%)	
Income €20,000 < €30,000	4411 (7.60%)	6573 (7.40%)	2425 (6.89%)	467 (7.00%)	
income €30,000 < €50,000	4427 (7.62%)	6819 (7.68%)	2494 (7.09%)	435 (6.52%)	
income ≥ €50.000	682 (1.17%)	928 (1.04%)	313 (0.89%)	80 (1.20%)	
Smokers	15,470 (26.65%)	31,034 (34.96%)	13,636 (38.78%)	2579 (38.68%)	< 0.0001
FEV_1 percentage predicted	96.33 [96.22–96.44]	65.30 [65.24–65.35]	41.49 [41.43–41.55]	24.70 [24.60–24.80]	< 0.0001
Pulmonary emphysema	3410 (5.87%)	9678 (10.90%)	8115 (23.07%)	2398 (35.94%)	< 0.0001
Cortisone DDD	15.29 [14.80–15.78]	22.72 [22.22–23.21]	43.84 [42.72–44.97]	77.41 [73.87–80.94]	< 0.0001
Charlson index	3.26 [3.24–3.28]	3.37 [3.35–3.38]	3.29 [3.26–3.32]	3.06 [3.00–3.12]	< 0.0001
DMP interruption	6209 (10.69%)	10,479 (11.80%)	3981 (11.32%)	753 (11.28%)	< 0.0001
BMI (kg/m^2)	29.21 [29.17–29.26]	29.13 [29.10–29.26]	27.81 [27.76–27.87]	26.17 [26.04–26.30]	< 0.0001
Normal weight (18.5 ≤ BMI < 25)	11,863 (20.43%)	19,935 (22.45%)	10,668 (30.33%)	2698 (40.43%)	< 0.0001
Overweight (25 ≤ BMI < 30)	22,636 (38.98%)	33,019 (37.18%)	12,652 (35.97%)	2124 (31.83%)	
Obese (BMI ≥ 30)	22,236 (40.02%)	34,954 (39.36%)	10,958 (31.15%)	1484 (22.24%)	
Underweight (BMI < 18.5)	332 (0.57%)	899 (1.01%)	900 (2.56%)	367 (5.50%)	
Total health care expenditures	€3430 [€3378-€3482]	€3931 [€3884-€3978]	€5008 [€4904-€5112]	€7544 [€7221-€7867]	< 0.0001
LABA	4275 (7.36%)	9982 (11.24%)	5298 (15.06%)	1025 (15.36%)	< 0.0001
LABA PDC-rate	3.15 [3.03–3.26]	5.07 [4.95–5.19]	7.63 [7.40–7.87]	9.20 [8.58–9.82]	< 0.0001
LABA + ICS	5169 (8.90%)	9788 (11.02%)	5112 (14.53%)	1161 (17.40%)	< 0.0001
LABA + ICS PDC-rate	4.44 [4.30–4.58]	5.97 [5.84–6.11]	8.62 [8.37–8.88]	11.34 [10.66–12.02]	< 0.0001

	GOLD grade 1	GOLD grade 2	GOLD grade 3	GOLD grade 4	p-value
ICS	6983 (12.03%)	11,505 (12.96%)	6180 (17.57%)	1469 (22.01%)	< 0.0001
ICS PDC-rate	4.60 [4.47–4.74]	5.69 [5.57–5.81]	8.80 [8.55–9.05]	12.66 [11.97–13.35]	< 0.0001
LAMA	9415 (16.21%)	25,203 (28.38%)	15,779 (44.85%)	3638 (54.52%)	< 0.0001
LAMA PDC-rate	9.96 [9.75–10.18]	17.69 [17.48–17.91]	30.23 [29.81–30.65]	39.81 [38.77–40.84]	< 0.0001
Short acting bronchodilators	14,770 (25.44%)	32,777 (36.91%)	19,410 (55.18%)	4538 (68.01%)	< 0.0001
Short acting bronchodilators PDC-rate	6.83 [6.68–6.99]	11.64 [11.48–141.80]	24.11 [23.75–24.47]	38.90 [37.91–39.88]	< 0.0001
Long acting bronchodilators	16,535 (28.48%)	37,526 (42.26%)	20,419 (58.04%)	4451 (66.70%)	< 0.0001
Long acting bronchodilators PDC-rate	16.51 [16.25–16.77]	26.54 [26.29–26.79]	41.47 [41.02–41.93]	52.62 [51.54–53.70]	< 0.0001
Oral bronchodilators	3114 (5.36%)	6284 (7.08%)	4356 (12.38%)	1181 (17.70%)	< 0.0001
Oral bronchodilators PDC-rate	3.13 [3.01–3.26]	4.21 [4.09–4.33]	7.84 [7.58–8.10]	11.74 [11.03–12.46]	< 0.0001

Percentage = (); Standard deviation = [].

2.6. Statistical analysis

Characteristics of patients with COPD in GOLD grades 1–4 were compared using analysis of variance (ANOVA) for continuous variables and Chi^2-tests for categorical variables. Unadjusted health care expenditures, including all time periods, were compared by non-parametric Kruskal-Wallis tests.

Stratified by GOLD grades 1–4, we estimated the effect of BMI, on health care expenditures and each cost category with a generalized additive mixed model (GAMM) with a smoothing function of BMI. As a sensitivity analysis we also conducted a not stratified analysis of the effect of BMI on health care expenditures. A GAMM is a generalized linear mixed model in which the linear predictor depends linearly on unknown smooth functions of the covariates of interest. For the smooth function, penalized regression spline type smoothers of moderate rank are used. For estimation purposes, the generalized component of each smooth is treated as a random effect term, while the unpenalized component is treated as fixed [49,50].

The models included age group, sex, income, smoking status, FEV_1 percentage predicted, pulmonary emphysema, corticosteroid DDDs, Charlson index, DMP interruption and year of observation, besides the spline for BMI, as covariates.

The GAMM was estimated using the statistical software R (version 3.5.1) and applying the gamm4 package [49].

3. Results

3.1. Study population

The selection of the study population is described in Fig. 1. The data set consisted of 50,801 patients who were enrolled in the DMP COPD. After applying the exclusion criteria, a study population of 30,682 patients with a total of 188,725 observations remained.

Table 1 gives the characteristics of the observational years of the study population by GOLD grades – 77.83% of 188,725 patient observation years were in grade 1 and 2. Direct comparison of the GOLD grades shows that the mean age ranged from 64.9 years in grade 4–68.3 years in grade 1. The percentage of women declined over GOLD grades from 52.5% in grade 1–31.9% in grade 4. More patients in higher disease grades were in lower income groups. The percentage of current smokers was higher in more severe grades. The Charlson comorbidity index was highest in GOLD grade 2 with 3.37, followed by grade 3 with 3.29, grade 1 with 3.26, and grade 4 with 3.06. For pulmonary emphysema the prevalence increased steadily from 5.9% in grade 1–35.9% in grade 4. Similarly, mean DDDs of corticosteroids increased from 15.3 in grade 1 to 77.4 in grade 4. The percentage of DMP interruptions was lowest in grade 1 with 10.7% and highest in grade two with 11.8%. There is also a decline in BMI from 29.2 in grade 1 to 26.2 in grade 4. The total unadjusted health care expenditures increased from €3430 in grade 1 to €7544 in grade 4.

3.2. Health care expenditures

The results of the GAMM on health care expenditures, stratified by GOLD grade, are presented in Table 2 and Fig. 2. Considered the effect of BMI in the different GOLD grades on health care expenditures patients with a BMI around 30 or slightly above had the lowest health care expenditures in grade 1–3, while the health care expenditures steadily decreased with increasing BMI in grade 4. The direction of the estimates and significance levels of the covariates were quite similar in the models for the four different GOLD grades. Our data indicates that increasing age reduced total health care expenditures, and females incurred higher health care expenditures than males, this is statistically significant in GOLD grade 2–4. Even if it was mostly not statistically significant, it appeared that there was an inverse U-shaped relationship between income and health care expenditures. Smokers caused lower health care expenditures than non-smokers, and a higher FEV_1 percentage predicted, within a GOLD grade, decreased health care expenditures, both effects were statistically significant in grade 2 and 3. The presence of pulmonary emphysema, a higher Charlson index, and a higher DDD for corticosteroids increased health care expenditures statistically significant in every GOLD grade. A DMP interruption increased health care expenditures in all GOLD grades, but statistically significant only in grade 1–3. No clear trend of the influence of year of observation on health care expenditures was found, generally health care expenditures increased over time, but this was statistically significant only for GOLD grade 1, 3, and 4.

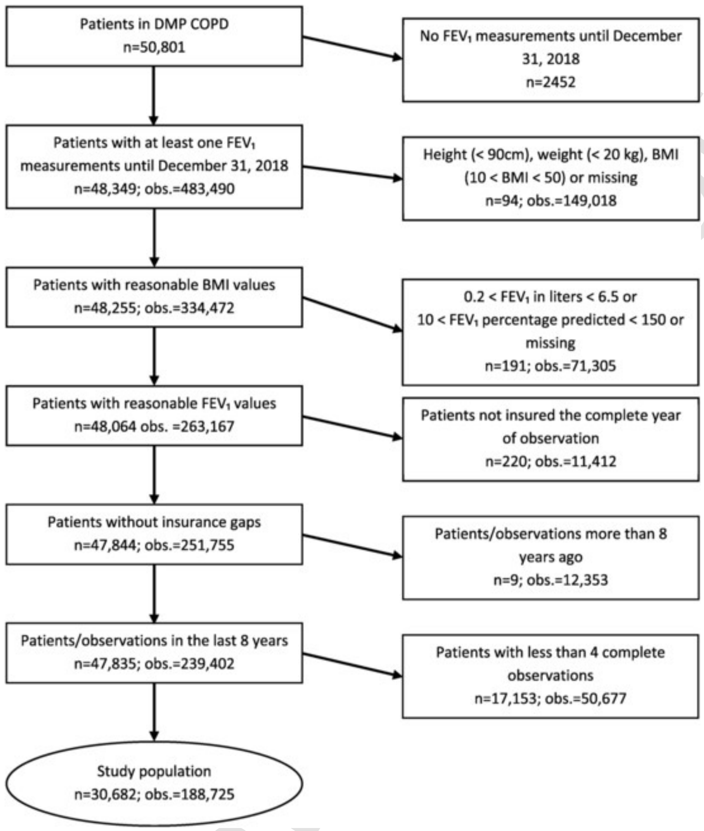

Fig. 1. Patient/observation selection.

For outpatient expenditures (appendix table 1 and Fig. 1), in GOLD grade 1 there was no effect of BMI on expenditures, in grade 2 expenditures slowly decreased with increasing BMI, while in grade 3 a marginal increase and in grade 4 a doubling of expenditures with increased BMI were observed.

For medication expenditures (appendix table 2 and Fig. 2) the shape of the curves was somehow similar to the total health care expenditures. The expenditures for medication were lowest at a BMI between 25 and 30 in GOLD grade 1, 2 and 3 and a declined with increasing BMI in grade 4.

The absolute level of inpatient expenditures increased with increasing GOLD grade (appendix table 3 and Fig. 3). While for grade 1 the minimum expenditures were at a BMI around 30 to 35, in grade 2–4 the hospital expenditures almost linearly declined with increasing BMI.

The level of expenditures for rehabilitation (appendix table 4 and Fig. 4) was higher in GOLD grade 1 and 2 than in grade 3 and 4. In grade 1 and 2 there seemed to be almost no effect of BMI on expenditures, besides a marginal increase with increasing BMI from 30 on. In grade 3 and 4 there was a linear decrease of expenditures with increasing BMI which is steeper in grade 4.

The level of expenditures for remedy and aids (appendix table 5 and Fig. 5) increased with increasing disease severity. In GOLD grade 1–3 the minimum expenditures were approximately at a BMI of 25, the expenditures were twice as high at a BMI of 50. In contrast to grade 4 were the expenditures linearly increased with an increasing BMI.

The level of travel expenditures (appendix table 6 and Fig. 6) was on a similar but lower level in GOLD grade 1–3 compared to grade 4. The expenditures were almost linearly decreasing with increasing BMI in every grade.

The same analysis we did for total health care expenditures and every single cost category could stratified for sex and age in an online appendix (Table A1 to A7 and figure A1 to A7 stratified for sex and Table B1 to B7 and figure B1 to B7 stratified for age groups).

4. Discussion

4.1. Main results

This study investigated the effect of BMI on overall health care expenditures in patients enrolled in a structured German DMP for COPD in different GOLD severity grades using real world data. In GOLD grade 1–3 patients with a BMI around 30 and slightly above had the lowest health care expenditures, in grade 4, however, we found an almost linear decline of health care expenditures with increasing BMI.

Table 2
Effect of BMI on total health care expenditures.

		GOLD grade 1			GOLD grade 2			GOLD grade 3			GOLD grade 4		
		β	s.e.	P-value	β	s.e.	P-value	β	s.e.	P-value	β	s.e.	P-value
(Intercept)		790.47	239.17	<0.0001	1617.76	242.96	<0.0001	3738.65	496.16	<0.0001	2267.94	1246.24	0.0688
BMI (smooth)		**See Fig. 1**		**0.0014**	**See Fig. 1**		**<0.0001**	**See Fig. 1**		**<0.0001**	See Fig. 1		0.0509
Age	**55 < 65**	−51.11	107.21	0.6336	−118.50	99.30	0.2327	−368.89	221.79	0.0963	−460.86	567.34	0.4167
	65 < 75	−38.28	116.66	0.7427	−181.21	109.85	0.0990	−470.69	244.45	0.0542	**−1242.45**	**633.43**	**0.0499**
	≥ 75	28.17	124.97	0.8217	**−381.79**	**120.05**	**0.0015**	**−1246.90**	**270.33**	**<0.0001**	**−2752.49**	**749.66**	**0.0002**
Sex	**male**	−119.65	72.50	0.0989	**−182.68**	**70.65**	**0.0097**	**−328.61**	**156.09**	**0.0353**	**−1236.43**	**434.97**	**0.0045**
Income	**€5,000 < €10,000**	−78.10	82.27	0.3425	122.27	76.33	0.1092	−234.40	160.68	0.1446	203.29	462.84	0.6605
	€10,000 <€15,000	33.78	95.61	0.7238	99.50	88.46	0.2607	245.90	188.60	0.1923	807.04	551.78	0.1436
	€15,000 < €20,000	27.86	121.52	0.8186	81.98	112.72	0.4670	261.95	242.76	0.2806	−284.15	735.28	0.6992
	€20,000 < €30,000	**−396.59**	**123.10**	**0.0013**	−109.63	113.16	0.3326	−403.96	244.29	0.0982	−787.32	715.30	0.2711
	€30,000 < €50,000	**−544.70**	**135.74**	**<0.0001**	**−488.54**	**124.50**	**<0.0001**	−462.28	263.49	0.0794	−228.37	761.74	0.7643
	≥ €50.000	**−621.76**	**280.01**	**0.0264**	−164.84	269.96	0.5415	−236.82	600.77	0.6934	389.91	1579.94	0.8051
Smoker	yes	−99.23	78.25	0.2048	**−199.68**	**68.42**	**0.0035**	**−334.62**	**137.20**	**0.0147**	−655.74	378.46	0.0832
FEV_1 percentage predicted		3.40	2.01	0.0908	**−12.63**	**2.95**	**<0.0001**	**−41.33**	**9.24**	**<0.0001**	25.64	38.21	0.5023
Pulmonary emphysema	yes	**1086.32**	**130.89**	**<0.0001**	**838.12**	**92.90**	**<0.0001**	**1202.02**	**148.12**	**<0.0001**	**1807.26**	**376.63**	**<0.0001**
Cortico-steroid DDD	yes	**12.60**	**0.46**	**<0.0001**	**9.97**	**0.34**	**<0.0001**	**10.87**	**0.51**	**<0.0001**	**15.20**	**1.14**	**<0.0001**
Charlson index	yes	**736.30**	**13.04**	**<0.0001**	**928.88**	**11.99**	**<0.0001**	**1147.67**	**25.40**	**<0.0001**	**1501.69**	**77.68**	**<0.0001**
DMP interruption	yes	**454.18**	**81.60**	**<0.0001**	**533.06**	**69.91**	**<0.0001**	**384.42**	**148.54**	**0.0097**	837.03	467.36	0.0733
Year of observation	**−1**	−139.61	94.56	0.1399	−117.14	81.08	0.1485	**−713.98**	**162.44**	**<0.0001**	−74.87	471.64	0.8739
	−2	**−242.53**	**94.85**	**0.0106**	4.87	81.11	0.9521	**−669.91**	**165.31**	**<0.0001**	108.77	495.37	0.8262
	−3	**−196.05**	**95.32**	**0.0397**	9.48	82.14	0.9081	**−633.96**	**168.85**	**0.0002**	126.40	525.21	0.8098
	−4	**−195.61**	**98.08**	**0.0461**	51.57	84.82	0.5432	**−590.25**	**177.38**	**0.0009**	−195.91	546.58	0.7201
	−5	−35.92	102.08	0.7251	109.36	88.31	0.2156	**−518.11**	**187.14**	**0.0056**	−313.00	595.89	0.5994
	−6	−37.89	107.34	0.7242	160.24	93.13	0.0854	**−505.02**	**199.47**	**0.0114**	**−1324.58**	**643.84**	**0.0397**
	−7	113.64	114.31	0.3201	**272.27**	**100.84**	**0.0069**	**−519.64**	**219.37**	**0.0179**	−1138.02	720.45	0.1143
		R-sq. (adj) = 0.0910, n = 58,067			R-sq. (adj) = 0.1000, n = 88,807			R-sq. (adj) = 0.0858, n = 35,178			R-sq. (adj) = 0.0954, n = 6,673		

Bold = P-value < 0.05.
Year before last FEV1 measurement = Year 0, the year before Year 0 = Year 1 and so on.

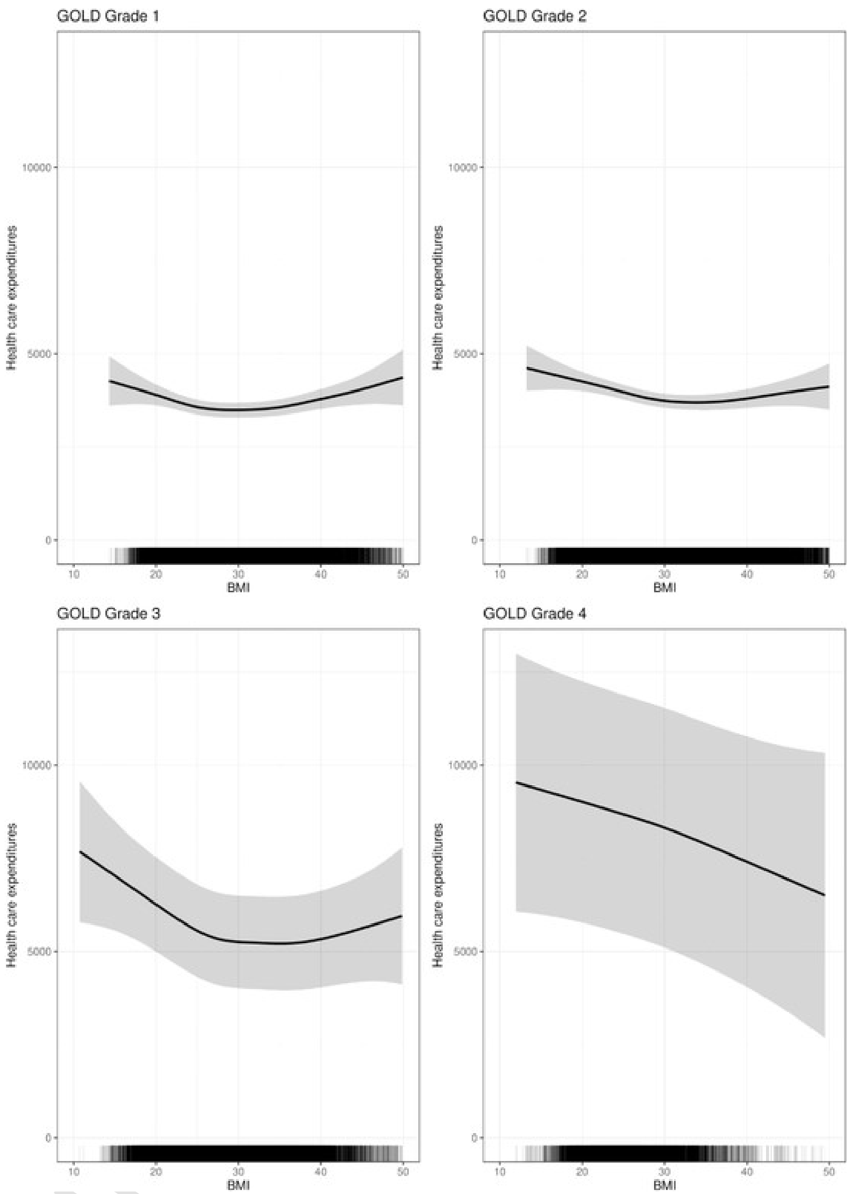

Fig. 2. Effect of BMI on health care expenditures.

4.2. Comparison of findings with literature

There is a quite limited body of literature which includes the BMI as a covariate in the statistical models, estimating the determinants of expenditures in patients with COPD. To the author's best knowledge so far, no study was published measuring the association between the BMI and total health care expenditures and each single expenditure category, stratified by GOLD grades.

We identified 11 studies [26,31–40], which estimated the effect of BMI on health care expenditures. The most important study characteristics such as author, country, study design, statistical methods, population, data basis, included covariates, and effect of BMI on health care expenditures are summarized in appendix table 8. All studies were published between 2006 [40] and 2019 [31,32]. The studies were conducted in Germany [31–34], USA [35,37,38], South Korea [26,36], Israel [39], and Northern Ireland [40]. All studies used a cross-sectional design and one study [32] additionally conducted a longitudinal analysis. The used statistical models were generalized linear regression models [22,31,32,34,35,38], multivariate linear regression models [26,37,40], a multivariate logistic regression model [39], a simple linear regression model [36], and a change score model [32]. The considered population ranged from 49 [40] to 39,307 [31] patients, which included two times [26,36] GOLD grade 1–2, and nine times [22,31,32,34,35,37–40] grade 1–4 patients. The basis of data were claims data [26,31,36,37,39], self-reported data [32–34,40] and a combination of both [35,38]. All studies estimated the influence on direct health care expenditures and three studies [31,33,34] additionally the influence on indirect health care expenditures. In the statistical analysis a wide variety of covariates was included, only one study [26] did not further adjust for covariates. In sum, the effect of BMI on health care expenditures was not conclusive.

When BMI was included as categorical variable in the models, the results pointed in both directions. Some studies found that overweight [26,31,38] and obesity [26,38] reduced direct health care expenditures. Other studies reported that overweight [34,35] and obesity [33] caused higher direct health care expenditures. For indirect health care expenditures only one study [31] reported a significant effect of BMI, that obesity increased health care expenditures.Whereas, when the BMI was included in the models as continuous variable, an increasing BMI reduced direct health care expenditures [36,37]. For indirect health care expenditures no statement can be made, as no model was conducted with BMI as a continuous variable.

Several studies reported no statistically significant effect of BMI on health care expenditures [32,39,40].

One advantage of our study, lacking in the previous literature, is the stratified analysis by GOLD grades. On the other hand the stratification limits the comparability of our results to the literature. As we included BMI as a continuous spline, a comparison with the studies including BMI only as categorical variable is even more restricted. Our non-stratified sensitivity analysis showed that the minimum health care expenditures were at a BMI around 35 (appendix Fig. 7). This is only slightly above the minimum of our stratified analysis for GOLD grade 1–3, which might be a result of the decreasing health care expenditures in grade 4 with increasing BMI. All in all, this fits quite well with the results of the studies that included BMI as continuous variables, as they report an increasing BMI reduced health care expenditures. To our knowledge we are the first to reveal that, in grade 4 the health care expenditures not start to increase again after a certain BMI threshold was met.

When considering the curves how the BMI affected total health care expenditures and each single cost category GOLD stage 1–3 had mostly a common shape, while grade 4 deviated most. This observation suggests that a weight reduction in extremely obese is meaningful in GOLD grades 1–3, but does not reduce health care expenditures in grade 4. Further the results of our statistical analysis were as expected. Interestingly, interruption of DMP enrollment increased health care expenditure (statistically significant in GOLD grade 1–3). This indicates potential for better managing DMP patients while the causes of discontinuity remain to be investigated in further studies.

Furthermore, considering each single included category of health care expenditures for potential savings through BMI management, following was found:

In outpatient expenditures a reduction of BMI in GOLD grade 1 and 2 had no potential for savings in expenditures, whereas weight reduction in a normal BMI range could reduce expenditures up to 20% in grade 3 and up to 50% in grade 4.

In medication expenditures in GOLD grade 1–3 a reduction of health care expenditures could be achieved by a reduction of the BMI in a normal range. This is up to 25% in grade 1 and 2 and up to 15% in grade 3, whereas in grade 4 no potential for reduction of expenditures was found.

Inpatient expenditures seems to be a category, were a BMI management, meaning a reduction of the BMI to a normal range, had no potential reduction in expenditures in any GOLD grade.

BMI management reduces expenditures for rehabilitation in GOLD grade 1 and 2 up to approximately 10%, however health care expenditures could not be reduced in grade 3 and 4 by a reduction of BMI.

For remedy and aid the saving potential in expenditures by an adequate BMI management showed to highest percentage in all GOLD grades. In grade 1 and 2 savings over 50%, in grade 4 almost 85%, and in grade 4 30% were possible by an adequate BMI management.

Similarly to inpatient expenditures travel expenditures showed no potential for a reduction in expenditures by BMI management.

This results of the expenditure categories, are mainly comprehensible, but sometimes contradictory. Logically the health care expenditures for medication and remedy and aid increase with a higher BMI as the propensity of comorbidities increase with a higher BMI which increases the number of necessary medications and remedy and aids. Also understandable are the lower expenditures for traveling, as a higher BMI normally reduces mobility, this should also reduce expenditures in outpatient care and should shift expenditures to inpatient care, as physician contacts caused by reduced mobility were avoided until it is too late. But in our analysis we did not found reduced expenditures with higher BMI in outpatient care or higher expenditures with higher BMI in inpatient care. Similarly with the same argument, of reduced mobility, we also would have expected lower expenditures for rehabilitation, with increased BMI, but this was only found in grade 3 and 4, whereas the expenditures are almost constant in grade 1 and 2 with increasing BMI.

4.3. Limitations and strengths of this study

Our analysis is also subject to several limitations. The results are based on claims data of just one large regional statutory health insurance fund. Therefore, the transferability of the findings might be limited. We compared as far as possible the descriptive statistics of our study population with two further studies [51,52] analyzing COPD data with data from statutory health insurances. Schwarzkopf et al. [51] used a research data base of Arvato health analytics GmbH – which includes claims data of seven German statutory health insurance funds, which should be representative for whole Germany, as confirmed by various tests concerning age, gender, morbidity and mortality. The study compared patients with COPD without (chronic ischemic heart disease) IHD with Persons with COPD and IHD. Patients with COPD without IHD were 65.2 years and with IHD 74.0 years old. 57.4% without IHD were female compared to 47.5% with additional IHD. The prevalence of pulmonary emphysema was for COPD patients without IHD and with IHD 8.5% and 9.9% respectively. Achelrod et al. [52] used data of the Barmer GEK, a nationwide operating sickness fund that covers more than 10% of the German population. They compared COPD patients enrolled and not-enrolled in the DMP COPD. The mean age of the patients enrolled was 67.4 years and the patients not-enrolled 65.7 years. The percentage of female was 55.5% in the DMP and 61.5% in the non-DMP group. The mean age of our population was 67.9 years, where 45.4% percent were female and 12.5% of patients had pulmonary emphysema. According to age, our population was the oldest with the lowest proportion of females in all three studies and with a higher prevalence of emphysema than Schwarzkopf et al. [51].

These differences are small but not neglectable, these differences and their tendency (older and more comorbid patients in our dataset) might be explained by the still existing historical structural differences in risk structure of statutory health insurance funds. Besides that, claims data are collected for administrative and billing processes rather than for research purposes.

Furthermore, the population consists of patients enrolled in the DMP COPD which is voluntary. Therefore, self-selection effects cannot be ruled out. For example, persons who are more health-conscious or more active overall are more likely to decide to enroll in a DMP. Moreover, physicians might enroll patients with specific characteristics, e.g. more adherent patients, more likely [53]. Therefore, our population might be prone to an underestimation of health care provision and expenditures, but this is unlikely to affect the effect of BMI on it. On the other hand, we used for our analysis a completely unselected cohort of DMP COPD patients, as the only exclusion criteria was missing or unreasonable values in covariates.

The prevalence of comorbidities in patients with COPD in claims data [31] seems to be higher than in cohort studies [33], as there are financial incentives for hospitals for up-coding. We best possibly mitigated this potential source of bias by using proven methods to estimate the prevalence of comorbidities [47], but still it might lead to an underestimation of the effect of comorbidities on health care expenditures.

We only had expenditure data for rehabilitation if the statutory health insurance was the third party payer, which only includes about 70% of all rehabilitation cases, which means that the effect of BMI on rehabilitation might be biased in both directions.

According to our dataset we only were able to include BMI as a measurement for obesity, which does not indicate body composition or body fat percentage [54] which had shown to be a better predictor e.g. for mortality [55].

Despite these limitations, we are strongly convinced of our claims data-based approach. We analyzed a large unselected data set, with over 30,000 patients with almost 200,000 observational years, which allowed us a stratification for GOLD grades while remaining with a sound sample size for the single strata.

Furthermore, clinical measures from DMP documentation forms were used which include measures such as FEV_1, weight and height. This allows a sound FEV_1 percentage prediction and BMI calculation.

The biggest strength, besides the unselected patient population, is that our direct health care expenditure calculations are based on real expenditures of a statutory health insurance but not on weighted average health care expenditures that are used to monetize care in survey-based cohort studies, which are prone to recall bias [56].

5. Conclusion

Our findings, which are the first measuring the effect on BMI on health care expenditures stratified by GOLD grades, are based on a large unselected real-world dataset of patients enrolled in a structured DMP for COPD. The results demonstrate that BMI affects health care expenditures differently in grade 1–3 than in grade 4. The minimum health care expenditures are on the boundary between overweight and obese patients in grade 1–3 while the health care expenditures decrease almost linear with increasing BMI in grade 4. These findings are robust for a wide variety of control variables. Based on these findings, weight reduction to a certain level remains a promising strategy to reduce health care expenditures in patients with COPD in Gold stage 1–3. In contrast, weight reduction seems to have no positive impact on expenditures for the most advanced, obese COPD patients. Eventual causes for the latter remain to be investigated in studies which, other than ours, also can take mortality into account.

Ethics approval and consent to participate

Data stem from the LQ-DMP-project that was approved by the Ethics Committee of the Ludwig-Maximilians-Universität München (vote-no. 17–358).

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due §75 SGB X to but are available from the corresponding author on reasonable request.

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Authors' contributions

FK analyzed and interpreted the patient data, performed the statistical analysis and wrote the manuscript. FK, RL, CK, LS, JL, and MH created the statistical analysis plan. AS provided the dataset and have been involved in drafting or revising the manuscript. All authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmed.2020.106194.

References

[1] A.E. Moran, M.H. Forouzanfar, G.A. Roth, G.A. Mensah, M. Ezzati, A. Flaxman, C.J. Murray, M. Naghavi, The global burden of ischemic heart disease in 1990 and 2010: the Global Burden of Disease 2010 study, Circulation 129 (14) (2014) 1493–1501.
[2] C.D. Mathers, D. Loncar, Projections of global mortality and burden of disease from 2002 to 2030, PLoS Med. 3 (11) (2006) e442.
[3] J.G. van Manen, P.J. Bindels, I.J. Cj, J.S. van der Zee, B.J. Bottema, E. Schade, Prevalence of comorbidity in patients with a chronic airway obstruction and controls over the age of 40, J. Clin. Epidemiol. 54 (3) (2001) 287–293.
[4] F. Garcia-Rio, J.B. Soriano, M. Miravitlles, L. Munoz, E. Duran-Tauleria, G. Sanchez, V. Sobradillo, J. Ancochea, Impact of obesity on the clinical profile of a population-based sample with chronic obstructive pulmonary disease, PloS One 9 (8) (2014) e105220.
[5] L.M. Cecere, A.J. Littman, C.G. Slatore, E.M. Udris, C.L. Bryson, E.J. Boyko, D.J. Pierson, D.H. Au, Obesity and COPD: associated symptoms, health-related quality of life, and medication use, COPD, J. Chronic Obstr. Pulm. Dis. 8 (4) (2011) 275–284.
[6] C. Landbo, E. Prescott, P. Lange, J. Vestbo, T.P. Almdal, Prognostic value of nutritional status in chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 160 (6) (1999) 1856–1861.
[7] K. Bhaskaran, I. Dos-Santos-Silva, D.A. Leon, I.J. Douglas, L. Smeeth, Association of BMI with overall and cause-specific mortality: a population-based cohort study of 3.6 million adults in the UK, Lancet Diabetes Endocrinol 6 (12) (2018) 944–953.
[8] K.H. Wade, D. Carslake, N. Sattar, G. Davey Smith, N.J. Timpson, BMI and mortality in UK biobank: revised estimates using mendelian randomization, Obesity (Silver Spring) 26 (11) (2018) 1796–1806.
[9] M. Laxy, C. Teuner, R. Holle, C. Kurz, The association between BMI and health-related quality of life in the US population: sex, age and ethnicity matters, Int. J. Obes. 42 (3) (2018) 318–326.
[10] S. Jalali-Farahani, Y.S. Chin, P. Amiri, M.N. Mohd Taib, Body mass index (BMI)-for-age and health-related quality of life (HRQOL) among high school students in Tehran, Child Care Health Dev. 40 (5) (2014) 731–739.

[11] A. Dee, K. Kearns, C. O'Neill, L. Sharp, A. Staines, V. O'Dwyer, S. Fitzgerald, I.J. Perry, The direct and indirect costs of both overweight and obesity: a systematic review, BMC Res. Notes 7 (2014) 242.
[12] S. Musich, S. MacLeod, G.R. Bhattarai, S.S. Wang, K. Hawkins, F.G. Bottone Jr., C.S. Yeh, The impact of obesity on health care utilization and expenditures in a medicare supplement population, Gerontol Geriatr Med 2 (2016) 2333721415622004.
[13] J. Abukhalaf, R. Davidson, N. Villalobos, P. Meek, H. Petersen, A. Sood, Y. Tesfaigzi, R. Vazquez Guillamet, Chronic obstructive pulmonary disease mortality, a competing risk analysis, Clin. Res. J 12 (11) (2018) 2598–2605.
[14] E. Abston, A. Comellas, R.M. Reed, V. Kim, R.A. Wise, R. Brower, S. Fortis, R. Beichel, S. Bhatt, J. Zabner, J. Newell, E.A. Hoffman, M. Eberlein, Higher BMI is associated with higher expiratory airflow normalised for lung volume (FEF25-75/FVC) in COPD, BMJ Open Respir Res 4 (1) (2017) e000231.
[15] P. Stoll, S. Foerster, J.C. Virchow, M. Lommatzsch, Overweight is a predictor of long-term survival in hospitalised patients with exacerbations of COPD, Respir. Med. 116 (2016) 59–62.
[16] M.J. Divo, C. Cabrera, C. Casanova, J.M. Marin, V.M. Pinto-Plata, J.P. de-Torres, J. Zulueta, J. Zagaceta, P. Sanchez-Salcedo, J. Berto, C. Cote, B.R. Celli, Comorbidity distribution, clinical expression and survival in COPD patients with different body mass index, Chronic Obstr Pulm Dis 1 (2) (2014) 229–238.
[17] G. Gudmundsson, C.S. Ulrik, T. Gislason, E. Lindberg, E. Brondum, P. Bakke, C. Janson, Long-term survival in patients hospitalized for chronic obstructive pulmonary disease: a prospective observational study in the Nordic countries, Int. J. Chronic Obstr. Pulm. Dis. 7 (2012) 571–576.
[18] M. Lainscak, S. von Haehling, W. Doehner, I. Sarc, T. Jeric, K. Ziherl, M. Kosnik, S.D. Anker, S. Suskovic, Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease, J Cachexia Sarcopenia Muscle 2 (2) (2011) 81–86.
[19] R.G. Galesanu, S. Bernard, K. Marquis, Y. Lacasse, P. Poirier, J. Bourbeau, F. Maltais, Obesity in chronic obstructive pulmonary disease: is fatter really better?, Canc. Res. J. 21 (5) (2014) 297–301.
[20] J.U. Lim, J.H. Lee, J.S. Kim, Y.I. Hwang, T.H. Kim, S.Y. Lim, K.H. Yoo, K.S. Jung, Y.K. Kim, C.K. Rhee, Comparison of World Health Organization and Asia-Pacific body mass index classifications in COPD patients, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 2465–2475.
[21] J. Sundh, S. Montgomery, M. Hasselgren, M. Kampe, C. Janson, B. Stallberg, K. Lisspers, Change in health status in COPD: a seven-year follow-up cohort study, NPJ Prim Care Respir Med 26 (2016) 16073.
[22] M.E. Wacker, R.A. Jorres, A. Karch, S. Wilke, J. Heinrich, S. Karrasch, A. Koch, H. Schulz, H. Watz, R. Leidl, C. Vogelmeier, R. Holle, Assessing health-related quality of life in COPD: comparing generic and disease-specific instruments with focus on comorbidities, BMC Pulm. Med. 16 (1) (2016) 70.
[23] A.A. Lambert, N. Putcha, M.B. Drummond, A.M. Boriek, N.A. Hanania, V. Kim, G.L. Kinney, M.N. McDonald, E.P. Brigham, R.A. Wise, M.C. McCormack, N.N. Hansel, Obesity is associated with increased morbidity in moderate to severe COPD, Chest 151 (1) (2017) 68–77.
[24] P.M. Boiselle, D.E. Litmanovich, G. Michaud, D.H. Roberts, S.H. Loring, H.M. Womble, M.E. Millett, C.R. O'Donnell, Dynamic expiratory tracheal collapse in morbidly obese COPD patients, COPD 10 (5) (2013) 604–610.
[25] Z. Wu, D. Yang, Z. Ge, M. Yan, N. Wu, Y. Liu, Body mass index of patients with chronic obstructive pulmonary disease is associated with pulmonary function and exacerbations: a retrospective real world research, J. Thorac. Dis. 10 (8) (2018) 5086–5099.
[26] Y.S. Jo, Y.H. Kim, J.Y. Lee, K. Kim, K.S. Jung, K.H. Yoo, C.K. Rhee, Impact of BMI on exacerbation and medical care expenses in subjects with mild to moderate airflow obstruction, Int. J. Chronic Obstr. Pulm. Dis. 13 (2018) 2261–2269.
[27] Y.F. Wei, Y.H. Tsai, C.C. Wang, P.H. Kuo, Impact of overweight and obesity on acute exacerbations of COPD - subgroup analysis of the Taiwan Obstructive Lung Disease cohort, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 2723–2729.
[28] Y.M. Oh, S.S. Sheen, J.H. Park, U.R. Jin, J.W. Yoo, J.B. Seo, K.H. Yoo, J.H. Lee, T.H. Kim, S.Y. Lim, H.I. Yoon, J.S. Lee, S.D. Lee, Emphysematous phenotype is an independent predictor for frequent exacerbation of COPD, Int. J. Tubercul. Lung Dis. 18 (12) (2014) 1407–1414.
[29] A. Jacob, C. Laurin, K.L. Lavoie, G. Moullec, M. Boudreau, C. Lemiere, S. Bacon, The impact of body mass index on inpatient- versus outpatient-treated chronic obstructive pulmonary disease exacerbations, Canc. Res. J. 20 (4) (2013) 237–242.
[30] L. Lacey, M. Tabberer, Economic burden of post-acute myocardial infarction heart failure in the United Kingdom, Eur. J. Heart Fail. 7 (4) (2005) 677–683.
[31] F. Kirsch, A. Schramm, L. Schwarzkopf, J.I. Lutter, B. Szentes, M. Huber, R. Leidl, Direct and indirect costs of COPD progression and its comorbidities in a structured disease management program: results from the LQ-DMP study, Respir. Res. 20 (1) (2019) 215.
[32] D. Byng, J.I. Lutter, M.E. Wacker, R.A. Jorres, X. Liu, S. Karrasch, H. Schulz, C. Vogelmeier, R. Holle, Determinants of healthcare utilization and costs in COPD patients: first longitudinal results from the German COPD cohort COSYCONET, Int. J. Chronic Obstr. Pulm. Dis. 14 (2019) 1423–1439.
[33] M.E. Wacker, R.A. Jorres, H. Schulz, J. Heinrich, S. Karrasch, A. Karch, A. Koch, A. Peters, R. Leidl, C. Vogelmeier, R. Holle, Direct and indirect costs of COPD and its comorbidities: results from the German COSYCONET study, Respir. Med. 111 (2016) 39–46.
[34] M.E. Wacker, K. Kitzing, R.A. Jorres, R. Leidl, H. Schulz, S. Karrasch, A. Karch, A. Koch, C.F. Vogelmeier, R. Holle, The contribution of symptoms and comorbidities to the economic impact of COPD: an analysis of the German COSYCONET cohort, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 3437–3448.
[35] J.J. Stephenson, D. Wertz, T. Gu, J. Patel, A.A. Dalal, Clinical and economic burden of dyspnea and other COPD symptoms in a managed care setting, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 1947–1959.
[36] C.K. Rhee, K. Kim, H.K. Yoon, J.A. Kim, S.H. Kim, S.H. Lee, Y.B. Park, K.S. Jung, K.H. Yoo, Y.I. Hwang, Natural course of early COPD, Int. J. Chronic Obstr. Pulm. Dis. 12 (2017) 663–668.
[37] K. Darnell, A.K. Dwivedi, Z. Weng, R.J. Panos, Disproportionate utilization of healthcare resources among veterans with COPD: a retrospective analysis of factors associated with COPD healthcare cost, Cost Eff. Resour. Allocation 11 (2013) 13.
[38] T.A. Omachi, S.E. Gregorich, M.D. Eisner, R.A. Penaloza, I.V. Tolstykh, E.H. Yelin, C. Iribarren, R.A. Dudley, P.D. Blanc, Risk adjustment for health care financing in chronic disease: what are we missing by failing to account for disease severity?, Med. Care 51 (8) (2013) 740–747.
[39] T. Simon-Tuval, S.M. Scharf, N. Maimon, B.J. Bernhard-Scharf, H. Reuveni, A. Tarasiuk, Determinants of elevated healthcare utilization in patients with COPD, Respir. Res. 12 (2011) 7.
[40] E. Murtagh, C. O'Neill, D. McAllister, F. Kee, J. Macmahon, L.G. Heaney, A cross-sectional comparison of direct medical care costs among COPD and asthma patients living in the community in northern Ireland, Treat. Respir. Med. 5 (6) (2006) 495–501.
[41] S.R. de Bruin, R. Heijink, L.C. Lemmens, J.N. Struijs, C.A. Baan, Impact of disease management programs on healthcare expenditures for patients with diabetes, depression, heart failure or chronic obstructive pulmonary disease: a systematic review of the literature, Health Pol. 101 (2) (2011) 105–121.
[42] S. Mattke, M. Seid, S. Ma, Evidence for the effect of disease management: is $1 billion a year a good investment?, Am. J. Manag. Care 13 (12) (2007) 670–676.
[43] P.H. Quanjer, S. Stanojevic, T.J. Cole, X. Baur, G.L. Hall, B.H. Culver, P.L. Enright, J.L. Hankinson, M.S. Ip, J. Zheng, J. Stocks, Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations, Eur. Respir. J. 40 (6) (2012) 1324–1343.
[44] H. Quan, V. Sundararajan, P. Halfon, A. Fong, B. Burnand, J.C. Luthi, L.D. Saunders, C.A. Beck, T.E. Feasby, W.A. Ghali, Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data, Med. Care 43 (11) (2005) 1130–1139.
[45] H. Kurosaki, T. Ishii, N. Motohashi, T. Motegi, K. Yamada, S. Kudoh, R.C. Jones, K. Kida, Extent of emphysema on HRCT affects loss of fat-free mass and fat mass in COPD, Intern. Med. 48 (1) (2009) 41–48.
[46] D.A. Lynch, C.M. Moore, C. Wilson, D. Nevrekar, T. Jennermann, S.M. Humphries, J.H.M. Austin, P.A. Grenier, H.U. Kauczor, M.K. Han, E.A. Regan, B.J. Make, R.P. Bowler, T.H. Beaty, D. Curran-Everett, J.E. Hokanson, J.L. Curtis, E.K. Silverman, J.D. Crapo, CT-based visual classification of emphysema: association with mortality in the COPDGene study, Radiology 288 (3) (2018) 859–866.
[47] German Federal Insurance Office, The New Risk Structure Equalisation, 2008. http://www.bundesversicherungsamt.de/risikostrukturausgleich.html.
[48] J.R. Curtis, A.O. Westfall, J. Allison, J.W. Bijlsma, A. Freeman, V. George, S.H. Kovac, C.M. Spettell, K.G. Saag, Population-based assessment of adverse events associated with long-term glucocorticoid use, Arthritis Rheum. 55 (3) (2006) 420–426.
[49] S. Wood, F. Scheipl, M.S. Wood, Package 'gamm4', Am. Stat. 45 (2017) 339.
[50] S. Wood, F. Scheipl, gamm4: generalized additive mixed models using mgcv and lme4, 2014 URL http://CRAN. R-project. org/package= gamm4.
[51] L. Schwarzkopf, M. Wacker, J. Ertl, J. Hapfelmeier, K. Larisch, R. Leidl, Impact of chronic ischemic heart disease on the health care costs of COPD patients - an analysis of German claims data, Respir. Med. 118 (2016) 112–118.
[52] D. Achelrod, T. Welte, J. Schreyögg, T. Stargardt, Costs and outcomes of the German disease management programme (DMP) for chronic obstructive pulmonary disease (COPD)-A large population-based cohort study, Health policy (Amsterdam, Netherlands) 120 (9) (2016) 1029–1039.
[53] W. Ullrich, U. Marschall, C. Graf, Versorgungsmerkmale des Diabetes mellitus in Disease-Management-Programmen, Diabetes, Stoffwechs. Herz 16 (6) (2007) 407–414.
[54] F.Q. Nuttall, Body mass index: obesity, BMI, and health: a critical review, Nutr. Today 50 (3) (2015) 117–128.
[55] R.S. Ahima, M.A. Lazar, The health risk of obesity—better metrics imperative, Science 341 (6148) (2013) 856–858.
[56] M.E. Goossens, M.P. Rutten-van Molken, J.W. Vlaeyen, S.M. van der Linden, The cost diary: a method to measure direct and indirect costs in cost-effectiveness research, J. Clin. Epidemiol. 53 (7) (2000) 688–695.