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Pre- and post-vaccination characteristics and risk factors for COVID-19 outcomes in a Swedish population-based cohort of COPD patients

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Tweetable abstract

This study delineates poorly understood risk factors that are clinically relevant for COPD patients and quantifies risks pre- and post-vaccination, with implications on informing clinical evaluation and improving treatment and prevention efforts.

Disclosures
CS has received personal fees from AstraZeneca, Boehringer-Ingelheim and Novartis for lectures at sponsored meetings. LV has received grants and personal fees from AstraZeneca and personal fees from GSK, Novartis, Boehringer-Ingelheim, Menarini, Resmed, Chiesi, AGA Linde, Zambon and Pulmonx. FN was an employee of AstraZeneca until 2019 and holds some AstraZeneca shares. SF is an employee of AstraZeneca as of October 2021 but the work in this paper relates to the period prior to this. BK, AS and HL have nothing to disclose.

This article has an online data supplement.

ABSTRACT

Rationale
Evidence on risk factors for Coronavirus disease 2019 (COVID-19) outcomes among patients with chronic obstructive pulmonary disease (COPD) in relation to COVID-19 vaccination remains limited.

Objectives
To characterize determinants of COVID-19 infection, hospitalization, intensive care unit (ICU) admission, and death in COPD patients in their unvaccinated state compared to when vaccinated.

Methods
We included all COPD patients in the Swedish National Airway Register (SNAR). Events of COVID-19 infection (test and/or healthcare encounter), hospitalization, ICU admission and death were identified 1Jan 2020 - 30Nov 2021. Using adjusted Cox regression, associations between baseline sociodemographics, comorbidities, treatments, clinical measurements, and COVID-19 outcomes, during unvaccinated and vaccinated follow-up time, were analyzed.

Results
The population-based COPD cohort included 87472 patients; among whom 6771 (7.7%) COVID-19 infections, 2897 (3.3%) hospitalizations, 233 (0.3%) ICU admissions, and 882 (1.0%) COVID-19 deaths occurred. During unvaccinated follow-up, risk of COVID-19 hospitalization and death increased with age, male sex, lower education, non-married status and being foreign-born. Comorbidities increased risk of several outcomes, e.g. respiratory failure for infection and hospitalization (adjusted HR 1.78, 95%CI 1.58-2.02 and 2.51, 2.16-2.91, respectively), obesity for ICU admission (3.52, 2.29-5.40) and cardiovascular disease for mortality (2.80, 2.16-3.64). Inhaled COPD therapy was associated with infection, hospitalization, and death. COPD severity was also associated with COVID-19, especially hospitalization and death. Although the risk factor panorama was similar, COVID-19 vaccination attenuated HRs for some risk factors.

Conclusion
This study provides population-based evidence on predictive risk factors for COVID-19 outcomes, and highlights the positive implications of COVID-19 vaccination for COPD patients.

INTRODUCTION

Studies early in the coronavirus disease 2019 (COVID-19) pandemic showed that patients with several chronic diseases are at high risk for infection, worse prognosis, and death [1–3]. However, many aspects of the risk for COVID-19 onset and severity remain poorly understood for individuals with chronic obstructive pulmonary disease (COPD), especially after

widespread vaccination. COPD patients are prone to exacerbations, which are associated with a decline in lung function [4], impaired quality of life [5], and contribute to increased morbidity and mortality. Respiratory virus infections, including some coronaviruses, are frequent triggers of COPD exacerbations [6]. Therefore, it is plausible that preexisting COPD may contribute to the risk of COVID-19 outcomes. However, previous studies on COVID-19 patients with COPD have yielded conflicting results, including some finding increased healthcare utilization [7] and higher risk for severe COVID-19 [8–10], while others did not find associations with negative COVID-19 outcomes [11,12]. This may reflect variability in studies conducted, including study period, sample size, and a focus on hospitalized COVID-19 cohorts, but leaves many questions without satisfactory answers.

Prior studies have reported clinical factors, such as the degree of symptoms and airflow limitation [13], or inhaler corticosteroids (linked to Angiotensin-Converting Enzyme-2 (ACE2) receptor downregulation) [14], may predict COVID-19 outcomes. Yet, population-based studies could better delineate the risk factor panorama differentiating COVID-19 risk in COPD patients by investigating a more extensive set of potential risk factors, including clinical variables, combined with multiple COVID-19 outcomes to explore risk across the COVID-19 disease spectrum. The present study followed a population-based cohort of COPD patients prospectively over 23 months, covering their pre- and post-vaccination states during the COVID-19 pandemic, using nationally representative register data, to systematically investigate determinants of COVID-19 infection, hospitalization, ICU admission, and death, of specific relevance for the COPD patient population.

METHODS

Study design

This study adopted a cohort design using data from the Swedish COVID-19 Investigation for Future Insights - Population Epidemiology Approach using Register Linkage (SCIFI-PEARL) project [15]. This database includes all individuals in Sweden, comprehensively identifies COVID-19 outcomes from different sources, including SmiNet (national database of notifiable diseases), the National Patient Register (NPR) with outpatient or inpatient care, or the Cause-of-Death Register (CDR), and also links additional data from various other registries, including the Swedish National Airway Register (SNAR). Ethical approval was obtained from the Swedish Ethical Review Authority.

Study population, outcomes, and follow-up

Our study population was restricted to COPD patients (International Classification of Diseases version 10, Swedish Edition (ICD-10-SE) code J44) ≥40-year old in the Swedish population diagnosed at all levels of care and registered in SNAR during 2015-2019 [16]. We defined 4 COVID-19 outcomes: COVID-19 infection based on COVID-19 (ICD-10-SE codes U07.1 or U07.2) as primary or secondary diagnosis from inpatient or specialist outpatient care in the NPR or underlying or contributing cause of death in the CDR, or positive test result for SARS-CoV-2 in SmiNet), hospitalization (primary or secondary COVID-19 diagnosis with the same ICD-10-SE codes from NPR inpatient care), intensive care unit (ICU) admission (COVID-19 diagnosis with the same codes from the Swedish Intensive care Register (SIR), and death (underlying or contributing cause of death due to COVID-19 with the same codes in the CDR). In our main analysis, unvaccinated follow-up included outcome events from 1 Jan 2020 (index date) until exiting the cohort on the earliest of: the studied outcome, death, emigration, first vaccination, or end of follow-up (30 Nov 2021). Vaccinated follow-up included outcome events in COPD patients still at risk from 14 days after their first vaccination date until exiting

the cohort. Unvaccinated time corresponded mainly to the period before and during the alpha variant predominance, vaccinated time mainly to alpha- and delta-dominated periods (Figure S1). The cohort design is illustrated in Figure 1.

Exposures and covariates

The potential determinants studied included sociodemographic characteristics, smoking status, pre-existing comorbidities, medications, and clinical measurements (Table E1). Sociodemographic information was obtained from the Longitudinal Integrated Database for Health Insurance and Labor Market Studies (LISA)[17], including education, age-stratified employment status (unemployed 40-64 years, employed 40-64, employed 65+ and retired), marital status, and region of birth (Table E1). Smoking status was derived from SNAR (never, former, and current smoking).

Information on pre-existing comorbidities from the NPR included: overall cardiovascular disease, hypertension, heart failure, diabetes, asthma, respiratory failure, interstitial lung disease, chronic kidney disease, immunologic disease, autoimmune diseases, cancer, depression, anxiety, and psychiatric conditions, and on sleep apnea syndrome diagnosis from SNAR (Table E1). From the National Prescribed Drug Register (NPDR), we obtained prescribed medications in the year before the index date for COPD medications of importance, and a few cardiovascular and depression medications that have been implicated as potential risk factors for COVID-19 (Table E1). Information on COVID-19 vaccination came from the National Vaccination Register.

Clinical measurements obtained from SNAR included dyspnea measured by the modified Medical Research Council (mMRC) dyspnea scale, symptom burden assessed with the COPD

Assessment Test (CAT), body mass index (BMI), and spirometry values. Spirometry included post-bronchodilator Forced Expiratory Volume in one second, percent of predicted (FEV_1% predicted), based on the Swedish Hedenström reference values [18]. Missing post-bronchodilator FEV_1 values were replaced with pre-bronchodilator values. FEV_1 was categorized into Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages: 1 = $FEV_1 \geq 80\%$; 2 = 50-79%; 3 = 30-49% and 4 = < 30%. GOLD ABCD classes were also created from SNAR data on number of total and hospitalized exacerbations in the year prior to index date, CAT and mMRC scores as described in Table E1. BMI was classified as underweight (<18.5); normal (18.5-24.9); overweight (25.0-29.9) and obese ($\geq$30.0 kg/m^2). For CAT, a cutoff at $\geq$10 was used [19] and mMRC was retained as a 0-4 score. The most recent measurements available before the index date were used, since smoking, BMI, spirometry, CAT and mMRC scores were not measured on every healthcare visit (Table E1).

Statistical analysis

Most variables had no missing by design, as absence of a registration of e.g., a comorbidity is interpreted as no comorbidity. Variables with some missing values in the study were education, smoking, BMI, FEV_1% predicted and GOLD stage. Descriptive statistics are presented as frequencies and percentages for categorical variables and means and standard deviations or medians and interquartile ranges for continuous variables, for the total COPD population cohort and for the COVID-19 outcome groups. Cox proportional hazards models with calendar time as the underlying timescale were used to examine associations between potential determinants and the four COVID-19 outcomes. Separate models were run for each potential determinant, and for unvaccinated and vaccinated COPD patients. All main models were adjusted for age, sex, diabetes, hypertension, smoking and BMI as potential confounders, based on prior knowledge. As a sensitivity analysis, an extensive post hoc multivariable model was also run,

including most of the studied risk factors (notably except GOLD stage and $FEV_{1,}$ due to more missing data in these variables). Results are reported as unadjusted and adjusted hazard ratios (HRs) with 95% confidence interval (CI), and statistical significance considered for two-sided $P<0.05$. A trend test for ordinal categorical variables was obtained by including the variable as an ordinal covariate in the regression model. All analyses were conducted on individuals with complete data with Stata (Version 16.1) and R (Version 4.0.2).

RESULTS

There were 87472 COPD patients identified, among whom 6068 infections, 2649 hospitalizations, 221 ICU admissions, and 803 deaths related to COVID-19 occurred during unvaccinated follow-up time (Table 1). In the overall cohort and among patients with COVID-19 infections in the unvaccinated period, a slight majority were women, while more men were hospitalized, ICU admitted and died of COVID-19 (Table 1). COPD patients who were hospitalized or died from COVID-19 were older than patients with COVID-19 infection, ICU admission or in the COPD population cohort. Following COVID-19 vaccination, 703 infections, 248 hospitalizations, 12 ICU admissions and 79 deaths occurred during vaccinated follow-up time (Table 1).

Higher BMI and prevalence of obesity were observed for ICU admissions (Table 2). COPD patients with poor COVID-19 outcomes also had a higher prevalence of most investigated comorbidities (e.g., cardiovascular diseases, diabetes, respiratory diseases, CKD, cancer, depression, anxiety and psychiatric disorders) except autoimmune and interstitial lung diseases, and more frequent use of most respiratory medications (e.g., oral and inhaled corticosteroids, bronchodilator agonists, muscarinic antagonists) than the underlying population COPD cohort

(Table 2, Table E2). Moreover, COVID-19 patients, admitted to ICUs were more likely to have high CAT scores, i.e., higher symptom burden, than the COPD population cohort (Table 2).

Associations of risk factors and COVID-19 outcomes in unvaccinated COPD patients

The adjusted HRs for COVID-19 hospitalization and mortality in unvaccinated COPD patients increased clearly with age, but this was not the case for COVID-19 infection and ICU admissions (Figure 2, Table E3). Women and those with higher education were at significantly lower risk for all COVID-19 outcomes except ICU admission, with a significant trend across education levels for hospitalization and death. Foreign-born individuals, especially from outside Europe, were at significantly higher risk for COVID-19 infection, hospitalization, and ICU admission, than Sweden-born. Among working-age (40-64-year-old) patients, employment was significantly associated risk with an increased risk of COVID-19 infection but otherwise with lower risk across different COVID-19 outcomes. Being married decreased the risk of hospitalization and death (Figure 2, Table E3).

Pre-existing comorbidities such as cardiovascular diseases, respiratory failure, CKD, diabetes, autoimmune disease, depression, anxiety and psychiatric disease, were significant predictors for most COVID-19 outcomes in the unvaccinated (HR range 1.28-2.80), except for ICU admissions (Figure 3, Table E3). Some predictors of COVID-19 death such as heart failure, and hypertension were not significantly predictive of ICU admission. Use of inhaled and oral corticosteroid drugs (ICS and OCS), short- and long-acting bronchodilator agonists (SABA and LABA), and short- and long-acting muscarinic antagonists (SAMA, and LAMA) was associated with a higher risk of COVID-19 infection and hospitalization (Figure 4, Table E3). Similar associations were observed with death, significant except for OCS, and for ICU admission, albeit significant only for ICS, OCS, LABA, and LAMA (Table E3).

Underweight patients were at an increased risk of all COVID-19 outcomes (HR range 1.21-1.69) but not for ICU admissions (Figure 5, Table E3). Obese patients had a higher risk for hospitalization (HR 1.19, 95% CI 1.07-1.32) and ICU admissions (3.52, 2.29-5.40). Clinical measures indicating severe disease, especially CAT score ≥10 and GOLD B, C and D classification, but also mMRC level 3, were positively associated with most outcomes and predicted hospitalization (HRs range 1.37-1.92) and death (HRs 1.38-2.39) (Figure 5, Table E4). COPD patients with lower FEV_1 % predicted (GOLD 3 and 4), also had a higher risk of COVID-19 infection, hospitalization, and death (Table E3).

In the sensitivity analysis, the full multivariable model that presents results conditional on most of the studied risk factors (Table E4), estimates for demographic risk factors were similar to the main results with predefined confounder adjustment (Table E3). Many comorbidities (overall cardiovascular disease, type 2 diabetes, respiratory failure, autoimmune disease, depression, psychiatric disease), prescribed medications (ICS, LABA, SAMA, LAMA, statins, ARB, antidepressants) and clinical features (CAT scores and BMI) remained significant risk factors.

Associations of risk factors and COVID-19 outcomes in vaccinated COPD patients

Overall, HRs for risk factors among the vaccinated were similar in direction to the unvaccinated, albeit with wider confidence intervals (Figures 2-5, Table E5). Risk factors to highlight include older age, comorbidities (e.g., cardiovascular diseases, respiratory failure, autoimmune disease, depression, anxiety, psychiatric disease), and clinical factors (e.g., CAT, underweight, GOLD C and D), where the HRs for the vaccinated were attenuated compared to the unvaccinated, and some confidence intervals included one (Figures 2, 3, 5). Conversely,

the magnitude of HRs for other factors, notably many prescribed medications,e.g., inhaled corticosteroids, were somewhat stronger in the vaccinated, although nonetheless sometimes nonsignificant due to reduced power (Figure 4).

DISCUSSION

This study is the first to examine a broader range of COVID-19 outcomes for COPD patients in a truly population-based setting and spanning the pre- and post- COVID-19 vaccination periods. SARS-CoV-2 variants were not specifically evaluated, but the vaccinated and unvaccinated follow-up roughly separates pre-alpha and alpha from delta-dominated periods. Among the unvaccinated, old age, male sex, lower education level, and being foreign-born were associated with COVID-19 outcomes. Moreover, the study highlights that severe COPD (i.e., reduced lung function, a greater symptom burden and exacerbation risk as defined by GOLD 1-4 and ABCD), underweight and obesity, various comorbidities, and some prior medications were associated with severe COVID-19 outcomes. Among the vaccinated, most determinants of COVID-19 risk were similar in the vaccinated, although with some evidence of attenuated risk after vaccination.

The increased risk observed among men and with older age in COPD patients is in line with previous studies reporting these as risk factors for severe COVID-19 [7,8,11,13,20,21]. The higher COVID-19 susceptibility of men may be due to biological mechanisms, including weaker immune response [22] and higher expression of the ACE-2 receptor [23]. Furthermore, sex differences in immune responses may be related to differential pathogenic processes, and therefore, differences in the general presentation of COVID-19 among men and women [24]. There is no clear age effect for being infected with COVID-19, as might be expected in a situation with widespread disease, but the increased risk for hospitalization and death with higher age is clear. It is worth noting that when age is examined in a study, its effect may be partially mediated by comorbidities and individual characteristics, which may obscure the full effect of age.

Our findings are consistent with previous Swedish studies that found higher education to be associated with a reduced risk of COVID-19 death in the general population, and being foreign-born to be associated with increased risks for COVID-19 infection and hospitalization [25,26]. Foreign-born individuals living in other high-income countries have similarly been found to be at higher risk for severe COVID-19 [25,27]. There is evidence that migrants are at higher risk due to: socioeconomic factors, such as work [25] and living conditions; lower awareness of preventive measures compared to native populations; and other barriers [27]. In this study, COPD patients also exhibit this socioeconomic pattern.

In unadjusted analyses, most comorbidities were associated with COVID-19 outcomes, but only some (e.g., cardiovascular diseases and diabetes) were significant after adjustments. Interestingly, most comorbidities that strongly predicted hospitalization or death (e.g., heart failure) were not associated with ICU admission. This finding could reflect patients with such conditions not being selected for ICU admission, potentially due to the assessed low likelihood of treatment success in the ICU. As in previous studies of COPD cohorts among COVID-19 patients [8,11], overall cardiovascular disease including hypertension and heart failure was associated with an increased risk of hospitalization and mortality. Our results demonstrate that among COPD patients, being underweight is associated with an increased risk of COVID-19 infection, hospitalization and death. This is consistent with earlier reporting of high COVID-19 mortality risk in underweight COPD patients [28], and underweight being a known risk factor for diverse negative clinical outcomes in COPD patients [29]. In contrast, obesity was a predictor for severe disease, i.e. hospitalization, ICU admission but not significantly for death. Adipose tissue has high expression of the ACE2 receptor [30] that enables COVID-19 viral entry, and obesity has been linked to ventilation difficulties [31], which may contribute to increased severity of COVID-19 and hospitalization.

Commonly prescribed inhalation therapy for COPD was mostly associated with increased risk, as has been described [32] [32,33], implying that heavier therapy is generally a good clinical marker for assessing potential COVID-19 risk, especially when other information on COPD severity or important comorbidity is unavailable. This effect, however, largely disappeared for most medications in the a posteriori full multivariable model, with consistent effects remaining only for ICS and SAMA conditional on other concurrent therapies, disease severity (mMRC, CAT) and comorbidities in the model. This may therefore indicate possible additional confounding by indication or severity, but this model should be interpreted with caution, since it may also include mediators for some combinations of risk factors as has been pointed out [34].

In agreement with a previous study based on SNAR data [13], we found that severe COPD, defined as a lower FEV_1% predicted and higher CAT scores, was associated with greater risk of severe COVID-19 (hospitalization and/or death). Further, we note that a lower FEV_1% predicted was associated with a *lower* risk of ICU admission. Interestingly, we also observed such significant or suggestive inverse associations between several other factors (including higher age and comorbidities including diabetes type 2, heart failure, and chronic kidney disease) and ICU admission, although most of the pre-existing comorbidities showed similar point estimates for ICU admission. Although these results should be interpreted with caution due to low power with wide confidence intervals, selection of patients for ICU admission, where frailty and low likelihood to benefit from ICU treatment are contraindications, is a potential explanation. Increased “shielding” and COVID-19 precautions such as social distance and hand hygiene by those with perceived poor lung function may also have contributed to lower ICU admission risk, as reported in another study [35]. Our study thus highlights ICU-

admitted COPD patients as a special population where predictors differ from COVID-19 infections, hospitalizations, and deaths and thus merit further investigation.

Analyses of vaccinated COPD patients show that breakthrough infections are possible. However, our findings suggest that old and potentially frail patients, with certain chronic ailments, and clinically severe lung disease may have lower risk due to these characteristics of COVID-19 infection, hospitalization and death during vaccinated follow-up compared to unvaccinated follow-up. While the vaccinated time analysis has lower power, this finding may reflect that COPD patients with markers of severe underlying disease could accrue particular benefit from COVID-19 vaccination. Thus, our results support a recommendation to vaccinate patients with COPD against COVID-19, with a particular focus on those with a more severe form of COPD.

Strengths of our study include evaluating diverse factors over 4 different COVID-19 outcomes among COPD patients over a long follow-up in a truly population-based setting. Moreover, the pre-and post-vaccination follow-up periods offer insight into the natural course of COVID-19 disease, *and* the effect of the vaccination intervention, although the latter aim was limited due to fewer outcomes among the vaccinated. Other limitations should also be considered. Missing data was not an issue, except for smoking, education, BMI, GOLD and FEV_1. We focused on a complete case analysis, in the main model adjusting for key confounders and variables with limited missing data (smoking and BMI), but models including the variables with more missing, e.g., GOLD stage and FEV_1, showed consistent findings (data not shown). Potential exposure misclassification is another concern. For instance, prescribed medication does not necessarily equate to actual use. However, all exposure and covariate data were routinely collected pre-pandemic. Misclassification is thus likely to be non-differential with

respect to COVID-19 events, which would tend to reduce statistical power and attenuate associations. Despite adjusting for identified substantial confounders, unmeasured and residual confounding remains a possibility. Our study, like many others [36], found a lower HR for current smokers, but this result is unclear and needs further investigation.

Conclusion

This study provides detailed and robust evidence on important predictors of four different COVID-19 outcomes in patients with COPD, and suggests that vaccination has a positive effect on the added risk associated with some of them. Given the elevated COVID-19 risk among COPD patients, our findings provide a better understanding of their risk factor profiles and may contribute to better clinical evaluation, interventions and individualized care to reduce their COVID-19 risk.

Table 1. Sociodemographic characteristics of a population-based cohort of COPD patients (≥40 years) in Sweden on 1 Jan 2020, and of individuals with four different COVID-19 outcome events that occurred during unvaccinated and vaccinated follow-up time from 1 Jan 2020 to 30 Nov 2021 in that cohort (N (%))**.**

	Total COPD cohort N = 87472	COPD patients with COVID-19 outcomes during vaccinated and unvaccinated follow-up time†							
		Infected		Hospitalized		ICU admitted		Death	
		Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
	(Vaccinated by end of follow-up N= 77355)	N = 6068	N = 703	N = 2649	N = 248	N = 221	N = 12	N = 803	N = 79
Age (Mean, SD)	72.2 (9.7)	71.3 (11.3)	72.2 (11.2)	75.3 (9.2)	76.7 (9.1)	69.6 (7.2)	75.8 (6.7)	79.3 (8.3)	81.3 (6.6)
Age categories									
40-49	1489 (1.7)	174 (2.9)	24 (3.4)	14 (0.5)	2 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
50-59	7861 (9.0)	809 (13.3)	81 (11.5)	137 (5.2)	8 (3.2)	25 (11.3)	0 (0.0)	11 (1.4)	1 (1.3)
60-69	22121 (25.3)	1572 (25.9)	141 (20.1)	510 (19.3)	35 (14.1)	77 (34.8)	3 (25.0)	90 (11.2)	3 (3.8)
70-79	36418 (41.6)	1990 (32.8)	264 (37.6)	1103 (41.6)	105 (42.3)	105 (47.5)	6 (50.0)	286 (35.6)	26 (32.9)
80-89	17354 (19.8)	1255 (20.7)	166 (23.6)	746 (28.2)	87 (35.1)	14 (6.3)	3 (25.0)	332 (41.3)	43 (54.4)
90+	2229 (2.5)	268 (4.4)	27 (3.8)	139 (5.2)	11 (4.4)	0 (0)	0 (0.0)	84 (10.5)	6 (7.6)
Gender									
Male	38151 (43.6)	2854 (47.0)	309 (44.0)	1362 (51.4)	129 (52.0)	124 (56.1)	5 (41.7)	432 (53.8)	44 (55.7)
Female	49321 (56.4)	3214 (53.0)	394 (56.0)	1287 (48.6)	119 (48.0)	97 (43.9)	7 (58.3)	371 (46.2)	35 (44.3)

Education ‡ [a]									
Primary	29703 (34.4)	2108 (35.3)	225 (32.8)	1004 (38.8)	92 (38.0)	85 (39.7)	6 (50.0)	337 (43.2)	40 (51.9)
Secondary	40967 (47.4)	2890 (48.4)	317 (46.1)	1200 (46.4)	106 (43.8)	96 (44.9)	5 (41.7)	344 (44.1)	30 (39.0)
Higher	15674 (18.2)	970 (16.3)	145 (21.1)	384 (14.8)	44 (18.2)	33 (15.4)	1 (8.3)	99 (12.7)	7 (9.1)
Marital status									
Non-married	51861 (59.3)	3588 (59.1)	403 (57.3)	1635 (61.8)	156 (62.9)	122 (55.5)	5 (41.7)	526 (65.5)	50 (63.3)
Married	35568 (40.7)	2478 (40.9)	300 (42.7)	1012 (38.2)	92 (37.1)	98 (44.5)	7 (58.3)	277 (34.5)	29 (36.7)
Employment status									
Unemployed (40-64 years)	7033 (8.04)	536 (8.84)	41 (5.8)	178 (6.72)	15 (6.0)	28 (12.7)	0 (0)	25 (3.11)	0 (0)
Employed(40-64 years)	11416 (13.1)	1199 (19.8)	130 (18.5)	166 (6.27)	11 (4.4)	19 (8.64)	1 (8.3)	11 (1.37)	1 (1.3)
Employed(65+ years)	12350 (14.1)	712 (11.7)	93 (13.2)	289 (10.9)	25 (10.1)	41 (18.6)	3 (25.0)	50 (6.23)	5 (6.3)
Retired(65+ years)	56630 (64.8)	3619 (59.7)	439 (62.4)	2014 (76.1)	197 (79.4)	132 (60.0)	8 (66.7)	717 (89.3)	73 (92.4)
Region of Birth									
Sweden	71679 (81.9)	4566 (75.2)	560 (79.7)	1967 (74.3)	195 (78.6)	141 (63.8)	11 (91.7)	627 (78.1)	59 (74.7)
Nordic	6063 (6.93)	423 (6.97)	48 (6.8)	200 (7.55)	20 (8.1)	18 (8.14)	1 (8.3)	66 (8.22)	9 (11.4)
EU	3214 (3.67)	251 (4.14)	21 (3.0)	132 (4.98)	9 (3.6)	19 (8.60)	0 (0)	43 (5.35)	2 (2.5)
Non-EU	6515 (7.45)	828 (13.6)	74 (10.5)	350 (13.2)	24 (9.7)	43 (19.5)	0 (0)	67 (8.34)	9 (11.4)
Smoking ‡ [b]									

Never smoker	12310 (15.7)	991 (18.7)	118 (19.2)	460 (20.2)	42 (21.1)	36 (18.1)	1 (8.3)	146 (22.4)	22 (33.3)
Former smoker	39734 (50.7)	2909 (54.9)	350 (57.0)	1320 (57.9)	116 (58.3)	123 (61.8)	7 (58.3)	374 (57.3)	37 (56.1)
Current smoker	26252 (33.5)	1403 (26.5)	146 (23.8)	498 (21.9)	41 (20.6)	40 (20.1)	4 (33.3)	133 (20.4)	7 (10.6)

COPD = chronic obstructive pulmonary disease; COVID-19 = Coronavirus disease 2019; SD = standard deviation; EU = Europe ; ICU= intensive care unit; SNAR= Swedish national airways register.

‡ Proportion of non-missing

[a] Missing data on education for 1128 (1.3%) for the COPD population.

[b] Missing data on smoking for 9176 (10.5%) for the COPD population.

Table 2. Comorbidities and clinical characteristics on 1 Jan 2020 of a population-based cohort of COPD patients (≥40 years) in Sweden, and of individuals with four different COVID-19 outcome events that occurred during unvaccinated and vaccinated follow-up time from 1 Jan 2020 to 30 Nov 2021 in that cohort (N (%)**).**

	Total COPD cohort N = 87472	COPD patients with COVID-19 outcomes during vaccinated and unvaccinated follow-up time†							
		Infected		Hospitalized		ICU admitted		Death	
		Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
	(Vaccinated by end of follow-up N= 77355)	N = 6068	N = 703	N = 2649	N = 248	N = 221	N = 12	N = 803	N = 79
Comorbidities									
Overall cardiovascular disease	43583 (49.8)	3432 (56.6)	394 (56.0)	1865 (70.4)	179 (72.2)	136 (61.5)	7 (58.3)	656 (81.7)	58 (73.4)
Hypertension	31323 (35.8)	2527 (41.6)	291 (41.4)	1410 (53.2)	135 (54.4)	99 (44.8)	6 (50.0)	499 (62.1)	47 (59.5)
Heart failure	9400 (10.7)	969 (16.0)	99 (14.1)	625 (23.6)	56 (22.6)	32 (14.5)	2 (16.7)	267 (33.3)	26 (32.9)
Type 1 diabetes	1123 (1.3)	111 (1.8)	12 (1.7)	64 (2.4)	9 (3.6)	4 (1.8)	1 (8.3)	26 (3.2)	8 (10.1)
Type 2 diabetes	10549 (12.1)	956 (15.8)	114 (16.2)	567 (21.4)	63 (25.4)	49 (22.2)	2 (16.7)	199 (24.8)	22 (27.8)
Asthma	8188 (9.4)	695 (11.5)	82 (11.7)	350 (13.2)	29 (11.7)	30 (13.6)	1 (8.3)	111 (13.8)	12 (15.2)
Respiratory failure	3176 (3.6)	346 (5.7)	26 (3.7)	239 (9.0)	15 (6.0)	13 (5.9)	2 (16.7)	88 (11.0)	6 (7.6)
Interstitial lung disease	529 (0.6)	40 (0.7)	8 (1.1)	27 (1.0)	4 (1.6)	1 (0.5)	1 (8.3)	12 (1.5)	2 (2.5)
Sleep apnea syndromes	2854 (3.3)	232 (3.8)	33 (4.7)	124 (4.7)	13 (5.2)	19 (8.6)	1 (8.3)	31 (3.9)	7 (8.9)
Chronic kidney disease	1065 (1.2)	116 (1.9)	16 (2.3)	78 (2.9)	13 (5.2)	5 (2.3)	0 (0.0)	37 (4.6)	3 (3.8)
Immunologic disease	150 (0.2)	10 (0.2)	2 (0.3)	8 (0.3)	2 (0.8)	0 (0.0)	0 (0.0)	4 (0.5)	0 (0.0)

Autoimmune disease	150 (0.2)	10 (0.2)	69 (9.8)	8 (0.3)	30 (12.1)	0 (0.0)	0 (0.0)	4 (0.5)	10 (12.7)
Cancer	6509 (7.4)	574 (9.5)	125 (17.8)	333 (12.6)	60 (24.2)	22 (10.0)	1 (8.3)	138 (17.2)	23 (29.1)
Depression	13456 (15.4)	933 (15.4)	35 (5.0)	510 (19.3)	13 (5.2)	28 (12.7)	0 (0.0)	167 (20.8)	3 (3.8)
Anxiety	3625 (4.1)	310 (5.1)	33 (4.7)	150 (5.7)	11 (4.4)	16 (7.2)	0 (0.0)	47 (5.9)	2 (2.5)
Psychiatric disorders	3979 (4.5)	339 (5.6)	45 (6.4)	167 (6.3)	17 (6.9)	15 (6.8)	0 (0.0)	56 (7.0)	3 (3.8)
Clinical characteristics									
GOLD ABCD[§ a]									
Group A	12759 (23.9)	769 (21.3)	100 (23.5)	253 (16.2)	21 (14.8)	19 (14.8)	2 (25.0)	59 (14.4)	10 (23.3)
Group B	26224 (49.1)	1729 (47.9)	209 (49.2)	776 (49.7)	78 (54.9)	63 (49.2)	4 (50.0)	199 (48.7)	18 (41.9)
Group C	3782 (7.1)	278 (7.7)	30 (7.1)	119 (7.6)	7 (4.9)	9 (7.0)	0 (0.0)	26 (6.4)	1 (2.3)
Group D	10635 (19.9)	837 (23.2)	86 (20.2)	414 (26.5)	36 (25.4)	37 (28.9)	2 (25.0)	125 (30.6)	14 (32.6)
FEV_1 % of predicted [§ ll b]									
Median [IQR]	62 [49.0, 74.0]	62 [48.0,74.0]	63 [49.0, 77.0]	58 [44.0, 71.0]	56 [43.0,68.0]	62 [50.5, 79.5]	56 [50.5,56.5]	58 [45.0, 70.0]	58 [46.0,73.0]
≥ 80 (GOLD 1)	9599 (16.2)	634 (16.3)	102 (21.5)	206 (12.8)	22 (14.2)	34 (25.2)	1 (9.1)	49 (12.4)	9 (19.1)
50-79 (GOLD 2)	33907 (57.2)	2195 (56.5)	248 (52.3)	850 (52.8)	74 (47.7)	72 (53.3)	8 (72.7)	218 (55.2)	22 (46.8)
30-49 (GOLD 3)	13129 (22.1)	865 (22.3)	101 (21.3)	442 (27.5)	49 (31.6)	23 (17.0)	2 (18.2)	103 (26.1)	12 (25.5)
<30 (GOLD 4)	2666 (4.5)	189 (4.9)	23 (4.9)	111 (6.9)	10 (6.5)	6 (4.4)	0 (0.0)	25 (6.3)	4 (8.5)
CAT									
< 10	27073 (31.0)	1712 (28.2)	226 (32.1)	649 (24.5)	64 (25.8)	46 (20.8)	3 (25.0)	196 (24.4)	25 (31.6)
≥ 10	60399 (69.0)	4356 (71.8)	477 (67.9)	2000 (75.5)	184 (74.2)	175 (79.2)	9 (75.0)	607 (75.6)	54 (68.4)
mMRC									
0	13035 (14.9)	862 (14.2)	108 (15.4)	349 (13.2)	29 (11.7)	26 (11.8)	1 (8.3)	98 (12.2)	11 (13.9)
1	38020 (43.5)	2587 (42.6)	300 (42.7)	1060 (40.0)	96 (38.7)	103 (46.6)	3 (25.0)	333 (41.5)	32 (40.5)
2	17673 (20.2)	1225 (20.2)	157 (22.3)	556 (21.0)	57 (23.0)	40 (18.1)	7 (58.3)	157 (19.6)	14 (17.7)

3	11125 (12.7)	841 (13.9)	83 (11.8)	434 (16.4)	39 (15.7)	34 (15.4)	0 (0.0)	135 (16.8)	15 (19.0)
4	7619 (8.7)	553 (9.1)	55 (7.8)	250 (9.4)	27 (10.9)	18 (8.1)	1 (8.3)	80 (10.0)	7 (8.9)
Body mass index (BMI in kg/m^2)[§ c]									
Mean BMI (SD)	27.2 (11.1)	27.6 (10.6)	28.44 (16.9)	27.6 (11.7)	27.95 (6.2)	30.4 (6.4)	29.44 (8.9)	26.9 (6.6)	28.1 (8.2)
Underweight (BMI < 18.5)	3627 (4.7)	254 (4.7)	205 (32.6)	143 (6.0)	66 (30.7)	4 (2.0)	4 (40.0)	51 (7.2)	23 (32.4)
Normal (BMI =18.5 to 24.0)	27415 (35.2)	1748 (32.4)	16 (2.5)	786 (32.9)	5 (2.3)	28 (13.8)	0 (0.0)	259 (36.7)	3 (4.2)
Overweight (BMI = 25.0 to 29.9)	26535 (34.0)	1811 (33.6)	215 (34.2)	718 (30.1)	70 (32.6)	77 (37.9)	2 (20.0)	196 (27.8)	21 (29.6)
Obese (BMI ≥ 30)	20408 (26.2)	1582 (29.3)	192 (30.6)	740 (31.0)	74 (34.4)	94 (46.3)	4 (40.0)	200 (28.3)	24 (33.8)

COPD = chronic obstructive pulmonary disease; COVID-19 = Coronavirus disease 2019; GOLD = global initiative for chronic obstructive lung disease; FEV_1=forced expiratory volume in 1 second; CAT = chronic obstructive pulmonary disease assessment test; BMI = body mass index; SD = standard deviation; mMRC = modified Medical Research Council dyspnea scale; IQR = interquartile range; ICU = intensive care unit.

[§] Proportions presented as percent of non-missing

[ll] Post bronchodilator FEV_1 values were used but if missing, pre bronchodilator FEV_1 values were used.

[a] Missing data = 34072 (39.0%) of the COPD population cohort.

[b] Missing data = 28171 (32.2%) of the COPD population cohort.

[c] Missing data = 9487 (10.8%) of the COPD population cohort.

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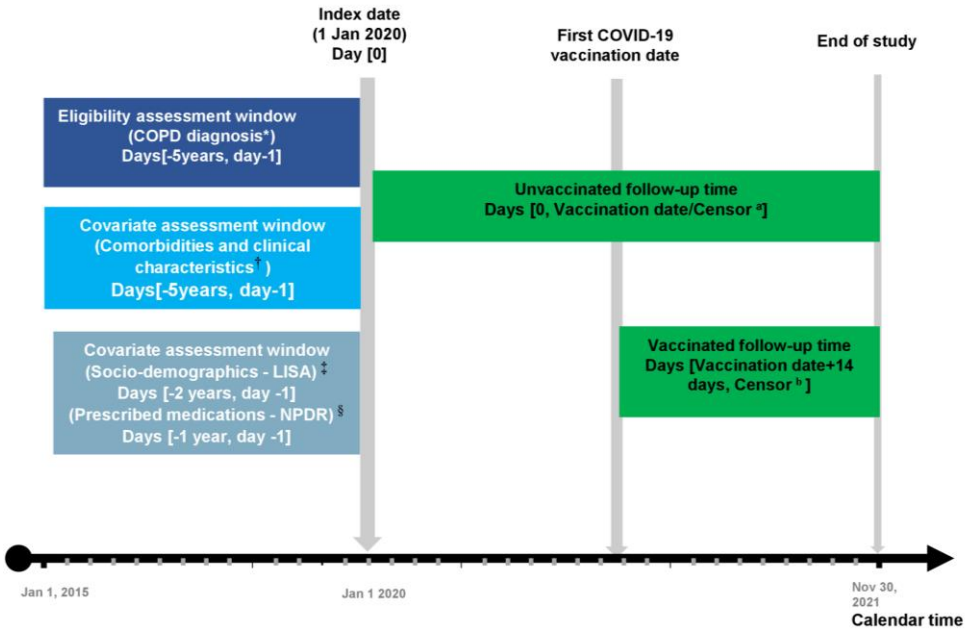
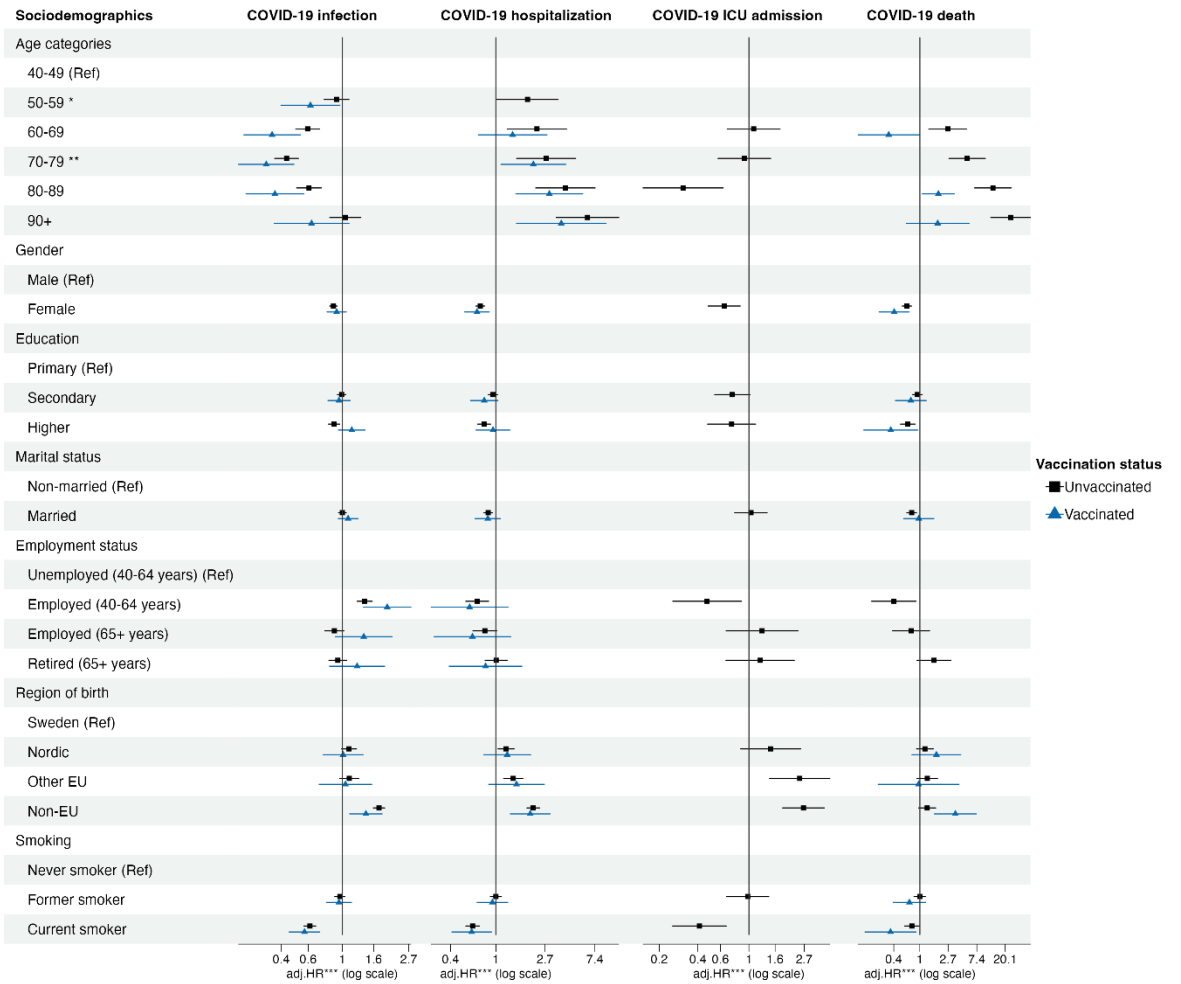


* Study population was defined as having a positive diagnosis of chronic obstructive pulmonary disease (COPD) prior to the index date in the Swedish National Airways Register (SNAR).
† Information on comorbidities available for 5 years prior to the index date were extracted from the National Patient Register and clinical data from SNAR.
‡ Sociodemographic data was collected in 2018 and 2019, and the latest available information for each individual was used.
§ Data on prescribed medication available was extracted from the Swedish national prescribed drug register (NPDR) one year pre-index.
a Unvaccinated follow-up time started from 1 Jan 2020 until exiting cohort on the earliest of: incident COVID-19 outcome- emigration- death- vaccination or end of study period (30 Nov 2021).
b. Vaccinated follow-up time started from 14 days after the first COVID-19 vaccination date until exiting cohort on the earliest of: incident COVID-19 outcome- emigration- death or end of study period (30 Nov 2021).
Coronavirus disease, 2019 (COVID-19) outcomes include infection, hospitalization, intensive care unit admission or death.

Figure 1. Illustration of cohort design for evaluation and follow-up of the study population



COVID-19 = Coronavirus disease 2019; EU = European; adj.HR = adjusted hazard ratio; Ref = reference category; ICU = intensive care unit; * Ref for COVID-19 ICU admission and death; ** = reference age category for COVID-19 deaths in vaccinated follow-up time; Ref for hospitalized vaccinated is the age 40-59;*** adjusted for age, sex, diabetes, hypertension, body mass index and smoking

Figure 2. Adjusted hazard ratios with 95% confidence intervals for associations between sociodemographic factors and four COVID-19 outcomes (infection, hospitalization, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 Jan 2020 to 30 Nov 2021. Note: hazard ratios for ICU admissions during the vaccinated follow-up period not estimated due to the small case numbers.

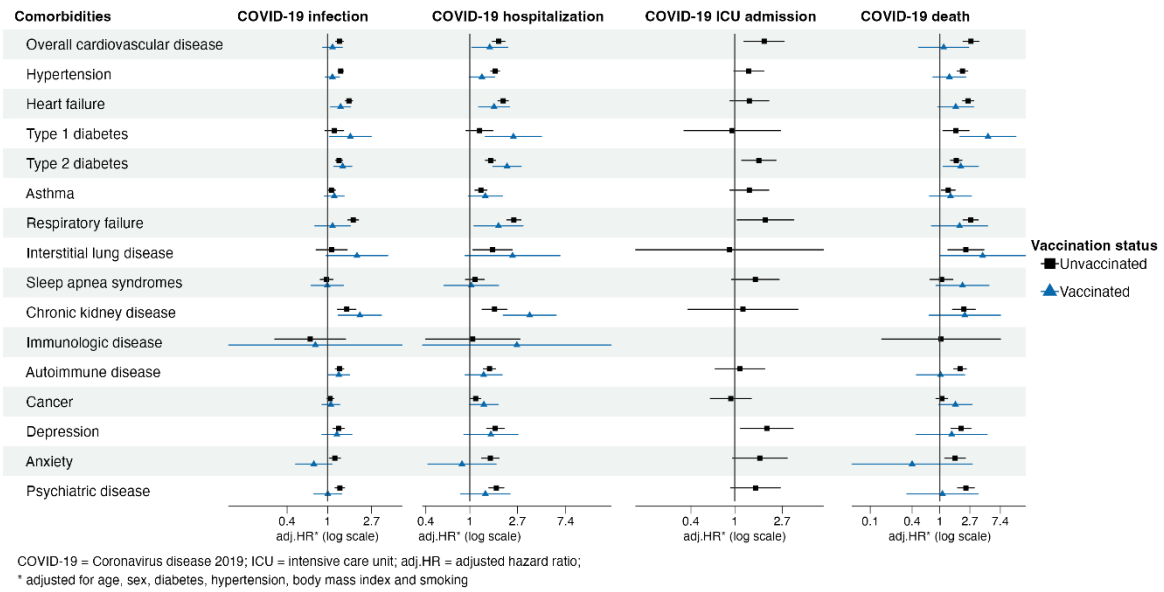
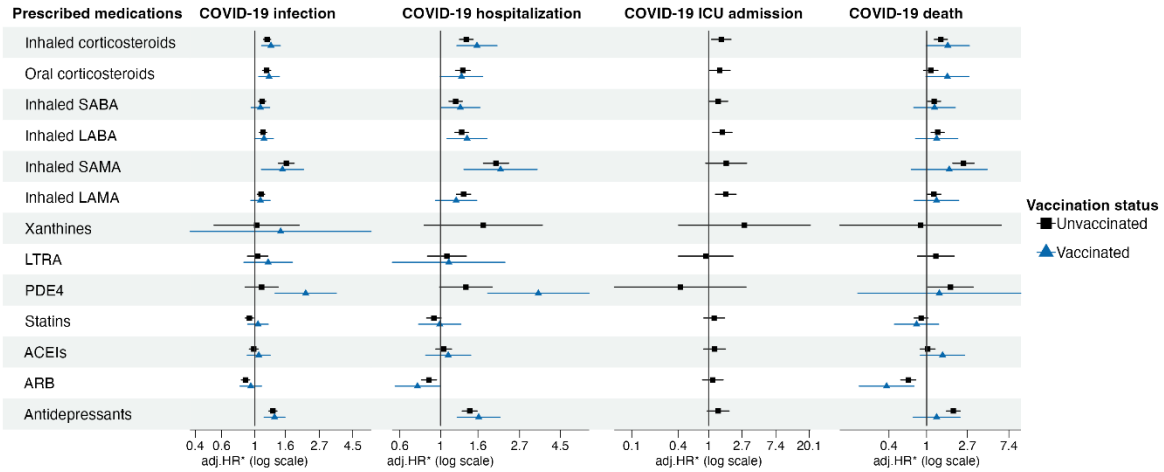
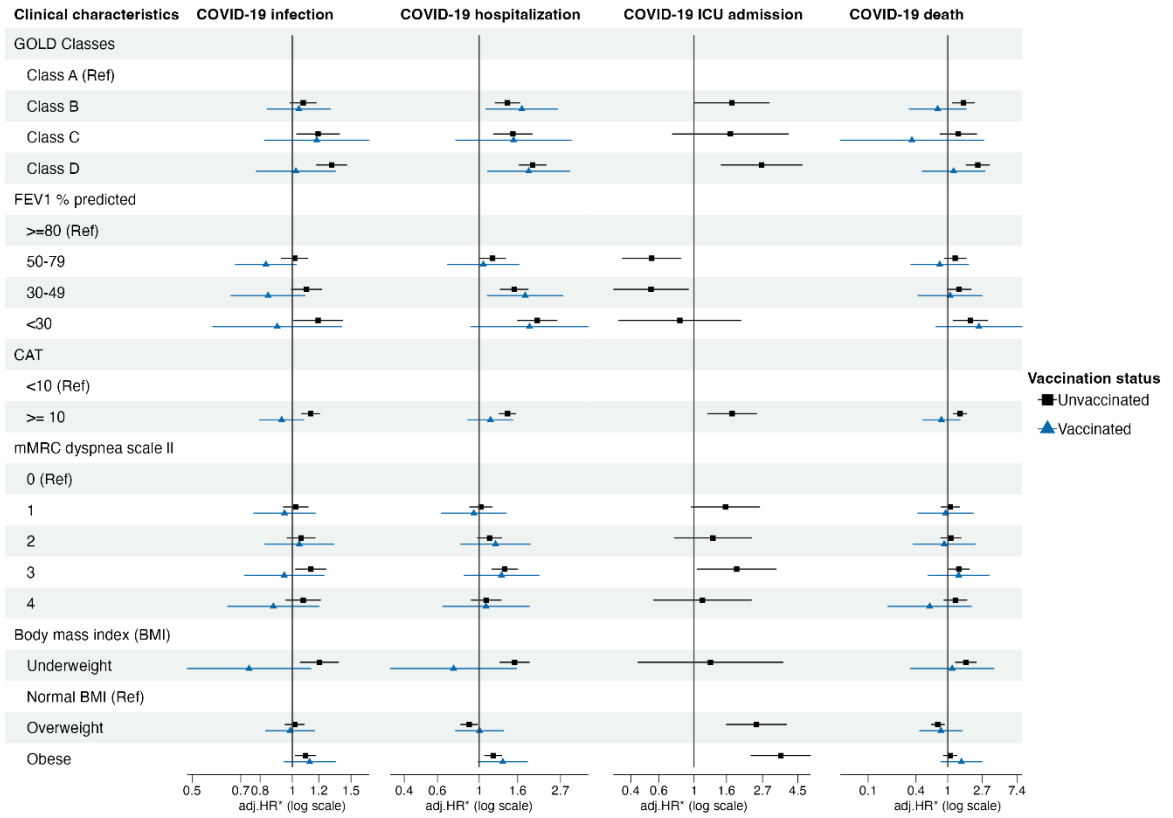


Figure 3. Adjusted hazard ratios with 95% confidence intervals for associations between comorbidities and four COVID-19 outcomes (infection, hospitalization, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 Jan 2020 to 30 Nov 2021. Note: hazard ratios for ICU admissions during the vaccinated follow-up period not estimated due to the small case numbers.



COVID-19 = Coronavirus disease 2019; ICU = intensive care unit; ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; SABA= short-acting bronchodilator agonists; LABA= long-acting bronchodilator agonists; SAMA = short-acting muscarinic antagonists; LAMA = long-acting muscarinic antagonists; LTRA=leukotriene receptor antagonists; PDE-4 = phosphodiesterase-4 inhibitors; adj.HR = adjusted hazard ratio; * adjusted for age, sex, diabetes, hypertension, body mass index and smoking

Figure 4. Adjusted hazard ratios with 95% confidence intervals for associations between prescribed medications and four COVID-19 outcomes (infection, hospitalization, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 Jan 2020 to 30 Nov 2021. Note: hazard ratios for ICU admissions during the vaccinated follow-up period not estimated due to the small case numbers.



COVID-19 = Coronavirus disease 2019; adj.HR = adjusted hazard ratios; ICU = intensive care unit; Ref= reference values; GOLD = global initiative for chronic obstructive lung disease; FEV1=forced expiratory volume in 1 second; ICU = intensive care unit; CAT = chonic obstructive pulmonary disease assessment test; mMRC = modified Medical Research Council; * adjusted for age, sex, diabetes, hypertension, body mass index and smoking; Reduced sample size for GOLD and FEV1 due to missing - refer Table E4 and Table E7

Figure 5. Adjusted hazard ratios with 95% confidence intervals for associations between clinical characteristics and four COVID-19 outcomes (infection, hospitalization, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 Jan 2020 to 30 Nov 2021. Note: hazard ratios for ICU admissions during the vaccinated follow-up period not estimated due to the small case numbers.

Online Data Supplement

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Table E1. Exposures and covariates selected for study in the evaluation of characteristics and risk factors for COVID-19 outcomes in a Swedish population-based cohort of COPD patients on 1 Jan 2020.

Covariate	Units and Categories	Source and definition	Lookback window before index date
Comorbidity	**Units/Categories**	**Register source; Description**	
Age	As a continuous variable and in 10-year categories	RTB	2 years
Sex	Male, female	RTB	2 years
Region of birth	Sweden, Nordic, EU, Non-EU	RTB	2 years
Education	Primary, secondary, and higher	LISA; Primary education included pre-secondary education shorter than 9 years, equal to 9 years or more than 9 years. Secondary educated included 2-year high school education, secondary education shorter than 3 years or longer than 3 years, and higher education included those with post-high-school education	2 years
Employment status	Unemployed (40-64 years), employed (40-64 years), employed (65+ years) and retired (65+ years)	Created using the LISA variable "employment" and stratified by age where; "employed" were either employed or with entrepreneurial income, and "unemployed" were the unemployed and without entrepreneurial income. This variable was further grouped by age that included: unemployed and unemployed aged 40-64 years; employed 65+ and retired 65+.	2 years
Marital status	Married and non-married	LISA; derived from "Civil Status" from the LISA register. A binary variable was then created which grouped individuals as either married (including the married, and those with a registered partner) and not married (divorced/separated, divorced partner, widow(er), and surviving partner)	2 years
Smoking	Never smoker Former smoker	SNAR; available as a variable in the SNAR dataset that was not measured for all visits that the patients made to the	5 years

	Current smoker	healthcare facilities, and therefore, the last observed smoking status before index was used for this variable. Never smokers had never been smokers; former smokers quit smoking for at least 6 months; current smokers includes infrequent (non-daily smokers) and frequent smokers (1 to >20 cigarettes daily).	
Comorbidity	**Units/Categories**	**Register source; ICD Codes**	
Overall cardiovascular disease	Yes/No	NPR; I00-I99	5 years
Hypertension	Yes/No	NPR; I10-I15	5 years
Heart failure	Yes/No	NPR; I50	5 years
Type 1 diabetes	Yes/No	NPR; E10	5 years
Type 2 diabetes	Yes/No	NPR; E11	5 years
Asthma	Yes/No	NPR; J45	5 years
Respiratory failure	Yes/No	NPR; J96	5 years
Interstitial lung disease	Yes/No	NPR; J84	5 years
Sleep apnea syndromes	Yes/No	SNAR variable	5 years
Chronic kidney disease	Yes/No	NPR; N184 N185 Z992	5 years
Autoimmune disease	Yes/No	NPR; M05-M14	5 years
Cancer	Yes/No	NPR; C00-C97	5 years
Depression	Yes/No	NPR; F32, F33	5 years
Anxiety	Yes/No	NPR; F41	5 years
Psychiatric disorders	Yes/No	NPR; F20 F21 F22 F23 F24 F25 F26 F27 F28 F29 F30 F31 F32 F33 F34 F35 F36 F37 F38 F39	5 years
Medications	**Units/Categories**	**NPDR; ATC Codes**	
Inhaled corticosteroids	Yes/No	R03BA, R03AK , R03AL08, R03AL09	1 year
Oral corticosteroids	Yes/No	H02AB	1 year
Inhaled SABA	Yes/No	R03AC02, R03AC03	1 year

Inhaled LABA	Yes/No	R03AC12, R03AK06, R03AC13, R03AK07, R03AK08, R03AK11, R03AL05, R03AL07, R03AL09, R03AL11, R03AC19, R03AL06, R03AC18, R03AK14, R03AK10	1 year
Inhaled SAMA	Yes/No	R03BB01, R03AL02	1 year
Inhaled LAMA	Yes/No	R03BB04, R03AL06, R03BB05, R03AL05, R03BB06, R03AL12, R03AL11, R03AL09, R03AL07, R03AL04, R03BB07, R03AL03, R03AL08	1 year
Xanthines	Yes/No	R03DA04	1 year
LTRA	Yes/No	R03DC03	1 year
Phospodiesterase 4 inhibitors	Yes/No	R03DX07	1 year
Statins	Yes/No	C10AA	1 year
ACEIs	Yes/No	C09A, C09B	1 year
ARBs	Yes/No	C09C, C09D	1 year
Antidepressants	Yes/No	N06A	1 year
Vaccination	Yes/No	Source: National vaccination register held by the Public Health Agency of Sweden; Vaccine types: BNT162b2, mRNA-1273 or AZD1222.	After index
Clinical measurements	**Categories**	**Source; Description**	
GOLD Classification	A = Mild, B = Moderate, C = Severe, D = Very severe	SNAR; GOLD ABCD classifications were created from SNAR data on number of total and hospitalized exacerbations in the year prior to index date, CAT and mMRC scores [E7]. A patient with one non-hospitalized exacerbation in the year before index date qualified for GOLD A or B, while GOLD C and D had ≥ 2 exacerbations or ≥ 1 hospitalized exacerbation in the prior year. GOLD A and C included patients who had a low symptom burden from CAT (<10) or a lower score on the mMRC scale (0-1), while GOLD B and D had higher symptom burden (CAT ≥10 or mMRC ≥2).	5 years

mMRC	Categorical variables numbered on a scale of 0 to 4	SNAR; defined as the most recent observations of the modified Medical Research Council dyspnea scale (mMRC). The scale is similar to the guidelines in the Global Inititative for Chronic Obstructive Lung Disease: 0 = Breathlessness with strenuous exercise; 1 = Breathlessness when climbing a slight hill; 2 = Breathlessness leads to slower walk than people of the same age with stops to catch breath when walking alone; 3 = Stopping for breath after walking 100 meters; and 4 = Too breathless to leave the house.	5 years
CAT	Continuous variable categorized into a binary variable <10 and ≥ 10	SNAR; defined as the most recent observations of the combined COPD assessment test (CAT). Used as a binary variable with a cutoff at CAT ≥ 10: <10 = lower symptom burden; and ≥ 10 higher symptom burden.	5 years
Spirometry	Categorical variable with levels; ≥ 80 (GOLD stage 1), 50-79 (GOLD stage 2), 30-49 (GOLD stage 3) and <30 (GOLD stage 4)	SNAR; Forced Expiratory Volume in one second, percent of predicted (FEV_1% predicted)	5 years
Body mass index (BMI)	Continuous variable	SNAR; available as a variable in the SNAR dataset that was not measured for all visits that the patients made to the healthcare facilities, and therefore, the last observed BMI value before index was used for this variable, with units in kg/m^2.	5 years
BMI categories	Underweight, Normal, Overweight, Obese	SNAR; This variable was created by grouping the last observed BMI values into four categories according to the WHO BMI classification as “underweight” (BMI < 18.5), “normal” (BMI =18.5 to 24.0), “overweight” (BMI = 25.0 to 29.9) and “obese” (BMI above 30).	5 years

RTB = register of total populations; LISA = longitudinal integrated database for health insurance and labor market studies; SNAR = Swedish national airways register; NPR = National Patient Register; NPDR = National Prescribed Drugs Register; ICD-10 = International Classification of Diseases, revision 10 ; ATC = anatomical therapeutic chemical; SABA = short-acting bronchodilator agonists; LABA = long-acting bronchodilator agonists; SAMA = short-acting muscarinic antagonists; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonists; ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; GOLD = Global initiative of chronic obstructive pulmonary disease; mMRC = modified Medical Research Council dyspnea scale; CAT = COPD Assessment Test ; BMI = body mass index; WHO = world health organization.

Table E2. Prescribed medications taken in the year before 1 Jan 2020 by a population-based cohort of COPD patients (≥40 years) in Sweden , and by individuals with four different COVID-19 outcome events that occurred during unvaccinated and vaccinated follow-up time from 1 Jan 2020 to 30 Nov 2021 in that cohort.

	Total COPD cohort N = 87472	COPD patients with COVID-19 outcomes during vaccinated and unvaccinated follow-up time†							
		Infected		Hospitalized		ICU admitted		Death	
		Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
N (%)	(Vaccinated by end of follow-up N= 77355)	N = 6068	N = 703	N = 2649	N = 248	N = 221	N = 12	N = 803	N = 79
Inhaled corticosteroids	41783 (47.8)	3208 (52.9)	379 (53.9)	1507 (56.9)	140 (56.5)	128 (57.9)	10 (83.3)	463 (57.7)	46 (58.2)
Oral corticosteroids	21275 (24.3)	1695 (27.9)	197 (28.0)	830 (31.3)	76 (30.6)	68 (30.8)	6 (50.0)	228 (28.4)	26 (32.9)
Inhaled SABA	37018 (42.3)	2734 (45.1)	311 (44.2)	1233 (46.5)	110 (44.4)	111 (50.2)	8 (66.7)	358 (44.6)	33 (41.8)
Inhaled LABA	42120 (48.2)	3106 (51.2)	361 (51.4)	1490 (56.2)	136 (54.8)	128 (57.9)	10 (83.3)	462 (57.5)	42 (53.2)
Inhaled SAMA	3502 (4.0)	382 (6.3)	36 (5.1)	219 (8.3)	18 (7.3)	13 (5.9)	0 (0.0)	93 (11.6)	5 (6.3)
Inhaled LAMA	49626 (56.7)	3470 (57.2)	408 (58.0)	1701 (64.2)	156 (62.9)	142 (64.3)	7 (58.3)	503 (62.6)	46 (58.2)
Xanthines	158 (0.2)	11 (0.2)	2 (0.3)	8 (0.3)	0 (0.0)	1 (0.5)	0 (0.0)	2 (0.2)	0 (0.0)
LTRA	2426 (2.8)	196 (3.2)	26 (3.7)	75 (2.8)	7 (2.8)	7 (3.2)	0 (0.0)	23 (2.9)	0 (0.0)
PDE4	910 (1.0)	68 (1.1)	17 (2.4)	40 (1.5)	12 (4.8)	1 (0.5)	0 (0.0)	15 (1.9)	2 (2.5)
Statins	33040 (37.8)	2233 (36.8)	272 (38.7)	1131 (42.7)	118 (47.6)	106 (48.0)	6 (50.0)	342 (42.6)	33 (41.8)
ACEIs	18181 (20.8)	1288 (21.2)	150 (21.3)	655 (24.7)	65 (26.2)	57 (25.8)	5 (41.7)	207 (25.8)	24 (30.4)
ARB	24059 (27.5)	1611 (26.5)	199 (28.3)	791 (29.9)	77 (31.0)	79 (35.7)	3 (25.0)	210 (26.2)	16 (20.3)
Antidepressants	20797 (23.8)	1719 (28.3)	207 (29.4)	773 (29.2)	74 (29.8)	56 (25.3)	1 (8.3)	285 (35.5)	22 (27.8)

ICU = intensive care unit; SABA = short-acting bronchodilator agonists; LABA = long-acting bronchodilator agonists; SAMA = short-acting muscarinic antagonists; LAMA = long-acting muscarinic antagonists; LTRA = leukotriene receptor antagonists; PDE-4 = phosphodiesterase-4 inhibitors; ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers.

Table E3. Association between sociodemographics, comorbidities, prescribed medications and clinical characteristics of a population-based COPD cohort in Sweden and four COVID-19 outcomes – infection and hospitalization (**E3a**), and intensive care unit (ICU) admission and death (**E3b**) - that occurred during unvaccinated follow-up time from 1 Jan 2020 until 30 Nov 2021.

E3a)

	COVID-19 infection				COVID-19 hospitalization			
Total number of events	6068				2649			
Person years	106981				108282			
	Unadj. HR [95% CI]	p-value	Adj. HR [95% CI] *	p-value	Unadj. HR [95% CI]	p-value	Adj.HR [95% CI] *	p-value
Sociodemographics								
Age categories †								
40-49	Ref. 40-49		Ref. 40-49		Ref. 40-49		Ref. 40-49	
50-59	0.95 [0.79-1.14]	0.571	0.92 [0.76-1.10]	0.367	2.15 [1.16-3.98]	0.015	1.90 [1.02-3.52]	0.042
60-69	0.67 [0.56-0.80]	<0.001	0.60 [0.50-0.71]	<0.001	2.93 [1.61-5.32]	<0.001	2.29 [1.26-4.17]	0.007
70-79	0.55 [0.47-0.66]	<0.001	0.43 [0.36-0.52]	<0.001	4.15 [2.29-7.53]	<0.001	2.76 [1.52-5.01]	0.001
80-89	0.86 [0.72-1.02]	0.082	0.61 [0.50-0.73]	<0.001	6.87 [3.78-12.48]	<0.001	4.08 [2.24-7.43]	<0.001
90+	1.59 [1.29-1.97]	<0.001	1.05 [0.83-1.32]	0.703	11.42 [6.16-21.2]	<0.001	6.37 [3.39-11.97]	<0.001
Gender †								
Male	Ref.		Ref.		Ref.		Ref.	
Female	0.87 [0.82-0.91]	<0.001	0.88 [0.83-0.93]	<0.001	0.73 [0.67-0.79]	<0.001	0.73 [0.67-0.79]	<0.001
Education a								
Primary	Ref.		Ref.		Ref.		Ref.	
Secondary	0.97 [0.91-1.03]	0.292	0.99 [0.93-1.05]	0.755	0.83 [0.76-0.91]	<0.001	0.94 [0.86-1.03]	0.196
Higher	0.87 [0.81-0.95]	0.001	0.88 [0.81-0.96]	0.004	0.72 [0.63-0.81]	<0.001	0.79 [0.69-0.90]	<0.001
Marital status								
Non-married	Ref.		Ref.		Ref.		Ref.	
Married	1.02 [0.97-1.08]	0.434	1.00 [0.95-1.06]	0.967	0.92 [0.85-1.00]	0.044	0.86 [0.78-0.93]	0.001
Employment status								

Unemployed (40-64 years)	Ref.		Ref.		Ref.		Ref.	
Employed (40-64 years)	1.43 [1.28-1.59]	<0.001	1.40 [1.25-1.57]	<0.001	0.61 [0.49-0.76]	<0.001	0.69 [0.54-0.86]	0.001
Employed (65+ years)	0.85 [0.75-0.96]	0.007	0.89 [0.77-1.02]	0.104	1.06 [0.87-1.30]	0.536	0.80 [0.63-1.02]	0.068
Retired (65+ years)	0.99 [0.89-1.09]	0.793	0.94 [0.82-1.07]	0.324	1.66 [1.41-1.96]	<0.001	1.01 [0.8-1.26]	0.956
Region of birth								
Sweden	Ref.		Ref.		Ref.		Ref.	
Nordic	1.11 [1.00-1.24]	0.046	1.11 [0.99-1.24]	0.07	1.22 [1.04-1.42]	0.012	1.23 [1.05-1.44]	0.012
Other EU	1.18 [1.03-1.35]	0.016	1.11 [0.96-1.28]	0.15	1.50 [1.25-1.80]	<0.001	1.42 [1.17-1.73]	<0.001
Non-EU	1.87 [1.73-2.03]	<0.001	1.73 [1.59-1.89]	<0.001	1.86 [1.65-2.10]	<0.001	2.13 [1.87-2.42]	<0.001
Smoking †								
Never smoker	Ref.		Ref.		Ref.		Ref.	
Former smoker	0.90 [0.84-0.97]	0.008	0.96 [0.89-1.04]	0.327	0.90 [0.81-1.00]	0.059	1.00 [0.89-1.11]	0.981
Current smoker	0.61 [0.56-0.66]	<0.001	0.62 [0.56-0.67]	<0.001	0.48 [0.42-0.54]	<0.001	0.62 [0.54-0.72]	<0.001
Comorbidities								
Overall cardiovascular disease	1.48 [1.40-1.56]	<0.001	1.30 [1.20-1.42]	<0.001	2.67 [2.45-2.92]	<0.001	1.82 [1.6-2.08]	<0.001
Hypertension †	1.44 [1.36-1.52]	<0.001	1.35 [1.27-1.43]	<0.001	2.24 [2.07-2.43]	<0.001	1.70 [1.55-1.86]	<0.001
Heart failure	1.95 [1.81-2.10]	<0.001	1.62 [1.49-1.76]	<0.001	3.13 [2.85-3.44]	<0.001	2.00 [1.80-2.23]	<0.001
Type 1 diabetes	1.48 [1.21-1.81]	<0.001	1.16 [0.94-1.43]	0.165	1.94 [1.49-2.53]	<0.001	1.23 [0.93-1.62]	0.154
Type 2 diabetes †	1.47 [1.37-1.58]	<0.001	1.30 [1.20-1.40]	<0.001	2.12 [1.93-2.34]	<0.001	1.54 [1.38-1.72]	<0.001
Asthma	1.29 [1.19-1.41]	<0.001	1.09 [1.00-1.19]	0.053	1.53 [1.36-1.72]	<0.001	1.26 [1.11-1.43]	<0.001
Respiratory failure	2.02 [1.80-2.26]	<0.001	1.78 [1.58-2.02]	<0.001	3.23 [2.81-3.71]	<0.001	2.51 [2.16-2.91]	<0.001
Interstitial lung disease	1.09 [0.77-1.56]	0.616	1.10 [0.77-1.56]	0.612	1.83 [1.21-2.76]	0.004	1.61 [1.07-2.43]	0.024
Sleep apnea syndromes	1.15 [1.00-1.32]	0.043	0.98 [0.85-1.13]	0.745	1.41 [1.17-1.70]	<0.001	1.11 [0.91-1.35]	0.288
Chronic kidney disease	2.02 [1.67-2.45]	<0.001	1.54 [1.25-1.90]	<0.001	3.06 [2.42-3.87]	<0.001	1.67 [1.29-2.17]	<0.001
Immunologic disease	0.99 [0.51-1.90]	0.974	0.67 [0.30-1.50]	0.335	1.74 [0.83-3.66]	0.143	1.06 [0.40-2.84]	0.903
Autoimmune disease	1.45 [1.32-1.58]	<0.001	1.31 [1.19-1.44]	<0.001	1.96 [1.74-2.21]	<0.001	1.51 [1.33-1.72]	<0.001
Cancer	1.12 [1.04-1.20]	0.003	1.06 [0.98-1.15]	0.145	1.45 [1.31-1.61]	<0.001	1.13 [1.01-1.26]	0.029

Depression	1.33 [1.18-1.50]	<0.001	1.28 [1.13-1.46]	<0.001	1.52 [1.28-1.80]	<0.001	1.70 [1.42-2.04]	<0.001
Anxiety	1.26 [1.12-1.41]	<0.001	1.18 [1.04-1.34]	0.011	1.39 [1.17-1.64]	<0.001	1.53 [1.28-1.84]	<0.001
Psychiatric disease	1.33 [1.20-1.47]	<0.001	1.32 [1.18-1.47]	<0.001	1.44 [1.24-1.67]	<0.001	1.74 [1.49-2.04]	<0.001
Prescribed medications								
Inhaled corticosteroids	1.27 [1.21-1.34]	<0.001	1.21 [1.14-1.28]	<0.001	1.48 [1.37-1.61]	<0.001	1.38 [1.27-1.51]	<0.001
Oral corticosteroids	1.26 [1.19-1.34]	<0.001	1.20 [1.13-1.28]	<0.001	1.47 [1.35-1.60]	<0.001	1.32 [1.21-1.45]	<0.001
Inhaled SABA	1.14 [1.08-1.20]	<0.001	1.12 [1.06-1.18]	<0.001	1.19 [1.10-1.29]	<0.001	1.21 [1.11-1.32]	<0.001
Inhaled LABA	1.18 [1.12-1.24]	<0.001	1.14 [1.07-1.20]	<0.001	1.42 [1.31-1.54]	<0.001	1.30 [1.20-1.42]	<0.001
Inhaled SAMA	1.89 [1.70-2.11]	<0.001	1.62 [1.44-1.83]	<0.001	2.47 [2.13-2.86]	<0.001	2.01 [1.71-2.35]	<0.001
Inhaled LAMA	1.08 [1.03-1.15]	0.003	1.10 [1.04-1.16]	0.001	1.45 [1.33-1.57]	<0.001	1.33 [1.22-1.46]	<0.001
Xanthines	1.13 [0.61-2.11]	0.693	1.03 [0.53-1.98]	0.934	2.05 [1.03-4.11]	0.042	1.71 [0.81-3.59]	0.157
LTRA	1.16 [0.99-1.34]	0.062	1.04 [0.89-1.22]	0.593	1.09 [0.86-1.38]	0.477	1.08 [0.85-1.38]	0.521
PDE4	1.17 [0.91-1.49]	0.218	1.11 [0.86-1.43]	0.417	1.48 [1.06-2.05]	0.02	1.37 [0.99-1.91]	0.059
Statins	1.00 [0.95-1.06]	0.964	0.92 [0.86-0.98]	0.009	1.26 [1.17-1.37]	<0.001	0.92 [0.84-1.01]	0.072
ACEIs	1.06 [0.99-1.13]	0.079	0.98 [0.92-1.05]	0.646	1.29 [1.17-1.41]	<0.001	1.04 [0.94-1.15]	0.44
ARB	0.97 [0.91-1.03]	0.322	0.87 [0.81-0.93]	<0.001	1.15 [1.05-1.25]	0.002	0.87 [0.79-0.95]	0.003
Antidepressants	1.32 [1.24-1.40]	<0.001	1.32 [1.24-1.41]	<0.001	1.37 [1.25-1.49]	<0.001	1.44 [1.31-1.59]	<0.001
Clinical measurements								
GOLD Classes b								
Class A	Ref.		Ref.		Ref.		Ref.	
Class B	1.10 [1.01-1.20]	0.027	1.08 [0.99-1.18]	0.098	1.52 [1.31-1.76]	<0.001	1.41 [1.22-1.64]	<0.001
Class C	1.22 [1.05-1.40]	0.008	1.19 [1.03-1.39]	0.018	1.58 [1.26-1.99]	<0.001	1.51 [1.19-1.91]	0.001
Class D	1.37 [1.24-1.52]	<0.001	1.31 [1.18-1.46]	<0.001	2.09 [1.78-2.45]	<0.001	1.92 [1.63-2.26]	<0.001
FEV1 % predicted c								
>=80	Ref.		Ref.		Ref.		Ref.	
50-79	0.99 [0.91-1.09]	0.877	1.02 [0.93-1.11]	0.734	1.17 [1.01-1.37]	0.039	1.18 [1.01-1.38]	0.04
30-49	1.06 [0.95-1.17]	0.296	1.10 [0.99-1.23]	0.068	1.65 [1.40-1.95]	<0.001	1.53 [1.29-1.82]	<0.001

<30	1.17 [0.99-1.37]	0.062	1.19 [1.01-1.41]	0.038	2.10 [1.67-2.65]	<0.001	2.03 [1.60-2.58]	<0.001
CAT								
<10			Ref.				Ref.	
≥ 10	1.17 [1.11-1.25]	<0.001	1.13 [1.07-1.21]	<0.001	1.45 [1.32-1.60]	<0.001	1.41 [1.28-1.56]	<0.001
mMRC dyspnea scale d							Ref.	
0	Ref.		Ref.		Ref.			
1	1.04 [0.95-1.12]	0.407	1.02 [0.94-1.12]	0.585	1.08 [0.95-1.22]	0.266	1.02 [0.89-1.17]	0.769
2	1.07 [0.98-1.18]	0.137	1.06 [0.96-1.17]	0.218	1.23 [1.07-1.42]	0.004	1.13 [0.98-1.32]	0.097
3	1.21 [1.09-1.34]	<0.001	1.14 [1.02-1.26]	0.017	1.59 [1.37-1.85]	<0.001	1.37 [1.17-1.60]	<0.001
4	1.12 [1.00-1.25]	0.055	1.08 [0.96-1.21]	0.215	1.26 [1.06-1.50]	0.009	1.09 [0.91-1.31]	0.358
Body mass index (BMI) e †								
Underweight	1.15 [1.01-1.32]	0.032	1.21 [1.06-1.38]	0.005	1.44 [1.21-1.73]	<0.001	1.54 [1.29-1.84]	<0.001
Normal BMI	Ref.		Ref.		Ref.		Ref.	
Overweight	1.05 [0.98-1.12]	0.158	1.02 [0.95-1.09]	0.637	0.92 [0.83-1.02]	0.125	0.88 [0.80-0.98]	0.019
Obese	1.17 [1.10-1.26]	<0.001	1.10 [1.02-1.18]	0.011	1.23 [1.11-1.36]	<0.001	1.19 [1.07-1.32]	0.001

E3b)

	COVID-19 ICU admission				COVID-19 death			
Total number of events	221				803			
Person years	109272				109342			
	Unadj. HR [95% CI]	p-value	Adj. HR [95% CI] *	p-value	Unadj. HR [95% CI]	p-value	Adj. HR [95% CI] *	p-value
Sociodemographics								
Age categories †								
40-49								
50-59	Ref. 50-59		Ref. 50-59		Ref. 50-59		Ref. 50-59	
60-69	1.31 [0.82-2.10]	0.251	1.09 [0.68-1.75]	0.724	3.51 [1.81-6.78]	<0.001	2.66 [1.37-5.18]	0.004

70-79	1.25 [0.79-1.97]	0.333	0.92 [0.57-1.48]	0.735	7.92 [4.2-14.94]	<0.001	5.27 [2.78-9.99]	<0.001
80-89	0.46 [0.23-0.89]	0.021	0.31 [0.15-0.63]	0.001	21.44 [11.37-40.43]	<0.001	13.04 [6.85-24.85]	<0.001
90+					43.55 [22.31-85.02]	<0.001	24.3 [12.10-48.80]	<0.001
Gender †								
Male	Ref.		Ref.		Ref.		Ref.	
Female	0.58 [0.44-0.76]	<0.001	0.64 [0.48-0.86]	0.003	0.65 [0.56-0.76]	<0.001	0.63 [0.54-0.75]	<0.001
Education a								
Primary	Ref.		Ref.		Ref.		Ref.	
Secondary	0.74 [0.54-1.00]	0.053	0.74 [0.54-1.02]	0.067	0.70 [0.60-0.82]	<0.001	0.92 [0.77-1.09]	0.316
Higher	0.73 [0.48-1.10]	0.132	0.73 [0.48-1.13]	0.159	0.54 [0.43-0.69]	<0.001	0.66 [0.51-0.85]	0.001
Marital status								
Non-married	Ref.		Ref.		Ref.		Ref.	
Married	1.21 [0.92-1.6]	0.169	1.04 [0.78-1.39]	0.804	0.81 [0.69-0.94]	0.007	0.75 [0.63-0.89]	0.001
Employment status								
Unemployed (40-64 years)	Ref.		Ref.		Ref.		Ref.	
Employed (40-64 years)	0.51 [0.28-0.93]	0.029	0.47 [0.25-0.87]	0.017	0.29 [0.14-0.62]	0.001	0.40 [0.18-0.87]	0.021
Employed (65+ years)	1.09 [0.65-1.84]	0.749	1.27 [0.67-2.42]	0.471	1.35 [0.81-2.27]	0.253	0.74 [0.39-1.41]	0.353
Retired (65+ years)	0.84 [0.54-1.33]	0.459	1.22 [0.66-2.26]	0.519	4.32 [2.79-6.69]	<0.001	1.64 [0.91-2.99]	0.102
Region of birth								
Sweden	Ref.		Ref.		Ref.		Ref.	
Nordic	1.56 [0.94-2.59]	0.085	1.48 [0.86-2.53]	0.155	1.30 [0.99-1.69]	0.056	1.19 [0.89-1.60]	0.233
Other EU	2.66 [1.58-4.48]	<0.001	2.49 [1.45-4.27]	0.001	1.59 [1.15-2.19]	0.005	1.30 [0.91-1.86]	0.15
Non-EU	3.18 [2.24-4.50]	<0.001	2.66 [1.83-3.87]	<0.001	1.10 [0.84-1.44]	0.489	1.29 [0.96-1.75]	0.09
Smoking †								
Never smoker	Ref.		Ref.		Ref.		Ref.	
Former smoker	1.05 [0.72-1.53]	0.79	0.98 [0.67-1.43]	0.917	0.80 [0.66-0.97]	0.026	1.00 [0.82-1.21]	0.961
Current smoker	0.41 [0.26-0.67]	<0.001	0.41 [0.25-0.67]	<0.001	0.41 [0.32-0.53]	<0.001	0.76 [0.59-0.98]	0.032

Comorbidities								
Overall cardiovascular disease	1.90 [1.43-2.53]	<0.001	1.85 [1.22-2.81]	0.004	5.30 [4.35-6.45]	<0.001	2.80 [2.16-3.64]	<0.001
Hypertension †	1.72 [1.30-2.27]	<0.001	1.34 [0.98-1.84]	0.065	3.41 [2.92-3.98]	<0.001	2.12 [1.78-2.52]	<0.001
Heart failure	1.88 [1.29-2.74]	0.001	1.36 [0.90-2.04]	0.145	5.06 [4.33-5.91]	<0.001	2.55 [2.13-3.05]	<0.001
Type 1 diabetes	1.63 [0.60-4.37]	0.336	0.95 [0.35-2.60]	0.918	2.68 [1.77-4.07]	<0.001	1.71 [1.11-2.63]	0.015
Type 2 diabetes †	2.24 [1.62-3.10]	<0.001	1.66 [1.15-2.37]	0.006	2.54 [2.15-3.01]	<0.001	1.72 [1.42-2.08]	<0.001
Asthma	1.69 [1.15-2.49]	0.008	1.36 [0.90-2.04]	0.145	1.70 [1.38-2.09]	<0.001	1.32 [1.05-1.66]	0.018
Respiratory failure	2.19 [1.25-3.84]	0.006	1.9 [1.05-3.45]	0.034	4.14 [3.30-5.20]	<0.001	2.77 [2.15-3.58]	<0.001
Interstitial lung disease	0.95 [0.13-6.79]	0.961	0.9 [0.13-6.41]	0.914	2.93 [1.61-5.31]	<0.001	2.37 [1.30-4.30]	0.005
Sleep apnea syndromes	2.69 [1.66-4.37]	<0.001	1.54 [0.93-2.54]	0.092	1.19 [0.82-1.72]	0.361	1.06 [0.72-1.55]	0.777
Chronic kidney disease	2.58 [1.06-6.28]	0.036	1.19 [0.38-3.76]	0.769	4.95 [3.52-6.95]	<0.001	2.21 [1.52-3.23]	<0.001
Immunologic disease	NA	NA	NA		2.51 [0.81-7.80]	0.112	1.04 [0.15-7.43]	0.966
Autoimmune disease	1.32 [0.81-2.14]	0.262	1.11 [0.66-1.87]	0.682	2.77 [2.28-3.36]	<0.001	1.95 [1.58-2.41]	<0.001
Cancer	0.99 [0.66-1.48]	0.961	0.92 [0.60-1.41]	0.705	1.61 [1.34-1.93]	<0.001	1.07 [0.88-1.30]	0.513
Depression	1.88 [1.11-3.18]	0.019	1.96 [1.13-3.40]	0.017	1.63 [1.20-2.20]	0.002	2.01 [1.45-2.80]	<0.001
Anxiety	1.58 [0.92-2.71]	0.101	1.69 [0.95-30.0]	0.072	1.51 [1.12-2.04]	0.007	1.66 [1.18-2.33]	0.004
Psychiatric disease	1.46 [0.89-2.41]	0.133	1.54 [0.92-2.60]	0.103	1.68 [1.31-2.17]	<0.001	2.37 [1.80-3.13]	<0.001
Prescribed medications								
Inhaled corticosteroids	1.56 [1.18-2.06]	0.002	1.45 [1.09-1.94]	0.012	1.55 [1.33-1.80]	<0.001	1.42 [1.20-1.66]	<0.001
Oral corticosteroids	1.42 [1.06-1.92]	0.021	1.39 [1.02-1.89]	0.038	1.32 [1.12-1.55]	0.001	1.11 [0.93-1.32]	0.261
Inhaled SABA	1.39 [1.06-1.83]	0.019	1.32 [1.00-1.76]	0.054	1.12 [0.96-1.29]	0.146	1.20 [1.03-1.41]	0.023
Inhaled LABA	1.51 [1.15-2.00]	0.004	1.50 [1.12-2.01]	0.007	1.49 [1.28-1.73]	<0.001	1.31 [1.12-1.54]	0.001
Inhaled SAMA	1.58 [0.86-2.90]	0.14	1.68 [0.91-3.10]	0.096	3.64 [2.90-4.57]	<0.001	2.45 [1.89-3.18]	<0.001
Inhaled LAMA	1.60 [1.20-2.15]	0.002	1.66 [1.22-2.27]	0.001	1.40 [1.20-1.64]	<0.001	1.20 [1.01-1.41]	0.037
Xanthines	3.07 [0.43-21.89]	0.263	2.90 [0.41-20.79]	0.289	1.71 [0.43-6.85]	0.449	0.86 [0.12-6.15]	0.884
LTRA	1.24 [0.59-2.65]	0.569	0.91 [0.40-2.06]	0.825	1.13 [0.74-1.72]	0.584	1.25 [0.80-1.96]	0.322
PDE4	0.49 [0.07-3.47]	0.472	0.43 [0.06-3.04]	0.395	2.08 [1.25-3.47]	0.005	1.79 [1.03-3.10]	0.039

Statins	1.54 [1.17-2.03]	0.002	1.17 [0.86-1.61]	0.312	1.34 [1.15-1.55]	<0.001	0.88 [0.74-1.04]	0.124
ACEIs	1.43 [1.05-1.96]	0.022	1.19 [0.86-1.65]	0.298	1.39 [1.18-1.65]	<0.001	1.03 [0.86-1.23]	0.775
ARB	1.57 [1.18-2.09]	0.002	1.13 [0.83-1.54]	0.446	0.97 [0.82-1.14]	0.676	0.64 [0.53-0.77]	<0.001
Antidepressants	1.24 [0.91-1.69]	0.18	1.32 [0.95-1.83]	0.094	1.78 [1.52-2.08]	<0.001	1.92 [1.62-2.27]	<0.001
Clinical measurements								
GOLD Classes b								
Class A	Ref.		Ref.		Ref.		Ref.	
Class B	1.64 [0.97-2.78]	0.064	1.73 [1.01-2.97]	0.046	1.67 [1.24-2.25]	0.001	1.58 [1.15-2.16]	0.004
Class C	1.78 [0.80-3.97]	0.157	1.69 [0.73-3.93]	0.219	1.40 [0.86-2.29]	0.18	1.36 [0.80-2.30]	0.256
Class D	2.48 [1.41-4.39]	0.002	2.67 [1.48-4.78]	0.001	2.69 [1.96-3.70]	<0.001	2.39 [1.71-3.35]	<0.001
FEV1 % predicted c								
>=80	Ref.		Ref.		Ref.		Ref.	
50-79	0.60 [0.40-0.90]	0.014	0.54 [0.35-0.83]	0.004	1.27 [0.93-1.73]	0.134	1.24 [0.91-1.70]	0.175
30-49	0.52 [0.31-0.89]	0.016	0.54 [0.31-0.92]	0.024	1.61 [1.14-2.26]	0.006	1.39 [0.98-1.96]	0.064
<30	0.69 [0.29-1.63]	0.395	0.81 [0.34-1.97]	0.65	1.97 [1.21-3.18]	0.006	1.93 [1.17-3.18]	0.01
CAT								
<10			Ref.				Ref.	
≥ 10	1.78 [1.27-2.51]	0.001	1.74 [1.22-2.47]	0.002	1.48 [1.24-1.76]	<0.001	1.43 [1.18-1.72]	<0.001
mMRC dyspnea scale d								
0	Ref.		Ref.		Ref.		Ref.	
1	1.47 [0.93-2.34]	0.102	1.58 [0.96-2.59]	0.071	1.16 [0.91-1.47]	0.237	1.08 [0.83-1.40]	0.581
2	1.31 [0.78-2.22]	0.306	1.32 [0.75-2.30]	0.335	1.22 [0.93-1.59]	0.153	1.10 [0.82-1.46]	0.539
3	1.75 [1.02-3.02]	0.042	1.86 [1.05-3.28]	0.034	1.67 [1.27-2.21]	<0.001	1.38 [1.03-1.86]	0.034
4	1.22 [0.63-2.35]	0.558	1.13 [0.56-2.29]	0.735	1.45 [1.05-1.99]	0.022	1.25 [0.90-1.74]	0.19
Body mass index (BMI) e †								
Underweight	1.13 [0.39-3.21]	0.824	1.27 [0.44-3.62]	0.656	1.55 [1.15-2.09]	0.004	1.69 [1.25-2.29]	0.001
Normal BMI	Ref.		Ref.		Ref.		Ref.	

Overweight	2.78 [1.80-4.28]	<0.001	2.47 [1.60-3.81]	<0.001	0.77 [0.64-0.92]	0.005	0.75 [0.62-0.90]	0.003
Obese	4.29 [2.82-6.55]	<0.001	3.52 [2.29-5.40]	<0.001	1.01 [0.84-1.21]	0.949	1.07 [0.88-1.30]	0.483

adj.HR = adjusted hazard ratios; CI = confidence interval; EU=Europe; Ref=Reference group;
ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; SABA= short-acting bronchodilator agonists; LABA= long-acting bronchodilator agonists; SAMA = short-acting muscarinic antagonists; LAMA = long-acting muscarinic antagonists; LTRA=leukotriene receptor antagonists; PDE-4 = phosphodiesterase-4 inhibitors. GOLD = global initiative for chronic obstructive lung disease; FEV_1=forced expiratory volume in 1 second; ICU = intensive care unit; CAT = chronic obstructive pulmonary disease assessment test; mMRC = modified Medical Research Council; NA= Not applicable

* Models adjusted for age, sex, smoking, BMI, diabetes, and hypertension. Models have reduced sample size due to missing values, see table E6.
† Models including the same variable are not adjusted for it.

[a] Significant trend across education levels for COVID-19 hospitalization ($p < 0.001$) and death ($p < 0.001$).
[b] Significant trend across GOLD ABCD for COVID-19 hospitalization ($p < 0.001$) and death ($p = 0.001$).
[c] Significant trend across FEV_1 % predicted levels for COVID-19 infection ($p = 0.011$), hospitalization ($p < 0.001$) and ICU admission ($p < 0.001$).
[d] Significant trend across mMRC dyspnea scale for COVID-19 infection ($p < 0.001$)
[e] Significant trend across BMI levels categories for COVID-19 infection ($p < 0.001$), hospitalization ($p < 0.001$) and ICU admission ($p < 0.001$).

Table E4 Association between sociodemographics, comorbidities, prescribed medications and clinical characteristics of a population-based COPD cohort in Sweden and four COVID-19 outcomes (infection, hospitalization, intensive care unit (ICU) admission and death) that occurred during unvaccinated follow-up time from from 1 Jan 2020 until 30 Nov 2021 from a multivariable regression model containing all investigated characteristics except GOLD[a] and FEV_1[a].

	COVID-19 infection		COVID-19 hospitalization		COVID-19 ICU admission		COVID-19 death	
Total number of events	6068		2649		221		803	
Person years	106981		108282		109272		109342	
	Adj. HR [95% CI] *	p-value	Adj.HR [95% CI] *	p-value	Adj. HR [95% CI] *	p-value	Adj. HR [95% CI] *	p-value
Sociodemographics								
Age categories								
40-49	Ref. 40-49		Ref. 40-49					
50-59	0.98 [0.82-1.18]	0.855	1.88 [1.01-3.49]	0.045	Ref. 50-59		Ref. 50-59	
60-69	0.79 [0.66-0.96]	0.017	2.09 [1.13-3.86]	0.019	0.72 [0.39-1.35]	0.312	1.77 [0.79-3.97]	0.163
70-79	0.68 [0.55-0.84]	<0.001	2.44 [1.30-4.59]	0.006	0.52 [0.25-1.09]	0.083	2.56 [1.08-6.08]	0.033
80-89	0.94 [0.75-1.17]	0.557	3.44 [1.82-6.50]	<0.001	0.18 [0.07-0.46]	<0.001	5.75 [2.41-13.72]	<0.001
90+	1.54 [1.19-2.01]	0.001	4.94 [2.54-9.62]	<0.001			10.04 [4.03-24.98]	<0.001
Gender								
Male	Ref.		Ref.		Ref.		Ref.	
Female	0.87 [0.82-0.93]	<0.001	0.69 [0.63-0.75]	<0.001	0.66 [0.48-0.90]	0.009	0.53 [0.44-0.63]	<0.001
Education								
Primary	Ref.		Ref.		Ref.		Ref.	
Secondary	1.00 [0.94-1.07]	0.961	0.97 [0.88-1.07]	0.541	0.80 [0.58-1.10]	0.164	0.94 [0.79-1.11]	0.453
Higher	0.87 [0.80-0.95]	0.001	0.80 [0.70-0.91]	0.001	0.71 [0.46-1.09]	0.118	0.70 [0.54-0.91]	0.007
Marital status								
Non-married	Ref.		Ref.		Ref.		Ref.	
Married	0.99 [0.94-1.05]	0.862	0.87 [0.79-0.95]	0.002	1.03 [0.77-1.39]	0.828	0.81 [0.68-0.96]	0.014
Employment status								
Unemployed (40-64 years)	Ref.		Ref.		Ref.		Ref.	
Employed (40-64 years)	1.72 [1.53-1.94]	<0.001	0.95 [0.75-1.20]	0.676	0.69 [0.36-1.30]	0.253	0.64 [0.29-1.41]	0.266
Employed (65+ years)	1.13 [0.98-1.31]	0.096	1.15 [0.90-1.47]	0.265	1.80 [0.92-3.52]	0.087	1.11 [0.57-2.16]	0.754
Retired (65+ years)	1.08 [0.94-1.23]	0.291	1.22 [0.97-1.53]	0.093	1.46 [0.78-2.73]	0.235	2.03 [1.11-3.72]	0.022

Region of birth								
Sweden	Ref.		Ref.		Ref.		Ref.	
Nordic	1.16 [1.04-1.30]	0.009	1.23 [1.05-1.45]	0.011	1.52 [0.89-2.62]	0.126	1.17 [0.87-1.58]	0.290
Other EU	1.14 [0.99-1.32]	0.07	1.43 [1.17-1.74]	0.001	2.63 [1.50-4.60]	0.001	1.31 [0.91-1.89]	0.146
Non-EU	1.84 [1.69-2.02]	<0.001	2.24 [1.95-2.57]	<0.001	2.53 [1.68-3.80]	<0.001	1.28 [0.92-1.77]	0.143
Smoking								
Never smoker	Ref.		Ref.		Ref.		Ref.	
Former smoker	0.98 [0.91-1.06]	0.568	1.00 [0.90-1.13]	0.946	1.08 [0.73-1.61]	0.705	0.99 [0.80-1.22]	0.919
Current smoker	0.62 [0.57-0.68]	<0.001	0.62 [0.53-0.71]	<0.001	0.42 [0.25-0.70]	0.001	0.72 [0.55-0.94]	0.014
Comorbidities								
Overall cardiovascular disease	1.37 [1.29-1.47]	<0.001	1.78 [1.60-1.98]	<0.001	1.48 [1.05-2.09]	0.024	2.70 [2.15-3.38]	<0.001
Type 1 diabetes	1.17 [0.95-1.45]	0.142	1.22 [0.92-1.62]	0.174	0.91 [0.33-2.52]	0.854	1.63 [1.05-2.53]	0.031
Type 2 diabetes	1.24 [1.14-1.35]	<0.001	1.38 [1.23-1.55]	<0.001	1.27 [0.87-1.86]	0.223	1.48 [1.21-1.81]	<0.001
Asthma	0.94 [0.85-1.03]	0.18	1.02 [0.90-1.17]	0.746	1.07 [0.70-1.66]	0.746	1.10 [0.87-1.39]	0.436
Respiratory failure	1.57 [1.38-1.78]	<0.001	1.97 [1.69-2.30]	<0.001	1.56 [0.84-2.89]	0.156	2.00 [1.53-2.61]	<0.001
Interstitial lung disease	0.97 [0.67-1.38]	0.847	1.30 [0.85-1.98]	0.223	0.74 [0.10-5.37]	0.769	1.93 [1.06-3.53]	0.033
Sleep apnea syndromes	0.93 [0.81-1.08]	0.355	1.05 [0.86-1.27]	0.660	1.42 [0.85-2.36]	0.178	1.03 [0.70-1.52]	0.867
Chronic kidney disease	1.46 [1.18-1.80]	0.001	1.52 [1.17-1.98]	0.002	1.09 [0.34-3.46]	0.888	1.96 [1.34-2.88]	0.001
Autoimmune disease	1.28 [1.16-1.42]	<0.001	1.43 [1.25-1.63]	<0.001	1.03 [0.60-1.77]	0.925	1.83 [1.47-2.28]	<0.001
Cancer	1.07 [0.99-1.16]	0.096	1.13 [1.01-1.26]	0.027	0.90 [0.58-1.39]	0.620	1.04 [0.85-1.26]	0.727
Depression	0.78 [0.62-0.98]	0.032	0.83 [0.59-1.17]	0.295	2.61 [0.58-11.64]	0.209	0.49 [0.28-0.87]	0.015
Anxiety	0.99 [0.87-1.14]	0.933	1.05 [0.86-1.27]	0.664	1.23 [0.64-2.35]	0.537	0.91 [0.64-1.32]	0.632
Psychiatric disease	1.43 [1.18-1.73]	<0.001	1.55 [1.16-2.08]	0.003	0.60 [0.15-2.48]	0.485	2.59 [1.61-4.15]	<0.001
Prescribed medications								
Inhaled corticosteroids	1.15 [1.06-1.24]	0.001	1.18 [1.05-1.32]	0.006	1.05 [0.71-1.55]	0.821	1.23 [0.99-1.53]	0.064
Oral corticosteroids	1.06 [0.99-1.14]	0.075	1.06 [0.96-1.17]	0.255	1.15 [0.82-1.62]	0.422	0.81 [0.67-0.98]	0.028
Inhaled SABA	1.04 [0.98-1.11]	0.201	1.03 [0.94-1.13]	0.559	1.07 [0.78-1.47]	0.678	1.04 [0.88-1.24]	0.641
Inhaled LABA	0.99 [0.91-1.06]	0.703	1.02 [0.91-1.14]	0.765	1.20 [0.82-1.77]	0.351	1.03 [0.83-1.27]	0.815
Inhaled SAMA	1.39 [1.23-1.58]	<0.001	1.45 [1.23-1.72]	<0.001	1.29 [0.68-2.45]	0.436	1.76 [1.34-2.32]	<0.001
Inhaled LAMA	1.04 [0.98-1.11]	0.188	1.19 [1.08-1.32]	<0.001	1.49 [1.06-2.09]	0.022	1.04 [0.86-1.25]	0.695
PDE4	0.86 [0.66-1.11]	0.239	0.88 [0.63-1.24]	0.463	0.27 [0.04-1.97]	0.198	1.22 [0.69-2.14]	0.492

Statins	0.90 [0.85-0.96]	0.002	0.87 [0.8-0.96]	0.005	1.09 [0.79-1.50]	0.613	0.83 [0.70-0.98]	0.030
ARB	0.92 [0.86-0.98]	0.010	0.94 [0.86-1.04]	0.230	1.12 [0.82-1.54]	0.464	0.72 [0.60-0.86]	<0.001
Antidepressants	1.30 [1.21-1.39]	<0.001	1.30 [1.17-1.43]	<0.001	1.16 [0.81-1.66]	0.432	1.64 [1.37-1.97]	<0.001
Clinical measurements								
CAT								
<10	Ref.		Ref.		Ref.		Ref.	
≥ 10	1.06 [0.99-1.13]	0.085	1.24 [1.12-1.38]	<0.001	1.46 [1.01-2.11]	0.042	1.30 [1.06-1.59]	0.011
mMRC dyspnea scale								
0	Ref.		Ref.		Ref.		Ref.	
1	1.00 [0.92-1.09]	0.935	0.97 [0.84-1.11]	0.645	1.37 [0.83-2.25]	0.221	1.06 [0.81-1.39]	0.648
2	1.01 [0.92-1.12]	0.791	1.00 [0.86-1.16]	0.976	1.08 [0.62-1.90]	0.784	0.99 [0.73-1.33]	0.944
3	1.04 [0.93-1.16]	0.464	1.11 [0.94-1.30]	0.224	1.34 [0.74-2.41]	0.331	1.10 [0.80-1.50]	0.560
4	0.94 [0.84-1.07]	0.368	0.81 [0.67-0.98]	0.031	0.73 [0.35-1.54]	0.414	0.91 [0.64-1.29]	0.593
Body mass index (BMI)								
Underweight	1.25 [1.09-1.44]	0.002	1.54 [1.27-1.87]	<0.001	1.23 [0.37-4.13]	0.733	1.66 [1.20-2.30]	0.002
Normal BMI	Ref.		Ref.		Ref.		Ref.	
Overweight	0.99 [0.92-1.06]	0.753	0.88 [0.79-0.98]	0.019	2.44 [1.52-3.93]	<0.001	0.76 [0.62-0.93]	0.008
Obese	1.02 [0.95-1.11]	0.524	1.09 [0.98-1.22]	0.125	2.93 [1.81-4.72]	<0.001	1.08 [0.87-1.33]	0.486

adj.HR = adjusted hazard ratios; CI = confidence interval; EU=Europe; Ref=Reference group;
ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; SABA= short-acting bronchodilator agonists; LABA= long-acting bronchodilator agonists; SAMA = short-acting muscarinic antagonists; LAMA = long-acting muscarinic antagonists; LTRA=leukotriene receptor antagonists; PDE-4 = phosphodiesterase-4 inhibitors. GOLD = global initiative for chronic obstructive lung disease; FEV_1=forced expiratory volume in 1 second; ICU = intensive care unit; CAT = chronic obstructive pulmonary disease assessment test; mMRC = modified Medical Research Council; NA= Not applicable

Models are based on unvaccinated COPD patients with larger sample sizes.
[a] Models containing GOLD or FEV_1 were consistent with the presented results and were excluded due to missingness that resulted in reduced sample sizes.
* Models adjusted for all variables shown except FEV_1 and GOLD
Note: Unadjusted hazard ratios are the same as in Table E3

Table E5. Association between sociodemographics, comorbidities, prescribed medications and clinical characteristics of a population-based COPD cohort in Sweden and three COVID-19 outcomes (infection, hospitalization, and death) that occurred during vaccinated follow-up time from from 1 Jan 2020 until 30 Nov 2021.

	COVID-19 infection				COVID-19 hospitalization				COVID-19 death			
Total number of events	703				248				77			
Person years	46315				46461				46544			
	Unadj. HR [95% CI]	p-value	Adj. HR [95% CI] *	p-value	Unadj. HR [95% CI]	p-value	Adj. HR [95% CI] *	p-value	Unadj. HR [95% CI]	p-value	Adj. HR [95% CI] *	p-value
Sociodemographics												
Age categories †												
40-49	Ref. 40-49		Ref. 40-49									
50-59	0.63 [0.42-0.95]	0.026	0.62 [0.40-0.97]	0.034	Ref. 40-59		Ref. 40-59					
60-69	0.41 [0.28-0.60]	<0.001	0.35 [0.23-0.53]	<0.001	1.35 [0.74-2.45]	0.329	1.40 [0.70-2.81]	0.340	0.23 [0.08-0.66]	0.006	0.33 [0.11-0.98]	0.046
70-79	0.43 [0.29-0.62]	<0.001	0.32 [0.21-0.48]	<0.001	2.43 [1.40-4.21]	0.002	2.13 [1.11-4.10]	0.023	Ref.		Ref.	
80-89	0.52 [0.35-0.76]	0.001	0.36 [0.24-0.56]	<0.001	3.79 [2.16-6.62]	<0.001	2.95 [1.50-5.79]	0.002	2.41 [1.46-3.98]	0.001	1.92 [1.09-3.38]	0.024
90+	0.78 [0.47-1.28]	0.321	0.63 [0.36-1.11]	0.108	3.92 [1.84-8.38]	<0.001	3.75 [1.52-9.26]	0.004	2.18 [0.88-5.41]	0.094	1.88 [0.62-5.69]	0.266
Gender †												
Male	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Female	0.91 [0.8-1.04]	0.178	0.92 [0.80-1.06]	0.252	0.66 [0.53-0.82]	<0.001	0.68 [0.53-0.87]	0.003	0.53 [0.34-0.84]	0.006	0.41 [0.24-0.69]	0.001
Education a												
Primary	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Secondary	0.94 [0.81-1.09]	0.402	0.95 [0.81-1.12]	0.563	0.70 [0.55-0.89]	0.004	0.79 [0.60-1.04]	0.097	0.57 [0.35-0.92]	0.021	0.73 [0.42-1.25]	0.252
Higher	1.12 [0.93-1.34]	0.231	1.15 [0.94-1.41]	0.165	0.82 [0.60-1.12]	0.214	0.94 [0.67-1.33]	0.739	0.35 [0.15-0.78]	0.010	0.36 [0.14-0.93]	0.035
Marital status												
Non-married	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Married	1.06 [0.93-1.21]	0.397	1.09 [0.94-1.26]	0.245	0.87 [0.69-1.09]	0.226	0.85 [0.66-1.10]	0.213	0.97 [0.61-1.55]	0.913	0.96 [0.57-1.63]	0.884
Employment status												
Unemployed (40-64 years)	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Employed (40-64 years)	1.91 [1.40-2.62]	<0.001	1.96 [1.37-2.79]	<0.001	0.47 [0.24-0.93]	0.029	0.58 [0.27-1.27]	0.174	NA [f]	NA [f]	NA [f]	NA [f]
Employed (65+ years)	1.26 [0.91-1.75]	0.163	1.38 [0.90-2.11]	0.137	0.92 [0.52-1.62]	0.766	0.62 [0.29-1.34]	0.225	NA [f]	NA [f]	NA [f]	NA [f]

Retired (65+ years)	1.24 [0.93-1.66]	0.145	1.25 [0.83-1.89]	0.292	1.51 [0.93-2.43]	0.094	0.81 [0.39-1.68]	0.569	NA [f]	NA [f]	NA [f]	NA [f]
Region of birth												
Sweden	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Nordic	0.99 [0.76-1.3]	0.957	1.01 [0.75-1.36]	0.933	1.26 [0.83-1.90]	0.274	1.26 [0.78-2.02]	0.341	1.72 [0.82-3.60]	0.152	1.79 [0.76-4.21]	0.183
Other EU	1.00 [0.69-1.45]	0.997	1.05 [0.71-1.55]	0.815	1.53 [0.91-2.58]	0.109	1.52 [0.86-2.66]	0.148	0.91 [0.22-3.73]	0.896	0.96 [0.23-3.96]	0.951
Non-EU	1.48 [1.19-1.85]	<0.001	1.42 [1.12-1.82]	0.005	1.58 [1.09-2.30]	0.016	2.00 [1.33-2.99]	0.001	2.61 [1.29-5.29]	0.008	3.48 [1.67-7.29]	0.001
Smoking †												
Never smoker	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Former smoker	0.93 [0.78-1.12]	0.452	0.95 [0.79-1.15]	0.603	0.87 [0.65-1.18]	0.386	0.93 [0.68-1.27]	0.658	0.59 [0.35-1.02]	0.058	0.69 [0.39-1.22]	0.206
Current smoker	0.57 [0.46-0.71]	<0.001	0.57 [0.45-0.71]	<0.001	0.45 [0.30-0.65]	<0.001	0.61 [0.41-0.92]	0.017	0.20 [0.09-0.47]	<0.001	0.36 [0.15-0.88]	0.025
Comorbidities												
Overall cardiovascular disease	1.31 [1.15-1.49]	<0.001	1.12 [0.90-1.39]	0.326	1.52 [1.04-2.20]	0.03	1.52 [1.04-2.20]	0.030	2.31 [1.38-3.87]	0.001	1.13 [0.49-2.60]	0.765
Hypertension †	1.29 [1.13-1.47]	<0.001	1.11 [0.95-1.31]	0.184	1.29 [0.99-1.68]	0.062	1.29 [0.99-1.68]	0.062	2.33 [1.47-3.70]	<0.001	1.37 [0.80-2.36]	0.254
Heart failure	1.60 [1.33-1.93]	<0.001	1.34 [1.07-1.68]	0.011	1.66 [1.20-2.29]	0.002	1.66 [1.20-2.29]	0.002	3.50 [2.16-5.66]	<0.001	1.69 [0.94-3.05]	0.081
Type 1 diabetes	2.01 [1.30-3.10]	0.002	1.67 [1.05-2.68]	0.032	2.48 [1.38-4.45]	0.002	2.48 [1.38-4.45]	0.002	7.68 [3.53-16.71]	<0.001	4.92 [1.95-12.42]	0.001
Type 2 diabetes †	1.46 [1.22-1.74]	<0.001	1.41 [1.15-1.73]	0.001	2.17 [1.62-2.92]	<0.001	2.17 [1.62-2.92]	<0.001	2.64 [1.61-4.34]	<0.001	2.00 [1.11-3.58]	0.020
Asthma	1.36 [1.11-1.66]	0.003	1.16 [0.93-1.45]	0.185	1.38 [0.97-1.97]	0.076	1.38 [0.97-1.97]	0.076	1.49 [0.79-2.82]	0.222	1.42 [0.71-2.84]	0.320
Respiratory failure	1.19 [0.83-1.71]	0.352	1.12 [0.75-1.67]	0.586	1.82 [1.09-3.04]	0.022	1.82 [1.09-3.04]	0.022	2.02 [0.87-4.67]	0.101	1.92 [0.76-4.88]	0.168
Interstitial lung disease	1.67 [0.83-3.35]	0.148	1.94 [0.97-3.90]	0.062	2.44 [0.91-6.56]	0.078	2.44 [0.91-6.56]	0.078	4.29 [1.05-17.50]	0.042	4.12 [1.00-16.99]	0.050
Sleep apnea syndromes	1.23 [0.88-1.71]	0.220	0.99 [0.69-1.43]	0.966	1.03 [0.58-1.83]	0.915	1.03 [0.58-1.83]	0.915	3.26 [1.50-7.10]	0.003	2.12 [0.88-5.10]	0.095
Chronic kidney disease	2.64 [1.75-4.00]	<0.001	2.08 [1.27-3.38]	0.003	3.49 [2.00-6.06]	<0.001	3.49 [2.00-6.06]	<0.001	2.98 [0.94-9.46]	0.064	2.28 [0.70-7.45]	0.170
Immunologic disease	1.32 [0.33-5.28]	0.696	0.76 [0.11-5.39]	0.782	2.67 [0.37-19.06]	0.328	2.67 [0.37-19.06]	0.328	NA [f]	NA [f]	NA [f]	NA [f]
Autoimmune disease	1.36 [1.09-1.70]	0.006	1.29 [1.01-1.65]	0.043	1.34 [0.91-1.96]	0.141	1.34 [0.91-1.96]	0.141	1.64 [0.84-3.19]	0.146	1.02 [0.46-2.27]	0.954
Cancer	1.22 [1.03-1.45]	0.025	1.08 [0.88-1.31]	0.474	1.34 [1.00-1.81]	0.053	1.34 [1.00-1.81]	0.053	2.18 [1.34-3.55]	0.002	1.67 [0.97-2.90]	0.066
Depression	1.20 [0.89-1.64]	0.234	1.23 [0.88-1.73]	0.222	1.55 [0.88-2.72]	0.126	1.55 [0.88-2.72]	0.126	0.83 [0.26-2.64]	0.754	1.48 [0.46-4.79]	0.512
Anxiety	0.93 [0.66-1.29]	0.658	0.73 [0.49-1.10]	0.136	0.85 [0.42-1.73]	0.654	0.85 [0.42-1.73]	0.654	0.23 [0.03-1.67]	0.147	0.40 [0.05-2.92]	0.366
Psychiatric disease	1.04 [0.79-1.38]	0.757	1.00 [0.73-1.38]	0.978	1.38 [0.83-2.31]	0.214	1.38 [0.83-2.31]	0.214	0.55 [0.17-1.75]	0.313	1.09 [0.34-3.53]	0.886

Prescribed medications												
Inhaled corticosteroids	1.32 [1.16-1.51]	<0.001	1.28 [1.11-1.48]	0.001	1.55 [1.24-1.93]	<0.001	1.58 [1.23-2.03]	<0.001	1.48 [0.94-2.34]	0.088	1.63 [0.99-2.67]	0.054
Oral corticosteroids	1.28 [1.11-1.48]	0.001	1.24 [1.06-1.46]	0.007	1.44 [1.14-1.82]	0.003	1.30 [1.00-1.70]	0.052	1.54 [0.96-2.47]	0.074	1.41 [0.85-2.34]	0.184
Inhaled SABA	1.10 [0.97-1.26]	0.146	1.09 [0.94-1.26]	0.24	1.16 [0.93-1.45]	0.179	1.28 [1.00-1.64]	0.047	0.98 [0.62-1.54]	0.927	1.27 [0.79-2.05]	0.324
Inhaled LABA	1.20 [1.05-1.36]	0.007	1.15 [1.00-1.33]	0.054	1.43 [1.15-1.78]	0.002	1.40 [1.09-1.79]	0.009	1.10 [0.70-1.72]	0.679	1.35 [0.83-2.20]	0.231
Inhaled SAMA	1.51 [1.12-2.03]	0.007	1.53 [1.11-2.11]	0.010	2.09 [1.37-3.20]	0.001	2.13 [1.34-3.37]	0.001	1.35 [0.54-3.37]	0.517	2.31 [1.05-5.09]	0.038
Inhaled LAMA	1.05 [0.92-1.19]	0.491	1.09 [0.94-1.26]	0.251	1.27 [1.01-1.59]	0.037	1.22 [0.94-1.58]	0.136	0.96 [0.61-1.50]	0.844	1.37 [0.82-2.31]	0.231
Xanthines	1.30 [0.33-5.22]	0.707	1.49 [0.37-5.96]	0.576	NA [f]	NA [f]	NA [f]	NA [f]	NA [f]	NA [f]	NA [f]	NA [f]
LTRA	1.34 [0.95-1.88]	0.096	1.23 [0.85-1.78]	0.281	1.23 [0.67-2.24]	0.505	1.11 [0.55-2.24]	0.779	NA [f]	NA [f]	NA [f]	NA [f]
PDE4	2.45 [1.60-3.73]	<0.001	2.18 [1.37-3.49]	0.001	4.08 [2.34-7.11]	<0.001	3.42 [1.81-6.46]	<0.001	2.29 [0.56-9.35]	0.247	1.25 [0.17-9.05]	0.825
Statins	1.07 [0.94-1.22]	0.301	1.05 [0.90-1.23]	0.551	1.48 [1.19-1.85]	<0.001	0.99 [0.76-1.29]	0.947	1.09 [0.69-1.71]	0.711	0.81 [0.49-1.36]	0.432
ACEIs	1.09 [0.93-1.27]	0.304	1.06 [0.89-1.27]	0.504	1.41 [1.10-1.81]	0.006	1.10 [0.83-1.46]	0.498	1.68 [1.03-2.72]	0.036	1.37 [0.82-2.31]	0.230
ARB	1.00 [0.87-1.16]	0.957	0.94 [0.80-1.11]	0.460	1.05 [0.83-1.34]	0.686	0.75 [0.57-0.99]	0.043	0.66 [0.38-1.14]	0.138	0.38 [0.20-0.72]	0.003
Antidepressants	1.35 [1.17-1.56]	<0.001	1.35 [1.15-1.59]	<0.001	1.33 [1.04-1.69]	0.022	1.61 [1.23-2.11]	<0.001	0.94 [0.56-1.56]	0.799	1.42 [0.84-2.42]	0.191
Clinical measurements												
GOLD Classes b												
Class A	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
Class B	1.01 [0.82-1.24]	0.944	1.05 [0.84-1.30]	0.686	1.71 [1.14-2.57]	0.010	1.68 [1.09-2.60]	0.019	0.81 [0.37-1.78]	0.603	0.83 [0.38-1.78]	0.626
Class C	1.10 [0.78-1.55]	0.587	1.18 [0.82-1.70]	0.360	1.49 [0.78-2.85]	0.232	1.52 [0.75-3.08]	0.245	0.32 [0.04-2.52]	0.281	0.35 [0.04-2.71]	0.312
Class D	1.03 [0.80-1.33]	0.817	1.02 [0.78-1.35]	0.861	1.89 [1.19-3.00]	0.007	1.83 [1.11-3.02]	0.018	1.48 [0.65-3.39]	0.350	1.21 [0.51-2.87]	0.663
FEV1 % predicted c												
>=80	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
50-79	0.80 [0.65-0.98]	0.033	0.83 [0.68-1.03]	0.089	1.03 [0.68-1.57]	0.882	1.05 [0.68-1.63]	0.814	0.66 [0.30-1.45]	0.302	0.89 [0.40-2.02]	0.785
30-49	0.78 [0.61-1.00]	0.052	0.85 [0.65-1.09]	0.201	1.76 [1.13-2.75]	0.012	1.76 [1.11-2.79]	0.016	0.83 [0.34-2.01]	0.681	1.23 [0.50-3.02]	0.645
<30	0.85 [0.55-1.30]	0.446	0.90 [0.58-1.41]	0.645	1.62 [0.81-3.25]	0.176	1.86 [0.91-3.80]	0.089	1.56 [0.48-5.08]	0.461	2.32 [0.67-8.02]	0.184
CAT												
<10	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
≥ 10	0.94 [0.82-1.08]	0.365	0.93 [0.8-1.08]	0.341	1.17 [0.92-1.49]	0.208	1.15 [0.87-1.51]	0.326	0.93 [0.57-1.49]	0.750	0.92 [0.55-1.54]	0.741
mMRC dyspnea scale d												

0	Ref.		Ref.		Ref.		Ref.		Ref.		Ref.	
1	0.98 [0.80-1.18]	0.804	0.95 [0.77-1.17]	0.620	0.95 [0.64-1.42]	0.818	0.94 [0.63-1.39]	0.749	0.97 [0.49-1.93]	0.934	1.00 [0.45-2.22]	0.992
2	1.06 [0.85-1.31]	0.617	1.05 [0.83-1.33]	0.689	1.24 [0.81-1.90]	0.319	1.22 [0.80-1.87]	0.355	0.82 [0.37-1.84]	0.636	1.12 [0.47-2.65]	0.797
3	0.98 [0.76-1.26]	0.866	0.95 [0.72-1.24]	0.690	1.34 [0.85-2.12]	0.201	1.31 [0.83-2.07]	0.241	1.46 [0.67-3.18]	0.341	1.48 [0.62-3.54]	0.380
4	0.93 [0.70-1.24]	0.641	0.88 [0.64-1.20]	0.415	1.14 [0.67-1.91]	0.633	1.09 [0.64-1.84]	0.757	0.82 [0.30-2.22]	0.694	0.74 [0.24-2.29]	0.605
Body mass index (BMI) e †												
Underweight	0.72 [0.47-1.10]	0.124	0.74 [0.48-1.14]	0.170	0.66 [0.31-1.43]	0.294	0.73 [0.34-1.58]	0.427	0.94 [0.28-3.14]	0.923	1.46 [0.50-4.22]	0.488
Normal BMI			Ref.				Ref.				Ref.	
Overweight	1.01 [0.85-1.19]	0.905	0.98 [0.83-1.17]	0.860	1.08 [0.80-1.44]	0.625	1.00 [0.75-1.35]	0.976	0.89 [0.49-1.64]	0.715	0.97 [0.54-1.72]	0.908
Obese	1.20 [1.01-1.43]	0.037	1.13 [0.94-1.35]	0.188	1.43 [1.07-1.91]	0.015	1.33 [0.99-1.80]	0.061	1.53 [0.86-2.71]	0.148	1.55 [0.87-2.76]	0.140

Unadj.HR = unadjusted hazard ratios ; adj.HR = adjusted hazard ratios; CI = confidence interval; EU=Europe; Ref=Reference group;
ACE = angiotensin converting enzyme inhibitors; ARB = angiotensin receptor blockers; SABA= short-acting bronchodilator agonists; LABA= long-acting bronchodilator agonists; SAMA = short-acting muscarinic antagonists; LAMA = long-acting muscarinic antagonists; LTRA=leukotriene receptor antagonists; PDE-4 = phosphodiesterase-4 inhibitors. GOLD = global initiative for chronic obstructive lung disease; FEV_1=forced expiratory volume in 1 second; ICU = intensive care unit; CAT = chronic obstructive pulmonary disease assessment test; mMRC = modified Medical Research Council; NA= Not applicable

*Models adjusted for age, sex, smoking, BMI, diabetes, and hypertension.
† Models including the same variable are not adjusted for it.

Note: hazard ratios for ICU admissions during the vaccinated follow-up period not estimated due to the small case numbers.

[a] Significant trend across education levels for COVID-19 hospitalization ($p < 0.001$).
[b] Significant trend across GOLD ABCD for COVID-19 hospitalization ($p < 0.001$) and death ($p = 0.001$).
[c] Significant trend across FEV_1 % predicted levels for COVID-19 infection ($p = 0.001$), hospitalization ($p < 0.001$) and death ($p < 0.001$).
[d] Significant trend across mMRC dyspnea scale for COVID-19 infection ($p < 0.001$)
[e] Significant trend across BMI levels categories for COVID-19 infection ($p < 0.001$), hospitalization ($p < 0.001$) and death ($p < 0.001$).
[f] NA introduced due to few observations.

Table E6. Sample sizes of observations in regression models for the unvaccinated follow-up time* assessing the association between different characteristics and the risk for four COVID-19 outcomes (infection, hospitalization, intensive care unit (ICU) admission and death) among patients in a population-based COPD cohort in Sweden from 1 Jan 2020 to 30 Nov 2021.

	COVID-19 infection				COVID-19 hospitalization				COVID-19 ICU admission				COVID-19 death			
	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]	Model 1[a]	Model 2[b]	Model 3[c]	Model 4[d]
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Age categories	6068	6068	6068	4995	2649	2649	2649	2178	221	221	221	199	803	803	803	621
Sex	6068	6068	6068	4995	2649	2649	2649	2178	221	221	221	199	803	803	803	621
Comorbidities[§]	6068	6068	6068	4995	2649	2649	2649	2178	221	221	221	199	803	803	803	621
Medications [ll]	6068	6068	6068	4995	2649	2649	2649	2178	221	221	221	199	803	803	803	621
Smoking	4995	4995	4995	4995	2178	2178	2178	2178	199	199	199	199	621	621	621	621
Body mass index	5395	5395	5395	4995	2387	2387	2387	2178	203	203	203	199	706	706	706	621

*Models are based on the unvaccinated follow-up time with larger sample sizes.

[a] Crude models
[b] Adjusted for age and sex
[c] Adjusted for age, sex, diabetes, and hypertension.
[d] Adjusted for age, sex, diabetes, hypertension, body mass index and smoking
[§] Include: Overall cardiovascular disease, hypertension, heart failure, type 1 and type 2 diabetes, asthma, chronic kidney disease, autoimmune diseases, cancer, psychiatric conditions, and anxiety.
[ll] Include: included inhaled (ICS) and systemic corticosteroids, long- and short-acting beta-agonists (LABA, SABA), long- and short- acting muscarinic antagonists (LAMA, SAMA), phosphodiesterase (PDE4) inhibitors, leukotriene receptor antagonists (LTRA), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), and statins

Table E7. Overview of register data sources for the present study on characteristics and risk factors of COVID-19 in a Swedish population-based cohort of COPD from 1 Jan 2020 to 30 Nov 2021.

Register Type	Register Name	Acronym	Administrator	Data	Assessment period*	Reference
Healthcare register	National Patient Register	NPR	Swedish National Board of Health and Welfare	Contains data of all in-patient care from public and private practitioners in Sweden	5 years for pre-index** comorbidities and after index data for COVID-19 outcomes	[E1]
Healthcare register	Swedish Cause-of-Death Register	SCDR	Swedish National Board of Health and Welfare	Database of all deaths registered in Sweden	5 years pre-index, and after index for COVID-19 outcomes	[E2]
Drug register	National Prescribed Drugs Register	NPDR	Swedish National Board of Health and Welfare	Contains information about all dispensed prescriptions in pharmacies	1 years before index	[E3]
Healthcare register	SmiNet (national register of notifiable diseases reporting)	SmiNet	The Public Health Agency of Sweden	Maintained by the public health agency of Sweden, contains reports of infectious diseases including COVID-19 and vaccination.	After index for COVID-19 outcomes	[E4]
General population register	Register of the Total Population	RTB	Statistics Sweden (SCB)	Has information on the Swedish population	Latest record in the past 5 years pre-index	[E5]
Socioeconomic register	Longitudinal Integrated Database for Health Insurance	LISA	Statistics Sweden (SCB)	Database with sociodemographic data such as household statistics, health	Latest record in the past 5	[E6]

	and Labor Market Studies			insurance, employment, income, and education	years pre-index	
Quality register	Swedish National Airways Register	SNAR	Swedish regions	Database with detailed data from individuals with chronic obstructive respiratory disease from primary, secondary, tertiary, and in-patient care	5 years pre-index	[E7]
Healthcare register	Swedish Intensive Care Registry	SIR	Region Värmland	A register for all intensive care unit cases	After index for COVID-19 outcomes	[E8]

COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease 2019.

*Selected duration for this study
** Index date is 1 Jan 2020.

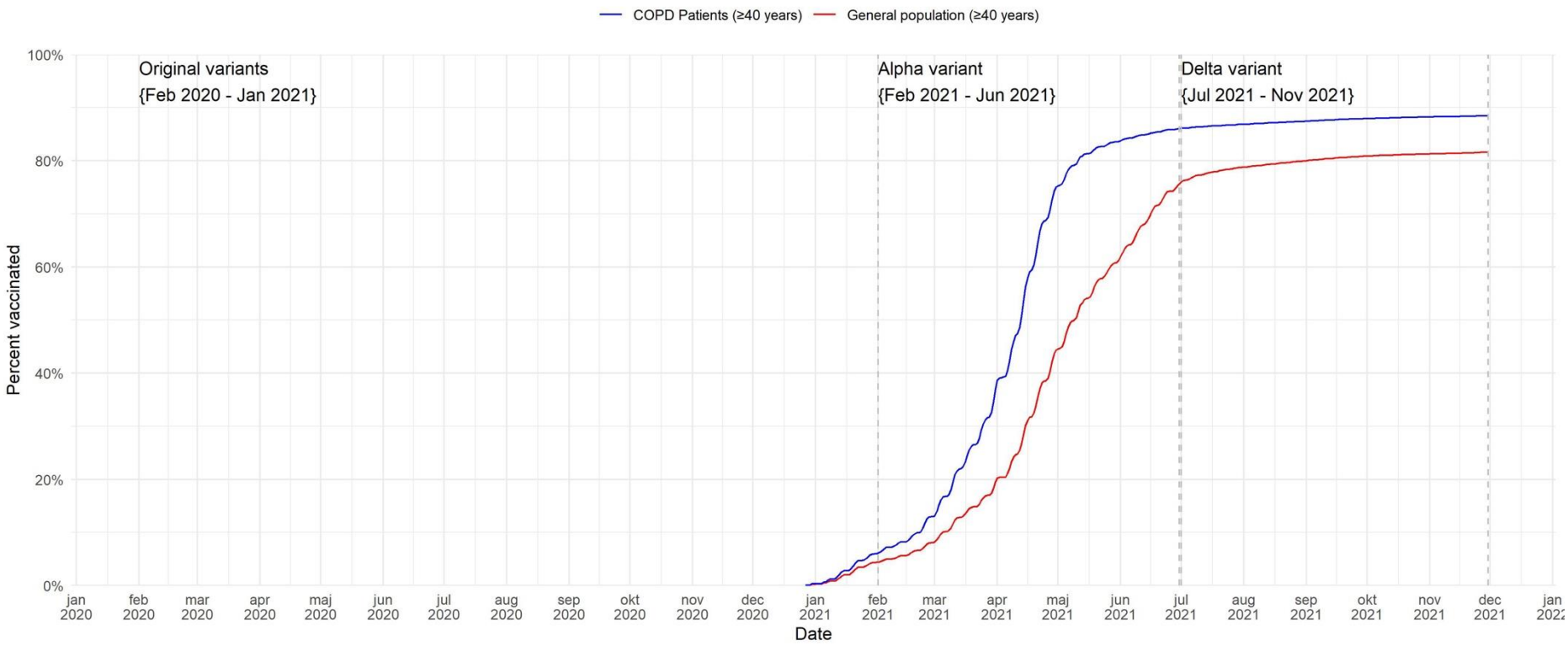

Figure S1: First Coronavirus vaccination uptake in COPD patients (≥40 years) and the general population (≥40 years) from Jan 1, 2020, to Nov 30, 2021 in Sweden.

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