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Predictors of mortality and hospitalised exacerbations in obstructive airway diseases

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Take home message: This nationwide cohort study including ≥1 million persons highlights the importance of tackling frailty, avoiding SABD overuse and encouraging smoking cessation in patients with asthma and COPD to reduce hospitalised exacerbations and mortality.

ABSTRACT

Background: In Belgium, age-standardised hospital admission and mortality rates for asthma and COPD are higher than the European average. Understanding the factors that lead to a hospitalised exacerbation and/or mortality is needed to optimize patient management.

Methods: Patients ≥18 years old obtaining 2 claims for drugs for obstructive airway diseases (ATC code R03) in one year between 2017 and 2022 were identified in Belgian nationwide claims-based data. A multivariable Cox model was used to investigate predictors of all-cause mortality and hospitalised exacerbation.

Results: Among 1,006,968 patients included in this study, 39,214 patients (3.9%) had a hospitalised exacerbation during follow-up and 145,021 patients (14.4%) died. Next to age, sex, Charlson Comorbidity index and socio-economic status, significant predictors for mortality were being frail (aHR 2.09, 95%CI 2.06-2.12), heavy overuse of short-acting bronchodilators (SABD) (≥6 packages/year, aHR 1.81, 95% CI 1.78-1.84), current smoking (aHR 1.64, 95%CI 1.61-1.66), a history of ≥2 outpatient exacerbations in the previous year (aHR 1.52, 95%CI 1.49-1.54). A recent hospitalised exacerbation (aHR 5.67, 95%CI 5.51-5.84), current smoking (aHR 3.69, 95% CI 3.60-3.78), heavy overuse of SABD (aHR 3.15, 95%CI 3.08-3.23) and being frail (aHR 1.07, 95%CI 1.03-1.10) were important additional risk factors for hospitalised exacerbation.

Conclusion: Previous exacerbations, (current) smoking, frailty and overuse of SABD were significantly associated with hospitalised exacerbations and mortality in patients with asthma and/or COPD. The results of this nationwide cohort study highlight the importance of achieving disease control, smoking prevention and tackling frailty in primary care.

Funding: none.

Keywords: asthma, COPD, exacerbations, hospitalization, mortality, primary care management

BACKGROUND

Chronic obstructive airway diseases (COAD), such as asthma and chronic obstructive pulmonary disease (COPD), are a significant cause of morbidity and mortality worldwide [1]. Since asthma and COPD can typically be managed outside hospital settings, hospital admissions and mortality related to COAD are considered preventable [2,3]. Effective management in primary care, including timely intervention and tailored preventive strategies (e.g. disease control [4,5], vaccination [6,7]), could significantly reduce exacerbations, potentially preventing hospitalizations [2,3,8,9]. In Belgium, age-standardised annual rates of hospital admission and mortality for COAD per 100,000 inhabitants are notably higher than the European average [2,10]. Identifying predictors for hospitalised exacerbations and mortality remains an ongoing challenge.

Many factors have been described which influence the risk of exacerbations and mortality in COAD patients [8,9,11-14]. Yet, limited studies investigated or presented the relative impact of different predictors in large sample sized cohorts [13-16]. Previous studies have demonstrated that the frequency and severity of exacerbations are strongly associated with future exacerbations and a higher risk of mortality in patients with asthma and COPD [12,14-16]. Consequently, research has often focused on specific subgroups, particularly those with established or severe disease [16-18]. However, even patients with mild or well-controlled symptoms face the risk of mortality and hospitalization due to exacerbations, though the estimates and preventive factors for these patients are less well-known [11,19]. This highlights the need for nationwide studies that encompass a broad spectrum of patients, including those treated in outpatient settings [15,18].

A comprehensive understanding of the multiple factors contributing to exacerbations and mortality is crucial for developing targeted multifaceted interventions that optimize primary care and reduce the burden on secondary and tertiary healthcare services. Therefore, we investigated predictors of mortality and hospitalised exacerbations in COAD patients using a Belgian nationwide claims-based cohort.

METHODS

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (Supplementary Table 1) [20].

Source population

The source population was provided by two nationwide databases, namely the InterMutualistic Agency (IMA) database and Minimal Hospital Dataset (MHD). The IMA centralizes all claims data from Belgian health insurance funds and manages three databases: (1) a population database containing socio-demographic characteristics (e.g., sex and age), (2) a healthcare database containing data on reimbursed ambulatory and hospital care (e.g. medical procedures, inpatient medication and other reimbursed care) and (3) a pharmaceutical database containing outpatient medication prescription claims (e.g., dispensing date, Anatomical Therapeutic Chemical [ATC] Classification code) [21]. Since health insurance is legally mandatory in Belgium, the source population represents all legal residents with reimbursed medication or care. The MHD, collected by the Belgian Ministry of Health, aggregates hospital discharge diagnoses of every hospital admission in Belgium, coded in International Classification of Diseases [ICD] codes [22]. The Trusted Third Party 'eHealth' was responsible for linking both databases using the national social security number as unique patient identifier. After applying an encrypting procedure for privacy protection, only pseudonymized data were available to the researchers on the secured IMA servers. This study was approved by the IMA and MHD database administrators and by the 'Social Security and Health Chamber of the Belgian Information Security Committee' (approval code IVC/KSZG/23/008), waiving the need for individual informed consents [23].

Study population

Adults in this nationwide observational cohort using the above-described population-based administrative data were followed from January 1st, 2017, to December 31st, 2021, latest. Inclusion criteria were (1) at least 2 ambulatory dispensed prescription claims for a drug for obstructive airway diseases (ATC code R03) in one year (~ 365 consecutive days) during the study period, (2) at least 18

years on the index date and (3) coverage of at least 1 year before the index date by a Belgian health insurance fund. The two prescription claims could have been filled for different ATC R03 drugs, both on the same day or on different days. To avoid immortal time bias, follow-up started for all on the date of the second outpatient delivery of a drug leading to inclusion (index date). Follow-up ended in case of death, emigration out of Belgium or end of the study period, whichever came first. Patients with missing data in key variables (age, sex) were excluded (eFigure 1).

Covariates

Baseline characteristics were assessed at the index date and included age, sex, socio-economic status (SES), comorbidities, medication history, smoking status, frailty and age-adjusted Charlson Comorbidity Index (CCI, excluding chronic pulmonary disease diagnosis in the calculation). The SES was based on the medical coverage and defined as low SES in case of increased reimbursements, which is in Belgium provided to individuals with low income. In case of missing data, medical coverage was derived from copayments for medication on the index date. Comorbidities and medication history were identified in the year before follow-up using ICD-coded diagnoses, medical procedure codes and/or ATC-coded medication prescription claims. Frailty was identified using the claims-based Frailty Indicator (CFI) [24-26] as it was not possible to define Fried's frailty phenotype using only administrative healthcare data. The CFI was developed to classify persons as frail and non-frail, validated against Fried's phenotype, and can be used in large datasets for risk prediction [24]. This algorithm consists of 21 variables using only administrative data (including demographics, physical and cognitive dysfunction and the CCI) with a cut-off of ≥0.20 to define frail patients [24-26]. More information on covariate definitions is provided in Supplementary Table 2, the study design is visualized in eFigure 2.

To assess preventive strategies in primary care, we evaluated smoking prevention and vaccination before follow-up. Patients were categorized as ever smoking if any ICD-code related to (history of) tobacco use or nicotine dependence, a nomenclature code for smoking cessation counselling or

medication for smoking cessation was registered between January 1st, 2010, and the index date. Current smokers were ever smokers with active smoking ICD-coding or smoking cessation attempts after the index date. Vaccination was limited to influenza vaccination in the year before follow-up as pneumococcal vaccination was not reimbursed in Belgium during the study period.

To assess disease control in primary care, we examined the use of short-acting bronchodilators (SABD) and patients' history of exacerbations. Use of SABD was classified as appropriate use (0-2 canisters/year), overuse (3-5 canisters/year) and heavy overuse (at least 6 canisters/year) in the year preceding follow-up [5]. Definitions for exacerbations were based on the 2024 Global Initiative of Asthma (GINA) (3) and 2024 Global Initiative of Chronic Obstructive Lung Disease (GOLD) reports (2) and formulated generally to be applicable to both diseases. Hospitalised exacerbations were defined as hospital admissions with a primary diagnosis of asthma or (acute) COPD exacerbation, COPD with acute lower respiratory infection or asthma with status asthmaticus (ICD-10: J44.0, J44.1, J45.X1, J45.X2, J45.901 or J45.902) or with a primary diagnosis for chronic lower respiratory disease (ICD-10: J40–J47) or respiratory failure (ICD-10: J96) and a secondary diagnosis for asthma or (acute) COPD exacerbation, COPD with acute lower respiratory infection or asthma with status asthmaticus (Supplementary Table 2). Outpatient exacerbations were defined as a prescription fill for an oral corticosteroid (OCS) (ATC code H02AB04, except parenteral use) with/without guideline-recommended antibiotics (29). Outpatient exacerbations followed by a hospital admission for a severe exacerbation within 14 days were counted only as hospitalised exacerbation, to avoid counting exacerbations twice. Patients were categorized into one of four mutually exclusive subgroups based on their exacerbation history in the preceding year before follow-up: (1) no exacerbations, (2) one outpatient exacerbation, (3) two or more outpatient exacerbations: individuals with at least 2 outpatient exacerbations in the preceding year and no hospitalised exacerbations and (4) at least 1 hospitalised exacerbation: individuals with at least one hospitalised exacerbation in the preceding year, irrespective of number of outpatient exacerbations.

Outcomes

All-cause-mortality and hospitalised exacerbations were the study outcomes, measured from index date until end of follow-up. The incident date of hospitalised exacerbations was defined as the date of hospital admission.

Statistical analysis

Mean and standard deviation or median and interquartile range were presented for continuous variables, and counts and percentages for categorical variables. We characterized patients with COAD treatment on their index date by the above-described covariates. A multivariable Cox proportional hazard regression model was used to investigate predictors of death and time to a new hospitalised exacerbation and to calculate adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs). The following covariates were included in the multivariable model: age, sex, SES, exacerbation history, influenza vaccination, SABD use, smoking history, frailty and age-adjusted CCI. The proportional hazard assumption was graphically checked. Collinearity between predictors was tested using the variation inflation factors (VIF) function in R, whereby all VIF values obtained were <5 indicating little multicollinearity [27]. To assess whether the 1-year and 3-year mortality prediction of patients with chronic obstructive airway diseases be improved beyond modelling age, sex and smoking status, we calculated receiver operating characteristic (ROC) curves with areas under the curve (AUCs). The nonparametric method described by DeLong et al. was used to compare differences in AUCs across different models [28].

To investigate whether the significant factors differed in those patients with and without an ICD-coded hospital diagnosis for COAD, analyses were repeated after stratification based on a hospital diagnosis for asthma (ICD-10: J45) and/or COPD (ICD-10: J44) in the 12 months preceding follow-up. Additionally, hospital diagnosed patients were further stratified into asthma, COPD or asthma-COPD overlap (ACO). To investigate whether predictors are consistent across patients with different COAD severity, analyses were repeated after stratification based on exacerbation history in the 12 months preceding follow-

up. Additionally, to investigate whether predictors are consistent across patients with different duration of disease, analyses were repeated after stratification by incident and prevalent patients. Prevalent patients were identified as patients with a hospital diagnosis of asthma and/or COPD more than 90 days prior to the index date or those who collected ATC R03 packages more than 90 days prior to the index date. Moreover, to evaluate the impact of the comorbidities included in the age-adjusted CCI, analyses were repeated adjusting our model for each comorbidity separately. Since the COVID-19 pandemic overlapped with the study period, a sensitivity analysis was conducted by limiting the inclusion and follow-up period to March 1st, 2020. Furthermore, a competing risk analysis was performed for time to a new hospitalised exacerbation using Fine-Gray subdistribution hazard model treating death as a competing risk. A two-sided p-value of <0.05 was considered statistically significant. All analyses were undertaken using R (R version 4.3.0, Vienna, Austria).

RESULTS

Baseline characteristics

A total of 1,006,968 patients were included in this study (Supplemental figure 1). Baseline characteristics of the patients are presented in Table 1. Patients who died during the study period were more likely to be older, male, of lower SES and a current or past smoker, compared to patients who survived. Those who died also had a higher age-adjusted CCI, used SABD more frequently, were more frail and were more vaccinated against influenza in the year before follow-up. Additionally, these patients experienced more exacerbations in the preceding 12 months compared to those who survived and received more frequently a hospital diagnosis of asthma or COPD.

Factors associated with mortality

Approximately 14.4% (145,021) patients died during a mean follow-up of 2.9 ± 1.5 years (2,904,141 persons-years). Figure 1 shows the aHRs for mortality for each variable evaluated.

High SABD use was associated with a significantly increased risk of death, with heavy overuse of SABD being one of the most important predictors of mortality (aHR 1.81, 95%CI 1.78-1.84). Next to that, being frail (aHR 2.09, 95%CI 2.06-2.12), current smoking (aHR 1.64, 95%CI 1.61-1.66) and two or more outpatient exacerbations in the previous year, compared to patients without exacerbations (aHR 1.52, 95%CI 1.49-1.54), were also associated with a significantly higher risk of death. Moreover, an increased age, age-adjusted CCI, low SES, being a past smoker (compared to no smoking history) and a recent hospitalised exacerbation were significantly associated with a higher risk of death, whereas female sex and influenza vaccination were associated with a significantly lower risk of death. Adding frailty, SABD use and exacerbation history to a model of age, sex and smoking status statistically improved the prediction of 1-year and 3-year mortality (eTable 3 and eFigure 3).

Factors associated with a new hospitalised exacerbation

During follow-up, 39,214 patients (3.9%) experienced a hospitalised exacerbation. Figure 2 shows the aHRs for a new hospital exacerbation for each variable evaluated.

Besides, age, sex, frailty, comorbidities and low SES, an exacerbation in the previous year was associated with a significantly higher risk of a new hospitalised exacerbation compared to patients without an exacerbation in the preceding year, which was most pronounced among subjects with a recent hospitalised exacerbation (aHR 5.67, 95% CI 5.51-5.84). Being a current smoker was associated with a 3.7-fold significantly increased risk of a new hospitalised exacerbation (aHR 3.69, 95% CI 3.60-3.78) compared to no smoking history. Furthermore, heavy SABD overuse was associated with a higher risk of new hospitalised exacerbations (aHR 3.15, 95% CI: 3.08-3.23).

Sensitivity analyses

Our results were largely confirmed in additional analyses stratified by disease label (no label, asthma, COPD, ACO), exacerbation history, duration of disease (incident/prevalent), when adjusting for each comorbidity of the CCI separately, when excluding the COVID-19 pandemic period or when using the Fine-Gray method (Supplementary file).

DISCUSSION

In this large nationwide study (N = 1,006,968), we investigated the risk of mortality and hospitalised exacerbations among treated COAD patients in the general Belgian population of adults aged 18 years or older. We found that heavy overuse of SABD, being a current smoker, a history of two or more outpatient exacerbations and being frail were the most important predictors of mortality. The risk of a new hospitalised exacerbation was highest in patients with a previous hospitalised exacerbation, being a current smoker and heavy overuse of SABD.

In the UK National Review of Asthma deaths at least half of the deaths were considered avoidable [29]. SABD overprescribing and prior hospitalisation were highlighted as opportunities for healthcare providers to prevent exacerbations and death [29,30]. Still, more than 20% of our study population overused SABD, whereof 8.5% of patients collected at least 6 SABD packages/year, suggesting poor disease control [31,32]. In line with previous research [4,33], (heavy) SABD overuse increased the risk of mortality and hospitalised exacerbations. This association remained irrespective of hospital diagnosis, showing the importance of identifying patients with SABD overuse in all care settings. Reducing SABD use could not only improve patient's disease control but also reduce the environmental impact associated with these pressurized metered-dose inhalers [5,34].

Similarly, as observed in other studies [11,12,14,16,17], we found that a history of exacerbations is a strong predictor for subsequent exacerbations, independently of COAD diagnosis. However, Tomisa et al. (2024) [16] reported no association between a history of outpatient exacerbations and a (new)

hospitalised exacerbation in patients with asthma and significant between-study variability has been observed for this association in patients with COPD [14]. While our findings, alongside those of Hurst et al. (2022) [14] suggest a significant role for exacerbation history in future risk, further studies are needed to unravel the impact of outpatient exacerbations on future events.

In terms of mortality, our finding that a history of exacerbations is strongly associated with an increased risk of mortality aligns with previous literature [12,13,15,17,18]. An UK population-based study in patients with COPD reported that experiencing one or more hospitalised COPD exacerbations was associated with a higher mortality risk compared to experiencing any number of outpatient exacerbations [19]. Interestingly, in our study, the risk of death associated with at least 1 hospitalised exacerbation in the preceding year was less pronounced than the risk in patients who experienced two or more outpatient exacerbations (but no hospitalised exacerbation). Additionally, when stratifying by disease duration, a hospitalised exacerbation in patients with COPD tended towards lower mortality risk in incident patients, in contrast to the increased mortality risk in incident COPD patients observed by Rothnie et al. [19] This discrepancy might reflect improved follow-up care after hospitalisation, which may differ by country.

In general, exacerbation and hospital admission rates significantly declined during the COVID-19 pandemic [35]. Our study period included the COVID-19 pandemic which may have had an impact on exacerbation and mortality rates. Nevertheless, results were consisted in sensitivity analysis restricting the study period up to March 1st, 2020.

While our study observed that an increasing Charlson Comorbidity index was associated with a higher mortality risk, which aligns with previous literature [36], the systematic review of Owusaa et al. (2022) [5] found no significant association. This inconsistency may be attributed to substantial between-study heterogeneity and limited sample sizes included in their analysis. Furthermore, as seen previously [37,38], frailty was found to be the second most important predictor of mortality next to increasing age bins.

Smoking cessation is a crucial strategy in the management of COAD [8,9]. In our dataset we were not able to correct for the quantity of smoking (pack-years), which could have left residual confounding by smoking intensity. Nevertheless, being a current smoker was associated with a 3.9-fold higher risk of hospitalised exacerbations and a 81% increased risk of mortality, compared to having no smoking history, highlighting the importance of smoking prevention. Annualized influenza vaccination is recommended and reimbursed in Belgium for all adults ≥65 years old and in patients with COPD or severe asthma [8,9,39]. Although we observed no protective effect of influenza vaccination on hospitalised exacerbations, being vaccinated against influenza was associated with a 11% reduced risk of mortality. Despite it being an important preventive measure, the proportion of unvaccinated patients remains substantial in Europe [40]. Around 40% of our study population was vaccinated against influenza. Healthcare provider recommendation can be important to increase vaccination rates in this high-risk population [41]. Additionally, the associations of influenza vaccination and death, and the association of smoking history and hospitalised exacerbation and death remained significant in sensitivity analyses based on stratification by hospital diagnosis. Therefore, our results highlight the importance of avoiding SABD overuse, smoking cessation and influenza vaccination in primary care to reduce hospitalised exacerbations and/or mortality.

This nationwide cohort study on chronic users of medication for obstructive lung diseases in Belgium is strengthened by the large sample size and the long-term follow-up up to 5 years for a total of 2,904,141 person-years at a full-population scale. Nevertheless, several limitations should be mentioned. First, the observational use of healthcare databases is inherently characterized by some limitations such as the probability of coding errors, misclassification bias, the inability to confirm if the patient actually used the dispensed medication and the lack of information about symptom control, blood values (such as eosinophilia), lung function variables or inhaler technique. Therefore, we could not account for disease severity markers such as FEV1 and blood eosinophil counts. We tried to mitigate this limitation by using proxies for diseases control, namely SABD overuse and exacerbation history. Furthermore, due to a lack of information, specific-cause mortality could not be determined

which would have been interesting as exacerbations may have a stronger association with respiratory or cardiovascular-related death. Although we thoroughly tried to adjust for confounders, there is a risk of unmeasured confounding due to missing information concerning important covariates such as educational level, occupational exposures, genetics and lifestyle factors (BMI, smoking pack-years). Second, although the study design was adapted to exclude patients without chronic disease (namely by including patients with at least two obstructive lung disease medication claims), the study population was not restricted to asthma or COPD patients with a registered ICD-coded diagnosis. This would have limited our study population to recently hospitalized patients, with exclusion of patients treated exclusively in ambulatory care (risk of selection bias). To investigate the effect of a registered diagnosis, stratified analyses were performed, yielding similar trends in patients with or without a COAD hospital diagnosis. Additionally, only treated patients were included. Our results can therefore not be generalized to COAD patients receiving no chronic treatment for obstructive lung diseases. Third, our study design incorporated patients at different stages and durations of disease. We tried to mitigate this limitation by performing additional sensitivity analyses after stratification by COAD severity (exacerbation history in the 12 months before follow-up) and after stratification by incident and prevalent patients, yielding similar results as our main analyses. Furthermore, as ICD-code registration in Belgium is not obligated for emergency department visits, exacerbations leading to an emergency department visit but without the need for hospitalization may have not been identified or identified as an outpatient exacerbation solely. Moreover, we identified multimorbidity and frailty based on the age-adjusted CCI and the validated CFI respectively, using only administrative data. These covariates may have a high specificity but a lower sensitivity, potentially underestimating the amount of multimorbid and/or frail patients, especially in non-diagnosed COAD patients. Lastly, we may have underestimated the effect of influenza vaccination by vaccinations provided at work or in nursing homes.

CONCLUSIONS

Previous exacerbations, (current) smoking and SABD overuse were significantly associated with mortality and hospitalised exacerbations in patients with COAD. Our results highlight the importance of achieving disease control, smoking cessation and tackling frailty in primary care to reduce hospitalised exacerbations and mortality.

DECLARATIONS

Ethics approval

This study involving human participants was reviewed and approved by the InterMutualistic Agency and Minimal Hospital Dataset database administrators as well as by the 'Social Security and Health Chamber of the Belgian Information Security Committee' (approval code IVC/ KSZG/23/008), waiving the need for individual informed consent [23].

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from the InterMutualistic Agency and Minimal Hospital Dataset, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Any further inquiries regarding data availability should be directed to Professor Lies Lahousse (lies.lahousse@ugent.be) or the administrators of the InterMutualistic Agency (IMA) database or Minimal Hospital Dataset.

Competing interests

Outside this manuscript, LL has been consulted as expert for AstraZeneca, GlaxoSmithKline and Sanofi, and has given lectures sponsored by Chiesi, IPSA vzw and Domus Medica vzw (non-profit organizations facilitating lifelong learning for health care providers), all paid to her institution. She received support for travel from Menarini. None of which are related to the content of this work. Outside this manuscript, DV received support for travel from FWO (Research Foundation Flanders) and is unpaid member of the European Respiratory Society and Belgian Respiratory Society. None of which are related to the content of this work. GJ reports consulting fees from GlaxoSmithKline, Chiesi and AstraZeneca, lecture honoraria from GlaxoSmithKline and AstraZeneca, and acts as chair of the operational Committee IRC (International Respiratory Coalition) for the European Respiratory Society,

outside the submitted work. All other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' contributions

DV, FVV and LL contributed to the concept and design of the study. DV and FVV performed the statistical analysis, interpretation and writing under supervision of LL. MG, GJ and LL provided feedback to optimise the design of the study. MG, GJ and LL revised the manuscript critically. All authors contributed to the article and approved the final version of the manuscript.

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Table 1: Baseline characteristics of included patients, stratified by survival status			
Patient characteristics	**Total n = 1,006,968**	**Survived n = 861,947**	**Died n = 145,021**
Age in years (SD)	59.8 (19.0)	56.7 (18.1)	78.8 (11.9)
Age categories			
<50 years	296,298 (29.4%)	293,512 (34.1%)	2,786 (1.9%)
50-59 years	173,567 (17.2%)	165,827 (19.2%)	7,740 (5.3%)
60-69 years	206,898 (20.5%)	185.015 (21.5%)	21,883 (15.1%)
70-79 years	169,034 (16.8%)	133.930 (15.5%)	35,104 (24.2%)
80 years or older	161,171 (16.0%)	83,663 (9.7%)	77,508 (53.4%)
Female	545,562 (54.2%)	475,279 (55.1%)	70,283 (48.5%)
Low SES	297,876 (29.6%)	228,194 (26.5%)	69,682 (48.0%)
Smoking status			
No smoker	764,257 (75.9%)	676,477 (78.5%)	87,780 (60.5%)
Past smoker	107,392 (10.7%)	78,459 (9.1%)	28,933 (20.0%)
Current smoker	135,319 (13.4%)	107,011 (12.4%)	28,308 (19.5%)
Hospital diagnosis of COAD			
Asthma	28,265 (2.8%)	24,758 (2.9%)	3,507 (2.4%)
ACO	10,420 (1.0%)	6,868 (0.8%)	3,552 (2.4%)
COPD	72,356 (7.2%)	42,072 (4.9%)	30,284 (20.9%)
Exacerbations in 12 months before follow-up			
No exacerbations	799,110 (79.4%)	703,663 (81.6%)	95,447 (65.8%)
One outpatient exacerbation	127,206 (12.6%)	105,204 (12.2%)	22,002 (15.2%)
Two or more outpatient exacerbations	57,185 (5.7%)	39,123 (4.5%)	18,062 (12.5%)
≥1 hospitalised exacerbation	23,467 (2.3%)	13,957 (1.6%)	9,510 (6.6%)
SABD use			
Appropriate (0-2 canisters/year)	788,679 (78.3%)	700,978 (81.3%)	87,701 (60.5%)
Overuse (3-5 canisters/year)	132,445 (13.2%)	102,124 (11.8%)	30,321 (20.9%)
Heavy overuse (≥6 canisters/year)	85,844 (8.5%)	58,845 (6.8%)	26,999 (18.6%)
Influenza vaccination	395,285 (39.3%)	304,834 (35.4%)	90,451 (62.4%)
Frailty	134,310 (13.3%)	60,146 (7.0%)	74,164 (51.1%)
Age-adjusted Charlson Comorbidity Index, median (IQR)	2 (0-4)	2 (0-3)	5 (4-7)
Follow-up time in years (SD)	2.9 (1.5)	3.1 (1.5)	1.6 (1.3)

ACO: asthma-COPD overlap, COAD: chronic obstructive airway disease, IQR: interquartile range, SABD: short-acting bronchodilators, SD: standard deviation, SES: socio-economic status

Figure legends

Figure 1: Risk of mortality in patients with COAD. aHR: adjusted hazard ratio, CCI: Charlson comorbidity index, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status.

Figure 2: Risk of next hospitalised exacerbation in patients with COAD. aHR: adjusted hazard ratio, CCI: Charlson comorbidity index, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status.

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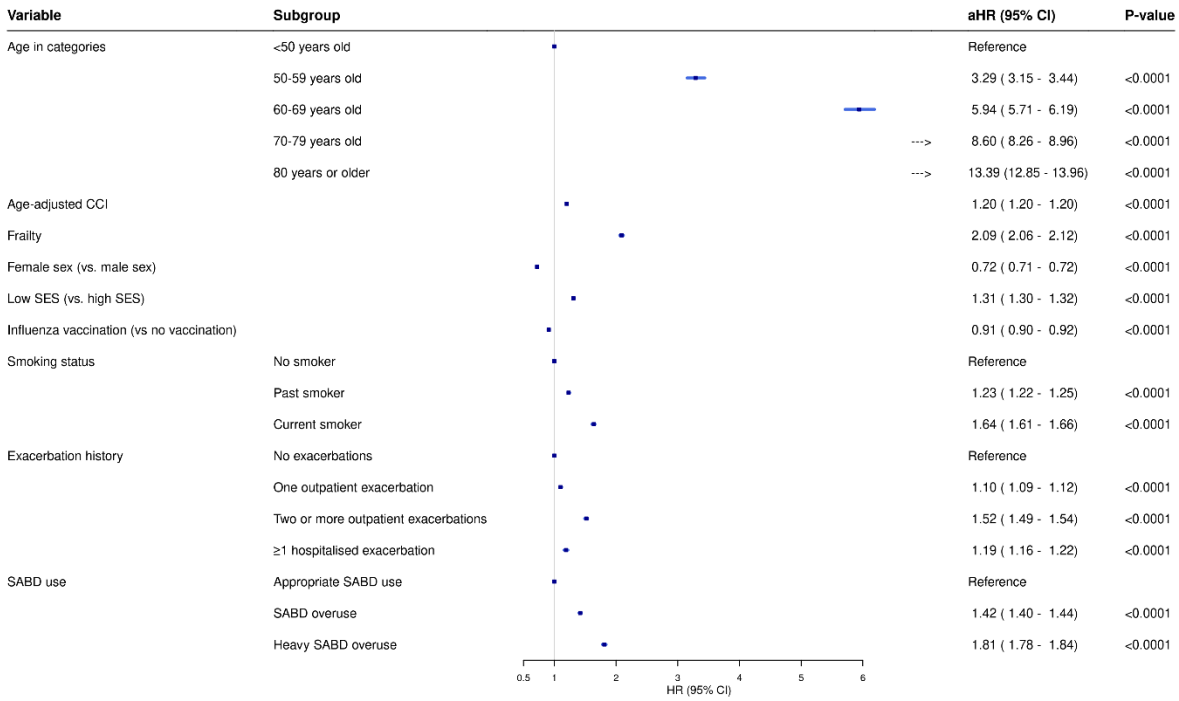

Figure 1

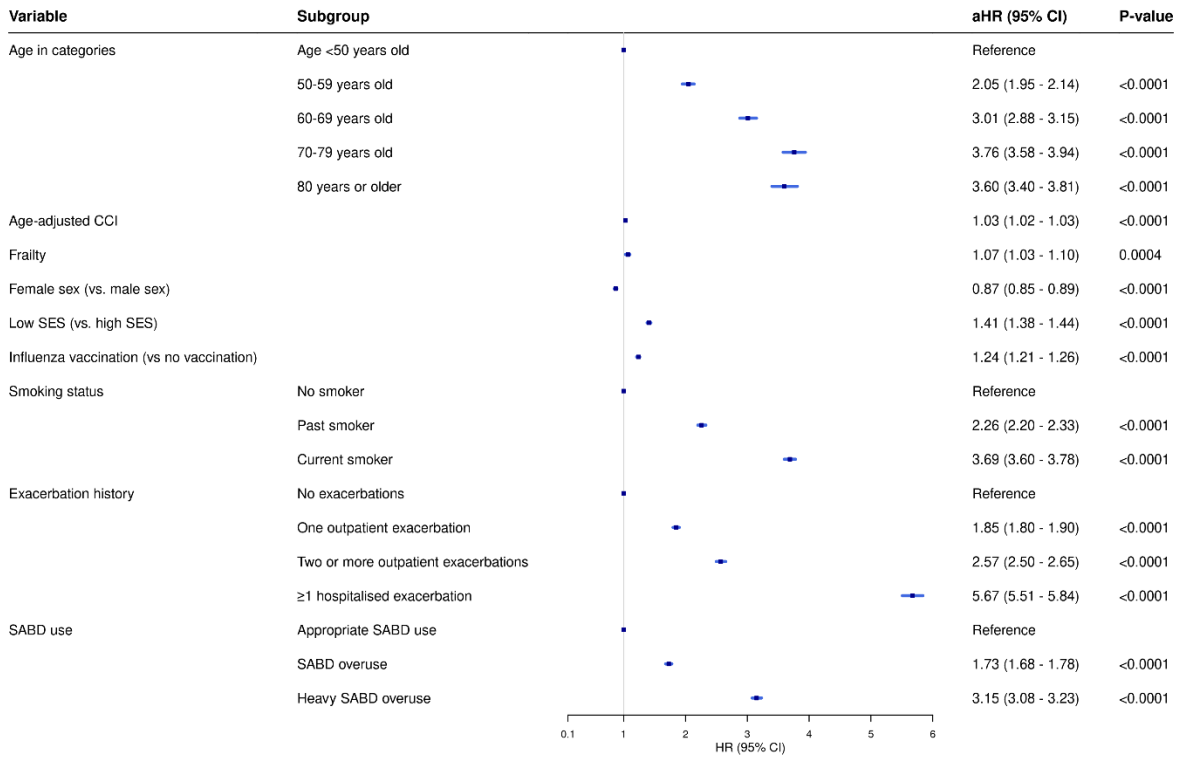

Figure 2

Supplemental materials

Predictors of mortality and hospitalized exacerbations in obstructive airway diseases

Table of contents

Supplemental tables

eTable 1: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline

eTable 1: Compliance to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guideline [1].

	Item No.	Recommendation	Page No.
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
INTRODUCTION			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
METHODS			
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	4-7, eFigure 1&2
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4-8, eTable 2
Bias	9	Describe any efforts to address potential sources of bias	5-8, 12-13
Study size	10	Explain how the study size was arrived at	4-5, eFigure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	5-8
		(*d*) If applicable, explain how loss to follow-up was addressed	/
		(*e*) Describe any sensitivity analyses	7-8
RESULTS			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8, eFigure 1

		(b) Give reasons for non-participation at each stage	/
		(c) Consider use of a flow diagram	eFigure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	/
		(c) Summarise follow-up time (eg, average and total amount)	8, Table 1
Outcome data	15*	Report numbers of outcome events or summary measures over time	8-9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8-9
		(*b*) Report category boundaries when continuous variables were categorized	/
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	/
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10, eTable 3-12
DISCUSSION			
Key results	18	Summarise key results with reference to study objectives	10-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10-13
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-13
OTHER INFORMATION			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	2, 16

eTable 2: Definition of in- and exclusion criteria, comorbidities, comedication and clinical risk scores

VARIABLE	ICD, ATC AND MEDICAL PROCEDURE CODES
INCLUSION CRITERIA [2,3]	
Drugs for obstructive airway diseases	**ATC:** R03 Categorized as: *Short-acting bronchodilators ~ ATC: R03AC02, R03AC03, R03AL01, R03AL02, R03BB01* *Long-acting bronchodilators ~ ATC: R03AC12, R03AC13, R03AC18, R03AC19, R03AL03-R03AL06, R03BB04-R03BB07* *Inhaled corticosteroids ~ ATC: R03BA01, R03BA02, R03BA05* *Combination therapy of long-acting β2-agonists and inhaled corticosteroids ~ due to use of the ATC for the specific categories or use of ATC: R03AK06 – R03AK08, R03AK10 – R03AK12, R03AK14* *Multiple R03 medication: R03AL08, R03AL09, R03AL11, R03AL12, R03BC01, R03CC02, R03CC03, R03DA01, R03DA04, R03DC01, R03DC03, R03DC53, R03DX05, R03DX08-R03DX10*
≥18 years	Age ≥18 years on index date
≥1 year coverage	≥1 year coverage by a Belgian health insurance fund
COPD (sensitivity analysis)	**ICD 10:** J44
Asthma (sensitivity analysis)	**ICD 10:** J45
DEMOGRAFICS (on index date)	
Age	Age on index date based on the year and month of birth, not the exact date due to patient privacy.
Sex	Sex on index date
Socio-economic status	Binomial variable derived from medical coverage, based on copayments for medical procedures and medication at the index date.
SMOKING STATUS [2-4]	

Smoking status	**ICD-9:** 305.1, V15.82
	ICD-10: F17, Z71.6, Z72.0, Z87.891
	ATC: N06AX12, N07BA
	Medical procedure code: 740434, 740445, 740456, 740460, 740471, 740482
	
	Categorized as past smoker if:
	• Past smoking ICD before index date without current smoking ICD during follow-up
	  ○ Past smoking ICD: history of tobacco use ~ **ICD-9**: V15.82 or **ICD-10**: F17.201, F17.211, F17.221, F17.291, Z87.891
	  ○ Current smoking ICD: **ICD-9**: 305.1 or **ICD-10**: F17.200, F17.203, F17.208, F17.209, F17.210, F17.213, F17.218, F17.219, F17.220, F17.228, F17.290, F17.293, F17.298, F17.299, Z71.6, Z72.0
	• Last smoking cessation attempt before index date and no current smoking ICD during follow-up: **ATC**: N06AX12, N07BA or **Medical procedure code**: 740434, 740445, 740456, 740460, 740471, 740482.

COMORBIDITIES (≤1 year before follow-up) [2-4]	
Myocardial infarction	**ICD-10:** I21, I22, I25.2
Congestive heart failure	**ICD-10:** I09.81, I11.0, I13.0, I13.2, I25.5, I42.0, I42.6-I42.9, I43, I50, P29.0 **ATC: combination of treatment of all of the following drug classes [5]:** **I) Beta blocker (selective or alpa and beta blocking):** C07AB, C07AG, C07BB, C07BG, C07CB, C07CG, C07DB, C07FB, C07FX03, C07FX04, C07FX05, C07FX06 **II) ACE inhibitor or angiotensin II receptor blocker:** C09A, C09BA, C09BB, C09C, C09DA, C09DB, C09DX01, C09DX02, C09DX03, C09DX04, C09DX06, C09DX07, C09DX08, C10BX04, C10BX06,

	C10BX07, C10BX10, C10BX11, C10BX12, C10BX13, C10BX14, C10BX15, C10BX16, C10BX17, C10BX18, C10BX19, C10BX20, C10BX21 **III) Loop diuretic:** C03C, C03EB **or use of ≥1 combination product (beta blocker + ACE inhibitor or beta blocker + angiotensin II receptor blocker)**: C09BX02, C09BX04, C09BX05, C09BX06, C09BX07, C09DX05 **and loop diuretic**
Peripheral vascular disease	**ICD-10:** I70, I71, I73.1, I73.8, I73.9, I74, I77, I79.0, K55.1, K55.8, K55.9, Z95.82, Z98.62 **Medical procedure code:** 229294, 229305, 229316, 229320, 229331, 229342, 235071, 235082, 235093, 235104, 235115, 235126, 235196, 235200, 235211, 235222, 236014, 236025, 236036, 236040, 236051, 236062, 237016, 237020, 237031, 237042, 237053, 237064, 237075, 237086, 237090, 237101, 237171, 237182, 589050, 589061, 589094, 589105, 589175, 589186, 589595, 589606, 589610, 589621, 589632, 589643, 589654, 589665
Cerebrovascular disease	**ICD-10:** G45, G46, H34.0, I60, I61, I62, I63, I65, I66, I67, I68, I69, Z86.73 **Medical procedure code:** 182136, 182140, 182151, 182162, 182173, 182184, 477724, 477746, 477761, 477783
Dementia	**ICD-10:** A81.0, F01, F02, F03, F05, G30, G31.0, G31.83, G31.85 **ATC**: N06D
Connective tissue disease	**ICD-10:** M05.0, M05.1, M05.2**,** M05.3, M05.8, M05.9, M06.0, M06.3, M06.9, M32, M33, M34, M35, M36.0, M36.8
Peptic ulcer disease	**ICD-10**: K22.1, K25, K26, K27, K28, Z87.11 **ATC:** A02BD04, A02BD08, A02BD11 **Medical procedure code:** 550093, 550104, 552370, 552381
Mild liver disease	**ICD-10:** B17.0, B17.10, B18, B19.10, B19.20, K70.0, K70.1, K70.2, K70.3, K70.9, K71.3, K71.4, K71.5, K71.6, K71.7, K71.8, K71.9, K73, K74, K75.2, K75.3, K75.4, K75.8, K75.9, K76.0, K76.2, K76.3, K76.4, K76.89, K76.9, Z94.4 **ATC:** J05AF07, J05AF08, J05AF10, J05AP **Medical procedure code:** 318076, 318080, 318334, 318345, 472113, 472124, 556754, 556765, 556776, 556780, 589352, 589363
Diabetes without vascular complications	**ICD-10:** E08.0, E08.1, E08.6, E08.9, E09.0, E09.1, E09.6, E09.9, E10.1, E10.6, E10.9, E11.0, E11.1, E11.6, E11.9, E13.0, E13.1, E13.6, E13.9
Diabetes with vascular complications	**ICD-10:** E08.2, E08.3, E08.4, E08.5, E08.8, E09.2, E09.3, E09.4, E09.5, E09.8, E10.2, E10.3, E10.4, E10.5, E10.8, E11.2, E11.3, E11.4, E11.5, E11.8, E13.2, E13.3, E13.4, E13.5, E13.8 **Medical procedure code:** 653671, 653682, 697093, 697104, 770070, 773393, 773496
Hemiplegia/paraplegia	**ICD-10:** G04.1, G11.4, G80.0, G80.1, G80.2, G81, G82, G83.0, G83.4, G83.9 **Medical procedure code:** 643414, 643425
Chronic kidney disease	**ICD-10:** I12.0, I13.11, I13.2, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N18, N19, N25.0, T86.1, Z48.22, Z49, Z91.15, Z94.0, Z99.2 **Medical procedure code:** 107096, 107111, 107133, 107155, 318010, 318021, 318290, 318301, 470293, 470304, 470315, 470326, 470330, 470341, 470352, 470374, 470385, 470400, 470422, 470433, 470444, 470466, 470470, 470481, 470875, 470890, 470901, 470912, 470934, 470945, 471111, 471122, 471133, 471144, 471155, 471166, 471170, 471181, 474714, 474725, 754294, 757433, 757492, 761272, 761283, 761456, 761471, 761493, 761515, 761526, 761530, 761552, 761574, 761596, 761655, 761670, 767594, 767616, 767631, 767664, 767686, 767701, 767723, 767734, 767756, 767782, 767804, 767815, 767826, 767830, 767841, 767955, 767966
Cancer	**ICD-10:** C00-C96, Z51.0, Z51.11, Z51.12 **ATC:** L01 **Medical procedure code:** 154873, 154884, 154895, 154906, 157231, 157242, 201191, 201202, 201213, 201224, 220275, 220286, 220371, 220382, 226914, 226925, 226936, 226940, 227216, 227220, 227275, 227286, 227636, 227640, 227651, 227662, 227673, 227684, 227695, 227706, 227710, 227721, 227732, 227743, 227754, 227765, 227776, 227780, 227791, 227802, 227813, 227824, 227835, 227846, 230473, 230484, 231033, 231044, 235152, 235163, 241231, 241242, 241415, 241426, 241430, 241441, 241452, 241463, 242012, 242023, 242034, 242045, 242292, 242303, 242314, 242325, 242830, 242841, 242852, 242863, 242874, 242885, 242896, 242900, 243051, 243062, 243073, 243084, 243235, 243246, 243736, 243740, 243751, 243762, 243773, 243784, 244016, 244020, 244031, 244042, 244075, 244086, 244311, 244322, 244856, 244860, 244893, 244904, 244915, 244926, 244930, 244941, 244952, 244963, 244974, 244985, 245512,

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Any malignancy including leukaemia and lymphoma	**ICD-10:** C00-C76, C80.1, C80.2, C81-C96, Z51.0, Z51.11, Z51.12 **ATC:** L01 **Medical procedure code:** see 'Cancer'
Metastatic cancer	**ICD-10:** C77-C79, C80.0
Moderate and severe liver disease	**ICD-10:** B15.0, B16.0, B16.2, B17.11, B19.0, B19.11, B19.21, I85, I86.4, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
HIV/AIDS	**ICD-10:** B20, B97.35, Z21 **ATC:** J05AE01, J05AE03, J05AE04, J05AE05, J05AE07, J05AE08, J05AE09, J05AE10, J05AF01, J05AF02, J05AF03, J05AF04, J05AF06, J05AF09, J05AF11, J05AF12, J05AG, J05AJ, J05AR, J05AX07, J05AX09, J05AX29
Impaired mobility	**ICD-10:** Z74.01, Z74.09, Z99.3 **Medical procedure code:** 520015, 520026, 520030, 520041, 520052, 520063, 520074, 520085, 520096, 520100, 520111, 520122, 520133, 520144, 520155, 520166, 520170, 520181, 520192, 520203, 520214, 520225, 520310, 520321, 520332, 520343, 520354, 520365, 520376, 520380, 520391, 520402, 520413, 520424, 520435, 520446, 520450, 520461, 520472, 520483, 520494, 520505, 520516, 520520, 520531, 520542, 520553, 520564, 520575, 520586, 520590, 520601, 520612, 520623, 520634, 520645, 520656, 520660, 520671, 520682, 520693, 520704, 520715, 520726, 520730, 520741, 520752, 520763, 520774, 520785, 520796, 520800, 520811, 520822, 520833, 520844, 520855, 520866, 520870, 520881, 520892, 520903, 520914, 520925, 520936, 520940, 520951, 520962, 520973, 520984, 520995, 521006, 521010, 521021, 521032, 521043, 521054, 521065, 521076, 521080, 521091, 521102, 521113, 521124, 521135, 521146, 521150, 521161, 521172, 521183, 521194, 521205, 521216, 521220, 521231, 521242, 521253, 521264, 521275, 521286, 521290, 521301, 521312, 521323, 521334, 521345, 521356, 521360, 521371, 521382, 521393, 521404, 521415, 521426, 521430, 521441, 521452, 521463, 521474, 521485, 521496, 521500, 521511, 521522, 521533, 521544, 521555, 521566, 521570, 521581, 521592,

	521603, 521614, 521625, 521636, 521640, 521651, 521662, 521673, 521684, 521695, 521706, 521710, 521721, 521732, 521743, 521754, 521765, 521776, 521780, 521791, 521802, 521813, 521824, 521835, 521846, 521850, 521861, 521872, 521883, 521894, 521905, 521916, 521920, 521931, 521942, 521953, 521964, 521975, 521986, 521990, 522001, 522012, 522023, 522034, 522045, 522056, 522060, 522071, 522082, 522093, 522104, 522115, 522126, 522130, 522141, 522152, 522163, 522174, 522185, 522196, 522200, 522211, 522222, 522233, 522244, 522255, 522266, 522270, 522281, 522292, 522303, 522314, 522325, 522336, 522340, 522351, 522362, 522373, 522384, 522395, 522406, 522410, 522421, 522432, 522443, 522454, 522465, 522476, 522480, 522535, 522550, 522572, 522583, 522594, 522605, 522616, 522620, 522631, 522642, 522653, 522664, 522675, 522686, 522734, 522745, 522756, 522760, 522771, 522782, 522793, 522804, 522815, 522826, 522830, 522841, 522852, 522863, 522874, 522885, 522896, 522900, 522911, 522922, 522933, 522944, 522955, 522966, 522970, 522981, 523014, 523025, 523036, 523040, 523051, 523062, 523073, 523084, 523095, 523106, 523110, 523121, 523132, 523143, 523154, 523165, 523176, 523180, 523191, 523202, 523213, 523224, 523235, 523246, 523250, 523261, 523272, 523283, 523294, 523305, 523316, 523320, 523331, 523342, 523353, 523364, 523375, 523386, 523390, 523401, 523412, 523423, 523434, 523445, 523456, 523460, 523471, 523482, 523493, 523504, 523515, 523526, 523530, 523541, 523552, 523563, 523574, 523585, 523596, 523600, 523611, 523622, 523633, 523644, 523655, 523666, 523670, 523681, 523692, 523703, 523714, 523725, 523736, 523740, 523751, 523762, 523773, 523784, 523795, 523806, 523810, 523821, 523832, 523843, 523854, 523865, 523876, 523880, 523891, 523902, 523913, 523924, 523935, 523946, 523950, 523961, 523972, 523983, 523994, 524005, 524016, 524020, 524031, 524042, 524053, 524064, 524075, 524086, 524090, 524101, 643451, 643462, 653656, 653660, 770394, 770405, 770416, 770420
Depression	**ICD-10:** F06.31, F06.32, F30, F31, F32, F33, F34.1, F43.21, F43.23, F53.0 **ATC**: N06AA, N06AB, N06AF, N06AG, N06AX01, N06AX02, N06AX03, N06AX04, N06AX05, N06AX06, N06AX07, N06AX08, N06AX09, N06AX10, N06AX11, N06AX13, N06AX14, N06AX15, N06AX16, N06AX17, N06AX18, N06AX19, N06AX21, N06AX22, N06AX23, N06AX24, N06AX25, N06AX26, N06AX27, N06AX28, N06AX29
Parkinson's disease	**ICD-10:** G20, G21, G23.1, G31.83, G31.85, G90.3 **ATC:** N04AB, N04AC, N04B
Arthritis (any type)	**ICD-10:** L40.5, M02.3, M05, M06, M08, M13.0, M13.1, M15-M19, M45, M46.1, M46.8, M46.9 **ATC**: L04AA13, L04AA24 **Medical procedure code:** 478030, 478041
Stroke	**ICD-10:** I61, I62, I63, I67.89, I69.1, I69.2, I69.3, I69.8, I69.9, I97.82, Z86.73 **Medical procedure code:** 182136, 182140, 182151, 182162, 182173, 182184, 477724, 477746, 477761, 477783
Schizophrenia & paranoia	**ICD-10:** F06.0, F06.2, F20, F22, F23, F24, F28, F29
Chronic skin ulcer	**ICD-10:** E08.621, E08.622, E09.621, E09.622, E10.621, E10.622, E11.621, E11.622, E13.621, E13.622, L89, L97, L98.4 **Medical procedure code:** 114074, 114085
Skin and soft tissue infection	**ICD-10:** A06.7, A28.1, A31.1, A43.1, A46, A50.06, A51.3, A60.1, A63.0, A66.2, L00, L01, L02, L03, L04, L05, L08, L88 **Medical procedure codes:** 145552, 145563, 145574, 145585, 220253, 220264, 244650, 244661
Mycosis	**ICD-10:** B35-B49 **ATC:** D01A, D01BA02
Gout or other crystal-induced arthropathy	**ICD-10:** M10, M11, M1A **ATC:** M04A
History of falling	**ICD-10:** R29.6, V00.141, V00.811, V00.831, V81.5, V81.6, V82.5, V82.6, V92.0, V93.3, V94.0, V97.0, W00, W01, W03, W05-W15, W16.0-W16.4, W17, W18, W19, Y21.1, Y21.3, Y30, Z91.81
Musculoskeletal problems	**ICD-10:** M02, M07, M12.0, M12.1, M12.2, M12.3, M12.4, M12.8, M12.9, M13, M14, M24.0, M24.3, M24.6, M24.7, M24.8, M24.9, M25, M36.1, M36.2, M36.3, M36.4, M45, M46.0, M46.1, M46.4, M46.8, M46.9, M47, M48, M49, M50, M51, M53, M54, M80, M81, M84.3, M84.4, M84.5, M84.6, Z87.31, Z87.39
Urinary tract infection	**ICD-10:** A56.01, N10, N12, N13.6, N15.1, N15.9, N16, N28.84, N28.85, N28.86, N30.0, N30.8, N30.9, N34, N39.0 **ATC:** J01XE01, J01XX01

CLINICAL RISK SCORE	
Charlson Comorbidity Index [6-10]	- **Myocardial infarction:** 1 point (definition mentioned above: 'Myocardial infarction') - **Congestive heart failure**: 1 point (definition mentioned above: 'Congestive heart failure') - **Peripheral vascular disease**: 1 point (definition mentioned above: 'Peripheral vascular disease) - **Cerebrovascular disease:** 1 point (definition mentioned above: 'Cerebrovascular disease') - **Dementia**: 1 point (definition mentioned above: 'Dementia') - **Connective tissue disease**: 1 point (definition mentioned above: 'Connective tissue disease') - **Peptic ulcer disease**: 1 point (definition mentioned above: 'Peptic ulcer disease') - **Mild liver disease**: 1 point (definition mentioned above: 'Mild liver disease') - **Diabetes without chronic complications**: 1 point (definition mentioned above: 'Diabetes' and/or 'Diabetes without vascular complications) - **Diabetes with chronic complications**: 2 points (definition mentioned above: 'Diabetes with vascular complications) - **Hemiplegia or paraplegia**: 2 points (definition mentioned above: 'Hemiplegia/paraplegia) - **Renal disease:** 2 points (definition mentioned above: 'Chronic kidney disease') - **Any malignancy, including leukaemia and lymphoma:** 2 points (definition mentioned above: 'Any malignancy, including leukaemia and lymphoma') - **Moderate or severe liver disease:** 3 points (definition mentioned above: 'Moderate or severe liver disease') - **Metastatic solid tumour:** 6 points (definition mentioned above: 'Metastatic cancer') - **AIDS/HIV:** 6 points (definition mentioned above: 'HIV') - **Age on the index date:** • <50 years: 0 points • 50-59 years: 1 point • 60-69 years: 2 points • 70-79 years: 3 points • ≥80 years: 4 points *The following comorbid conditions were mutually exclusive: diabetes with chronic complications and diabetes without chronic complications; mild liver disease and moderate or severe liver disease; and any malignancy and metastatic solid tumour. Patients with diabetes without specific ICD-codes linked to diabetes with or without chronic complications were considered as patients with diabetes without chronic complications. As it is suspected that all patients included in our study cohort have chronic pulmonary disease, this factor was not taken into account to calculate the Charlson Comorbidity Index.*
John Hopkins Claims-based Frailty Indicator [11-15]	- **Impaired mobility**: beta coefficient 1.24 (definition mentioned above: 'Impaired mobility') - **Depression**: beta coefficient 0.54 (definition mentioned above: 'Depression') - **Congestive heart failure**: beta coefficient 0.50 (definition mentioned above: 'Congestive heart failure') - **Parkinson's disease**: beta coefficient 0.50 (definition mentioned above: 'Parkinson's disease') - **White race**: beta coefficient -0.49: not available - **Arthritis (any type):** beta coefficient 0.43 (definition mentioned above: 'Arthritis') - **Cognitive impairment**: beta coefficient 0.33 (combination of definitions mentioned above: 'Dementia' and 'Cognitive deterioration') • **ICD-10:** A81.0, F01, F02, F03, F05, G30, G31.0, G31.1, G31.83, G31.84, G31.85, G31.89, G31.9, R41.81 • **ATC:** N06D - **Charlson comorbidity index (> 0)**: beta coefficient 0.31 - **Stroke**: beta coefficient 0.28 (definition mentioned above: 'Stroke') - **Paranoia**: beta coefficient 0.24 (definition mentioned above: 'Schizophrenia & paranoia') - **Chronic skin ulcer**: beta coefficient 0.23 (definition mentioned above: 'Chronic skin ulcer') - **Pneumonia**: beta coefficient 0.21 • **ICD-10:** A01.03, A02.22, A37.01, A37.11, A37.81, A37.91, A50.04, A54.84, B01.2, B05.2, B06.81, B77.81, J09.X1, J09.X2, J09.X3, J10.0, J11.0, J12, J13, J14, J15, J16, J17, J18, J84.11, J84.2, J85.1, J95.851, Z87.01

	- **Male sex**: beta coefficient -0.19 - **Skin and soft tissue infection**: beta coefficient 0.18 (definition mentioned above: 'Skin and soft tissue infection') - **Mycoses**: beta coefficient 0.14 (definition mentioned above: 'Mycosis') - **Age (for every 1 year increase)**: beta coefficient 0.09 - **Admission in past 6 months**: beta coefficient 0.09 - **Gout or other crystal-induced arthropathy**: beta coefficient 0.08 (definition mentioned above: 'Gout or other crystal-induced arthropathy') - **Falls**: beta coefficient 0.08 (definition mentioned above: 'History of falling') - **Musculoskeletal problems**: beta coefficient 0.05 (definition mentioned above: 'Musculoskeletal problems') - **Urinary tract infection**: beta coefficient 0.05 (definition mentioned above: 'Urinary tract infection)
COMEDICATION USE (≤1 year before follow-up) [2]	
Influenza vaccination	**ATC:** J07BB02
Use of short-acting bronchodilators (SABD)	**ATC**: R03AC02, R03AC03, R03AL01, R03AL02, R03BB01 Categorized as appropriate (0-2 canisters/year), overuse (3-5 canisters/year) or heavy overuse (≥6 canisters/year)
OUTCOMES	
Mortality	All-cause mortality.
Hospitalised/severe exacerbations	Hospital admissions with a primary diagnosis code of asthma or (acute) COPD exacerbation, COPD with acute lower respiratory infection or asthma with status asthmaticus **ICD-10:** J44.0, J44.1, J45.21, J45.22, J45.31, J45.32, J45.41, J45.42, J45.51, J45.52, J45.901 or J45.902 *OR* with a primary diagnosis code for chronic lower respiratory disease (**ICD-10**: J40-J47) or respiratory failure (**ICD-10:** J96) and a secondary diagnosis code of asthma or (acute) COPD exacerbation, COPD with acute lower respiratory infection or asthma with status asthmaticus. Hospitalizations with concomitant pneumonia diagnosis were excluded. **ICD-10**: A01.03, A02.22, A37.01, A37.11, A37.81, A37.91, A50.04, A54.84, B01.2, B05.2, B06.81, B77.81, J09.X1, J09.X2, J09.X3, J10.0, J11.0, J12, J13, J14, J15, J16, J17, J18, J84.11, J84.2, J85.1, J95.851.
Outpatient/moderate exacerbations	Outpatient prescription fill for an oral corticosteroid ~ **ATC**: H02AB04, except parenteral use (defined on package level) with/without guideline recommended antibiotics ~ **ATC**: J01CA, J01CR, J01DC, J01FA, J01MA, except continuous azithromycin therapy (defined on package level with increased copayments). Prescription fills needed to be separated by at least 14 days to be considered as separate events. Outpatient exacerbations followed by a hospital admission for a severe exacerbation within 14 days were counted only as hospitalised exacerbation, to avoid counting exacerbations twice.

eTable 3: Diagnostic accuracy for predicting 1-year and 3-year mortality in patients with COAD

eTable 3: Diagnostic accuracy for predicting 1-year and 3-year mortality				
	1-year mortality		3-year mortality	
	AUC (95% CI)	P-value	AUC (95% CI)	P-value
Model 1				
Age, sex, smoking status	84.6 (84.5-84.8)		86.0 (85.9-86.1)	
+ Frailty	85.6 (85.5-85.8)	<0.0001	86.7 (86.6-86.8)	<0.0001
+ SABD use	85.0 (84.9-85.1)	<0.0001	86.4 (86.3-86.5)	<0.0001
+ Exacerbation history	85.0 (84.9-85.2)	<0.0001	86.3 (86.2-86.4)	<0.0001
Model 2				
Age, sex, smoking status, frailty	85.6 (85.5-85.8)		86.7 (86.6-86.8)	
+ SABD use	86.0 (85.9-86.1)	<0.0001	87.1 (87.0-87.2)	<0.0001
+ Exacerbation history	86.2 (86.1-86.4)	<0.0001	87.1 (87.0-87.2)	<0.0001
Model 3				
Age, sex, smoking status, frailty, exacerbation history	86.2 (86.1-86.4)		87.1 (87.0-87.2)	
+ SABD use	86.5 (86.4-86.6)	<0.0001	87.4 (87.3-87.5)	<0.0001
Model 4				
Age, sex, smoking status, frailty, exacerbation history, SABD use	86.5 (86.4-86.6)		87.4 (87.3-87.5)	

AUCs for predicting 1-year and 3-year mortality in patients with COAD are presented. Model 1 is adjusted for age, sex and smoking status. The variables frailty, exacerbation history and SABD use are separately added to model 1. Model 2, 3 and 4 are adjusted for variables of the previous model, producing the highest AUC. *AUC: area under the curve, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status*

eTable 4: Sensitivity analysis - risk of mortality in patients with COAD, stratified by registration of a hospital diagnosis for asthma and/or COPD.

eTable 4: Risk of mortality in patients with COAD, stratified by registration of a hospital diagnosis for asthma and/or COPD

Variable	Not hospital diagnosed		Hospital diagnosed	
	aHR (95% CI)	P-value	aHR (95% CI)	P-value
Aged 50-59 years (vs aged <50 years)	3.05 (2.91-3.20)	<0.0001	2.63 (2.38-2.91)	<0.0001
Aged 60-69 years (vs aged <50 years)	5.62 (5.38-5.88)	<0.0001	3.64 (3.31-4.01)	<0.0001
Aged 70-79 years (vs aged <50 years)	9.15 (8.75-9.57)	<0.0001	3.96 (3.59-4.36)	<0.0001
Aged 80 years or older (vs aged <50 years)	14.76 (14.1-15.46)	<0.0001	4.91 (4.45-5.43)	<0.0001
Age-adjusted Charlson Comorbidity Index	1.21 (1.20-1.21)	<0.0001	1.20 (1.19-1.20)	<0.0001
Frailty	2.34 (2.30-2.38)	<0.0001	1.63 (1.59-1.68)	<0.0001
Female sex (vs male sex)	0.68 (0.67-0.69)	<0.0001	0.76 (0.75-0.80)	<0.0001
Low SES (vs high SES)	1.33 (1.32-1.35)	<0.0001	1.16 (1.13-1.18)	<0.0001
Past smokers (vs no smokers)	1.23 (1.20-1.25)	<0.0001	1.25 (1.21-1.28)	<0.0001
Current smokers (vs no smokers)	1.69 (1.66-1.72)	<0.0001	1.42 (1.38-1.46)	<0.0001
One outpatient exacerbation (vs no exacerbation history)	1.10 (1.08-1.12)	<0.0001	1.10 (1.06-1.13)	<0.0001
Two or more outpatients exacerbations (vs no exacerbation history)	1.55 (1.52-1.58)	<0.0001	1.46 (1.41-1.50)	<0.0001
≥ 1 hospitalised exacerbation (vs no exacerbation history)	*NA*	*NA*	1.26 (1.22-1.29)	<0.0001
Influenza vaccination	0.89 (0.87-0.90)	<0.0001	0.94 (0.92-0.96)	<0.0001
Overuse of SABD (vs appropriate use)	1.45 (1.42-1.47)	<0.0001	1.28 (1.24-1.31)	<0.0001
Heavy SABD overuse (vs appropriate use)	1.91 (1.88-1.95)	<0.0001	1.67 (1.63-1.71)	<0.0001

aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status

eTable 4b: Sensitivity analysis - risk of mortality in patients with COAD, stratified by registration of a hospital diagnosis for asthma and/or COPD.

eTable 4b: Risk of mortality in patients with diagnosed COAD, stratified by asthma, COPD or asthma-COPD (ACO) overlap			
Variable	**COPD aHR (95% CI)**	**Asthma aHR (95% CI)**	**ACO aHR (95% CI)**
Aged 50-59 years (vs aged <50 years)	1.47 (1.28-1.68)	1.96 (1.58-2.43)	1.35 (1.05-1.72)
Aged 60-69 years (vs aged <50 years)	1.82 (1.60-2.07)	2.73 (2.23-3.33)	1.52 (1.20-1.92)
Aged 70-79 years (vs aged <50 years)	1.93 (1.69-2.20)	3.51 (2.86-4.30)	1.49 (1.17-1.89)
Aged 80 years or older (vs aged <50 years)	2.29 (2.01-2.62)	4.88 (3.93-6.05)	1.90 (1.48-2.44)
Age-adjusted Charlson comorbidity Index	1.18 (1.17-1.18)	1.27 (1.26-1.29)	1.21 (1.19-1.22)
Frailty	1.55 (1.50-1.60)	2.21 (1.99-2.46)	1.77 (1.61-1.95)
Female sex (vs male sex)	0.80 (0.78-0.82)	0.80 (0.74-0.86)	0.84 (0.78-0.90)
Low SES (vs high SES)	1.12 (1.09-1.14)	1.15 (1.07-1.23)	1.14 (1.07-1.22)
Past smokers (vs no smokers)	1.07 (1.04-1.10)	1.19 (1.09-1.30)	1.15 (1.06-1.25)
Current smokers (vs no smokers)	1.12 (1.09-1.16)	1.33 (1.19-1.49)	1.23 (1.12-1.35)
One outpatient exacerbation (vs no exacerbation history)	1.10 (1.06-1.14)	*1.01 (0.93-1.11)**	*1.10 (0.99-1.22)**
Two or more outpatients exacerbations (vs no exacerbation history)	1.43 (1.38-1.48)	1.49 (1.35-1.63)	1.53 (1.39-1.69)
≥ 1 hospitalised exacerbation (vs no exacerbation history)	1.23 (1.19-1.26)	*0.95 (0.84-1.07)**	1.27 (1.17-1.38)
Influenza vaccination	0.93 (0.91-0.95)	0.90 (0.83-0.96)	*0.95 (0.89-1.02)**
Overuse of SABD (vs appropriate use)	1.28 (1.24-1.32)	1.34 (1.23-1.46)	1.17 (1.06-1.28)
Heavy SABD overuse (vs appropriate use)	1.67 (1.63-1.72)	1.76 (1.62-1.92)	1.54 (1.43-1.67)

**Non-significant results (p-value <0.05) are presented in italic.*
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status

eTable 5: Sensitivity analysis - risk of mortality in patients with COAD, stratified by exacerbation history

eTable 5: Risk of mortality in patients with COAD, stratified by history of exacerbations in the previous 12 months

Variable	No exacerbation history aHR (95% CI)	One outpatient exacerbation aHR (95% CI)	Two or more outpatient exacerbations aHR (95% CI)	At least one hospitalised exacerbation aHR (95% CI)
Aged 50-59 years (vs aged <50 years)	3.37 (3.2-3.56)	3.18 (2.84-3.57)	1.79 (1.59-2.00)	2.40 (1.98-2.92)
Aged 60-69 years (vs aged <50 years)	6.59 (6.27-6.92)	4.81 (4.32-5.36)	2.65 (2.39-2.95)	3.40 (2.82-4.10)
Aged 70-79 years (vs aged <50 years)	10.61 (10.09-11.14)	7.05 (6.32-7.85)	3.13 (2.82-3.48)	3.57 (2.96-4.31)
Aged 80 years or older (vs aged <50 years)	17.33 (16.48-18.24)	10.7 (9.57-11.96)	4.16 (3.73-4.64)	4.04 (3.32-4.9)
Age-adjusted Charlson comorbidity Index	1.18 (1.18-1.19)	1.24 (1.23-1.24)	1.23 (1.23-1.24)	1.16 (1.15-1.17)
Frailty	2.40 (2.35-2.44)	1.85 (1.78-1.93)	1.43 (1.37-1.49)	1.65 (1.56-1.75)
Female sex (vs male sex)	0.68 (0.67-0.69)	0.72 (0.70-0.74)	0.79 (0.76-0.81)	0.79 (0.75-0.82)
Low SES (vs high SES)	1.35 (1.33-1.36)	1.25 (1.22-1.28)	1.20 (1.17-1.24)	1.15 (1.10-1.20)
Past smokers (vs no smokers)	1.27 (1.25-1.30)	1.19 (1.15-1.24)	1.27 (1.23-1.32)	1.33 (1.22-1.38)
Current smokers (vs no smokers)	1.68 (1.83-1.90)	1.60 (1.54-1.65)	1.43 (1.37-1.49)	1.30 (1.22-1.38)
Influenza vaccination	0.89 (0.88-0.90)	0.85 (0.82-0.87)	0.91 (0.91-0.97)	*1.01 (0.96-1.05)**
Overuse of SABD (vs appropriate use)	1.48 (1.46-1.50)	1.34 (1.29-1.38)	1.26 (1.21-1.31)	1.24 (1.17-1.32)
Heavy SABD overuse (vs appropriate use)	1.86 (1.83-1.90)	1.76 (1.70-1.82)	1.65 (1.59-1.70)	1.80 (1.72-1.89)

**Non-significant results (p < 0.05) are presented in italic.*
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status

eTable 6: Sensitivity analysis - risk of mortality in patients with COAD, stratified in incident and prevalent patients

eTable 6: Risk of mortality in patients with COAD, stratified in incident and prevalent patients				
	Incident (n = 210,004)		Prevalent (n = 796,964)	
Variable	aHR (95% CI)	P-value	aHR (95% CI)	P-value
Aged 50-59 years (vs aged <50 years)	2.87 (2.62-3.14)	<0.0001	3.39 (3.22-3.56)	<0.0001
Aged 60-69 years (vs aged <50 years)	4.91 (4.52-5.34)	<0.0001	6.19 (5.91-6.48)	<0.0001
Aged 70-79 years (vs aged <50 years)	6.83 (6.28-7.42)	<0.0001	9.09 (8.68-9.52)	<0.0001
Aged 80 years or older (vs aged <50 years)	10.59 (9.73-11.54)	<0.0001	14.08 (13.43-14.77)	<0.0001
Age-adjusted Charlson comorbidity Index	1.21 (1.20-1.21)	<0.0001	1.19 (1.19-1.20)	<0.0001
Frailty	2.21 (2.14-2.28)	<0.0001	2.01 (1.97-2.04)	<0.0001
Female sex (vs male sex)	0.71 (0.69-0.73)	<0.0001	0.71 (0.70-0.72)	<0.0001
Low SES (vs high SES)	1.22 (1.20-1.25)	<0.0001	1.33 (1.31-1.35)	<0.0001
Past smokers (vs no smokers)	1.16 (1.12-1.19)	<0.0001	1.29 (1.27-1.31)	<0.0001
Current smokers (vs no smokers)	1.53 (1.48-1.59)	<0.0001	1.69 (1.67-1.72)	<0.0001
One outpatient exacerbation (vs no exacerbation history)	1.11 (1.08-1.15)	<0.0001	1.10 (1.08-1.12)	<0.0001
Two or more outpatients exacerbations (vs no exacerbation history)	1.55 (1.49-1.61)	<0.0001	1.53 (1.51-1.56)	<0.0001
≥ 1 hospitalised exacerbation (vs no exacerbation history)	0.92 (0.83-1.01)	0.0666	1.24 (1.21-1.27)	<0.0001
Influenza vaccination	0.86 (0.84-0.88)	<0.0001	0.95 (0.93-0.96)	<0.0001
Overuse of SABD (vs appropriate use)	1.36 (1.32-1.39)	<0.0001	1.49 (1.47-1.51)	<0.0001
Heavy SABD overuse (vs appropriate use)	1.49 (1.36-1.62)	<0.0001	1.96 (1.93-1.99)	<0.0001
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status				

eTable 7: Sensitivity analysis for risk of mortality, with exclusion of COVID-19 period

eTable 7: Sensitivity analysis for risk of mortality, with exclusion of COVID-19 period		
Variable	**aHR (95% CI)**	**P-value**
Aged 50-59 years (vs aged <50 years)	3.23 (3.05-3.43)	<0.0001
Aged 60-69 years (vs aged <50 years)	5.70 (5.39-6.02)	<0.0001
Aged 70-79 years (vs aged <50 years)	7.74 (7.33-8.18)	<0.0001
Aged 80 years or older (vs aged <50 years)	11.71 (11.07-12.39)	<0.0001
Age-adjusted Charlson comorbidity Index	1.21 (1.21-1.22)	<0.0001
Frailty	2.09 (2.05-2.13)	<0.0001
Female sex (vs male sex)	0.74 (0.73-0.75)	<0.0001
Low SES (vs high SES)	1.28 (1.26-1.30)	<0.0001
Past smokers (vs no smokers)	1.26 (1.24-1.28)	<0.0001
Current smokers (vs no smokers)	1.59 (1.56-1.62)	<0.0001
One outpatient exacerbation (vs no exacerbation history)	1.13 (1.11-1.15)	<0.0001
Two or more outpatients exacerbations (vs no exacerbation history)	1.58 (1.55-1.62)	<0.0001
≥ 1 hospitalised exacerbation (vs no exacerbation history)	1.23 (1.19-1.26)	<0.0001
Influenza vaccination	0.88 (0.87-0.90)	<0.0001
Overuse of SABD (vs appropriate use)	1.46 (1.44-1.49)	<0.0001
Heavy SABD overuse (vs appropriate use)	1.90 (1.87-1.94)	<0.0001
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status		

eTable 8: Risk of a new hospitalised exacerbation in patients with COAD, stratified by registration of a hospital diagnosis for asthma and/or COPD

eTable 8: Risk of a new hospitalised exacerbation in patients with COAD, stratified by registration of a hospital diagnosis for asthma and/or COPD				
	Not hospital diagnosed		**Hospital diagnosed**	
Variable	**aHR (95% CI)**	**P-value**	**aHR (95% CI)**	**P-value**
Aged 50-59 years (vs aged <50 years)	2.39 (2,25-2,54)	<0.0001	1.56 (1,44-1,68)	<0.0001
Aged 60-69 years (vs aged <50 years)	4.19 (3,95-4,45)	<0.0001	1.96 (1,81-2,11)	<0.0001
Aged 70-79 years (vs aged <50 years)	6.23 (5,82-6,67)	<0.0001	2.13 (1,97-2,31)	<0.0001
Aged 80 years or older (vs aged <50 years)	7.06 (6,51-7,66)	<0.0001	1.98 (1,81-2,17)	<0.0001
Age-adjusted Charlson comorbidity Index	0.93 (0.92-0.94)	<0.0001	1.02 (1.01-1.02)	<0.0001
Frailty	0.86 (0.82-0.91)	<0.0001	1.22 (1.16-1.27)	0.0342
Female sex (vs male sex)	0.83 (0.80-0.85)	<0.0001	0.94 (0.91-0.97)	0.0016
Low SES (vs high SES)	1.45 (1.41-1.49)	<0.0001	1.30 (1.27-1.34)	<0.0001
Past smokers (vs no smokers)	1.79 (1.72-1.87)	<0.0001	1.76 (1.68-1.84)	<0.0001
Current smokers (vs no smokers)	3.64 (3.52-3.75)	<0.0001	2.33 (2.23-2.43)	<0.0001
One outpatient exacerbation (vs no exacerbation history)	1.88 (1.82-1.94)	<0.0001	1.49 (1.42-1.56)	<0.0001
Two or more outpatients exacerbations (vs no exacerbation history)	2.57 (2.47-2.67)	<0.0001	2.01 (1.91-2.11)	<0.0001
≥ 1 hospitalised exacerbation (vs no exacerbation history)	*NA*	*NA*	3.43 (3.30-3.55)	<0.0001
Influenza vaccination	1.27 (1.23-1.31)	<0.0001	1.16 (1.13-1.20)	<0.0001
Overuse of SABD (vs appropriate use)	1.78 (1.71-1.85)	<0.0001	1.52 (1.46-1.59)	<0.0001
Heavy SABD overuse (vs appropriate use)	3.61 (3.49-3.73)	<0.0001	2.39 (2.31-2.47)	<0.0001
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status				

eTable 8b: Risk of a new hospitalised exacerbation in patients with COAD, stratified by registration of a hospital diagnosis for asthma and/or COPD

eTable 8b: Risk of a new hospitalised exacerbation in patients with diagnosed COAD, stratified by asthma, COPD or asthma-COPD (ACO) overlap

Variable	COPD aHR (95% CI)	Asthma aHR (95% CI)	ACO aHR (95% CI)
Aged 50-59 years (vs aged <50 years)	1.12 (1.00-1.26)	*1.06 (0.89-1.28)**	*1.00 (0.84-1.19)**
Aged 60-69 years (vs aged <50 years)	1.32 (1.18-1.48)	*1.22 (1.00-1.49)**	*1.05 (0.88-1.25)**
Aged 70-79 years (vs aged <50 years)	1.40 (1.25-1.57)	1.40 (1.11-1.76)	*1.15 (0.95-1.40)**
Aged 80 years or older (vs aged <50 years)	1.28 (1.13-1.44)	1.67 (1.25-2.22)	*0.94 (0.75-1.19)**
Age-adjusted Charlson comorbidity Index	*1.01 (1.00-1.01)**	*1.02 (0.99-1.06)**	1.03 (1.01-1.06)
Frailty	1.12 (1.06-1.17)	*1.10 (0.89-1.36)**	1.29 (1.14-1.47)
Female sex (vs male sex)	*0.97 (0.93-1.00)**	1.28 (1.13-1.45)	*1.02 (0.94-1.11)**
Low SES (vs high SES)	1.22 (1.18-1.26)	1.64 (1.47-1.83)	1.29 (1.19-1.41)
Past smokers (vs no smokers)	1.43 (1.35-1.51)	1.36 (1.17-1.59)	1.35 (1.19-1.52)
Current smokers (vs no smokers)	1.75 (1.66-1.85)	1.61 (1.40-1.85)	1.78 (1.57-2.00)
One outpatient exacerbation (vs no exacerbation history)	1.44 (1.36-1.52)	1.82 (1.54-2.14)	1.40 (1.20-1.63)
Two or more outpatients exacerbations (vs no exacerbation history)	1.87 (1.77-1.97)	3.00 (2.55-3.54)	1.94 (1.68-2.24)
≥ 1 hospitalised exacerbation (vs no exacerbation history)	3.01 (2.89-3.13)	6.11 (5.34-6.99)	3.28 (2.94-3.66)
Influenza vaccination	1.14 (1.10-1.18)	1.22 (1.08-1.38)	1.11 (1.01-1.21)
Overuse of SABD (vs appropriate use)	1.53 (1.46-1.60)	1.86 (1.62-2.14)	1.23 (1.09-1.40)
Heavy SABD overuse (vs appropriate use)	2.35 (2.26-2.44)	2.71 (2.38-3.08)	2.24 (2.03-2.47)

**Non-significant results(p-value < 0.05) are presented in italic.*
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status

eTable 9: Sensitivity analysis - Risk of a new hospitalised exacerbation in patients with COAD, stratified by exacerbation history

eTable 9: Risk of a new hospitalised exacerbation in patients with COAD, stratified by history of exacerbations in the previous 12 months

Variable	No exacerbation history aHR (95% CI)	One outpatient exacerbation aHR (95% CI)	Two or more outpatient exacerbations aHR (95% CI)	At least one hospitalised exacerbation aHR (95% CI)
Aged 50-59 years (vs aged <50 years)	2.16 (2.02-2.31)	1.87 (1.68-2.08)	1.84 (1.62-2.09)	1.26 (1.13-1.40)
Aged 60-69 years (vs aged <50 years)	3.55 (3.33-3.79)	2.83 (2.55-3.15)	2.47 (2.17-2.80)	1.38 (1.24-1.53)
Aged 70-79 years (vs aged <50 years)	4.66 (4.34-5.00)	3.68 (3.29-4.12)	3.13 (2.74-3.57)	1.38 (1.23-1.54)
Aged 80 years or older (vs aged <50 years)	4.52 (4.17-4.91)	3.37 (2.95-3.85)	2.96 (2.55-3.45)	*1.14 (1.00-1.30)**
Age-adjusted Charlson comorbidity Index	1.06 (1.03-1.14)	1.02 (1.00-1.03)	*0.99 (0.98-1.01)**	1.02 (1.01-1.03)
Frailty	1.08 (1.03-1.14)	1.09 (1.00-1.19)	*1.01 (0.93-1.11)**	1.13 (1.05-1.21)
Female sex (vs male sex)	0.83 (0.80-0.85)	0.86 (0.82-0.91)	0.89 (0.84-0.93)	0.95 (0.90-0.99)
Low SES (vs high SES)	1.49 (1.44-1.53)	1.37 (1.31-1.44)	1.32 (1.25-1.39)	1.22 (1.17-1.28)
Past smokers (vs no smokers)	2.24 (2.15-2.34)	2.09 (1.95-2.23)	2.11 (1.97-2.26)	1.58 (1.47-1.70)
Current smokers (vs no smokers)	4.38 (4.23-4.53)	3.56 (3.37-3.76)	3.11 (2.92-3.30)	1.85 (1.72-1.99)
Influenza vaccination	1.21 (1.17-1.24)	1.28 (1.21-1.35)	1.31 (1.24-1.39)	1.14 (1.09-1.19)
Overuse of SABD (vs appropriate use)	1.74 (1.67-1.81)	1.65 (1.55-1.76)	1.90 (1.76-2.05)	1.47 (1.38-1.57)
Heavy SABD overuse (vs appropriate use)	3.32 (3.19-3.44)	3.10 (2.93-3.28)	3.78 (3.56-4.02)	2.41 (2.29-2.53)

**Non-significant results (p < 0.05) are presented in italic.*

aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status

eTable 10: Sensitivity analysis - Risk of a new hospitalised exacerbation in patients with COAD, stratified in incident and prevalent patients

eTable 10: Risk of a new hospitalised exacerbation in patients with COAD, stratified in incident and prevalent patients				
	Incident (n = 210,004)		**Prevalent (n = 796,964)**	
Variable	**aHR (95% CI)**	**P-value**	**aHR (95% CI)**	**P-value**
Aged 50-59 years (vs aged <50 years)	1.98 (1.71-2.28)	<0.0001	2.07 (1.97-2.17)	<0.0001
Aged 60-69 years (vs aged <50 years)	2.77 (2.41-3.19)	<0.0001	3.05 (2.91-3.20)	<0.0001
Aged 70-79 years (vs aged <50 years)	3.61 (3.09-4.21)	<0.0001	3.78 (3.59-3.98)	<0.0001
Aged 80 years or older (vs aged <50 years)	2.79 (2.31-3.37)	<0.0001	3.72 (3.51-3.95)	<0.0001
Age-adjusted Charlson comorbidity Index	1.02 (1.00-1.04)	0.0599	1.03 (1.03-1.04)	<0.0001
Frailty	1.03 (0.9-1.18)	0.6342	1.09 (1.05-1.13)	<0.0001
Female sex (vs male sex)	0.68 (0.63-0.73)	<0.0001	0.89 (0.87-0.91)	<0.0001
Low SES (vs high SES)	1.58 (1.47-1.70)	<0.0001	1.40 (1.37-1.43)	<0.0001
Past smokers (vs no smokers)	1.69 (1.45-1.83)	<0.0001	2.26 (2.19-2.33)	<0.0001
Current smokers (vs no smokers)	4.23 (3.67-4.33)	<0.0001	3.61 (3.52-3.71)	<0.0001
One outpatient exacerbation (vs no exacerbation history)	1.63 (1.49-1.79)	<0.0001	1.87 (1.81-1.92)	<0.0001
Two or more outpatients exacerbations (vs no exacerbation history)	1.63 (1.40-1.89)	<0.0001	2.59 (2.51-2.67)	<0.0001
≥ 1 hospitalised exacerbation (vs no exacerbation history)	6.08 (5.26-6.74)	<0.0001	5.53 (5.37-5.7)	<0.0001
Influenza vaccination	0.96 (0.89-1.04)	0.2895	1.24 (1.21-1.27)	<0.0001
Overuse of SABD (vs appropriate use)	1.56 (1.43-1.72)	<0.0001	1.68 (1.63-1.73)	<0.0001
Heavy SABD overuse (vs appropriate use)	2.46 (1.81-3.22)	<0.0001	2.92 (2.85-3.00)	<0.0001
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status				

eTable 11: Sensitivity analysis for risk of a new hospitalised exacerbation, with exclusion of COVID-19 period

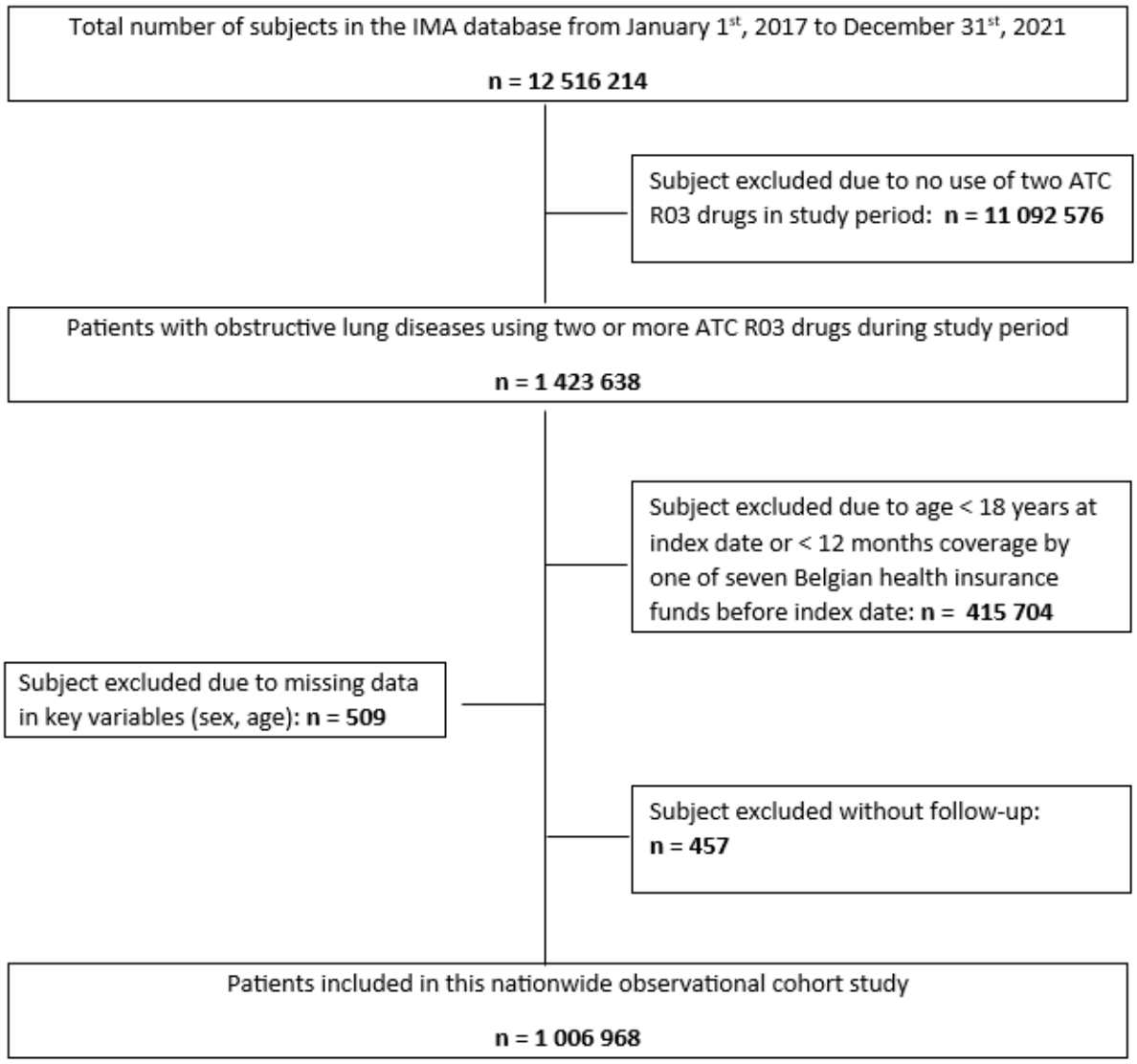
eTable 11: Sensitivity analysis for risk of (next) hospitalised exacerbation, with exclusion of COVID-19 period		
Variable	**aHR (95% CI)**	**P-value**
Aged 50-59 years (vs aged <50 years)	2.00 (1.89-2.12)	<0.0001
Aged 60-69 years (vs aged <50 years)	2.87 (2.72-3.03)	<0.0001
Aged 70-79 years (vs aged <50 years)	3.55 (3.35-3.76)	<0.0001
Aged 80 years or older (vs aged <50 years)	3.44 (3.23-3.68)	<0.0001
Age-adjusted Charlson comorbidity Index	1.03 (1.02-1.04)	<0.0001
Frailty	1.05 (1.01-1.10)	<0.0001
Female sex (vs male sex)	0.89 (0.87-0.91)	<0.0001
Low SES (vs high SES)	1.38 (1.35-1.41)	<0.0001
Past smokers (vs no smokers)	2.32 (2.25-2.40)	<0.0001
Current smokers (vs no smokers)	3.55 (3.45-3.65)	<0.0001
One outpatient exacerbation (vs no exacerbation history)	1.93 (1.87-1.99)	<0.0001
Two or more outpatients exacerbations (vs no exacerbation history)	2.75 (2.65-2.84)	<0.0001
≥ 1 hospitalised exacerbation (vs no exacerbation history)	6.12 (5.91-6.32)	<0.0001
Influenza vaccination	1.24 (1.21-1.28)	<0.0001
Overuse of SABD (vs appropriate use)	1.70 (1.65-1.76)	<0.0001
Heavy SABD overuse (vs appropriate use)	3.01 (2.93-3.09)	<0.0001
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status		

eTable 12: Sensitivity analysis for risk of a new hospitalised exacerbation, with death as competing risk (Fine-Gray subdistribution hazard model)

eTable 12: Sensitivity analysis for risk of (next) hospitalised exacerbation, with death as competing risk (Fine-Gray subdistribution hazard model)		
Variable	**aHR (95% CI)**	**P-value**
Aged 50-59 years (vs aged <50 years)	2.21 (2.11-2.32)	<0.001
Aged 60-69 years (vs aged <50 years)	3.34 (3.19-3.50)	<0.001
Aged 70-79 years (vs aged <50 years)	4.30 (4.09-4.52)	<0.001
Aged 80 years or older (vs aged <50 years)	3.99 (3.76-4.23)	<0.001
Age-adjusted Charlson comorbidity Index	0.97 (0.96-0.97)	<0.001
Frailty	0.92 (0.89-0.96)	<0.001
Female sex (vs male sex)	0.92 (0.89-0.96)	<0.001
Low SES (vs high SES)	1.38 (1.35-1.40)	<0.001
Past smokers (vs no smokers)	2.16 (2.10-2.30)	<0.001
Current smokers (vs no smokers)	3.59 (3.50-3.68)	<0.001
One outpatient exacerbation (vs no exacerbation history)	1.86 (1.80-1.91)	<0.001
Two or more outpatients exacerbations (vs no exacerbation history)	2.44 (2.36-2.51)	<0.001
≥ 1 hospitalised exacerbation (vs no exacerbation history)	5.55 (5.37-5.73)	<0.001
Influenza vaccination	1.30 (1.27-1.33)	<0.001
Overuse of SABD (vs appropriate use)	1.75 (1.70-1.80)	<0.001
Heavy SABD overuse (vs appropriate use)	3.14 (3.06-3.22)	<0.001
aHR: adjusted Hazard ratio, CI: confidence interval, SABD: short-acting bronchodilators, SES: socio-economic status		

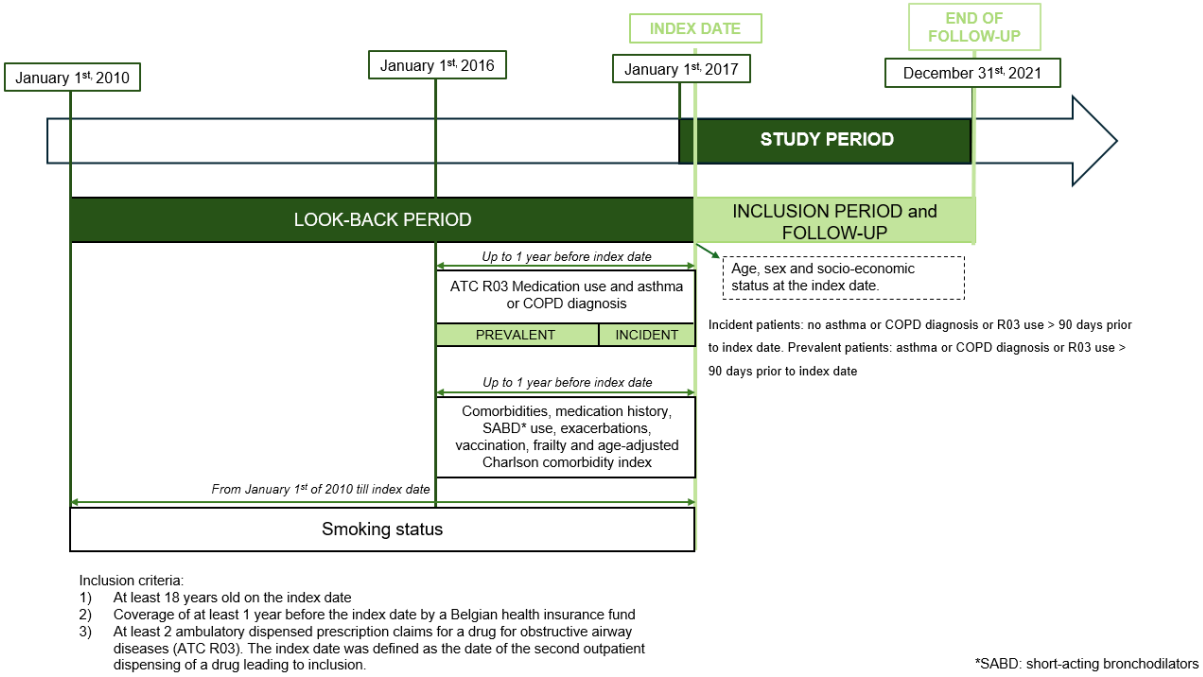
Supplemental figures

eFigure 1: Flowchart of inclusion of study population



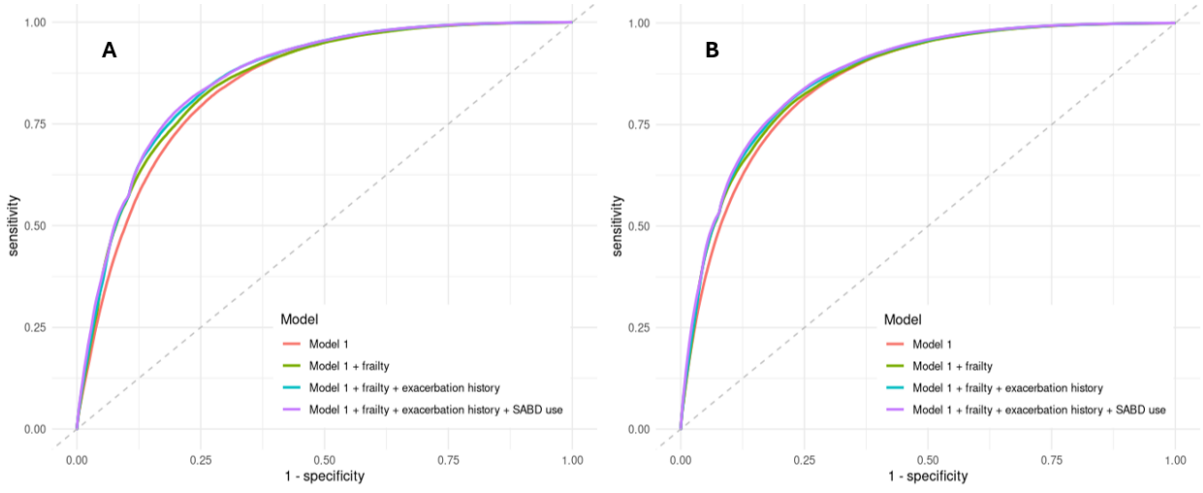
eFigure 1: Flowchart of inclusion of study population

eFigure 2: Study design of our cohort study with specification of incident and prevalent patients



eFigure 2: Study design of our cohort study with specification of incident and prevalent patients.

eFigure 3: Receiver operating characteristics (ROC) curves for prediction of 1-year and 3-year mortality in patients with COAD



eFigure 3: ROC curve for prediction of (A) 1-year mortality and (B) 3-year mortality in patients with COAD

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