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ORIGINAL RESEARCH

Major Adverse Cardiovascular Events and Cause-Specific Mortality After Hospitalisation in COPD

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Purpose: People with chronic obstructive pulmonary disease (COPD) are at elevated risk of cardiovascular events and mortality. We aimed to determine, in a COPD population, the relationship between hospitalization and post-discharge one-year rates of (i) major adverse cardiovascular events (MACE) and (ii) cause-specific mortality.

Patients and Methods: We conducted a prospective cohort study on a COPD population, between 01/01/2010 and 31/12/2019, using nationally-representative, routinely collected electronic healthcare records in England (Clinical Practice Research Datalink Aurum primary care data, linked with secondary care [Hospital Episode Statistics], and mortality [Office of National Statistics] data). The exposure was ≥one hospitalization, and the control group was no hospitalization. Outcomes were one-year rates of (i) non-fatal MACE (acute coronary syndrome, arrhythmia, heart failure, or ischemic stroke) and (ii) cause-specific mortality. Exposures were stratified by hospitalization type (elective and emergency) and cause (all-cause, cardiovascular, respiratory, and non-cardiorespiratory). We implemented adjusted Cox proportional hazard regression models, and sensitivity doubly robust propensity score-adjusted models.

Results: Hospitalized COPD patients had significantly higher rates (incidence rate [IR, per 1000 person-years]; adjusted hazard ratio {aHR} [95% confidence interval {95% CI}] of MACE in the year following hospitalization, whether elective (IR=33.3; 7.04 [6.19–8.07]) or emergency (IR=70.0; 8.85 [7.78–10.06]), versus those without hospitalization (IR=3.4). Emergency hospitalization was associated with increased all-cause mortality (IR=146.5; 2.49 [2.37–2.61]), regardless of hospitalization cause, compared to those not hospitalized (IR=30.3). Elective hospitalization was also associated with increased all-cause mortality (IR=54.6; 1.32 [1.25–1.38]), except for cardiovascular elective hospitalization (1.00 [0.89–1.12]). Cause-specific mortality was influenced largely by hospitalization cause.

Conclusion: Hospitalized COPD patients experienced increased subsequent one-year MACE and mortality rates, regardless of hospitalization cause or type. Hospitalization for any reason in COPD patients provides an opportunity to provide primary prevention for MACE.

Keywords: COPD, MACE, cause-specific mortality, hospitalization

Introduction

Hospitalization rates among the general population in the UK have increased faster than population growth.[1] From 1999 to 2019, there has been a 105% increase in rate of hospitalization for respiratory diseases,[1,2] rising from ninth to fourth most common cause of hospitalization. By 2019, UK respiratory hospitalizations (31,597.7 admissions per million people) were more common than endocrine, nutritional, and metabolic disease hospitalizations (including type-II diabetes mellitus [T2DM], at 7288.3 admissions per million people), and circulatory system hospitalizations (26,627.5 admissions per million people). Chronic obstructive pulmonary disease (COPD) affects approximately 5% of UK residents aged 40 years and older[3] and contributes greatly to hospitalization admission and readmission rates. Additionally, prevalence of COPD[3] and hospital admission rates within COPD[4] have risen.

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Comorbid cardiovascular disease (CVD) is frequent in people with COPD (9% to 60%, depending on CVD type).[5] COPD is also associated with major adverse cardiovascular events (MACE),[6] and, moreover, severe exacerbations of COPD requiring hospitalization are associated with 3.18-fold increase in subsequent non-fatal MACE over a mean of 1.2 years.[7] In addition to COPD-associated morbidity, COPD also has a high mortality burden, accounting for 30,000 deaths annually in the UK.[8] Significant predictors of COPD mortality (in addition to age, male sex, and CVD) include hospitalization for acute exacerbation and hospital readmission within 30 days.[9]

Given the severity of outcomes associated with COPD and the burden of COPD hospitalizations on health systems, understanding the effect of hospitalization amongst people with COPD has important implications for clinical practice as this may provide an opportunity to optimize care and prevent re-admissions and death. We, therefore, aimed, in a COPD population from a large UK-based primary care longitudinal dataset broadly representative of the English population, to investigate the association between hospitalization (by hospitalization type [elective or emergency], and hospitalization cause [cardiovascular, respiratory, or non-cardiorespiratory]) and subsequent risk of (i) non-fatal MACE and (ii) mortality.

Materials and Methods

Data Source

The study population was defined from primary care records using the Clinical Practice Research Datalink (CPRD) Aurum database (May 2022 build).[10] CPRD Aurum data are de-identified, routinely collected, electronic healthcare records covering ~20% of the UK population, and are representative of age, sex, and region.[11] Aurum data were linked with Hospital Episodes Statistics (HES) secondary care data,[12] Index of Multiple Deprivation (IMD) socioeconomic data,[13] and Office of National Statistics (ONS) mortality data[14] (see pg. 2 in the supplementary document for linkage practices).

Study Participants

Inclusion criteria were (1) COPD diagnosis (validated methodology,[15] codelist: https://github.com/NHLI-Respiratory-Epi/Hospitalisations-MACE-in-COPD), (2) aged ≥40-years-old, (3) current or ex-smokers, (4) data in CPRD between 1st January 2010 to 31st December 2019, (5) registered at primary care provider ≥one year before study start, and (6) data of "research quality"[11] (see supplement for CPRD practices).

Exposures, Outcomes, and Study Design

Study Groups and Design

We conducted a prospective cohort study. Broadly, the exposure was hospitalization. We stratified hospitalization by type (elective or emergency), cause (all-cause, respiratory, cardiovascular, and non-cardiorespiratory, using ICD-10 codes), and cause-type (eg, cardiovascular-emergency). For the exposed group, start of follow-up was date of hospital discharge (after meeting inclusion criteria). For the control group (no hospitalization), start of follow-up was the latest date on which all inclusion criteria were met. In the absence of the outcome, patients were followed up for one year, or until end of CPRD registration or study period (Figure 1).

Outcomes

Outcomes included (i) non-fatal MACE, and (ii) mortality (codelists: https://github.com/NHLI-Respiratory-Epi/Hospitalisations-MACE-in-COPD). MACE was defined using secondary care ICD-10 codes as acute coronary syndrome (ACS), arrhythmia, heart failure (HF), or ischemic stroke (stroke). People who died during follow-up for the non-fatal MACE analysis were censored. Mortality was defined using ICD-10 codes in ONS data, and was stratified into all-cause mortality, COPD-specific mortality, and cardiovascular-specific mortality.

Statistical Analysis

Baseline Characteristics and Covariates

Baseline characteristics were taken nearest as possible to start of follow-up date (see supplement for specific time-related definitions). Characteristics were described as mean (standard deviation) for continuous data, and as counts (percentage) for categorical data. We described age, sex, smoking status (ex or current), body mass index (BMI, underweight:<18.5kg.m^{-2};

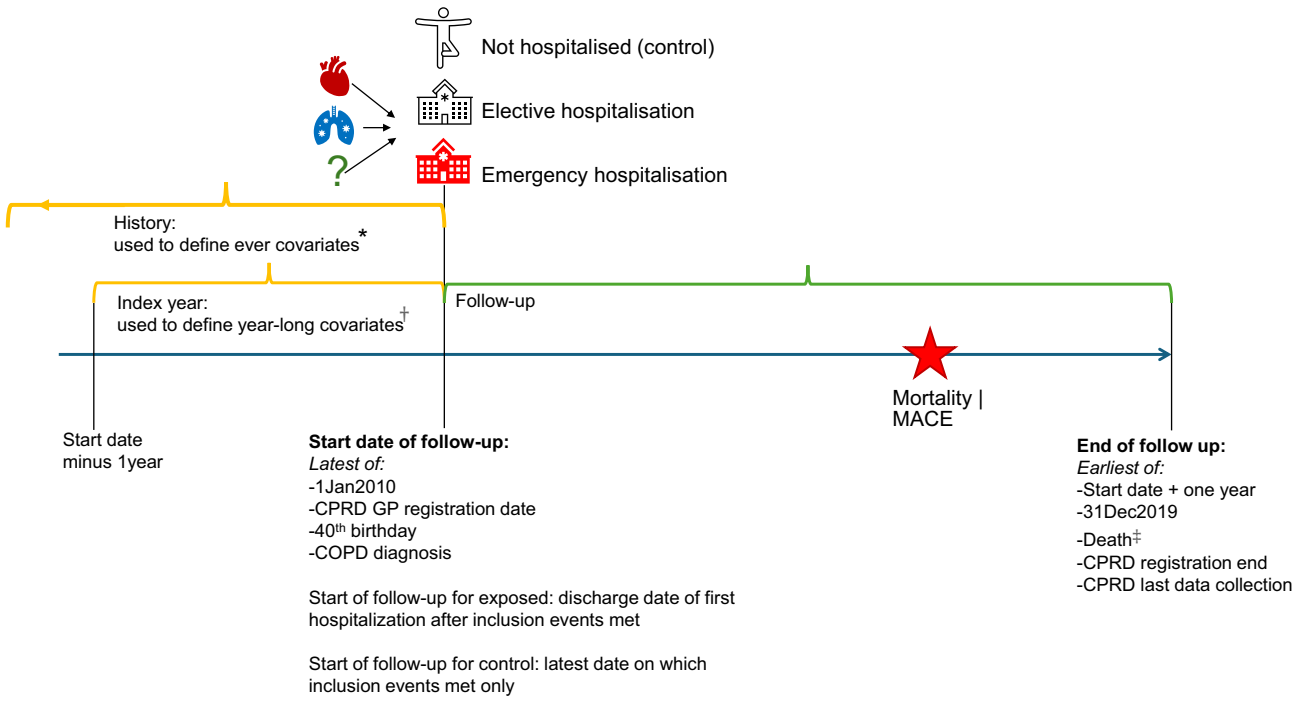

Figure 1 Study design. *Ever covariates: anxiety, asthma, cardiovascular disease history, depression, gastro-oesophageal reflux disease (GORD), hypertension, lung cancer, type II diabetes mellitus, smoking status (most recent), and body mass index (most recent). †Index year covariates: COPD exacerbation group, COPD long-acting medication, COPD short-acting medication. Other covariates obtained from primary care record or linked data: age, sex, and socioeconomic deprivation. ‡Death was censored for MACE outcome analysis.
Abbreviation: MACE, Major Adverse Cardiovascular Event (acute coronary syndrome OR heart failure OR arrhythmia OR ischaemic stroke).

healthy weight: 18.5–24.9kg.m^{-2}; overweight: 25.0–29.9kg.m^{-2}; obese:>30kg.m^{-2}), socioeconomic deprivation (IMD quintiles, IMD1=least deprived to IMD5=most deprived); COPD acute exacerbations, MRC dyspnea scale, GOLD airflow obstruction group, short-acting bronchodilators, COPD medications (long-acting bronchodilators and inhaled corticosteroids), asthma, depression, anxiety, gastro-esophageal reflux disease (GORD/GERD), lung cancer, hypertension, T2DM, and cardiovascular history (ACS, arrhythmia, MI, HF, or stroke; recorded in primary or secondary care) (codelists:https://github.com/NHLI-Respiratory-Epi/Hospitalisations-MACE-in-COPD).

Primary Analysis

We calculated absolute event rates (number and percentage), incidence rates (IR, per 1000-person-years), and implemented Cox proportional hazard regressions for (i) MACE and (ii) mortality (all-cause, cardiovascular-specific, and COPD-specific). Cox models were adjusted for aforementioned baseline characteristics except BMI, MRC score, and GOLD group due to missing-not-at-random. Analyses were done using Stata 17.[16]

Sensitivity Analyses

We conducted multiple sensitivity analyses, including (i) regressions adjusted for all covariates (including BMI, MRC score, and GOLD group), (ii) regressions amongst individuals without hospitalization in the year preceding follow-up, and (iii) doubly robust propensity score-adjusted regressions[17] to address confounding by indication in those hospitalized versus those not hospitalized. We applied Bonferroni corrections.

Secondary Analysis

We conducted a descriptive analysis, calculating percentage of primary cause of death of people in each study substratum (eg, emergency-cardiovascular hospitalization).

Ethical Approval and Patient Consent

CPRD has NHS Health Research Authority (HRA) Research Ethics Committee (REC) approval to allow the collection and release of anonymised primary care data for observational research [NHS HRA REC reference number: 05/MRE04/87]. Each year CPRD obtains Section 251 regulatory support through the HRA Confidentiality Advisory Group (CAG), to enable patient identifiers, without accompanying clinical data, to flow from CPRD contributing GP practices in England to NHS Digital, for the purposes of data linkage [CAG reference number: 21/CAG/0008]. The protocol for this research was approved by CPRD's Research Data Governance (RDG) Process (protocol number: 22_002514) and the approved protocol is available upon request. Linked pseudonymised data was provided for this study by CPRD. Data is linked by NHS Digital, the statutory trusted third party for linking data, using identifiable data held only by NHS Digital. Select general practices consent to this process at a practice level with individual patients having the right to opt-out.

Results

Descriptive Characteristics

Amongst 312,121 COPD patients, 238,831 (76.5%) had at least one hospitalization (Figure 2). Patients hospitalized were approximately five years older than those not hospitalized. More men (53.5%) than women (46.5%) were hospitalized. Prevalence of hypertension was higher amongst those hospitalized (51.6%) than not hospitalized (38.1%). Similarly, cardiovascular history was higher in people hospitalized (28.2%, aligning approximately with the population [24.0%]) versus those not hospitalized (10.4%). COPD exacerbations distribution differed slightly between groups, where those hospitalized tended to have fewer people in the "no exacerbations" group and more in the "any moderate, 1 severe" group. Additionally, people admitted as emergency cases tended to have fewer people in the "no exacerbations" group and more in the "any moderate, 1 severe" group, across hospitalization causes. Finally, patients not hospitalized (10.1%) had a low prevalence of triple therapy prescription versus those hospitalized (30.4%). Cause- and type-specific hospitalization descriptive statistics are available in the supplement (Table E1).

Sensitivity Analyses

We conducted several sensitivity analyses. Regression outputs were almost identical across the primary analysis and sensitivity analyses. We, therefore, report primary analysis outputs within this manuscript, and we report all sensitivity analysis results in the online data supplement (Tables E2–E6).

Hospitalization and MACE

Elective and Emergency Hospitalization and MACE

Across the whole cohort, there were 12,059 (3.9%) MACEs. The number of events amongst people hospitalized and not hospitalized was 11,881 (5.0%) and 248 (0.3%), with an incidence rate per 1000 person-years (IR) [95% confidence interval {95% CI}] of 51.0 [50.1, 51.9] and 3.4 [3.0, 3.8], respectively. MACE rate (IR [95% CI]) was 33.3 [32.3, 34.4] among electively hospitalized patients, and 70.0 [68.4, 71.6] in emergency hospitalized patients. There was a similar trend in MACE rates between patients hospitalized electively and as emergencies across all specific hospitalization causes (cardiovascular, respiratory, or non-cardiorespiratory), the highest rates of which were in cardiovascular hospitalizations, followed by respiratory hospitalizations and non-cardiorespiratory hospitalizations (Table E7 for individual event rates).

Hospitalization was strongly associated with subsequent MACE, whether elective (adjusted hazard ratio {aHR} [95% CI]=7.04 [6.19, 8.07]) or emergency (aHR [95% CI]=8.85 [7.78, 10.06]). Across all hospitalization causes, emergency hospitalization was more strongly associated with subsequent MACE versus elective hospitalization. Although all hospitalization causes and types were associated with subsequent MACE, cardiovascular hospitalizations were most strongly associated (elective: aHR [95% CI]=17.90 [15.45, 20.74]; emergency: aHR [95% CI]=19.83 [16.76, 22.40]), than were respiratory (elective: aHR [95% CI]=6.61 [5.31, 8.22]; emergency: aHR [95% CI]=7.22 [6.19, 8.43]) and non-cardiorespiratory (elective: aHR [95% CI]=6.17 [5.42, 7.03]; emergency: aHR [95% CI]=7.44 [6.52, 8.49]) (Figure 3).

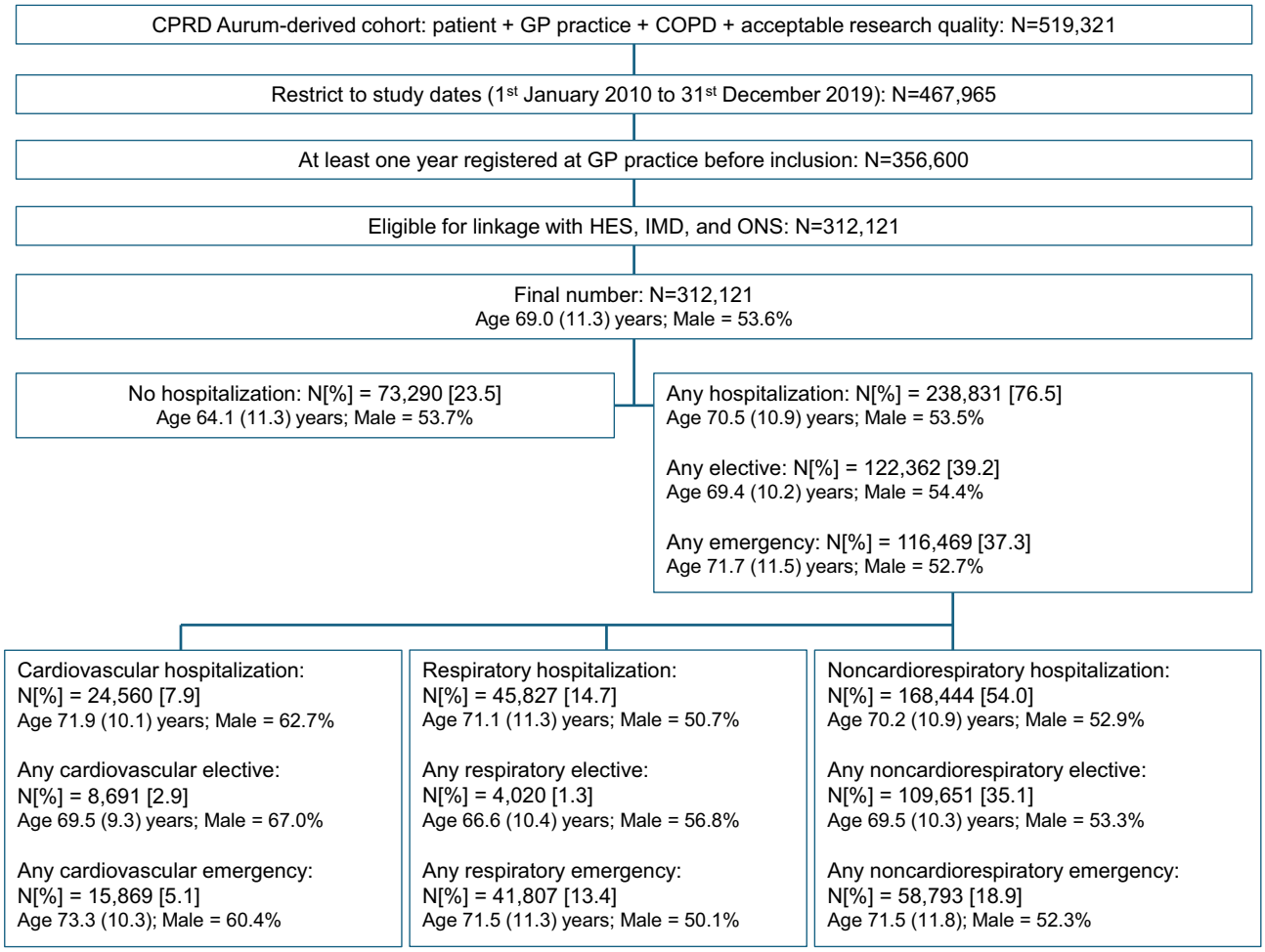

Figure 2 Description of inclusion criteria, study cohort, and individual study groups. Summary statistics are presented as Number [percentage] or as mean (standard deviation). Additional details of CPRD data research quality can be found in the supplement.
Abbreviations: CPRD, Clinical Practice Research Datalink; GP, General Practitioner; COPD, chronic obstructive pulmonary disease; HES, Hospital Episode Statistics; IMD, Index of Multiple Deprivation; ONS, Office of National Statistics.

Hospitalization and Mortality

Elective (All-Cause) Hospitalization and Mortality

Across 122,362 electively hospitalized patients, there were 6511 (5.3% of elective hospitalizations) subsequent all-cause deaths (IR [95% CI]=54.6 [53.3, 56.0]) (Table E8). COPD-specific mortality following any elective hospitalization accounted for 843 deaths (0.7% of elective hospitalizations) and accounted for 3.5% of all deaths (Table E9). Cardiovascular-specific mortality following elective hospitalization accounted for 1084 deaths (0.9% of elective hospitalizations) and accounted for 4.4% of all deaths (Table E10). In general, mortality rates were lower following elective hospitalizations than emergency hospitalizations, across all hospitalization causes.

All-cause elective hospitalization was associated with increased all-cause mortality (aHR [95% CI]=1.32 [1.25, 1.38]), but deceased COPD-specific (aHR [95CI%]=0.58 [0.53, 0.65]) and cardiovascular-specific mortality (aHR [95% CI]=0.56 [0.51, 0.61]) (Figure 4).

Elective (Cardiovascular-, Respiratory-, and Noncardiorespiratory-Specific) Hospitalization and Mortality

(i) All-cause mortality

The highest rate (IR [95% CI]) of all-cause mortality amongst patients electively hospitalized were amongst those hospitalized for respiratory causes (83.1 [74.4, 92.7), followed by non-cardiorespiratory causes (54.3 [53.0, 55.8]) and cardiovascular causes (45.3 [41.0, 50.1) (Table E8). There was a significant association between all-cause mortality and

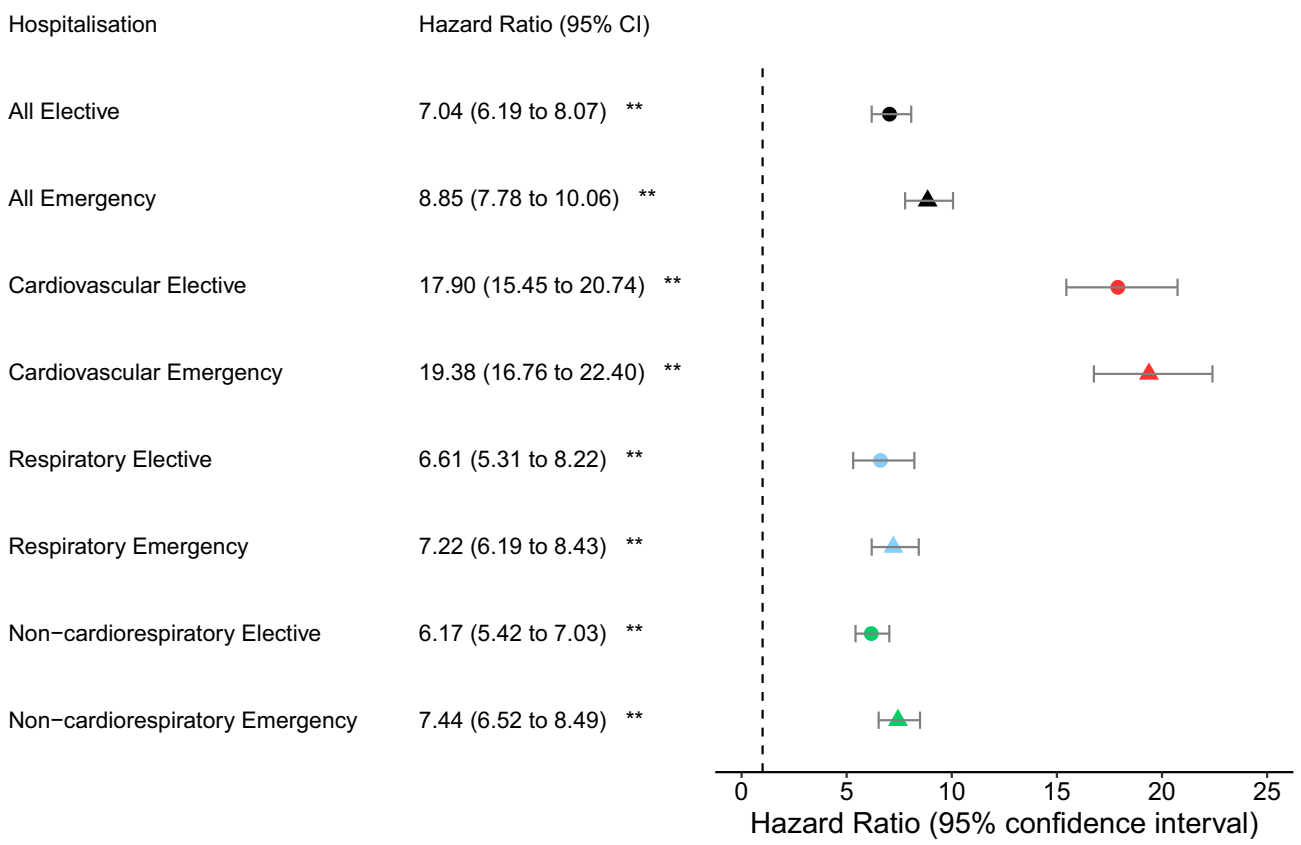

Figure 3 Association between hospitalization cause and type and subsequent MACE among people with COPD. Each hospitalization group substratum (eg, cardiovascular elective hospitalization) is compared with people with COPD without hospitalization as the control group. **Indicates statistical significance.
Abbreviation: MACE, Major Adverse Cardiovascular Event (acute coronary syndrome OR heart failure OR arrhythmia OR ischaemic stroke).

all-cause elective hospitalization (aHR [95% CI]=1.32 [1.25, 1.38]), respiratory elective hospitalization (aHR [95% CI] =1.99 [1.77, 2.24]) and non-cardiorespiratory elective hospitalization (aHR [95% CI]=1.31 [1.25, 1.38]), but not cardiovascular electively hospitalization (Figure 4).

(ii) COPD-specific mortality

COPD-specific mortality rate (IR [95% CI]) was highest amongst patients electively hospitalized for respiratory causes (14.5 [11.2, 18.8]), followed by non-cardiorespiratory causes (6.7 [6.2, 7.2]) and cardiovascular causes (6.6 [5.1, 8.5]) (Table E9). Elective hospitalization was associated with a reduction in COPD-specific mortality for any hospitalization cause (aHR [95% CI]=0.58 [0.53, 0.65]), cardiovascular cause (aHR [95% CI]=0.53 [0.40, 0.70]), and non-cardiorespiratory cause (aHR [95% CI]=0.53 [0.45, 0.59]), but not respiratory cause (Figure 4).

(iii) Cardiovascular disease-specific mortality

Cardiovascular-specific mortality rate (IR [95% CI]) was highest amongst patients electively hospitalized for cardiovascular causes (19.8 [17.0, 23.0]), followed by respiratory causes (11.5 [8.6, 15.4]), and non-cardiorespiratory causes (7.9 [7.4, 8.5]) (Table E10). There were significantly fewer cardiovascular-specific deaths among elective hospitalizations (aHR [95% CI]=0.56 [0.51, 0.61]) and non-cardiorespiratory elective hospitalizations (aHR [95% CI] =0.50 [0.45, 0.55]), but there was no association between COPD-specific mortality and respiratory elective hospitalizations or cardiovascular elective hospitalizations (Figure 4).

Emergency (All-Cause) Hospitalization and Mortality

Amongst 116,469 emergency hospitalized patients, there were 15,672 (13.5% of emergency hospitalizations) subsequent all-cause deaths (IR [95% CI]=146.5 [144.2, 148.8]) (Table E8). COPD-specific mortality following any emergency hospitalization accounted for 4545 deaths (3.9% of emergency hospitalizations) and accounted for 18.7% of all deaths

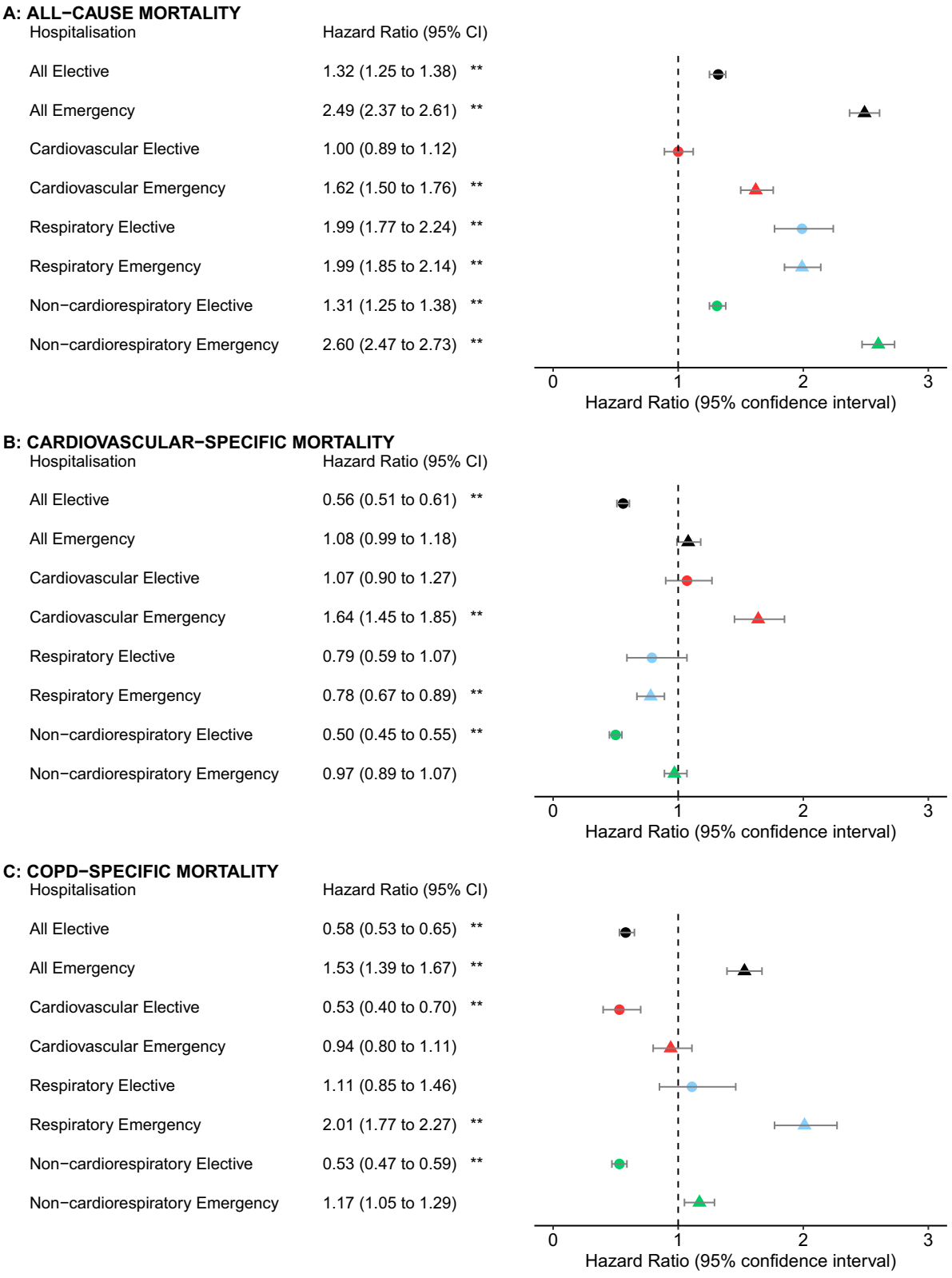

Figure 4 Association between hospitalization cause and type and subsequent mortality ((**A**) All-cause mortality, (**B**) Cardiovascular-specific, and (**C**) COPD-specific mortality) among people with COPD. Each hospitalization group substratum (eg, cardiovascular elective hospitalization) is compared with people with COPD without hospitalization as the control group.
Note: **Indicates statistical significance.

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(Table E9). Cardiovascular-specific mortality following any emergency hospitalization accounted for 3265 deaths (2.8% of emergency hospitalizations) and accounted for 13.4% of all deaths (Table E10). Moreover, compared with those not hospitalized, all-cause emergency hospitalization was associated with an increased all-cause mortality (aHR [95% CI] =2.49 [2.37, 2.61]), COPD-specific mortality (aHR [95% CI]=1.53 [1.39, 1.67]), but not cardiovascular-specific mortality (aHR [95% CI]=1.08 [0.99, 1.18]) (Figure 4).

Emergency (Cardiovascular-, Respiratory-, and Noncardiorespiratory-Specific) Hospitalization and Mortality

(i) All-cause mortality

When stratified by emergency hospitalization cause, mortality rate (IR [95% CI]) was highest in patients hospitalized for respiratory causes (161.0 [157.0, 165.1), followed by all emergency hospitalizations (146.5 [144.2, 148.8]); and were similar in non-cardiorespiratory causes (139.5 [136.4, 142.7]) and cardiovascular causes (134.8 [129.0, 140.9]) (Table E8). Emergency hospitalization was associated with increased all-cause mortality across all hospitalization causes (aHR [95% CI]: all-cause=2.49 [2.37, 2.61]; non-cardiorespiratory=2.60 [2.47 to 2.73]; respiratory=1.99 [1.85, 2.14]; cardiovascular=1.99 [1.85, 2.14]) (Figure 4).

(ii) COPD-specific mortality

COPD-specific mortality rates (IR [95% CI]) were highest in respiratory emergency hospitalizations (68.6 [66.1, 71.2]), followed by all-cause hospitalization (39.9 [38.8, 41.1]), and similar rates in non-cardiorespiratory causes (24.1 [22.9, 25.4]) and cardiovascular causes (25.0 [22.6, 27.6]) (Table E9). COPD-specific mortality was associated with respiratory emergency hospitalization (aHR [95% CI]=2.01 [1.77, 2.27]) and all-cause emergency hospitalization (aHR [95% CI]=1.53 [1.39, 1.67]), but not with cardiovascular emergency hospitalization or non-cardiorespiratory emergency hospitalization (Figure 4).

(iii) Cardiovascular disease-specific mortality

Cardiovascular-specific mortality rate (IR [95% CI] was highest for patients admitted as cardiovascular emergencies (57.2 [53.5, 61.1]), followed by similar rates in all-cause emergency hospitalizations (28.5 [27.5, 29.5]), respiratory emergency hospitalizations (24.3 [22.8, 25.8]), and non-cardiorespiratory emergency hospitalizations (24.0 [22.7, 25.2]) (Table E10). In addition, cardiovascular emergency hospitalizations were associated with increased cardiovascular mortality (aHR [95% CI]=1.64 [1.45, 1.85]), but respiratory emergency hospitalizations were associated with reduced cardiovascular hospitalizations (aHR [95% CI]=0.78 [0.67, 0.89]). There was no association between cardiovascular mortality and all-cause emergency hospitalization or non-cardiorespiratory hospitalization (Figure 4).

Cause of Death

We conducted a descriptive analysis of the primary cause of death stratified by hospitalization cause and type. Amongst patients who were hospitalized, 24,364 (7.8%) died, versus 2181 (3.0%) of people not hospitalized. The ICD-10 chapters with the highest frequency of events included Chapter II (neoplasms), Chapter IX (circulatory system), and Chapter X (respiratory system) (Figure 5). Although the number of deaths differed between study groups, distribution of cause was similar. Across all hospitalization causes, the proportion of deaths was greater amongst emergency hospitalizations versus elective hospitalizations (Figure 5 and Table E11).

Discussion

Statement of Principal Findings

We demonstrated, in a nationally representative population of people with COPD, that hospitalization for any cause is strongly associated with subsequent one-year MACE rates. Scaling our results according to the wider COPD population,[3,18] approximately two million people with COPD will have some type of hospitalization, and, amongst them, approximately 106,000 will have a MACE within one year, suggesting a missed opportunity for optimizing cardiovascular care in this population. Secondly, we demonstrated that the relationship between hospitalization and subsequent one-year mortality is influenced by hospitalization cause and type. Emergency hospitalization was generally associated with increased one-year all-cause mortality, with cause-specific mortality aligning with the reason for

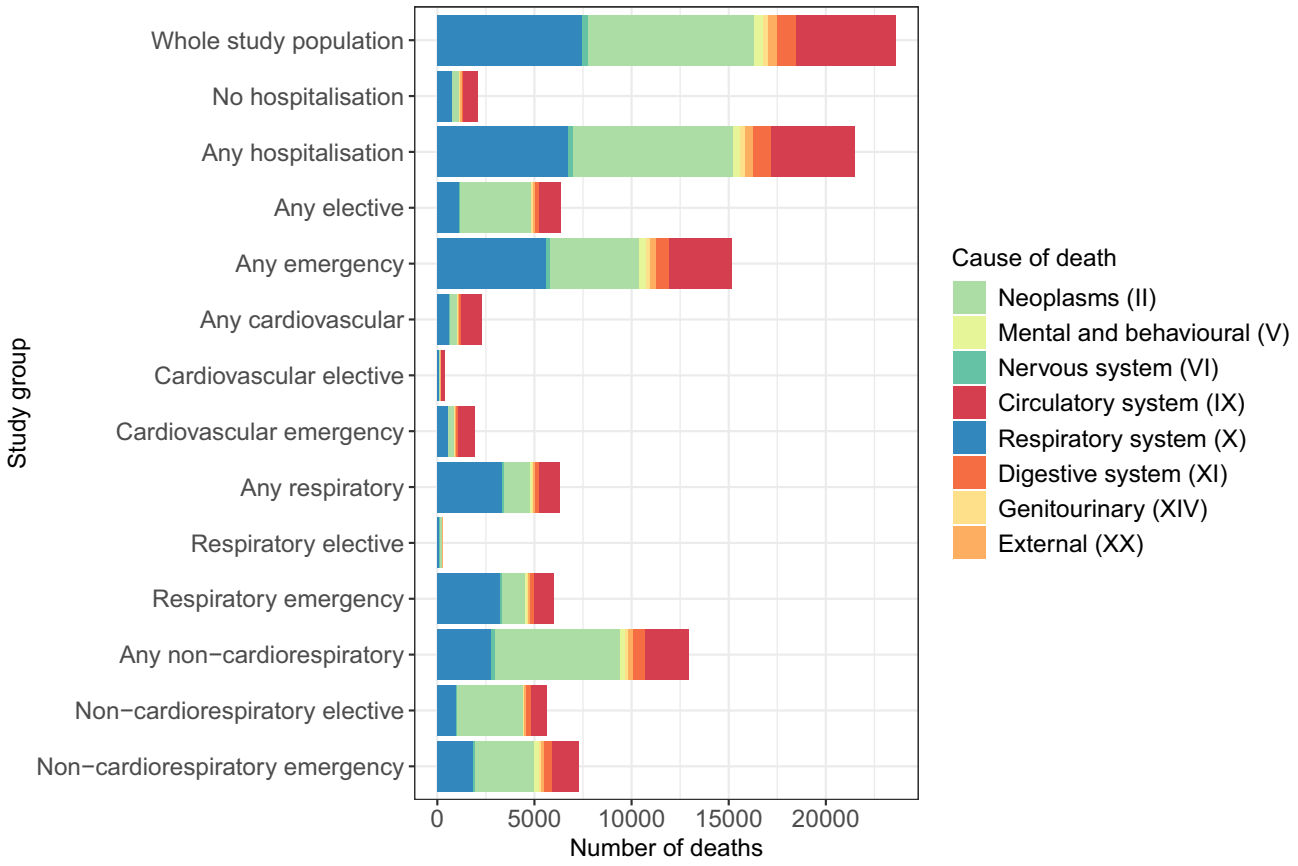

Figure 5 Primary cause of death amongst people with COPD by ICD10 chapter and hospitalization cause and type. Cause of death obtained from first position ICD10 code in Office of National Statistics linked data. Figure shows only causes of death that represented at least 1% of deaths within the whole population. More granular information can be found in Table E11.

hospitalization. This may be a recording artifact as cause of death likely mirrors the reason for hospitalization. In a COPD population, physicians do not routinely look for CVDs when the reason for admission is a COPD exacerbation, while cardiologists also do not frequently consider COPD and its pathophysiological consequences on CVD.[5] All-cause and non-cardiorespiratory elective hospitalizations were associated with reduced cause-specific mortality, likely as people will be at their "fittest" for an elective procedure. Nevertheless, elective hospitalizations were associated with increased all-cause mortality. Finally, for respiratory and cardiovascular hospitalizations, subsequent cause-specific mortality patterns reflected initial hospitalization cause. We are not suggesting that hospitalizations cause MACE and mortality; rather, we are highlighting that people who are ill enough to be hospitalized are more at risk of these adverse outcomes, and that the hospitalization itself is a point of contact with the healthcare system for adverse event-vulnerable patients to receive more effective management of disease.

Contextualization with Literature

To our knowledge, this is the first study to examine adverse outcomes (MACE and cause-specific mortality) of COPD patients following various types and causes of hospitalization. MACE risk increases significantly following hospitalization for an acute exacerbation of COPD,[7] however this study highlights that risk is not limited to exacerbations. Previous literature has demonstrated that hospitalization for transient conditions, such as infection, are associated with subsequent MACE.[19–22] COPD has been highlighted as a risk factor for post-hospitalization MACE following infection.[20,23] We have demonstrated that MACE risk in the COPD population (2.8% to 15.7% depending on hospitalization cause and type) is far higher than risk identified in previous literature for a general population and that it is, furthermore, comparable with MACE risk amongst a population of medium-to-high frailty (6.9% to 9.1%).[24] We have also demonstrated that MACE risk in people with COPD is high, irrespective of hospitalization cause and type.

We also demonstrated the relationship between hospitalization cause and type with mortality. To our knowledge, ours is the first study to evaluate the relationship between admission type subsequent cause-specific mortality. Other studies investigating mortality amongst different cause-specific hospitalized populations (ranging from infectious hospitalizations [Covid-19 and influenza[25] or tuberculosis[26]]; to chronic disease-related hospitalizations [cancer,[27] acute pancreatitis,[28] and alcoholic liver disease[29]]) demonstrated that mortality risk is largely linked to the condition itself, with cardiovascular death ranking after causes related to the condition in question. For example, people hospitalized with alcoholic liver disease were most likely to die of malignancies in the gastrointestinal tract or T2DM,[29] both of which frequently occur in people with alcohol disorders. There may, however, be unmeasured factors mediating coded causes of death, as CVD has previously been coded as an underlying cause of death amongst diabetic patients if patients died in hospital, had an autopsy, or were from geographical areas known to have higher prevalence of cardiovascular risk factors (higher BMI and systolic blood pressure).[30] Rates of all-cause mortality in our study were comparable with cardiovascular cohorts hospitalized for acute coronary syndromes.[31] Whilst, on the whole, people admitted electively are likely to be at their fittest for optimal management, those admitted electively for a respiratory hospitalization (eg, for lung volume reduction surgery), are likely to be sicker than those admitted for a cardiovascular cause.

Limitations and Strengths

Limitations of this study include potential misclassification of disease (due to overlapping symptomatic presentation in cardiovascular and respiratory events), and hospitalization cause tending to align with listed cause of death. Cause of death may have been misdiagnosed based on the hospitalization (eg, if someone was hospitalized for a pre-existing COPD-related cause, their cause of death may also have been COPD-related, resulting in a potential underestimation of cardiovascular-related deaths in a COPD population). We did not consider hospitalizations that may have occurred between first hospitalization of follow-up (exposure) and the outcome, the cause of which may have been associated with MACE or mortality. We could not consider medications or CVD-related risk management decisions taken whilst patients were in hospital for their initial exposure hospitalization. We acknowledge that it is not possible to determine, from this analysis, whether hospitalization itself is the risk factor for subsequent MACE, or whether the people hospitalized are at greater risk of MACE due to unmeasured confounding. However, (i) elective procedures and hospitalizations would typically occur amongst people who are healthier, yet these patients still demonstrate elevated MACE risk, and (ii) the messaging of our paper does not change: awareness of elevated MACE (and mortality) risk following hospitalization remains important for all clinicians treating COPD patients. Despite limitations, our study had several strengths. We investigated several aspects of the relationship between hospitalization and adverse outcomes in people with COPD (hospitalization cause and type, and cause-specific mortality and MACE). Our data source is representative of the UK population with high completeness of diagnostic coding. Our methodology (including cohort identification,[15] codelist design,[32] and covariate algorithms[33]) has been used and validated in previous research. We conducted several sensitivity analyses to ensure findings remained robust, including incorporating propensity scores within models to address confounding by indication.

Clinical and Policy Implications

People with COPD who are hospitalized, regardless of cause or type of hospitalization, are at high risk of subsequent MACE, providing an opportunity for primary prevention either at the point of initial hospitalization or immediately following. CVD is also under-recognized and undertreated amongst people with COPD,[5] amplifying the importance of taking advantage of opportunities to increase diagnostic screening, before adverse events (such as MACE and mortality) occur. Every healthcare encounter for people with COPD should be considered an opportunity to address and mitigate potential underlying CVD, COPD itself, and the COPD-CVD pathophysiological interplay. Furthermore, given the elevated MACE and mortality risk, there is an invisible burden of hospitalization of people with COPD that may not be immediately obvious, particularly when the hospitalization was an emergency but was not COPD-related.

Conclusion

Hospitalization of people with COPD, regardless of cause and type, is associated with one-year MACE and is most strongly associated following a cardiovascular hospitalization. Addressing MACE risk at every healthcare interaction is a critical part of COPD care. Hospitalization type and cause play a role in mortality of COPD patients, where elective

hospitalizations are generally associated with reduced cardiorespiratory mortality, emergency hospitalizations are generally associated with increased mortality. Cause-specific mortality is generally associated with the initial hospitalization cause. Attention to the increased risk adverse outcomes in the year after hospitalization amongst COPD patients, particularly MACE outcomes, may provide a policy opportunity to provide primary prevention.

Data Sharing Statement

Datasets generated and/or analysed in this study are not publicly available, however, data are available on request from the CPRD. Their provision requires the purchase of a license, and this license does not permit the authors to make them publicly available to all. This work used data from the version collected in May 2022 and has clearly specified the data selected in the Methods section. To allow identical data to be obtained by others, via the purchase of a license, the codelists will be provided upon request. Licenses are available from the CPRD (http://www.cprd.com): The Clinical Practice Research Datalink Group, The Medicines and Healthcare products Regulatory Agency, 10 South Colonnade, Canary Wharf, London E14 4PU.

AI Statement

No artificial intelligence (AI) was used in any stage of this research, nor in the write-up of the manuscript or supplementary materials.

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

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