

# Comorbidities and Cause of Death in COPD Patients Compared to Non-COPD Controls: An 8-year Observational Retrospective Healthcare Claims Database Cohort Study

Claus F Vogelmeier<sup>1</sup>, Felix W Friedrich<sup>2</sup>, Patrick Timpel<sup>3</sup>, Nils Kossack<sup>3</sup>, Joanna Diesing<sup>3</sup>, Marc Pignot<sup>4</sup>, Melanie Abram<sup>2</sup>, Michael Gediga<sup>2</sup>, Marija Halbach<sup>2</sup>

<sup>1</sup>Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-Universität Marburg, German Center for Lung Research (DZL), Marburg, Hessen, Germany; <sup>2</sup>AstraZeneca GmbH, Hamburg, Germany; <sup>3</sup>WIG2 GmbH Scientific Institute for Health Economics and Health System Research, Leipzig, Saxony, Germany; <sup>4</sup>ZEG – Center for Epidemiology and Health Research Berlin GmbH, Berlin, Germany

Correspondence: Michael Gediga, AstraZeneca GmbH, Friesenweg 26, Hamburg, 22763, Germany, Email michael.gediga@astrazeneca.com

**Purpose:** Patients with COPD suffer from various comorbidities, seemingly leading to a collective increase in morbidity and mortality. However, comorbidities with COPD have been largely unreported.

**Patients and Methods:** Using healthcare claims data, only the deceased among around 250,000 COPD patients diagnosed in 2011–2018 were evaluated by cause of death (cumulative incidence without competing risk) across a period of up to eight years. Results were compared with 1:1 propensity score-matched controls. Additionally, the prevalence of comorbidities in deceased patients was compared.

**Results:** On average, deceased COPD patients and matched controls lived to be 75.7 and 78.0 years, respectively, and COPD patients had more comorbidities prior to death (mean 4.53 and 3.65). Both respiratory and cardiovascular-related deaths were more likely in COPD patients than in their matched controls (3.3 and 1.6 percentage points higher after eight years), and this was more extreme (9.8 and 3.4 percentage points higher, respectively) in the COPD subgroup with multiple/severe exacerbations; cumulative incidence of death increased with increasing COPD severity. Comorbidity prevalence, especially cardiovascular-related, was higher in COPD patients than in matched controls; COPD patients had a 42% higher risk of heart failure (RR 1.42; 1.38–1.47), 30% higher risk of ischemic heart disease (RR 1.30; 1.25–1.35), and 27% increased risk of atrial fibrillation (RR 1.27; 1.21–1.32).

**Conclusion:** In this real-world observational retrospective cohort study, we found patients with COPD died at a younger age, and developed more comorbidities, than matched controls.

**Plain language summary:** People affected by COPD have other health issues. We studied a cohort of deceased insureds, comparing the health status of those with, to those without COPD, before death. The database had data from 250,000 COPD patients, over a period of up to eight years. More people with COPD died from respiratory or heart-related causes. They also died younger and had more additional health issues, compared to the non-COPD cohort, regardless of cause of death.

The COPD cohort had higher rates of asthma, pneumonia, various heart conditions, dementia, depression, cancer, and osteoporosis, compared to the non-COPD cohort; they were more likely to have these comorbidities diagnosed particularly before death. For example, the risk of pneumonia, atrial fibrillation, and heart failure was up to 83% higher in the COPD cohort. The risk of depression was also 78% higher in those with COPD than in the cohort without COPD.

This information shows a clear link between COPD and other health issues, especially those related to the lungs and heart. Treatment guidelines for COPD patients should target multiple health issues at once.

**Keywords:** exacerbations, mortality, cardiovascular disease, respiratory death, cardiovascular death, multimorbidity

## Introduction

COPD shares mutual risk factors with other diseases,<sup>1–3</sup> which puts patients with COPD at greater risk for cardiovascular (CV) diseases.<sup>4–6</sup> Heart failure,<sup>7</sup> ischemic heart disease and arrhythmias,<sup>8</sup> peripheral artery disease,<sup>9</sup> stroke,<sup>10</sup> as well as osteoporosis,<sup>9,11</sup> depression,<sup>9,12,13</sup> and lung cancer,<sup>14,15</sup> further impact morbidity and mortality.<sup>16–18</sup> COPD can therefore be seen as part of a group of diseases that share pathobiological mechanisms,<sup>19</sup> referred to as chronic systemic inflammatory syndrome.<sup>20</sup> Shared risk factors and chronic systemic pulmonary inflammation contribute to their mutual association,<sup>21–24</sup> particularly between CV and metabolic diseases.<sup>25</sup> The term inflammageing refers to the link between systemic inflammation and accelerated aging associated with chronic diseases like COPD and cardiovascular disease (CVD).<sup>25–27</sup> When these comorbidities cluster, mortality also increases.<sup>16</sup>

The specific features or characteristics of COPD patients who also suffer from CVDs are unclear.<sup>5</sup> Some CVDs seem to be related to COPD progression, while others occur across the range of disease severity.<sup>24,28</sup> COPD patients are also likely to be diagnosed with some comorbidities at a younger age.<sup>2,29</sup> Furthermore, CVD or lung cancer exceed respiratory failure as cause of death in COPD patients,<sup>30,31</sup> therefore comorbidity treatment in COPD patients should be a central part of their treatment plan.<sup>3,32</sup> Additionally, the prevalence of comorbidities like heart failure differs depending on history of exacerbations,<sup>33,34</sup> in COPD patients, there is a sustained increased risk of CV events directly after a COPD exacerbation,<sup>35</sup> particularly high in the first seven days (adjusted hazard ratio, HR, of 8.6; 95% confidence interval, 95% CI, 8.3–8.9).<sup>6</sup> This increased risk was even observed in newly diagnosed COPD patients, with each further exacerbation resulting in an incremental increase in risk.<sup>6,36,37</sup> This increased risk even in mild COPD disease highlights the importance of early comorbidity prevention.

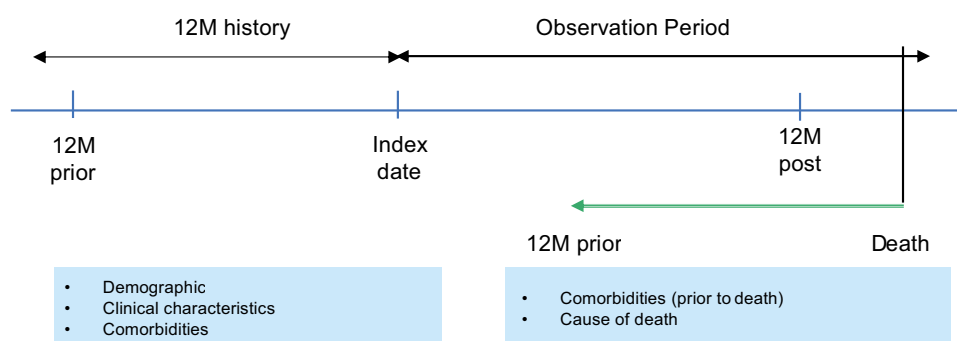
Our recent analysis of German claims data found that COPD increases the all-cause mortality risk by almost 60% (HR 1.57 (95% CI 1.55–1.59)) over matched non-COPD controls. Within three months prior to death, 17.2% and 34.8% of all deceased COPD patients had experienced a severe and moderate exacerbation, respectively.<sup>4</sup> Comorbidity patterns over time and their link to exacerbations in COPD remain largely unknown.<sup>38,39</sup>

This study retrospectively analyzes changes in comorbidities in COPD prior to death, and by cause of death, comparing this to a matched non-COPD population (thereby pinpointing the potential role of COPD). We differentiated between cardiac, respiratory, and cancer-related deaths, meanwhile investigating exacerbation history and comorbidities.

## Materials and Methods

We analyzed previously collected data of deceased patients from the AvoidEx study.<sup>4,40</sup> Healthcare claims data in the WIG2 research database include anonymous longitudinal inpatient and outpatient data from about 4.5 million German Statutory Health Insurance patients. The database and AvoidEx study methods have been reported previously.<sup>4,40</sup>

From the AvoidEx study, patients aged  $\geq 40$  years with a COPD diagnosis from 2011 to 2018 were followed up for at least 12 months ( $n = 250,723$ ), and up to eight years (see Figure 1 for Study Design). The number and severity of



**Figure 1** Study Design. The index date was defined as the first COPD diagnosis recorded after 01 January 2011 and was not considered part of the baseline period. A minimum of 12 months of data prior to the index date (baseline, blue line) as well as a minimum of 12 months of subsequent follow-up period (observation period, blue line) for the study cohort starting at the index date was required. The 12 months prior to death used for analysis is represented by the green line. (Source: Own presentation).

**Abbreviation:** M, Months.

exacerbations during a 12-month baseline period were used to form subgroups: A—no previous exacerbations; B—1 moderate exacerbation; C/D—1 severe exacerbation (D) and/or  $\geq 2$  moderate and/or severe exacerbations (C). Moderate exacerbations were identified by a prescription for either an oral corticosteroid or respiratory antibiotics, and a severe exacerbation was defined by a COPD-related hospitalization or emergency visit.

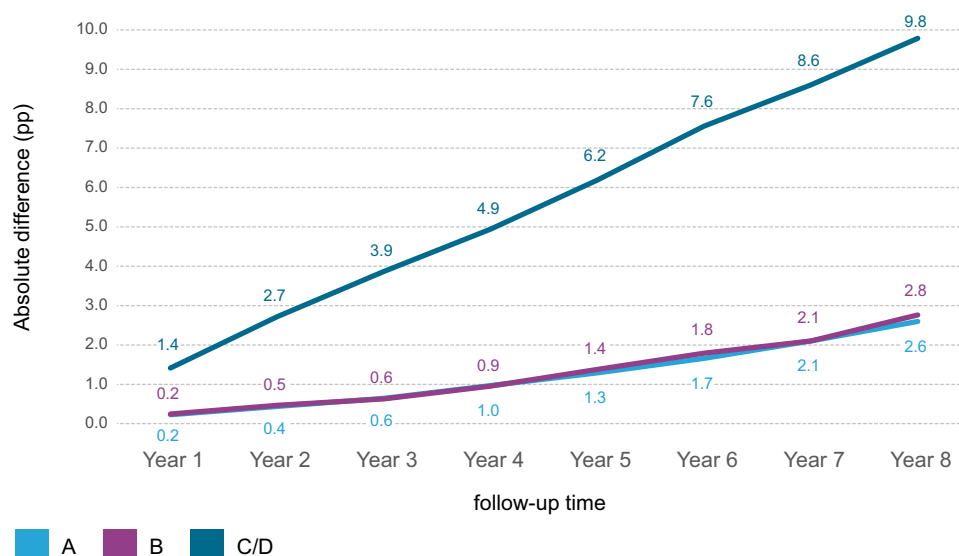
We analyzed cumulative incidence of specific types of death without competing risk of other deaths, using the COPD population and a 1:1 propensity score-matched (PSM) control cohort of non-COPD patients, by exacerbation history. We described cause of death as either respiratory, CV, oncological, other, or unknown, and reported the most commonly documented inpatient discharge ICD-10 code (International Classification of Diseases, 10th Revision) by these categories. Unknown cause of death refers to deaths for which no discharge reason was documented, and other causes of death were those that did not fit into the other categories we defined.

We also analyzed deceased patients (COPD and controls) for prevalence of pre-defined comorbidities in the 12 months prior to death: pneumonia, asthma, osteoporosis, type 2 diabetes mellitus, ischemic heart disease, peripheral artery disease, stroke, atrial fibrillation, heart failure, hypertension, dementia, malignant neoplasm, depression, and anxiety.<sup>4,40</sup> We compared the risk of having the comorbidity of each of COPD and control groups by exacerbation history in the 12 months prior to death, using the relative risk (RR) of COPD to control groups, with 95% confidence intervals (95% CI).

## Results

### Baseline Characteristics

Of the 250,723 patients with COPD identified in our database, 246,701 were matched with the same number of controls. As reported previously,<sup>4</sup> baseline characteristics of COPD patients and controls showed good overall comparability before and after PSM (see [Tables S1](#) and [S2](#) in supplement for matching details and exacerbation subgroup proportions). Of the population studied, 59,025 COPD patients and 41,025 controls died in the eight-year follow-up. This population was stratified into baseline exacerbation subgroups, along with their matched controls. Though all patients' health gradually declined before death, we found COPD patients had more comorbidities than matched controls prior to death and a larger increase in the timeframe. Moreover, milder COPD patients (subgroup A) had the largest increase in comorbidities compared to COPD patients with more severe disease (exacerbation subgroups B and C/D). Differences of cumulative incidence of respiratory-related death between COPD and matched controls, stratified by exacerbation subgroup, are shown in [Figure 2](#).



**Figure 2** Difference (pp) of cumulative incidence of respiratory-related death between COPD and matched controls across follow-up, stratified by exacerbation subgroup. **Abbreviations:** pp, percentage points; A, exacerbation subgroup A (with 0 pre-index exacerbations); B, exacerbation subgroup B (with 1 moderate pre-index exacerbation); C/D, exacerbation subgroup C/D (with  $\geq 2$  moderate and/or  $\geq 1$  severe pre-index exacerbation(s)).

## Cause of Death

Of the 59,025 COPD patients who died, more than half ( $n = 32,031$ ) died in-hospital. Just under half (19,608) of the deceased control patients ( $n = 41,025$ ) died in-hospital.

While chronic lower respiratory diseases accounted for 5.1% of deaths in COPD patients, forms of heart disease other than ischemic heart disease or cerebrovascular disease (4.6%), and malignant neoplasms of respiratory and intrathoracic organs (4.4%) were also found to be common causes of death (Table 1).

Cumulative incidence analyses of specific types of death revealed slight differences between respiratory-, CV-, and cancer-related deaths (Figure 3). We observed highest cumulative incidence of death in the COPD population for respiratory (4.6%; Figure 3 and Table S3 in supplement) and CV-related (4.5%; see Figure 3 and Table S4 in supplement) deaths at year eight. The difference in respiratory death incidence increased over time, with the cumulative incidence being 0.4 pp higher in COPD than in controls at year one rising to 3.3 pp higher at year eight. After eight years, the cumulative incidence of CV-related deaths was 1.6 pp higher in COPD patients than in matched controls.

Cumulative incidence of all-cause death (see Table S5 in supplement) was lowest in COPD exacerbation subgroups A and B, and highest in subgroup C/D throughout the eight years, as reported previously.<sup>4</sup> While this was true for all causes of death we investigated, the difference in respiratory-related deaths in COPD patients to controls was highest in exacerbation subgroup C/D (Figure 2); incidence of death was 1.4 pp higher than controls after the first year, and reached an increased rate 9.8 pp higher than controls by year eight.

Compared to controls, the proportion of CV-related deaths after eight years in the overall COPD cohort was 1.6 pp and 1.5 pp greater in exacerbation subgroup A, respectively (see Figure 3 and Table S6 in supplement). We found the highest exacerbation subgroup differences between COPD and non-COPD control cohorts in subgroup C/D after eight years (3.4 pp) (see Table S6 in supplement).

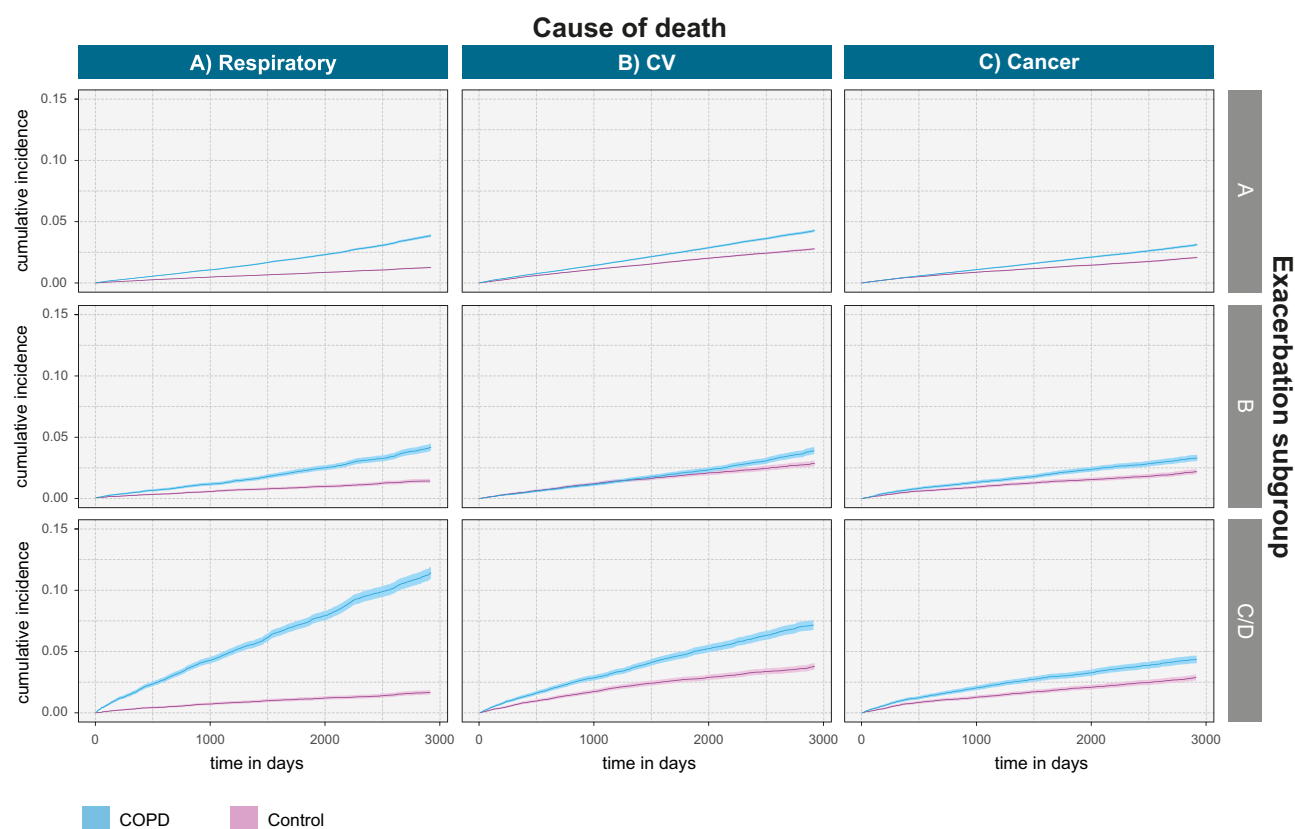
We found less prominent subgroup differences for cancer-related causes of death (see Table S6 in supplement), which were about 1.0 pp to 1.1 pp higher overall for exacerbation subgroups A and B, when compared to respective control patients without COPD. Cumulative incidence of death was 1.5 pp more in COPD C/D patients than controls.

The cumulative incidence of unknown cause of death was higher than other investigated causes (see Tables S7 and S8 and Figure S1 in supplement). However, the difference between COPD and controls increased over time, and subgroup

**Table 1** Top 3 Causes of Death per Category in All Deceased Patients with COPD ( $N = 59,025$ )

| Cause of Death        | Top 3 | ICD-10 Code | Description                                                         | N (%)       |
|-----------------------|-------|-------------|---------------------------------------------------------------------|-------------|
| Respiratory-related   | 1     | J40-J47     | Chronic lower respiratory diseases                                  | 2989 (5.1%) |
|                       | 2     | J09-J18     | Influenza and pneumonia                                             | 2918 (4.9%) |
|                       | 3     | J90-J94     | Other diseases of pleura                                            | 725 (1.2%)  |
| CV-related            | 1     | I30-I52     | Other forms of heart disease                                        | 2744 (4.6%) |
|                       | 2     | I20-I25     | Ischemic heart diseases                                             | 1169 (2.0%) |
|                       | 3     | I60-I69     | Cerebrovascular diseases                                            | 754 (1.3%)  |
| Cancer-related        | 1     | C30-C39     | Malignant neoplasms of respiratory and intrathoracic organs         | 2575 (4.4%) |
|                       | 2     | C15-C26     | Malignant neoplasms of digestive organs                             | 1388 (2.4%) |
|                       | 3     | C76-C80     | Malignant neoplasms of ill-defined, secondary and unspecified sites | 561 (1.0%)  |
| Other causes of death | 1     | A30-A49     | Other bacterial diseases                                            | 1559 (2.6%) |
|                       | 2     | K55-K64     | Other diseases of intestines                                        | 809 (1.4%)  |
|                       | 3     | N17-N19     | Renal failure                                                       | 759 (1.3%)  |

**Abbreviations:** ICD-10 code, International Classification of Diseases, 10th Revision; N, Number of Patients; % indicates the percentage deceased from that cause among all deceased patients.



**Figure 3** Cumulative incidence of death by cause of death category (respiratory-, CV-, and cancer-related), for each exacerbation subgroup (A with 0 pre-index exacerbations; B with 1 moderate pre-index exacerbation; C/D with  $\geq 2$  moderate and/or  $\geq 1$  severe pre-index exacerbation(s)).

**Abbreviations:** CV, cardiovascular; A, B, and C/D, baseline exacerbation subgroups (A: with 0 pre-index exacerbations; B: with 1 moderate pre-index exacerbation; C/D with  $\geq 2$  moderate and/or  $\geq 1$  severe pre-index exacerbation(s)).

C/D showed the highest increase compared to controls (9.9 pp difference after eight years). Other causes of death that do not fall into our pre-defined categories (respiratory-, CV-, or cancer-related) followed a similar pattern, and incidence was higher than that of CV- and cancer-related deaths.

## Comorbidities During 12-month Baseline and in the 12 months Leading up to Death

We analyzed the comorbidity prevalence from baseline (12 months) to the 12-month period preceding death in each of the COPD and control cohorts (by exacerbation subgroup A, B, or C/D), reporting the risk of the prevalence at each timepoint and for each cohort, as well as the RR with 95% CIs ([Table S9](#) in supplement and [Table 2](#)).

## Comparative Evolution of Comorbidities in Exacerbation Subgroups

Patients with no documented exacerbations at baseline (subgroup A) comprised the largest proportion of our deceased COPD population (72%). Patients with one moderate pre-index exacerbation (subgroup B) made up 10% of the population, while 18% of patients had  $\geq 2$  moderate and/or  $\geq 1$  severe exacerbations (pooled subgroup C/D) ([Table 3](#)).

When comparing sociodemographic characteristics of COPD exacerbation subgroups with those of non-COPD controls at baseline and prior to death, we saw that COPD patients were on average younger than matched controls in the overall population (75.7, compared to 78.0 in controls) and exacerbation subgroups, B and C/D ([Table 3](#)). The average number of comorbidities at baseline increased with exacerbation history severity; 2.71, 3.05, and 3.49 for subgroups A, B, and C/D, respectively. Across follow-up, controls experienced increased average comorbidities between 0.56 and 0.71. However, the increase in comorbidities in COPD subgroups was 1.73, 1.62, and 1.35, in subgroups A, B and C/D, respectively, with subgroup A experiencing the greatest increase in number of comorbidities from baseline to

**Table 2** Risk of Comorbidity Occurrence in Each of the COPD and Control Cohorts in the 12 Months Prior to Death, by Exacerbation Subgroup (SUB), and Relative Risk in COPD to Control Cohorts, with 95% Confidence Intervals (CI)

| Comorbidity                       | SUB | Risk (COPD) | Risk (Control) | Relative RISK (95% CI) |
|-----------------------------------|-----|-------------|----------------|------------------------|
| Respiratory-related comorbidities |     |             |                |                        |
| AST                               | A   | 15%         | 6%             | 2.41 (2.30–2.53)       |
|                                   | B   | 22%         | 7%             | 3.28 (2.92–3.70)       |
|                                   | C/D | 27%         | 8%             | 3.31 (3.02–3.63)       |
| PNEU                              | A   | 31%         | 21%            | 1.45 (1.42–1.49)       |
|                                   | B   | 35%         | 21%            | 1.64 (1.53–1.75)       |
|                                   | C/D | 38%         | 21%            | 1.83 (1.73–1.94)       |
| CV-related comorbidities          |     |             |                |                        |
| AF                                | A   | 40%         | 31%            | 1.28 (1.26–1.31)       |
|                                   | B   | 41%         | 30%            | 1.37 (1.30–1.44)       |
|                                   | C/D | 41%         | 32%            | 1.27 (1.21–1.32)       |
| HF                                | A   | 55%         | 41%            | 1.33 (1.31–1.35)       |
|                                   | B   | 57%         | 41%            | 1.38 (1.32–1.43)       |
|                                   | C/D | 62%         | 43%            | 1.42 (1.38–1.47)       |
| HTN                               | A   | 86%         | 83%            | 1.03 (1.03–1.04)       |
|                                   | B   | 87%         | 84%            | 1.03 (1.02–1.05)       |
|                                   | C/D | 87%         | 85%            | 1.02 (1.01–1.04)       |
| IHD                               | A   | 48%         | 37%            | 1.28 (1.26–1.30)       |
|                                   | B   | 50%         | 38%            | 1.32 (1.26–1.38)       |
|                                   | C/D | 50%         | 38%            | 1.30 (1.25–1.35)       |
| PAD                               | A   | 22%         | 14%            | 1.57 (1.52–1.63)       |
|                                   | B   | 22%         | 13%            | 1.71 (1.57–1.87)       |
|                                   | C/D | 22%         | 15%            | 1.47 (1.37–1.58)       |
| STR                               | A   | 15%         | 15%            | 1.05 (1.02–1.09)       |
|                                   | B   | 14%         | 14%            | 0.98 (0.89–1.07)       |
|                                   | C/D | 13%         | 14%            | 0.92 (0.85–1.00)       |
| Other comorbidities               |     |             |                |                        |
| DEM                               | A   | 26%         | 23%            | 1.12 (1.09–1.15)       |
|                                   | B   | 22%         | 23%            | 0.94 (0.87–1.01)       |
|                                   | C/D | 22%         | 22%            | 1.01 (0.95–1.07)       |

(Continued)

**Table 2** (Continued).

| Comorbidity | SUB | Risk (COPD) | Risk (Control) | Relative RISK (95% CI) |
|-------------|-----|-------------|----------------|------------------------|
| DEP         | A   | 30%         | 22%            | 1.34 (1.31–1.38)       |
|             | B   | 34%         | 22%            | 1.56 (1.46–1.67)       |
|             | C/D | 36%         | 20%            | 1.78 (1.68–1.88)       |
| MAL NE      | A   | 43%         | 39%            | 1.10 (1.08–1.12)       |
|             | B   | 49%         | 39%            | 1.26 (1.20–1.31)       |
|             | C/D | 40%         | 39%            | 1.04 (1.00–1.09)       |
| OST         | A   | 16%         | 13%            | 1.25 (1.21–1.30)       |
|             | B   | 19%         | 13%            | 1.45 (1.32–1.59)       |
|             | C/D | 31%         | 13%            | 2.42 (2.25–2.61)       |
| T2DM        | A   | 17%         | 18%            | 0.94 (0.92–0.97)       |
|             | B   | 16%         | 18%            | 0.94 (0.86–1.02)       |
|             | C/D | 16%         | 19%            | 0.83 (0.78–0.89)       |

**Abbreviations:** AF, Atrial fibrillation; AST, Asthma; CI, Confidence Interval; DEP, Depression and anxiety; DEM, Dementia; HF, Heart failure; HTN, Hypertension; IHD, Ischemic heart disease; MAL NE, Malignant neoplasm; N, Number of Patients; OST, Osteoporosis; PAD, Peripheral artery disease; PNEU, Pneumonia; SUB, Baseline exacerbation subgroups (A: with 0 pre-index exacerbations; B: with 1 moderate pre-index exacerbation; C/D with  $\geq 2$  moderate and/or  $\geq 1$  severe pre-index exacerbation(s)); STR, Stroke; T2DM, Type 2 diabetes mellitus.

**Table 3** Sociodemographic Description of Baseline Exacerbation Subgroups at Baseline and Prior to Death

| SUB | Period                                                                     | COPD          | Control       |
|-----|----------------------------------------------------------------------------|---------------|---------------|
| All | N                                                                          | 59,025 (100%) | 41,025 (100%) |
|     | Age before death, mean (SD)                                                | 75.7 (10.6)   | 78.0 (11.3)   |
|     | % male                                                                     | 65.8%         | 60.0%         |
|     | Average number of comorbidities from baseline to before death              | 2.88 / 4.53   | 3.06 / 3.65   |
|     | Increase in average number of comorbidities from baseline to before death* | + 1.65        | + 0.59        |
| A   | N                                                                          | 42,718 (72%)  | 30,560 (74%)  |
|     | Age before death, mean (SD)                                                | 76.0 (10.7)   | 75.7 (10.6)   |
|     | % male                                                                     | 66.7          | 65.8          |
|     | Average number of comorbidities from baseline to before death              | 2.71 / 4.44   | 3.08 / 3.64   |
|     | Increase in average number of comorbidities from baseline to before death* | + 1.73        | + 0.56        |
| B   | N                                                                          | 5707 (10%)    | 4707 (11%)    |
|     | Age before death, mean (SD)                                                | 75.1 (10.6)   | 78.4 (11.5)   |
|     | % male                                                                     | 65.2          | 59.5          |
|     | Average number of comorbidities from baseline to before death              | 3.05 / 4.67   | 3.03 / 3.62   |
|     | Increase in average number of comorbidities from baseline to before death* | + 1.62        | + 0.59        |

(Continued)



**Table 3** (Continued).

| SUB | Period                                                                     | COPD         | Control     |
|-----|----------------------------------------------------------------------------|--------------|-------------|
| C/D | N                                                                          | 10,600 (18%) | 5758 (14%)  |
|     | Age before death, mean (SD)                                                | 75.3 (10.1)  | 78.5 (10.9) |
|     | % male                                                                     | 62.3         | 60.5        |
|     | Average number of comorbidities from baseline to before death              | 3.49 / 4.84  | 2.98 / 3.69 |
|     | Increase in average number of comorbidities from baseline to before death* | + 1.35       | + 0.71      |

**Notes:** Before death refers to the 12 months prior to death. \*including: pneumonia, asthma, osteoporosis, type 2 diabetes mellitus, ischemic heart disease, peripheral artery disease, stroke, atrial fibrillation, heart failure, hypertension, dementia, malignant neoplasm, depression and anxiety.

**Abbreviations:** N, Number of Patients; SUB, Baseline Exacerbation Subgroups (A: with 0 pre-index exacerbations; B: with 1 moderate pre-index exacerbation; C/D with  $\geq 2$  moderate and/or  $\geq 1$  severe pre-index exacerbation(s)); SD, standard deviation.

before death. While the mean number of comorbidities prior to death was highest in patients with several and/or severe prior exacerbations (C/D) (4.84), the increase from baseline was lowest.

In the 12 months before death, COPD patients had a higher risk of being diagnosed with most comorbidities than their matched controls; respiratory- and CV-related comorbidities were more likely to be diagnosed in COPD patients, except for stroke and hypertension where the RR ratio was less pronounced. The RR of pneumonia was up to 1.83 in subgroup C/D (95% CI 1.73–1.94). The RR of PAD in the time before death was high, ranging from 1.47 in subgroup C/D (95% CI 1.37–1.58) to 1.71 in subgroup B (1.57–1.87). In particular, depression and osteoporosis were substantially more likely in COPD patients compared to matched controls, with up to 78% more COPD patients suffering from depression (95% CI 1.68–1.88) in subgroup C/D and the risk of osteoporosis in COPD patients before death was over double than their matched control counterparts (subgroup C/D, RR 2.42, 95% CI 2.25–2.61).

## Discussion

We found that patients with COPD died at a younger age and acquired more comorbidities than matched controls. CV and respiratory comorbidity prevalence were higher and caused more deaths in the COPD cohort than in the control cohort. Although cumulative incidence of death and comorbidity rates were highest in high-risk COPD patients (with severe and/or frequent exacerbations, subgroup C/D), the highest relative increases in comorbidities were found in patients with none, or one moderate prior exacerbation (subgroups A or B, respectively). Comorbidities, even in COPD patients without exacerbations, pose a substantial health risk, and should be treated proactively and just as aggressively, as patients with more active COPD. This also underlines the importance of a COPD diagnosis and adequate treatment at an early stage.

## Cause of Death

Our previous study indicated a substantial association between COPD and increased all-cause mortality risk (by 57%, HR 1.57; 95% CI 1.55–1.59) compared to matched non-COPD controls, when adjusting for comorbidities, age, and sex,<sup>4</sup> which we found again in the present analysis. COPD patients not only died more frequently from respiratory causes than controls, but this difference was already apparent after one year of our observation. CV death occurred more often in COPD patients than in matched controls, which had previously been observed.<sup>41–45</sup> CVD, together with lung cancer, account for up to two-thirds of all deaths in mild-to-moderate COPD patients, while respiratory failure is only predominant in advanced COPD.<sup>21,23,46</sup> In this regard, the cumulative incidence of CV-related death, especially in the frequent and/or severe exacerbators found in our analysis, underlines the importance of adequate comorbidity-specific and exacerbation-preventing treatments to reduce disease burden and mortality rates. Although other studies revealed that COPD is associated with both ischemic and hemorrhagic stroke<sup>47</sup> and about 4% of all deaths in COPD patients are



related to an incident ischemic stroke—<sup>48</sup> our analyses found minimal differences in the RR of stroke between COPD patients and non-COPD controls, especially in subgroup C/D (the most advanced disease subgroup).

In addition to the individual comorbidities assessed, an increased mortality risk in patients with multiple comorbidities was previously reported.<sup>49</sup> As specific comorbidity patterns were previously found to be associated with elevated mortality risk,<sup>50</sup> our findings may contribute to an improved understanding of the disease burden and mortality risk in COPD patients. While our multiple/severe exacerbation subgroup showed the highest mean number of comorbidities at baseline (3.49, increasing to 4.84 prior to death, an increase in mean comorbidities of 1.35), our subgroup with no baseline exacerbations showed the biggest increase in mean number of comorbidities from baseline to before death (+ 1.73). Since we might expect patients without previous COPD exacerbations to be under less intensive medical monitoring than those with frequent or severe exacerbations (defined as COPD-related emergency visit or hospitalization), the larger apparent increase in comorbidities in this timeframe may be a side effect of previously unrecognized comorbidities coming to light with increased healthcare monitoring through COPD care.

At the same time, both the baseline number of comorbidities (3.08, 3.03, 2.98) and the increase in comorbidities to the time up to death (+ 0.56, + 0.59, + 0.71) were similar among the exacerbation subgroup matched controls, showing the effect exacerbations in COPD have on comorbidities. Timely diagnosis and treatment are therefore crucial in slowing down deterioration in all COPD patients, regardless of apparent disease severity measured by exacerbation history.

While we saw a substantially increased cumulative incidence of death in the multiple and/or severe exacerbation cohort (compared to controls and patients with one moderate or no baseline exacerbations), the data on comorbidity development in patients with no or one moderate prior exacerbation, adds to evidence from the EXACOS study. They found that the risk of severe CV events or death was elevated even after one moderate exacerbation—especially in the first seven days (adjusted HR of 1.17; 95% CI 1.05 to 1.31)—and the risk remained elevated up to six months following the moderate exacerbation.<sup>6</sup> These results emphasize the serious risk patients face, even early in their disease course.

## Evolution of Comorbidities with COPD

When analyzing the risk of certain comorbidities prior to death, patients with COPD had a substantially higher risk, compared to their matched controls, and this varied depending on exacerbation history of COPD patients. In previous studies, patients with specific comorbidities like heart failure, had a significantly increased risk of moderate and severe exacerbations compared to COPD patients without heart failure.<sup>51,52</sup> While we did not collect data about the correlation between incident comorbidities and exacerbation development, we did notice that patients with a history of multiple and/or severe exacerbations at baseline had a substantial increase in the prevalence of heart failure during follow-up, resulting in a 42% higher risk in prevalence prior to death.

Comorbidities have a strong relation to disease burden (exacerbations),<sup>51,52</sup> and increased risk of death in patients with COPD.<sup>9</sup> This is evidence that points to targeting exacerbation history for therapeutic management<sup>4,40,53,54</sup> while still recognizing the ties between COPD (even without prior exacerbations) and worsening health status. Underuse of CV medications, particularly beta-blockers, in patients with COPD and CV indications has been described.<sup>55,56</sup> Our results of the elevated CVD burden emphasize a need for more intensive use of therapeutic methods to better manage COPD and concomitant diseases to reduce future exacerbations, worsening comorbidities (especially CV-related), and the risk of death. With significant delays in the diagnosis and management of heart failure in patients with COPD,<sup>57</sup> future studies should focus on associated therapeutic management and prevalence of related comorbid conditions. COPD treatment goals should include not only COPD-specific therapies (to prevent future exacerbations and slow down disease progression) but also a full work-up of associated comorbidity risk-assessment and implementing prevention and/or treatment options for these simultaneously.

## Increased Disease Burden in COPD Vs Non-COPD

Some comorbidities were more prevalent in the COPD cohort: pneumonia, CVD (specifically peripheral artery disease, ischemic heart disease, atrial fibrillation and heart failure), depression and osteoporosis. In all cases, the risk was substantially greater in the COPD population compared to controls. Although prevalence of pneumonia was high before death in both groups (COPD and non-COPD patients), the RR was up to 1.83 in subgroup C/D. COPD patients are at

higher risk due to the altered microbiome in COPD patients and COPD-typical therapies such as inhaled corticosteroids.<sup>58</sup> Interestingly, patients with no previous exacerbations and COPD had a higher increase in pneumonia prevalence than patients with several or severe previous exacerbations.

We identified a relative risk of depression and anxiety in patients with COPD compared to non-COPD controls of up to 1.78 in the 12 months before death (Table 2). This is supported by global epidemiological data, indicating that the odds of depression in COPD patients were 3.53 times higher than in non-COPD participants (95% CI: 2.35–5.29).<sup>59</sup> The presence of depressive symptoms was found to be associated with subsequent exacerbations and hospital admissions in individuals with COPD across the following three years (independent of previous exacerbations history),<sup>60</sup> and even associated with mortality.<sup>61</sup> Therefore, the increase in prevalence towards death we observed is not surprising and demands clinical intervention. While the RR was highest in patients with a history of multiple and/ or severe exacerbations (subgroup C/D), patients with no prior or only one moderate exacerbation still had a RR of 1.34 and 1.56 (subgroups A and B, respectively) of depression and anxiety before death. While we evaluated exacerbation history at baseline only, and do not know how COPD developed in these patients after baseline, the small risk difference among COPD and matched controls at baseline (with subgroup A controls even having a higher risk at baseline), reinforce the importance of targeting healthcare resources to patients, even if they have low (COPD) disease activity.

However, the increased prevalence of dementia in patients with COPD in our study is in line with analyses of other groups and may be strongly associated with increased age.<sup>62</sup> In accordance with other studies, we also detected no difference between COPD and non-COPD controls in terms of diabetes frequency.<sup>63</sup>

CV comorbidities are substantially more common in the COPD cohort and cause more deaths than in the control cohort. Our findings are also supported by analyses that found lung disease is independently associated with ischemic heart disease and heart failure,<sup>64</sup> and evidence showing associations between CV and respiratory diseases, particularly for ischemic heart disease and heart failure, which were found to substantially contribute to all-cause mortality.<sup>64</sup> The increasing prevalence of ischemic heart disease and heart failure from baseline leading up to death that we observed—especially in non- and moderate exacerbators (subgroups A and B)—underline the additive contribution of concomitant diseases that elevate disease burden. At the same time, analyses show that patients with lung disease are less likely to receive coronary revascularization or cardio-selective beta-blockers, which may also affect disease progression.<sup>64–66</sup>

## Limitations

We looked only at a population of deceased COPD patients, which may create a selection bias for patients with underlying factors contributing to the worsening in comorbidity prevalence. However, this should nonetheless be considered when treating patients with seemingly stable or less-active COPD.

Adding to the previously described strengths and weaknesses of our methodological approach,<sup>4</sup> the following additional limitation should be considered: Although we used PSM to compare COPD patients to matched controls and matching indicated general comparability of COPD and non-COPD groups prior to analysis, results may suffer from residual confounding; either due to incomplete adjustment or confounding by unknown/unmeasured characteristics. Due to the elevated mortality rate in patients with COPD, baseline characteristics of deceased patients differed slightly in our analysis; we found higher mortality rates among patients with less comorbidity burden, if COPD is present additionally. These differences might also have affected clinical patterns observed prior to death.

## Conclusion

We describe comorbidity prevalence in a cohort of deceased COPD insureds and matched deceased non-COPD controls. COPD appears as a “systemic” disease, with a higher prevalence of certain comorbidities than in matched controls, in the time before death. Our results emphasize the role key therapeutic targets at an early stage to address both exacerbations and comorbidities that play a crucial role in mortality risk, thereby improving disease outcomes.

## Abbreviations

CI, confidence intervals; CVD, cardiovascular disease(s); CV, cardiovascular; HR, hazard ratio; pp, percentage point; PSM, propensity score-matched/matching; RR, relative risk.

## Data Sharing Statement

Our epidemiology data is drawn from calculations from a large dataset. The pseudonymized healthcare data was made available to us for the purpose of this project, and is stringently protected in a physical location. Due to data protection reasons, it cannot be made available to the public. This is to comply with European General Data Protection Regulation and preserve individuals' privacy.

## Ethics Approval and Informed Consent

No primary patient data was collected for the conduct of this research. According to the 10th chapter of book V of social code in Germany (SGB V, Sozialgesetzbuch), anonymised healthcare claims data can be used for research purposes, therefore ethics approval of this secondary data were not required. Only WIG2 employees were granted access to the data for the research, and only aggregated results were generated and presented.

## Consent for Publication

This work has not been published previously, and it is not under consideration for publication elsewhere. If accepted, it will not be published elsewhere in the same form in English or in any other language including electronically, without the written consent of the copyright holder. The publication and all data, visualizations and content have been approved for publication by all authors.

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One of the authors, Patrick Timpel, was employed by WIG2 GmbH at the time of the analyses and his drafting of the manuscript, however, is now affiliated with fbeta GmbH, Akazienstr. 31, 10823, Berlin, Deutschland, since January 1<sup>st</sup>, 2024.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

JD, PT, and NK are employees of WIG2 GmbH. WIG2 was contracted by AstraZeneca to support designing the study, run the analyses and develop/adapt the manuscript draft. MP is an employee of ZEG Berlin GmbH. ZEG Berlin was contracted by AstraZeneca to support managing and designing the study. FWF, MA, and MH are employed by AstraZeneca. CFV reports grants and/or personal fees from Aerogen, AstraZeneca, Boehringer Ingelheim, CSL Behring, Chiesi, GlaxoSmithKline, Grifols, Insmmed, Menarini, Novartis, Nuaira, MedUpdate, Aerogen, Sanofi, and Roche outside the submitted work. The authors report no other conflicts of interest in this work.

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