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# The revised GOLD 2017 COPD categorization in relation to comorbidities

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## ABSTRACT

*Introduction:* The COPD classification proposed by the Global Initiative for Obstructive Lung Disease was recently revised, and the A to D grouping is now based on symptoms and exacerbations only. Potential associations with comorbidities have not been assessed so far.

Thus the aim of the present study was to determine the relationship between the revised (2017) GOLD groups A-D and major comorbidities.

*Methods:* We used baseline data from the COPD cohort COSYCONET. Comorbidities were identified from patient self-reports and disease-specific medication: gastrointestinal disorders, asthma, sleep apnea, hyperuricemia, hyperlipidemia, diabetes, osteoporosis, mental disorders, heart failure, hypertension, coronary artery disease. The A-D groups were based on either the COPD Assessment Test or the modified Medical Research Council scale. Exacerbations were also categorized as per GOLD recommendations.

*Results:* Data from 2228 patients were analyzed. Using GOLD group A as a reference, group D was associated with nearly all comorbidities, followed by group B and C. When groups A-D were dichotomized as AC vs. BD (symptoms) and AB vs. CD (exacerbations), all comorbidities correlated with symptoms and/or exacerbations. This was true for both mMRC- and CAT-based categorizations.

*Conclusions:* These findings suggest that the recently modified GOLD categorization is clinically relevant beyond being purely an assessment of symptoms and exacerbations. As the A-D groups correlated with the risk of important comorbidities, with some differences in terms of the correlation with symptoms and exacerbations, the findings underline the importance of identifying comorbidities in COPD, particularly in non-responders to therapy who have high symptoms and/or exacerbation rates.

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## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is frequently associated with comorbidities, the presence of which impair overall prognosis [1,2]. The association of comorbidities with COPD is putatively derived from shared risk factors, systemic interactions (e.g. a pro-inflammatory state) and direct interactions (e.g. physiological and mechanical); side-effects of COPD therapy may also play a role [3,4]. Comorbidities occur across all spirometric Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades, and the ECLIPSE study [5] found no close relationship of these grades to dyspnea, health status or the number of exacerbations. The GOLD classification of groups A-D has recently been revised by separating spirometric grading from symptoms and exacerbations [6]. In the revised classification the evaluation of future risk of exacerbations is purely based on exacerbation history, while symptoms are quantified via COPD Assessment Test (CAT) score or modified Medical Research Council (mMRC) score. If the revised classification also shows associations with comorbidities this would improve its usefulness. Until now, however, to the best of our knowledge no data evaluating this question is available.

The German **CO**PD and **Sy**stemic **Co**nsequences-Comorbidities **Net**work (COSYCONET) is a large cohort study with a focus on the role of comorbidities in COPD [7]. It is therefore well suited to assess the association of comorbidities with the GOLD categorizations, taking into account major risk factors of COPD. We analyzed the relationship of the revised GOLD groups A-D to a panel of comorbidities and potential or known risk factors like $FEV_1$% predicted, BMI, gender, age and pack-years, using cross-sectional data from the COSYCONET cohort.

## 2. Methods

### 2.1. Study population

We used visit 1 (baseline) data of the German COPD cohort COSYCONET [7]. Only patients with a forced expiratory volume in 1 s ($FEV_1$) to forced vital capacity (FVC) ratio < 0.7 [8] and with complete data for both mMRC and CAT [6] and for 12-month exacerbation history were included in the analysis. The study was approved by the ethical committees of all 31 study centers, and all patients gave their written informed consent [7].

### 2.2. Assessments

A broad panel of tests was applied to determine the patients' clinical and functional state [7]; all assessments were guided by standard operating procedures on the basis of established guidelines. Post-bronchodilator spirometry [7] comprised $FEV_1$, FVC and $FEV_1$/FVC. Predicted values of spirometric lung function parameters were taken from the Global Lung Function Initiative [9]; the fixed value criterion for $FEV_1$/FVC of < 0.7 as proposed by GOLD was kept for the definition of COPD.

The GOLD groups were defined in accordance with GOLD 2017 recommendations [6]. Since a number of previous studies have shown that patients can be classified differently based on CAT compared with mMRC [10,11], we included both questionnaires in our analyses. Exacerbation risk was based on the 12-month history of exacerbations of all severities, including hospitalization, as described in GOLD (with high risk indicated by a history of two non-hospitalized exacerbations, or one exacerbation leading to hospital admission). To identify exacerbations the patients were asked for “acute respiratory worsening in the last 12 months, with acute worsening for several days and the need for specific measures including changes in medication, e.g. prednisolone treatment”. Furthermore, the patients were asked whether they visited the general physician or the emergency department because of this respiratory worsening. To identify severe exacerbations, patients were asked for the number of past hospital admissions due to acute respiratory worsening.

### 2.3. Definition of comorbidities

Comorbidities were assessed via a predefined list, and were identified based on patients' self-reports of doctors' diagnoses (see Ref. [7]) and, as far as feasible, disease-specific medication. Details of the procedure and the categorization of medication have been given previously [12]. The combination of self-reported comorbidity and/or disease-specific medication was applied to the comorbidities gastrointestinal disorders, asthma, hyperuricemia, diabetes mellitus, hyperlipidemia, osteoporosis, mental disorders (comprising different disease entities, in particular depression and anxiety, but also other disorders), arterial hypertension, and coronary artery disease. For sleep apnea and heart failure we used patients' reports only, given the absence of sufficiently disease-specific medication and information on therapy.

### 2.4. Statistical analysis

Comparisons were performed using chi-square statistics and contingency tables for categorical data, and one-way analysis of variance for continuous variables. Comorbidities were treated as binary outcomes, and the relationship to the independent variables was assessed via multiple logistic regression analysis. In a first step we incorporated GOLD groups A-D in terms of categorical variables, including $FEV_1$% predicted, BMI, age, gender and packyears as confounders and taking GOLD group A as reference within the categorical variables A-D, since there is no natural order except for assuming that GOLD “A” represents the lowest and “D” the highest category. In a second step we aimed to explicitly account for symptoms and exacerbations within the GOLD A-D grouping. We therefore collapsed the A-D groups into two binary subgroups: AC vs. BD (to compare the influence of low symptoms vs. high symptoms) and AB vs. CD (to compare the influence of no/few exacerbations vs. more exacerbations). This permitted analysis via binary predictors (instead of four categories) and had the advantage to facilitate the interpretation of the results. Statistical significance was assumed for $p < 0.05$. All analyses were performed using the software package SPSS Statistics 23 (IBM Corp., Armonk, NY, USA).

## 3. Results

### 3.1. Baseline characteristics

The recruitment of the COSYCONET study (ClinicalTrials.gov, Identifier: NCT01245933) was conducted from September 2010 to December 2013. The study population of the present analysis comprised 2228 patients from the originally recruited 2741 patients [7]; 452 patients were excluded on the basis of $FEV_1$/FVC ratio ≥0.7 or missing data of $FEV_1$ or FVC (n = 450) or implausible lung function data (n = 2), and 61 patients were excluded due to incomplete data for exacerbation history, CAT or mMRC. GOLD grades 1–4 [6] were present in 201/948/853/226 of the 2228 patients.

The relationship between the CAT- and mMRC-based A-D groups is shown in Table 1. A high number of patients (n = 641) were categorized as group A according to mMRC but changed categorization to group B according to CAT, with more than half of those considered group B according to CAT changing to group A according to mMRC (641/1177). Conversely, few patients (n = 22) were in group A according to CAT but in group B according to mMRC. Furthermore, almost all patients categorized as group C according to mMRC were re-categorized as group D by CAT (n = 257), whereas few patients changed from group C according to CAT into group D according to mMRC (n = 5).

**Table 1**
Relationship between GOLD groups A-D according to CAT and mMRC.

| GOLD grouping according to CAT | GOLD grouping according to mMRC | | | |
|---|---|---|---|---|
| | A (n = 863) | B (n = 558) | C (n = 291) | D (n = 516) |
| A (n = 244) | 222 | 22 | 0 | 0 |
| B (n = 1177) | 641 | 536 | 0 | 0 |
| C (n = 39) | 0 | 0 | 34 | 5 |
| D (n = 768) | 0 | 0 | 257 | 511 |

The table shows the absolute numbers for the total population of 2228 patients.

### 3.2. Baseline characteristics according to groups A-D

The baseline characteristics of the population are given in Table 2 based on CAT or mMRC. In case of CAT-based groups the distribution of gender was borderline to non-significant different in A-D groups, although this was not the case in the mMRC-based categorization. Age significantly depended on both A-D categorizations, whereas BMI and pack-years of cigarette smoking were significantly different across A-D groups only in the mMRC-based categorization. In both GOLD categorizations, there were significant differences across GOLD groups for $FEV_1$, FVC and $FEV_1$/FVC (Table 2, all $p < 0.001$).

### 3.3. The relation between GOLD groups and comorbidities

When using the GOLD groups A-D (A as reference) in the logistic regression analysis, group B was significantly ($p < 0.05$ each) associated with gastrointestinal disorders, coronary artery disease and mental disorders for both CAT and mMRC-based categorizations (Table 3). For CAT there was only an association with asthma and sleep apnea, and for mMRC only with hyperuricemia and heart failure. Group C was linked to diabetes when using CAT, and to gastrointestinal disorders, asthma and heart failure when using mMRC ($p < 0.05$ each). No comorbidities were significantly associated with group C with both categorizations (Table 3). The highest agreement between CAT and mMRC-based categorizations was achieved for group D, with significant ($p < 0.05$ each) associations between GOLD category and comorbidity prevalence for gastrointestinal disorders, asthma, sleep apnea, osteoporosis, hyperlipidemia, hyperuricemia, coronary artery disease, heart failure and mental disorder. Hypertension was associated with D only for CAT, and diabetes only for mMRC (Table 3).

When using the CAT-based dichotomized GOLD subgroups AC vs. BD (symptoms) and AB vs. CD (exacerbations) as independent variables, the presence of gastrointestinal disorders, asthma, sleep apnea, osteoporosis, mental disorder and heart failure were significantly ($p < 0.05$ each) associated with both symptoms and exacerbations (Fig. 1, Table 4). Hyperuricemia, hyperlipidemia, hypertension and diabetes were associated only with exacerbations, whereas coronary artery disease was linked only to symptoms. When the symptoms subgroups were based on mMRC the pattern of relationships was very similar, with the exception of asthma and heart failure which were linked to exacerbations only.

## 4. Discussion

Using data from a large COPD cohort we found that the revised GOLD A-D groups, either based on CAT or mMRC, were related to a number of common comorbidities of COPD. Using group A as a reference for comparison, group D was associated with most of the comorbidities, and this was true for both CAT and mMRC. Group B was linked to a lower number of comorbidities, and there were more differences between CAT and mMRC. Irrespective of this, the number of associations was substantially higher than in group C. When data were analyzed according to the binary categories “symptoms” (using CAT) and “exacerbations”, eleven of twelve comorbidities were found to correlate with exacerbation risk, seven with symptoms and six with both symptoms and exacerbations. In the mMRC analyses, the pattern of relationships between exacerbations and comorbidities was similar to in the CAT-based grouping, however, there were fewer correlations with symptoms. To the best of our knowledge this is the first such analysis of the GOLD 2017 categorization. The findings suggest that the revised GOLD groups A-D are clinically informative beyond being a mere description of symptoms and exacerbations. They underline the importance of identifying comorbidities in COPD.

Symptoms and exacerbation history were defined in accordance with the revised GOLD recommendations, which suggest that either CAT or mMRC can be used to assess the impact of symptoms [13]. However, there are data suggesting that CAT and mMRC might not be equivalent [10,11], and we therefore performed analyses for both. Our results are consistent with the previous findings, in that about one half of the patients categorized as group B according to CAT were re-

**Table 2**
Baseline characteristics of the study cohort (n = 2228) according to GOLD groups A-D based on CAT and mMRC.

| Parameter | All n = 2228 | GOLD 2017 grouping according to CAT | | | | | GOLD 2017 grouping according to mMRC | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | GOLD A n = 244 | GOLD B n= 1177 | GOLD C n = 39 | GOLD D n = 768 | p-value | GOLD A n = 863 | GOLD B n = 558 | GOLD C n = 291 | GOLD D n = 516 | p-value |
| Gender (m/f) | 1361/867 (61/39) | 163/81 (67/33) | 730/447 (62/38) | 20/19 (51/49) | 448/320 (58/42) | 0.050 | 546/317 (63/37) | 347/211 (62/38) | 174/117 (60/40) | 294/222 (57/43) | 0.117 |
| Age (y) | 65.1 ( ± 8.4) | 66.7 ( ± 8.3) | 65.3 ( ± 8.4) | 66.0 ( ± 8.6) | 64.2 ( ± 8.4) | < 0.001 | 65.0 ( ± 8.5) | 66.3 ( ± 8.1) | 63.6 ( ± 9.0) | 64.6 ( ± 7.9) | < 0.001 |
| BMI ($kg/m^2$) | 26.7 ( ± 5.2) | 26.2 ( ± 4.1) | 26.8 ( ± 5.2) | 25.5 ( ± 4.5) | 26.6 ( ± 5.6) | 0.201 | 26.2 ( ± 4.6) | 27.4 ( ± 5.6) | 25.9 ( ± 4.5) | 27.0 ( ± 6.0) | < 0.001 |
| Pack-years | 49.1 ( ± 35.7) | 47.9 ( ± 37.3) | 50.2 ( ± 35.5) | 57.3 ( ± 36.9) | 47.6 ( ± 35.6) | 0.233 | 47.5 ( ± 34.6) | 53.2 ( ± 37.4) | 44.8 ( ± 33.2) | 49.8 ( ± 36.9) | 0.006 |
| $FEV_1$ (% predicted) | 52.8 ( ± 18.5) | 63.5 ( ± 18.2) | 54.6 ( ± 18.2) | 59.1 ( ± 17.8) | 46.3 ( ± 16.5) | < 0.001 | 61.4 ( ± 17.8) | 47.9 ( ± 16.5) | 54.6 ( ± 16.8) | 42.7 ( ± 15.3) | < 0.001 |
| $FEV_1$/FVC (%) | 51.4 ( ± 10.9) | 55.0 ( ± 9.6) | 52.1 ( ± 10.9) | 53.4 ( ± 12.3) | 49.1 ( ± 10.8) | < 0.001 | 54.8 ( ± 9.9) | 47.9 ( ± 16.5) | 54.5 ( ± 16.8) | 42.7 ( ± 15.3) | < 0.001 |
| FVC (% predicted) | 78.5 ( ± 19.0) | 88.1 ( ± 18.2) | 80.1 ( ± 18.3) | 86.1 ( ± 16.8) | 72.6 ( ± 18.6) | < 0.001 | 86.0 ( ± 18.0) | 74.6 ( ± 17.1) | 82.1 ( ± 16.8) | 68.3 ( ± 17.9) | < 0.001 |

The table shows mean values ( ± standard deviations), for gender absolute numbers (percentages). The comparisons of age, BMI, smoking history in terms of pack-years and lung function parameters between GOLD A-D were performed by unadjusted analysis of variance; gender was compared by the chi-squared statistics. BMI = body-mass index, $FEV_1$ = forced expiratory volume in 1 s, FVC = forced vital capacity, $FEV_1$/FVC = ratio of $FEV_1$ and FVC. For GOLD groups A-D the p-values refer to the comparisons of all four groups. Post-hoc comparisons between the GOLD groups A-D (either based on CAT or mMRC) using the Tukey and Duncan post-hoc comparisons showed no significant differences ($p < 0.05$) in the post-hoc analyses of age, gender, packyears and BMI between the GOLD groups A-D.

**Table 3**
Odds ratios for comorbidities in relation to GOLD groups B-D according to CAT and mMRC.

| Comorbidities | GOLD 2017 grouping according to CAT | | | GOLD 2017 grouping according to mMRC | | |
|---|---|---|---|---|---|---|
| | GOLD B | GOLD C | GOLD D | GOLD B | GOLD C | GOLD D |
| Gastrointestinal disorders | **1.418*** | 1.030 | **2.652*** | **1.569*** | **1.687*** | **2.828*** |
| Asthma | **3.596*** | 2.406 | **5.816*** | 1.177 | **1.951*** | **1.887*** |
| Hyperuricemia | 1.359 | 2.074 | **1.909*** | 1.329 | **1.940*** | **1.548*** |
| Osteoporosis | 1.404 | 0.435 | **2.171*** | 1.408 | 1.173 | **2.254*** |
| Sleep apnea | **2.252*** | – | **3.433*** | 1.476 | 1.543 | **2.141*** |
| Hyperlipidemia | 1.137 | 0.748 | **1.503*** | 0.921 | 1.185 | **1.299*** |
| Heart failure | 2.556 | – | **4.877*** | **1.858*** | **2.295*** | **3.008*** |
| Hypertension | 1.200 | 1.846 | **1.451*** | 0.965 | 1.265 | 1.221 |
| Coronary artery disease | **1.757*** | 0.272 | **2.306*** | **1.882*** | 1.196 | **2.322*** |
| Diabetes | 0.856 | **2.957*** | 1.141 | 1.066 | 1.108 | **1.619*** |
| Mental disorder | **2.491*** | 0.470 | **3.351*** | **1.525*** | 1.228 | **2.075*** |

Results of binary logistic regression analyses with comorbidities as dependent variables and GOLD groups B-D as categorical independent variables, with group A as reference. In these analyses, the risk factors $FEV_1$% predicted, BMI, gender, age and pack-years were included as confounders for adjustment. The table shows the Odds ratios. The associations marked with (*) were statistically significant ($p < 0.05$), those marked with "-" could not be estimated.

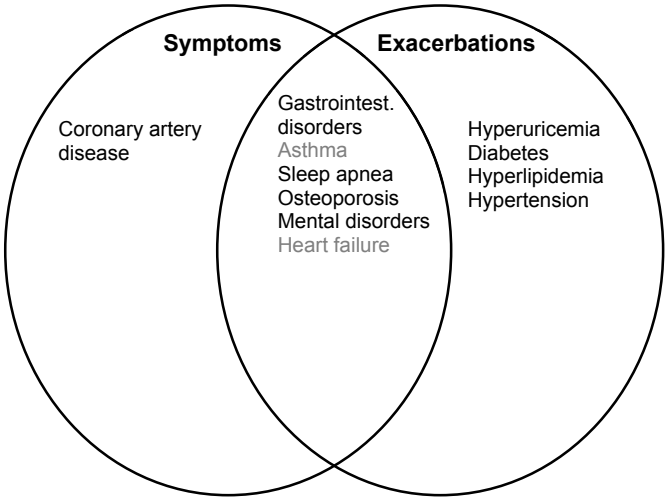


**Fig. 1. Associations between comorbidities, symptoms and exacerbations.**
This figure illustrates the results of logistic regression analyses in which the binary GOLD categories BD vs. AC (symptoms) and CD vs. AB (exacerbations) were taken as predictors, together with BMI, gender, age, pack-years and $FEV_1$% predicted, and the single comorbidities as dependent variables. Only statistically significant ($p < 0.05$; see Table 4) associations are shown in this Venn diagram. The grey shading indicates that the associations were significant only for CAT and not for mMRC.

categorized as group A according to mMRC. Furthermore, about one third of patients in group D according to CAT were re-categorized into group C when using mMRC.

In view of this, it is noteworthy that the major associations between GOLD groups and comorbidities were statistically significant for both CAT and mMRC, particularly the binary subgroups. Correlations with symptoms seemed to be stronger with CAT compared to mMRC (cf. Table 4) which provides additional validity to our findings, suggesting that patients with low symptoms according to mMRC but high symptoms according to CAT were patients with a greater burden of comorbidities. CAT appears to be a broader measure of the impact of the disease than mMRC which is a measure purely of the impact of breathlessness. Our findings are compatible with the assumption that patients with low symptoms according to mMRC but high according to CAT are experiencing a broader impact of COPD from comorbidities resulting in a more clear separation of groups B and C. When using CAT group C comprised only few patients, in contrast to the result when using mMRC. This might underly the finding that diabetes was associated with either group C or D for the two questionnaires. Despite these conflicting data the major result was that exacerbations seem to be linked to diabetes, as clearly confirmed by the binary score which yielded similar results for CAT and mMRC (see Table 4).

The characteristics of the patients recruited into COSYCONET [7] are similar to those recruited into other large cohorts [14], and it is likely that the present findings are not specific for the cohort studied. We observed a number of correlations between baseline characteristics and GOLD categories, including age in both symptoms-based groups, and BMI and pack-years in the mMRC-based GOLD characterization, in addition to lung function in terms of $FEV_1$% predicted. However, although on the basis of the large sample size the correlations were statistically significant, differences between groups were small and probably of limited clinical relevance. Despite this, as a conservative approach we adjusted for the baseline characteristics and confounders in the multivariate analyses.

Obviously, group D was associated with most of the comorbidities independent of the symptom score used. Less consistent results were obtained for group B, whereas for group C the association with comorbidities was completely dependent on the symptoms score used for its definition, as reflected in the differences between CAT and mMRC in Table 3. This may have been partially due to the fact that this group had a very small sample size when using CAT. However, the relatively low impact of comorbidities in group C in our analyses is consistent with other work that has suggested that in patients who have either high symptoms alone (group B) or high exacerbation risk alone (group C), symptoms are more likely to correlate with greater disease burden. For example, when using the former (2011) GOLD groups A-D [15], an analysis of ECLIPSE data suggested that the percentage of patients with any (self-reported) comorbidity was highest in group B, despite having milder airflow limitation than groups C or D [14]. Moreover, in a general population study, the prevalence of ischemic heart disease and myocardial infarction was significantly higher in 2011 GOLD groups B and D than in groups A and C, with mortality from cardiovascular disease and cancer also highest in the B and D groups [16].

To evaluate the relative role of symptoms and exacerbations we used the two binary scores from which GOLD groups are defined. For this purpose we compared the two low versus two high symptom groups, and the two low versus two high exacerbation groups. All comorbidities showed an association with symptoms or exacerbations, with up to one half correlating with both.

Few studies have found associations between purely spirometric GOLD grades and comorbidities [16,17], or markers of comorbidities such as the ankle-brachial index [18]. Also, our data revealed a poor correlation between GOLD grades 1–4 and comorbidities, if GOLD grades 1–4 were taken as predictors in logistic regression analyses, together with BMI, gender, age, packyears, the binary subgroups GOLD

**Table 4**
Odds ratios for comorbidities in relation to symptoms and exacerbations.

| Comorbidities | GOLD 2017 grouping according to CAT | | GOLD 2017 grouping according to mMRC | | Overall prevalence % |
|---|---|---|---|---|---|
| | BD vs. AC (symptoms) | CD vs. AB (exacerbations) | BD vs. AC (symptoms) | CD vs. AB (exacerbations) | |
| Gastrointestinal disorders | **1.548**** [1.167; 2.053] | **1.801***** [1.489; 2.179] | **1.607***** [1.317; 1.961] | **1.750***** [1.445; 2.119] | 46.3 |
| Asthma | **3.314***** [1.973; 5.568] | **1.641***** [1.287; 2.093] | 1.079 [0.831; 1.400] | **1.762***** [1.380; 2.151] | 17.7 |
| Hyperuricemia | 1.275 [0.866; 1.877] | **1.439**** [1.119; 1.851] | 1.092 [0.839; 1.421] | **1.454**** [1.130; 1.871] | 18.1 |
| Osteoporosis | **1.700*** [1.062; 2.720] | **1.465**** [1.126; 1.905] | **1.592***** [1.197; 2.117] | **1.421**** [1.090; 1.852] | 15.8 |
| Sleep apnea | **2.747**** [1.404; 5.372] | **1.463*** [1.065; 2.008] | **1.441*** [1.025; 2.027] | **1.485*** [1.079; 2.044] | 10.4 |
| Hyperlipidemia | 1.231 [0.930; 1.629] | **1.275*** [1.051; 1.548] | 0.981 [0.803; 1.199] | **1.304**** [1.074; 1.584] | 42.8 |
| Heart failure | **3.228*** [1.144; 9.111] | **1.840**** [1.203; 2.813] | 1.591 [0.995; 2.543] | **1.852**** [1.205; 2.845] | 9.9 |
| Hypertension | 1.132 [0.853; 1.502] | **1.234*** [1.018; 1.518] | 0.965 [0.786; 1.185] | **1.265*** [1.035; 1.546] | 56.6 |
| Coronary artery disease | **2.020**** [1.306; 3.127] | 1.256 [0.976; 1.616] | **1.902***** [1.452; 2.493] | 1.220 [0.947; 1.573] | 17.1 |
| Diabetes | 0.742 [0.492; 1.118] | **1.424*** [1.066; 1.901] | 1.197 [0.883; 1.623] | **1.344*** [1.007; 1.793] | 13.0 |
| Mental disorder | **2.839***** [1.852; 4.351] | **1.303*** [1.046; 1.625] | **1.585***** [1.253; 2.007] | **1.304*** [1.044; 1.629] | 24.2 |

Results of binary logistic regression analyses with comorbidities as dependent variables and the dichotomized GOLD subgroups AC vs. BD and AB vs. CD as independent variables. In these analyses, the risk factors $FEV_1$% predicted, BMI, gender, age and pack-years were included as confounders for adjustment. The left part refers to the categorization according to CAT, the right part according to mMRC. The table shows the odds ratios of the binary subcategories, referring to the presence of a comorbidity as well as the 95% confidence intervals; for example the risk for sleep apnea was 2.747-fold elevated for group BD patients according to CAT and 1.441-fold higher for BD patients according to mMRC. The rightmost column shows the prevalence of comorbidities in the population investigated. *$p < 0.05$, **$p < 0.01$, ***$p \leq 0.001$. For the sake of clarity, statistically significant odds ratios of GOLD subgroups and grades were marked in bold.

BD (symptoms) and GOLD CD (exacerbations), and the single comorbidities as dependent variables. Indeed, the change in approach by GOLD was based on the observation that $FEV_1$ alone is not a strong predictor of exacerbation risk; consequently pharmacotherapy recommendations are now based on exacerbations and symptoms alone [6]. In view of the link between exacerbation risk and comorbidities, the revised approach is also in line with previous observations that spirometry alone does not correlate strongly with individual comorbidities [19,20].

Comorbidities definitely play a role in the impact and burden COPD, with cardiovascular events being one of the main causes of mortality [21,22]. We also found significant associations of comorbidities with both the A-D groups and binary groups of symptoms and exacerbations, events that are linked to mortality [23]. In view of this, the associations between the A-D groups and comorbidities appear plausible, in particular as comorbidities might be one of the driving factors for exacerbations. This emphasizes the importance of the identification of comorbidities and might even be helpful to motivate the assessment of suspected comorbidities, especially those of low or intermediate prevalence. Interestingly, when using the binary categories, metabolic disorders such as diabetes, hyperlipidemia and hyperuricemia were associated with exacerbations; all of these disorders are associated with a systemic pro-inflammatory state and therefore may contribute to the development of COPD exacerbations [24–27].

Several mechanisms may underly the observed associations based on CAT. Arterial hypertension was associated with exacerbations, particularly group D, which is in line with recent data on arterial hypertension as a predictor of re-exacerbation [28] and low-grade systemic inflammation as a pathogenetic factor for both entities [1]. Gastrointestinal disorders and sleep apnea were associated with symptoms and exacerbations (group B, stronger with group D). Both can lead to unwitnessed pulmonary aspiration [29,30] and pulmonary infections, and could, therefore, increase symptom burden and exacerbation rates. In line with findings on higher symptom burden and exacerbation rates in patients with Asthma-COPD overlap syndrome [31], we found asthma to be associated with groups B and D which might also be related to chronic airway inflammation. Osteoporosis was associated primarily with group D. It is known that COPD-related systemic inflammation and the risk of osteoporosis are linked, independent from lung function [32]. Heart failure was associated with group D, whereby inflammation could be a major factor [33], in line with results on inflammation in the Framingham study [34]. The risk for coronary artery disease was higher in group B and D. Again, inflammation is a major risk factor for atherosclerosis and coronary artery disease as well as COPD exacerbations. Groups B and D also showed a higher risk of mental disorders. Indeed, COPD patients with a high symptom burden appear to show an increased prevalence of mental disorders [35], probably due to physiological arousals caused by a misinterpretation of their symptoms.

The major strengths of the present study are the large sample size and broad panel of comorbidities assessed. In order to get robust results we only included comorbidities with a prevalence of at least 10%. However, as a cross-sectional and non-interventional study, the results are descriptive and do not permit the inference of causal relationships between A-D groups and comorbidities. Moreover, when using patients' reports of doctors' diagnoses, one of the weaknesses is the lack of independent assessments which could not be performed within COSYCONET. We addressed this to some extent by taking into account disease-specific medication and assuming the presence of comorbidities even in the absence of a report if such medication was taken. This procedure for extracting information from observational studies was followed for all comorbidities for which disease-specific medication could be defined [12]. When using only the reported diagnoses for all comorbidities, the same associations were observed, partially since few patients had disease-specific medication without reporting a corresponding comorbidity. The data available within COSYCONET also did

not permit a definitive diagnosis of Asthma-COPD overlap (ACO) [36], and we could only evaluate the simultaneous occurrence of COPD and asthma.

## 5. Conclusion

The revised GOLD groups A-D, evaluated either separately or in terms of low/high symptoms and low/high exacerbation risk, were related to a broad panel of comorbidities. This was true for both CAT or mMRC as used in the definition of symptoms. The results underline the importance of determining the presence of comorbidities, since many are associated with worse symptoms or higher exacerbation risk, and some of them with both. In patients in GOLD groups B and D who have symptoms and/or exacerbations that do not respond to therapy, the presence of comorbidities should be suspected. Our findings suggest that the revised GOLD groups A-D are clinically informative beyond just as a description of symptoms and exacerbations, with comorbidities likely to play a major role for both.

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