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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Shareable abstract (@ERSpublications)
This study delineates poorly understood risk factors that are clinically relevant for COPD patients, and quantifies risks pre- and post-vaccination, with implications for informing clinical evaluation, and improving treatment and prevention efforts https://bit.ly/42Zxa6R

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Abstract

Rationale Evidence on risk factors for Coronavirus disease 2019 (COVID-19) outcomes among patients with COPD in relation to COVID-19 vaccination remains limited. The objectives of the present study were to characterise determinants of COVID-19 infection, hospitalisation, 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), hospitalisation, ICU admission and death were identified from 1 January 2020 to 30 November 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 analysed.

Results The population-based COPD cohort included 87 472 patients, among whom 6771 (7.7%) COVID-19 infections, 2897 (3.3%) hospitalisations, 233 (0.3%) ICU admissions and 882 (1.0%) COVID-19 deaths occurred. During unvaccinated follow-up, risk of COVID-19 hospitalisation 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 hospitalisation (adjusted hazard ratios (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, hospitalisation and death. COPD severity was also associated with COVID-19, especially hospitalisation 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 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 pre-existing 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 utilisation [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 hospitalised 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, hospitalisation, 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 years old in the Swedish population diagnosed at all levels of care and registered in SNAR during 2015–2019 [16]. We defined four 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; hospitalisation (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 January 2020 (index date) until exiting the cohort on the earliest of: the studied outcome, death, emigration, first vaccination or end of follow-up (30 November 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 (supplementary 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 (supplementary 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 (supplementary Table E1). Smoking status was derived from SNAR (never-, former and current smoker).

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, immunological disease, autoimmune diseases, cancer, depression, anxiety and psychiatric conditions, and on sleep apnoea syndrome diagnosis from SNAR (supplementary 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 (supplementary Table E1). Information on COVID-19 vaccination came from the National Vaccination Register.

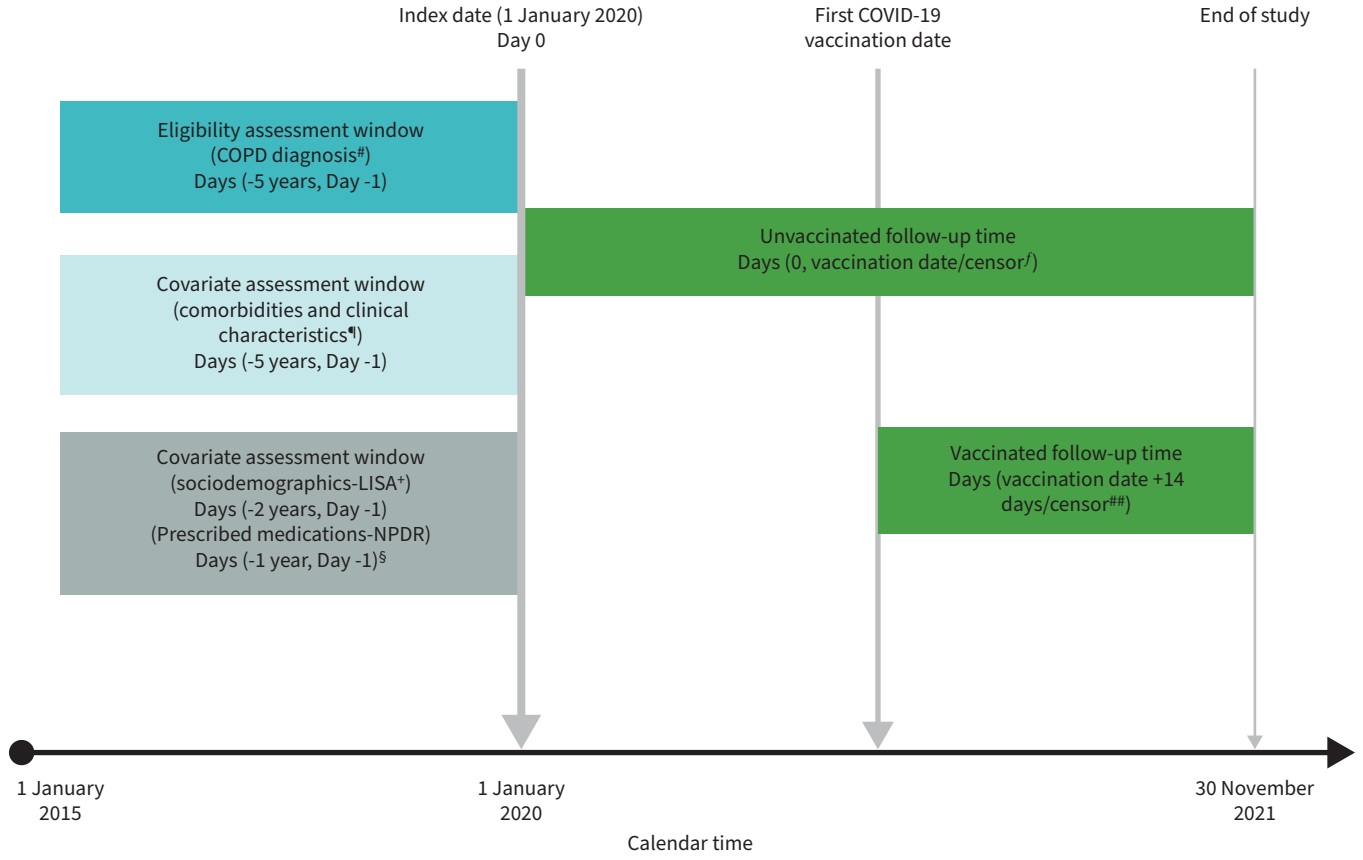

FIGURE 1 Illustration of cohort design for evaluation and follow-up of the study population. LISA: Longitudinal Integrated Database for Health Insurance and Labor Market Studies. #: study population was defined as having a positive diagnosis of COPD prior to the index date in the Swedish National Airways Register (SNAR); ¶: information on comorbidities available for 5years prior to the index date were extracted from the National Patient Register and clinical data from SNAR; +: sociodemographic data were collected in 2018 and 2019, and the latest information for each individual was used; §: data on prescribed medication available was extracted from the Swedish National Prescribed Drug Register (NPDR) 1 year pre-index; f: unvaccinated follow-up time started from 1 January 2020 until exiting cohort on the earliest of: incident COVID-19 outcome, emigration, death, vaccination or end of study period (30 November 2021); ##: 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 November 2021). COVID-19 outcomes include infection, hospitalisation, intensive care unit admission or death.

Clinical measurements obtained from SNAR included dyspnoea measured by the modified Medical Research Council (mMRC) dyspnoea 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 1 s per cent 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 categorised into Global Initiative for Chronic Obstructive Lung Disease (GOLD) stages: 1=FEV_1 ⩾80%; 2=50–79%; 3=30–49% and 4=<30%. GOLD ABCD classes were also created from SNAR data on number of total and hospitalised exacerbations in the year prior to index date, CAT and mMRC scores as described in supplementary Table E1. BMI was classified as underweight (<18.5 $kg \cdot m^{-2}$), normal (18.5–24.9 $kg \cdot m^{-2}$), overweight (25.0–29.9 $kg \cdot m^{-2}$) and obese (⩾30.0 $kg \cdot m^{-2}$). For CAT, a cut-off at ⩾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 (supplementary Table E1).

Statistical analysis

Most variables had no missing data by design, as absence of a registration of, for example, 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 n (%) for categorical variables and mean±$_{SD}$ or median (IQR) 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 87 472 COPD patients identified, among whom 6068 infections, 2649 hospitalisations, 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 hospitalised, ICU admitted and died of COVID-19 (table 1). COPD patients who were hospitalised 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 hospitalisations, 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, chronic kidney disease (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, supplementary 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 hospitalisation 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, supplementary 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 hospitalisation and death. Foreign-born individuals, especially from outside Europe, were at significantly higher risk for COVID-19 infection, hospitalisation and ICU admission than Sweden-born. Among working-age (40–64 years old) patients, employment was significantly associated with an increased risk of COVID-19 infection but otherwise with lower risk across different COVID-19 outcomes. Being married decreased the risk of hospitalisation and death (figure 2, supplementary 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, supplementary 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 hospitalisation (figure 4, supplementary 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 (supplementary 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, supplementary Table E3). Obese patients had a higher risk for hospitalisation (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 hospitalisation (HRs range 1.37–1.92) and death (HRs 1.38–2.39) (figure 5, supplementary Table E4). COPD patients with lower FEV_1% predicted (GOLD 3 and 4) also had a higher risk of COVID-19 infection, hospitalisation and death (supplementary Table E3).

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TABLE 1 Sociodemographic characteristics of a population-based cohort of COPD patients (⩾40 years old) in Sweden on 1 January 2020, and of individuals with four different COVID-19 outcome events that occurred during unvaccinated and vaccinated follow-up time from 1 January 2020 to 30 November 2021 in that cohort

	Total COPD cohort[#]	COPD patients with COVID-19 outcomes during vaccinated and unvaccinated follow-up time							
		Infected		Hospitalised		ICU admitted		Death	
		Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Patients n	87 472	6068	703	2649	248	221	12	803	79
Age years, 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 years									
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	22 121 (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	36 418 (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	17 354 (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)
Sex									
Male	38 151 (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	49 321 (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[¶,+]									
Primary	29 703 (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	40 967 (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	15 674 (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									
Unmarried	51 861 (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	35 568 (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)	11 416 (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)	12 350 (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)	56 630 (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	71 679 (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[¶,§¶]									
Never-smoker	12 310 (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	39 734 (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	26 252 (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)

Data are presented as n (%) unless indicated otherwise. COVID-19: coronavirus disease 2019; ICU: intensive care unit. [#]: vaccinated by end of follow-up n=77 355.[¶]: proportion of non-missing; [+]: missing data on education for 1128 (1.3%) for the COPD population; [§]: missing data on smoking for 9176 (10.5%) for the COPD population.

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TABLE 2 Comorbidities and clinical characteristics on 1 January 2020 of a population-based cohort of COPD patients (⩾40 years old) in Sweden, and of individuals with four different COVID-19 outcome events that occurred during unvaccinated and vaccinated follow-up time from 1 January 2020 to 30 November 2021 in that cohort

	Total COPD cohort[#]	COPD patients with COVID-19 outcomes during vaccinated and unvaccinated follow-up time							
		Infected		Hospitalised		ICU admitted		Death	
		Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Patients n	87 472	6068	703	2649	248	221	12	803	79
Comorbidities									
Overall cardiovascular disease	43 583 (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	31 323 (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	10 549 (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 apnoea 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	13 456 (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[¶,+]									
Group A	12 759 (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	26 224 (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	10 635 (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[¶,§,f]									
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)	33 907 (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)	13 129 (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	27 073 (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	60 399 (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	13 035 (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	38 020 (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	17 673 (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	11 125 (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)

Continued

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TABLE 2 Continued

	Total COPD cohort[#]	COPD patients with COVID-19 outcomes during vaccinated and unvaccinated follow-up time							
		Infected		Hospitalised		ICU admitted		Death	
		Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Vaccinated
Body mass index kg·m^{-2}[¶,##]									
Mean±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)	27 415 (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)	26 535 (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)	20 408 (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)

Data are presented as n (%) unless indicated otherwise. COVID-19: coronavirus disease 2019; ICU: intensive care unit; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; CAT: chronic obstructive pulmonary disease assessment test; mMRC: modified Medical Research Council dyspnoea scale; BMI: body mass index. [#]: vaccinated by end of follow-up n=77 355; [¶]: proportions presented as per cent of non-missing; [+]: missing data=34 072 (39.0%) of the COPD population cohort; [§]: post-bronchodilator FEV_1 values were used but if missing, pre-bronchodilator FEV_1 values were used; [f]: missing data=28 171 (32.2%) of the COPD population cohort; [##]: missing data=9487 (10.8%) of the COPD population cohort.

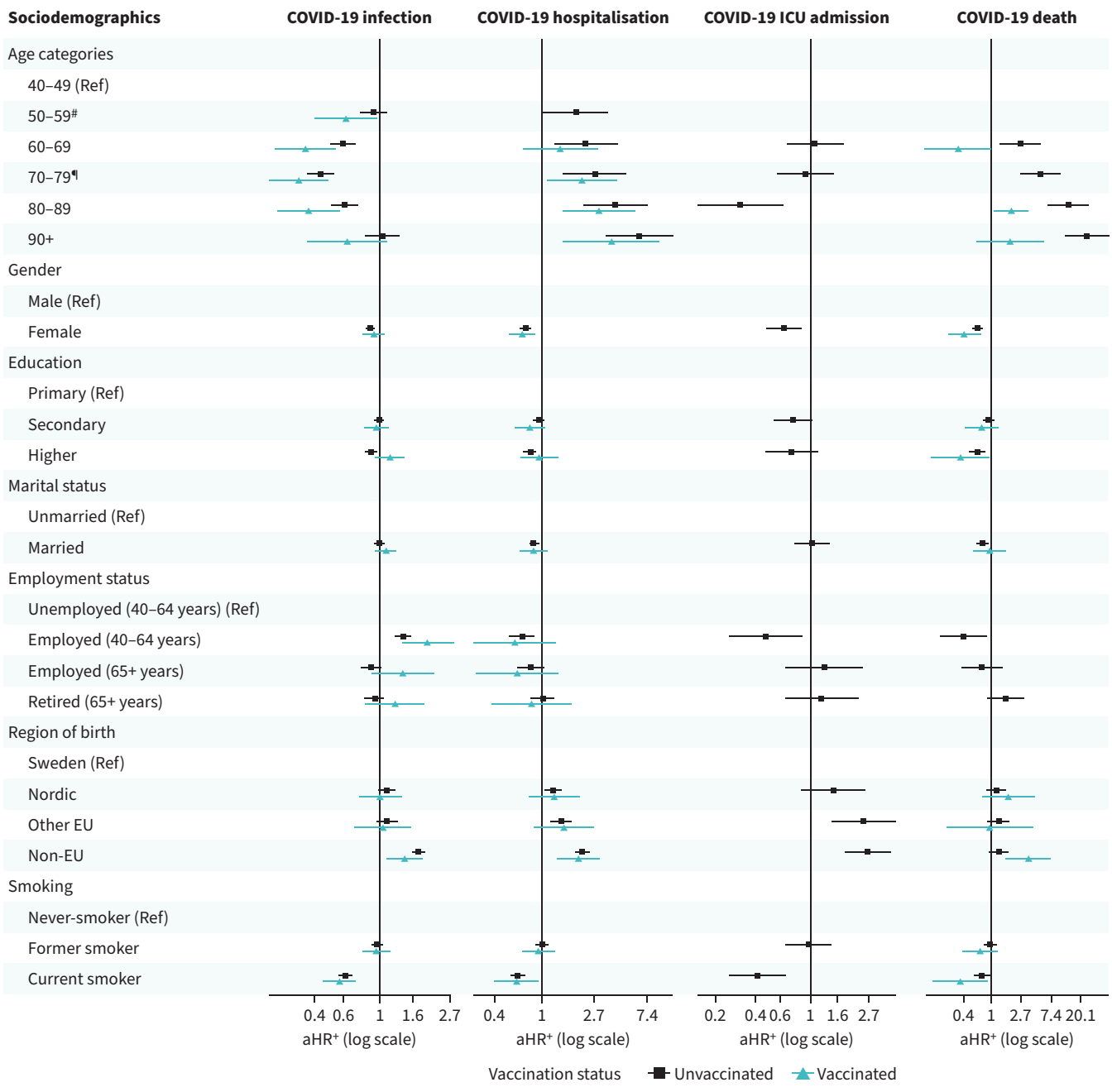

FIGURE 2 Adjusted hazard ratios with 95% confidence intervals for associations between sociodemographic factors and four COVID-19 outcomes (infection, hospitalisation, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 January 2020 to 30 November 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; aHR: 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 hospitalised vaccinated is age 40–59 years; +: adjusted for age, sex, diabetes, hypertension, body mass index and smoking.

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

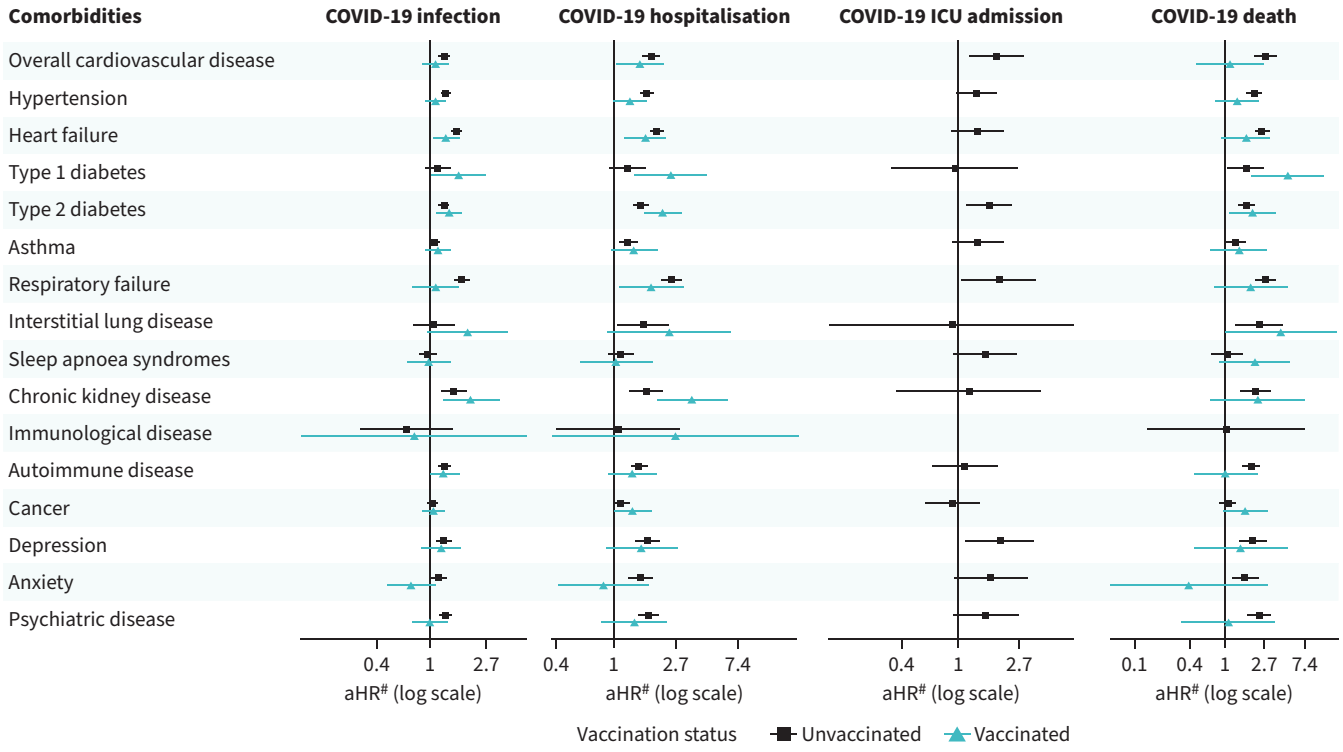

FIGURE 3 Adjusted hazard ratios with 95% confidence intervals for associations between comorbidities and four COVID-19 outcomes (infection, hospitalisation, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 January 2020 to 30 November 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; aHR: adjusted hazard ratio; ICU: intensive care unit. #: adjusted for age, sex, diabetes, hypertension, body mass index and smoking.

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, supplementary 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 and 5). Conversely, the magnitude of HRs for other factors, notably many prescribed medications, *e.g.*, inhaled corticosteroids, was somewhat stronger in the vaccinated, although 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 ACE2 receptor [23]. Furthermore, sex differences in immune responses may be

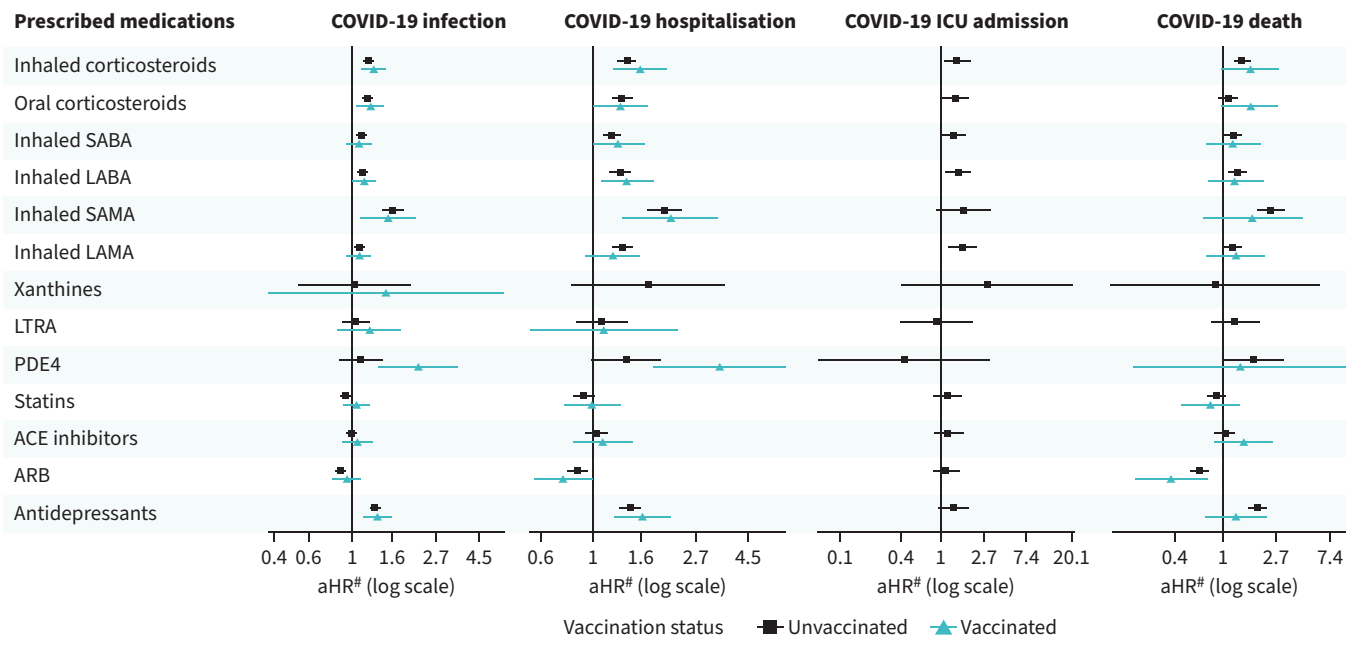

FIGURE 4 Adjusted hazard ratios with 95% confidence intervals for associations between prescribed medications and four COVID-19 outcomes (infection, hospitalisation, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 January 2020 to 30 November 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; aHR: adjusted hazard ratio; ICU: intensive care unit; ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; SABA: short-acting bronchodilator agonist; LABA: long-acting bronchodilator agonist; SAMA: short-acting muscarinic antagonists; LAMA: long-acting muscarinic antagonists; LTRA: leukotriene receptor antagonists; PDE4: phosphodiesterase-4 inhibitors. #: adjusted for age, sex, diabetes, hypertension, body mass index and smoking.

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 hospitalisation 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 hospitalisation [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 hospitalisation 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 hospitalisation and mortality. Our results demonstrate that among COPD patients, being underweight is associated with an increased risk of COVID-19 infection, hospitalisation 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.* hospitalisation, 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 hospitalisation.

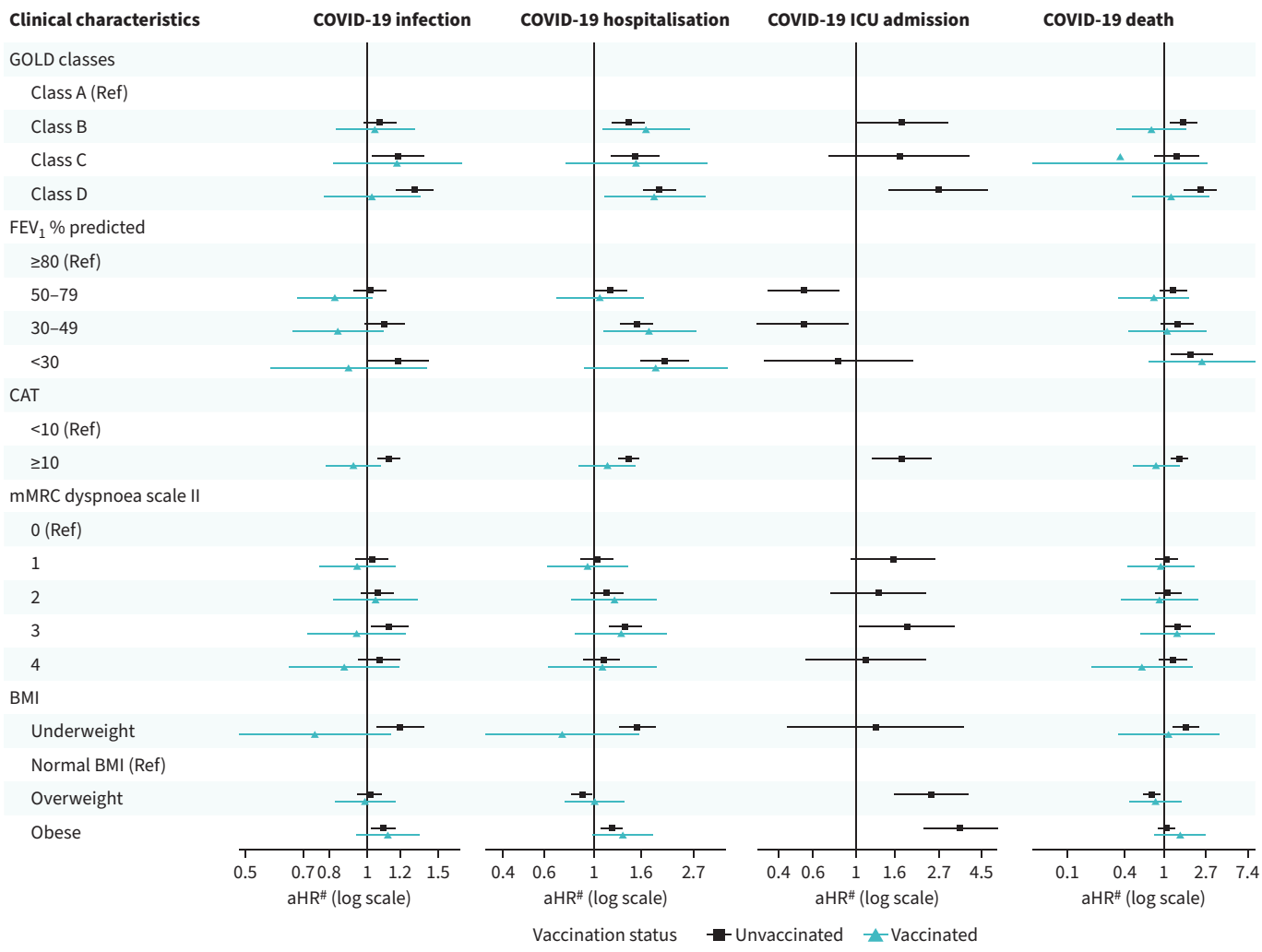

FIGURE 5 Adjusted hazard ratios with 95% confidence intervals for associations between clinical characteristics and four COVID-19 outcomes (infection, hospitalisation, intensive care unit (ICU) admission and death), by vaccination status, in a population-based COPD cohort in Sweden from 1 January 2020 to 30 November 2021. Note: hazard ratios for ICU admissions during the vaccinated follow-up period not estimated due to the small case numbers. Reduced sample sizes for GOLD and FEV_1 due to missing data – refer to supplementary Table E4 and E7. COVID-19: coronavirus disease 2019; aHR: adjusted hazard ratio; ICU: intensive care unit; Ref.: reference value; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV_1: forced expiratory volume in 1 s; CAT: chronic obstructive pulmonary disease assessment test; mMRC: modified Medical Research Council dyspnoea scale; BMI: body mass index. #: adjusted for age, sex, diabetes, hypertension, body mass index and smoking.

Commonly prescribed inhalation therapy for COPD was mostly associated with increased risk, as has been described [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 (hospitalisation 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, hospitalisations 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, hospitalisation 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 four 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 individualised care to reduce their COVID-19 risk.

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Conflict of interest: L.E.G.W. Vanfleteren has received grants and personal fees from AstraZeneca, and personal fees from GSK, Novartis, Boehringer Ingelheim, Menarini, Resmed, Chiesi, AGA Linde, Zambon and Pulmonx. S. Franzén is an employee of AstraZeneca as of October 2021 but the work in this paper relates to the period prior to this.

C. Stridsman has received personal fees from AstraZeneca, Boehringer Ingelheim and Novartis for lectures at sponsored meetings. F. Nyberg was an employee of AstraZeneca until 2019 and holds some AstraZeneca shares. B.K. Kirui, A. Santosa and H. Li have nothing to disclose.

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