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Associations of statin use with 30-day adverse outcomes among 4,801,406 Veterans with and without SARS-CoV-2

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ABSTRACT

Objective: To estimate associations of statin use with hospitalization, intensive care unit (ICU) admission, and mortality at 30 days among individuals with and without a positive test for SARS-CoV-2

Design: Retrospective cohort study

Setting: U.S. Veterans Health Administration (VHA)

Participants: All Veterans receiving VHA health care with ≥1 positive nasal swab for SARS-CoV-2 between March 1, 2020 and March 10, 2021 (cases; n=231,154) and a comparator group of controls comprising all Veterans who did not have a positive nasal swab for SARS-CoV-2 but who did have ≥1 clinical lab test performed during the same time period (n=4,570,252).

Main outcomes: Associations of (1) Any statin use, (2) use of specific statins, or (3) low-/moderate- vs. high-intensity statin use at the time of positive nasal swab for SARS-CoV-2 (cases) or result of clinical lab test (controls) assessed from pharmacy records with hospitalization, ICU admission, and death at 30 days.

Results: Among individuals who tested positive for SARS-CoV-2, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]) but not with hospitalization or ICU admission. Over the same time period, associations were significantly stronger among individuals without a positive test for SARS-CoV-2: hospitalization OR 0.79 (95%CI 0.77–0.80), ICU admission OR 0.86 (95%CI 0.81–0.90), and death 0.60 (95%CI 0.58–0.62), p for interaction all <0.001. Among SARS-CoV-2–positive individuals, associations were similar comparing use of specific statins to no statin. Compared to low-/moderate-intensity statin use, high-intensity statin use was not associated with lower odds of ICU admission or death.

Conclusions: Associations of statin use with lower adverse 30-day outcomes are weaker among individuals who tested positive for SARS-CoV-2 compared to individuals without a positive test, indicating that statins do not exert SARS-CoV-2–specific effects.

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SUMMARY BOXES

What is already known on the topic:

-Statin use at diagnosis is associated with lower risk of hospitalization, mortality in many observational studies conducted among individuals with COVID-19.

-Whether these associations are similar in individuals with and without COVID-19 is unknown

What this study adds:

-In this observational study among 231,154 Veterans with a positive nasal swab for SARS-CoV-2 and a negative control population of 4,570,252 Veterans without a positive test for SARS-CoV-2, statin use was associated with lower odds of adverse 30-day outcomes in both groups, but associations of statin use with lower 30-day outcomes were substantially weaker among SARS-CoV-2–positive individuals compared to individuals without a positive test.

-Statins may not exert SARS-CoV-2–specific effects. Existing evidence suggesting a protective association of statin use with adverse outcomes after COVID-19 may be an artifact of bias, likely due to residual confounding.

Strengths and limitations of this study

- Large, well characterized national (U.S.) sample
- First study to formally assess and compare statin effects seen in SARS-CoV-2 infection using a negative control
- Observational design cannot exclude the possibility of residual confounding
- Did not capture hospitalizations or diagnoses occurring outside VHA

INTRODUCTION

New cases of COVID-19/SARS-CoV-2 infection continue to occur at high rates in the United States and worldwide with few treatments available to decrease mortality. Statin use at the time of COVID-19 diagnosis has been associated with a lower risk of short-term mortality in observational studies[1] and systematic reviews[2], and may have promise for this purpose. However, preliminary findings from a randomized placebo-controlled trial of patients admitted to the ICU did not show a protective effect of atorvastatin 20 mg/day on 30-day mortality after COVID-19 diagnosis, among patients not taking statins prior to admission[3]. These paradoxical findings may reflect the presence of residual confounding in observational studies. In addition, effects of statins on mortality after COVID-19 may differ across populations, for example, among individuals with or without cardiovascular disease (CVD), or specific to certain statins but not all medications in this class. Therefore, observational studies with comprehensive strategies to reduce bias from unmeasured confounding and examine associations by comorbidities and statin type are needed to improve estimates of the potential causal effect of statin use at diagnosis on mortality after COVID-19.

To address these gaps, we used national data from the Veterans Health Administration (VHA) to quantify the independent association of statin use at diagnosis with adverse outcomes from COVID-19 at 30 days, including hospitalization, intensive-care unit (ICU) admission, and mortality. We used the following strategies to mitigate or estimate bias: 1) directed-acyclic graphs to guide the choice of potential confounders; 2) comparison of associations among SARS-CoV-2 infected individuals (n=231,154) with associations among an uninfected comparator sample (n=4,570,252); and 3) a dose-response analysis comparing low- or moderate-intensity statin use to high-intensity use. In additional analyses, we investigated associations of individual statins with 30-day outcomes after COVID-19 and evaluated the magnitude of the statin-mortality association in strata of sex, age, race, BMI, clinical comorbidities, and C-reactive protein (CRP) level prior to diagnosis.

METHODS

Study setting and population

The Veterans Health Administration (VHA)—the largest integrated healthcare system in the United States—provides care to more than 7 million Veterans at 170 medical centers and 1,074 outpatient sites[4]. We used

data from the Corporate Data Warehouse (CDW), a data repository derived from VHA's integrated electronic medical record, including a COVID-19 Shared Data Resource, which contains analytic variables for all enrollees tested for SARS-CoV-2[5]. The study was approved by the institutional review board at VA Puget Sound Health Care System. The requirement for informed consent was waived.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Selection of the SARS-CoV-2–positive cohort

We identified all enrollees with one or more positive nasal swabs for SARS-CoV-2 between March 1, 2020, and March 10, 2021. The index date was defined as the date the first positive test was performed. Most tests were performed in VA laboratories using US Food and Drug Administration (FDA)–approved RealTime (Abbott Laboratories) or Xpert-Xpress (Cepheid) SARS-CoV-2 assays. A small number were sent to outside laboratories.

Selection of the SARS-CoV-2–negative cohort

Individuals without a positive nasal swab for SARS-CoV-2 and with any clinical lab test available in the medical record between March 1, 2020, and March 31, 2021, were chosen as a comparison group. A negative nasal swab for SARS-CoV-2 was not required for inclusion. Participants without a positive nasal swab for SARS-CoV-2 were assigned an index month during the study period for which they had a lab result, and a random index date during the index month which was used as the start of follow-up.

Exposure

Statin use was defined as receipt of a statin prescription with a fill date prior to the index date and a quantity prescribed that would extend past the index date. Statin intensity was defined as low, moderate, or high using definitions from the American Heart Association/American College of Cardiology guidelines on management of

cholesterol[6]. Prescribing data were available for the following specific statins: Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin.

Covariates

We collected data on age, sex, race/ethnicity, VHA facility location, and urban, rural, or highly rural residence using a validated classification scheme that has been previously described[7]. Body mass index (BMI) was defined as weight in kg divided by (height in meters)^2. Smoking status was classified as current, former, or never based on VHA health factors data. If no smoking code was entered, the participant was classified as never smoked. At-risk drinking was defined using a score ≥3 for men and ≥4 for women on the Alcohol Use Disorders Identification Test consumption questions (AUDIT-C)[8]. Comorbidities (hypertension (HTN), CVD, and heart failure) were identified using ICD-9-CM and -10 codes entered after October 1, 1999, the date when VHA began using a universal electronic health record[9]. We defined chronic kidney disease (CKD) by categories of estimated glomerular filtration rate[10] using the most recent creatinine at least 3 days, but not more than 1 year, before the index date. For individuals with data available on CRP at least 14 days but not more than six months before the index date (n=27,630), we dichotomized CRP values as normal or elevated based on cut points provided for each assay at the testing site because a variety of assays for these biomarkers are used across the VA system. We also controlled for prior statin use to approximate a comparison of incident users and non-users. We defined prior statin use as receipt of a statin prescription with a fill date that included the time period six months prior to the index date.

Outcomes

We collected data on all hospitalizations, ICU admissions, and deaths occurring through March 10, 2021. Deaths were verified by official sources including VHA Patient Treatment File, the Beneficiary Identification Records Locator Subsystem (BIRLS), and VA/CMS Medicare Vital Status File; Social Security Administration (SSA) Death Master File; death certificates, and VHA National Cemetery Administration[11].

Statistical analyses

We summarized baseline characteristics for SARS-CoV-2 infected and uninfected participants, stratified by statin use at the index date. We used multiple imputation with 10 sets of imputations for analyses that included BMI or CKD due to approximately 20% missing values for each of these variables. We used DAGitty[12] to generate a directed acyclic graph (DAG) to assist in variable selection. We fit separate logistic regression models for individuals with and without a positive swab for SARS-CoV-2, testing the association of statin use at index date with occurrence of hospitalization, ICU admission, and death, adjusting for the minimal sufficient covariate set to estimate the total effect of statin use according to our DAG (statin use ≥ six months prior to diagnosis, sex, age, race/ethnicity, BMI, tobacco use, facility location, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder) separately. In combined models, we tested for the presence of multiplicative first-order interactions to determine whether the association between statins and odds of hospitalization, ICU admission, and death at 30 days differed between persons with and without a positive swab for SARS-CoV-2. In a sensitivity analysis, we examined associations of statin use at diagnosis with occurrence of hospitalization, ICU admission, and death in models that were not adjusted for statin use six months prior to diagnosis.

Among individuals with a positive swab for SARS-CoV-2, we fit logistic regression models examining associations of specific statins compared to no statin use with outcomes adjusted for sex, age, race/ethnicity, BMI, tobacco use, facility location, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder, as well as models comparing low-intensity to moderate- or high-intensity statin use. We evaluated the magnitude of the statin-mortality association in strata of sex, age, race, BMI, clinical comorbidities, and prior CRP concentration and tested for first-order multiplicative interactions by using interaction terms in combined models.

Role of the funding source

The analysis was funded by VA Clinical Science Research & Development, which had no role in its design, conduct, analysis, or reporting.

RESULTS

SARS-CoV-2 infected participants were 60.9 years old (±16.5) on average, and 10% percent (n= 23,974) were female. Thirty percent (69,263) had an active statin prescription at enrollment. During the 30 days after diagnosis, 14% (32,490) of SARS-CoV-2 infected participants were hospitalized, 3% (6,140) were admitted to the ICU, and 5% (12,111) died. SARS-COV-2 uninfected participants were 61.6 years old (±16.7) on average, and 13% (577,718) were female. Thirty percent (1,389,364) had an active statin prescription at enrollment. During the 30 days after the index date, 2% (91,604) were hospitalized, 0.2% (9,298) were admitted to the ICU, and 0.4% died (n=19,298) (**Table 1**).

Among SARS-COV-2 positive individuals, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]), but not with hospitalization or ICU admission. Among SARS-COV-2 negative individuals, statin use was associated with lower odds of hospitalization (OR 0.79 [95%CI 0.77–0.80]), ICU admission (OR 0.86 [95%CI 0.81–0.90]), and death at 30 days (OR 0.60 [95%CI 0.58–0.62]). (**Table 2a**). Compared to persons with SARS-CoV-2 infection, OR for all three outcomes were significantly lower in persons without SARS-CoV-2 infection, as reflected by p<0.001 for the interaction term of SARS-CoV-2*statin use in all three models. Among individuals with and without SARS-CoV-2 infection, adjustment for receipt of statin six months prior to baseline attenuated the magnitude of the association of statin use at diagnosis with all outcomes (**Fig. 1, Table 2b**). Among persons with SARS-CoV-2 infection, associations with outcomes were similar for individual statins (**Table 3**). Compared to low-/moderate-intensity, high-intensity statin use was associated with higher odds of hospitalization (1.06 [95%CI 1.01–1.10]) but not with ICU admission or death (**Table 4**). Among persons with SARS-CoV-2 infection, associations of statin use with hospitalization differed across strata of sex, age, race (Black vs. non-Black), and eGFR (e.g., OR for hospitalization in Black participants 0.98 [95%CI 0.92–1.03], OR for hospitalization in non-Black participants 0.92 [95%CI 0.89–0.95], p for interaction = 0.022). Associations of statin use with ICU admission differed across strata of sex and ethnicity (Latinx vs. not Latinx) (e.g., OR for ICU admission in Latinx participants 0.77 [95%CI 0.62–0.95], OR for ICU admissioni in non-Latinx participants 0.94 [95%CI 0.89–1.00], p for interaction = 0.044). Associations of statin use with mortality differed across strata of age, race/ethnicity (white vs. non-white and Black vs. non-Black), and BMI (e.g., OR for mortality in Black participants 0.83 [95%CI 0.76–0.92], OR for mortality in non-

Black participants 0.77 [95%CI 0.74–0.81], p for interaction = 0.006). Associations did not differ across strata of prevalent diabetes, hypertension, or CVD (**Supplementary Fig. 1–3**).

CONCLUSIONS

In this cohort of U.S. Veterans with (n=231,154) and without (n=4,570,252) a positive respiratory swab for SARS-CoV-2, statin use was independently associated with lower odds of death at 30 days compared to no statin use, but this association over a similar time period was significantly stronger among Veterans without a positive respiratory swab for SARS-CoV-2. Among individuals with and without a positive respiratory swab for SARS-CoV-2, adjusting for prior statin use attenuated the association of statin use with all outcomes; however, in every case the magnitude of the association remained substantially greater among individuals without a diagnosis of COVID-19. Associations were similar for specific statins, and receipt of high-potency statin was not associated with lower odds of any outcome compared to moderate and low potency, except for a small difference in the odds of hospitalization. Associations were not significantly different in strata of prevalent diabetes, hypertension, or cardiovascular disease. Furthermore, the lack of a gradient of effect with statin potency also does not support a potential causal benefit of statin use. Taken together, these results suggest that while statin use is associated with lower mortality among individuals with a positive swab for SARS-CoV-2, the benefit is actually smaller for than it is for those without evidence of SARS-CoV-2 infection and does not support a possible anti-COVID effect of statin treatment.

Use of negative controls is an important technique to detect confounding or other sources of bias in epidemiological studies[13] that has gone underutilized in the era of COVID-19 research. An instructive example is the association of pneumonia or influenza vaccination with all-cause mortality seen in elderly individuals despite rigorous control for confounding by factors related to overall health status[14]. Using negative controls, Jackson et al. examined the association of vaccination with a negative control outcome: mortality prior to influenza season[15]. They found a stronger association with mortality during the period prior to influenza season compared to during or after, a biologically implausible result that was attributed by the authors to preferential receipt of vaccines by healthy individuals. This source of bias is now recognized in studies of this topic[16]. While

the use of a negative control outcome is not precisely analogous to the methods used in the current study, the example can inform interpretation of the current findings.

Several recent systematic reviews and meta-analyses have examined the association of prior statin use with short-term outcomes after COVID-19[2,17-22]. Many of these reported an inverse association of statin use at diagnosis with mortality. For example, statin use was associated with a lower hazard of death (HR 0.72 [95%CI 0.69–0.75]) in a large population-based study of English patients with diabetes independent of age and co-morbid CVD[23]. In a recent nationwide U.S. study of hospitalized individuals (n=10,541), outpatient statin, either alone or with blood pressure-lowering medications, was associated with lower odds of in-hospital death (OR 0.59 [95%CI 0.50–0.69]). The magnitude of the association of statin use at diagnosis with mortality reported in these and other analyses is quite similar to the OR in the current report among individuals with COVID-19 in models that were not adjusted for prior statin use (OR for death at 30 days 0.78 [95% CI 0.75–0.82]), likely reflecting similar strategies for confounder adjustment. The lower COVID-19 mortality risk among statin users, however, is not a universal finding. In fact, among French hospitalized patients with diabetes, statin use at diagnosis was associated with higher odds of death at 28 days (OR 1.46 [95% CI 1.08–1.95])[24]. Reasons for these disparate findings are unclear but may be due in part to differences in timing, as early in the pandemic, treatments such as dexamethasone and remdesivir were not widely used. Consistent with this, in the French cohort mortality was about 21% at 28 days, considerably higher than our overall 30-day mortality rate of about 7%. No prior study to our knowledge has examined outcomes following statin use comparing SARS-CoV-2 infected and uninfected statin users.

We noted several differences in outcomes associated with statin use by certain characteristics such as sex, age, and race (Supplementary Fig. 1-3). As our main analysis did not show evidence of a lower risk of outcomes associated with statin use confined to COVID-19 infected participants, these interactions likely reflect associations independent of presence of this infection and therefore reflecting effect modification between statin use, stratum variables, and outcomes of interest.

Our study has several strengths, most importantly a large, well characterized national sample. To our knowledge, this is the largest observational study of prior statin use and adverse outcomes from SARS-CoV-2 in the United States (n=4,801,406) as well as the first to formally assess and compare statin effects seen in SARS-CoV-2 infection using a negative control (non-infected statin users). Second, we used several methods designed to mitigate or quantify bias due to unmeasured confounding. We: 1) constructed a DAG to estimate the minimal sufficient adjustment set to estimate the total effect of statin use on 30-day outcomes; 2) compared associations in SARS-CoV-2 infected individuals and an uninfected comparator sample; and 3) conducted dose-response analyses using statin potency to reflect dose. In addition, most VHA enrollees receive medical care and medications without cost, which likely decreases the contribution of unmeasured financial factors to differences in the quality of care received and most importantly to receipt of statin medications. Our results should be considered within the context of several limitations. The VHA population is generally older, with lower income and socioeconomic status [25] than the U.S. population as a whole, and our findings may not be generalizable to non-VHA populations. Additionally, the proportion of women was low (13%); however, although women comprised only a small proportion of the sample, the number of female participants (n=601,765) is adequate for robust statistical inference. We were also unable to capture hospitalizations or some outpatient prescriptions that occurred outside VHA, although VHA users are asked to provide notification within 72 hours of an outside hospital admission, and when possible are transferred to a VHA facility, which would then be captured in the VHA electronic health record. Finally, not all individuals in the comparator group were tested for SARS-CoV-2, so we were unable to exclude the possibility that some participants were misclassified. We elected to include individuals without SARS-CoV-2 tests because individuals with indications for SARS-CoV-2 testing may represent a particular (and sicker) population than the general group of VA enrollees as a whole. Further, based on the current results, inclusion of individuals with undiagnosed COVID-19 in the SARS-CoV-2–negative comparator group would be expected to attenuate observed associations of statin use with adverse outcomes. It is unlikely that exclusion of participants with undiagnosed COVID-19 from the comparator group would have resulted in a reduction in the observed negative association between statin use and mortality, as this would have required an opposite association to be present between undiagnosed COVID-19 infection and mortality, a possibility for which there is little reason or evidence to support.

In conclusion, statin use is associated with lower odds of 30-day mortality both among U.S. Veterans with or without a positive respiratory swab for SARS-CoV-2 indicating that statins may not exert COVID-19-specific beneficial effects.

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COMPETING INTERESTS. There are no relevant conflicts of interest to disclose.

DATA AVAILABILITY. Access to VA electronic health records data is limited to researchers with active, VA appointments and an IRB-approved protocol.

CONTRIBUTORSHIP. PLW conceived the project, designed the overall research plan, and wrote the first draft of the manuscript. EL analyzed the data and reviewed/edited the manuscript, LB contributed to the conception of the work and reviewed/edited the manuscript, LTP contributed to the conception of the work and reviewed/edited the manuscript, AK contributed to design/interpretation of the analyses and reviewed/edited the manuscript, AP contributed to the design/interpretation of the analyses and reviewed/edited the manuscript. SEK contributed to the conception of the work and reviewed/edited the manuscript. GD contributed to the design/interpretation of the analyses and reviewed/edited the manuscript. EJB conceived the project, designed the overall research plan, and reviewed/edited the manuscript.

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ETHICS STATEMENT. The study was approved by the institutional review board at VA Puget Sound Health Care System, Seattle, WA, USA (#01897). The requirement for informed consent was waived.

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Table 1. Characteristics of VHA Veterans with and without a positive respiratory swab for SARS-CoV-2 (March 1, 2020–March 10, 2021), stratified by presence of an active statin prescription at enrollment

	Overall		No positive respiratory swab for SARS-CoV-2				≥1 positive respiratory swab for SARS-CoV-2			
	n=4,801,406		No statin prescription n=3,180,888		Active statin prescription n=1,389,364		No statin prescription n=161,891		Active statin prescription n=69,263	
Age, years	61.6	±16.7	58.3	±17.7	69.3	±10.8	57.8	±17.5	68.0	±11.4
Age category, years										
19-39	661,777	14%	613,885	19%	15,272	1%	31,645	20%	975	1%
40-49	482,871	10%	402,201	13%	54,467	4%	22,718	14%	3,485	5%
50-59	728,340	15%	516,328	16%	172,006	12%	29,099	18%	10,907	16%
60-69	993,105	21%	600,530	19%	346,361	25%	28,785	18%	17,429	25%
70-79	1,408,065	29%	735,949	23%	610,855	44%	33,303	21%	27,958	40%
80+	525,548	11%	311,010	10%	189,825	14%	16,204	10%	8,509	12%
Sex at birth, female	601,692	13%	509,443	16%	68,275	5%	20,598	13%	3,376	5%
Race/ethnicity										
White	3,335,105	69%	2,122,989	67%	1,055,742	76%	106,448	66%	49,926	72%
Black	860,829	18%	582,091	18%	226,384	16%	38,080	24%	14,274	21%
Hispanic	333,593	7%	230,848	7%	79,866	6%	17,770	11%	5,109	7%
Other	542,562	11%	430,377	14%	94,575	7%	13,410	8%	4,200	6%
Body-mass index, kg/m²	30.2	±6.09	29.8	±6.04	30.8	±6.06	30.9	±6.35	31.9	±6.26
Body-mass index category, kg/m²										
<18.5	28,116	1%	20,717	1%	6,230	1%	951	1%	218	0%
18.5-24.9	553,988	17%	379,204	20%	152,657	14%	16,249	15%	5,878	11%
25-29.9	1,107,238	35%	687,781	36%	367,799	34%	34,949	32%	16,709	30%
30-34.9	869,628	27%	507,893	26%	313,277	29%	30,944	29%	17,514	32%
35-39.9	399,754	13%	224,651	12%	149,833	14%	15,734	15%	9,536	17%
≥ 40	208,950	7%	113,491	6%	80,708	8%	9,077	8%	5,674	10%
Tobacco use										
Never	1,747,387	36%	1,338,452	42%	328,440	24%	62,782	39%	17,713	26%
Former	1,729,275	36%	984,318	31%	651,438	47%	58,321	36%	35,198	51%
Current	1,323,044	28%	857,133	27%	408,908	29%	40,651	25%	16,352	24%
Urban/rural/highly rural ZIP code										
Highly rural	57,047	1%	34,211	1%	20,620	1%	1,360	1%	856	1%
Rural	1,561,076	33%	975,607	31%	518,394	37%	43,690	27%	23,385	34%
Urban	3,172,176	66%	2,163,063	68%	847,474	61%	116,643	72%	44,996	65%
Unknown	9,407	0%	7,022	0%	2,298	0%	61	0%	26	0%
Estimated glomerular filtration rate, ml/min/1.73 m²										
≥ 90	938,310	27%	654,399	31%	235,893	20%	36,230	32%	11,788	19%
60-89	1,718,393	49%	1,034,287	49%	599,357	50%	54,598	48%	30,151	48%
45-59	520,635	15%	268,392	13%	226,556	19%	13,799	12%	11,888	19%
30-44	212,116	6%	100,776	5%	100,175	8%	5,626	5%	5,539	9%
15-29	58,464	2%	27,223	1%	27,527	2%	1,906	2%	1,808	3%
<15 or dialysis	25,765	1%	12,803	1%	10,449	1%	1,503	1%	1,010	2%
Active statin prescription six months prior to enrollment	1,375,009	29%	259,070	8%	1,046,850	75%	17,020	11%	52,069	75%

Table 1 CONTINUED. Characteristics of VHA Veterans with and without a positive respiratory swab for SARS-CoV-2 (March 1, 2020–March 10, 2021), stratified by presence of an active statin prescription at enrollment

Diabetes	1,482,197	31%	679,909	21%	716,920	52%	44,364	27%	41,004	59%
Hypertension	2,874,378	60%	1,551,529	49%	1,176,398	85%	86,382	53%	60,069	87%
Cardiovascular disease	1,749,197	36%	857,912	27%	794,940	57%	53,635	33%	42,710	62%
Heart failure	352,710	7%	144,971	5%	183,128	13%	12,388	8%	12,223	18%
Alcohol use disorder	909,010	19%	629,005	20%	238,333	17%	31,212	19%	10,460	15%
Statin prescribed										
None	3,341,657	70%	3,179,903	100%	0	0%	161,754	100%	0	0%
Atorvastatin	872,981	18%			829,795	60%			43,186	62%
Fluvastatin	364	<1%			348	0%			16	0%
Lovastatin	15,375	<1%			14,751	1%			624	1%
Pitavastatin	801	<1%			748	<1%			53	<1%
Pravastatin	123,779	3%			118,039	8%			5,740	8%
Rosuvastatin	173,943	4%			165,066	12%			8,877	13%
Simvastatin	270,806	6%			260,039	19%			10,767	16%
High-potency statin (vs. low- or moderate-potency)*	616,824	42%	0	<1%	585,224	42%	0	<1%	31,600	46%
Mean hsCRP in the prior six months, mg/L**	17.3	±136	16.4	±151	18.2	±120	19.9	±49.6	21.0	±52.9
hsCRP in the prior six months ≥2 mg/L**	390,796	41%	217,408	40%	145,787	42%	17,407	44%	10,194	45%
Mean hsCRP at or after the index date, mg/L***	29.3	±54.1	22.2	±46.6	25.6	±50.8	57.8	±70.8	65.2	±71.1
hsCRP at or after the index date ≤2 mg/L***	125,178	52%	61,501	46%	34,630	49%	18,260	75%	10,787	79%
OUTCOMES										
Hospital admission within 30 days	124,094	3%	61,651	2%	29,953	2%	20,280	13%	12,210	18%
ICU admission within 30 days	15,438	<1%	5,710	<1%	3,588	<1%	3,754	2%	2,386	3%
Death w/in 30 days	31,409	1%	13,074	<1%	6,224	<1%	7,815	5%	4,296	6%

Data are presented as mean ± standard deviation (SD) for continuous variables and n (%) for categorical variables

p-values for global differences in participant characteristics across categories of COVID diagnosis and prior statin use all <0.001

* based on estimated % LDL-c reduction

** up to 14 days prior to index date (Overall n=958,343)

*** Overall n=224,930

Table 2a. Odds ratios from logistic regression models testing the association of active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2, including adjustment for prior statin use

	No positive swab, n=4,568,689						≥1 positive swab, n=231,017					
	Hospital admission		ICU admission		Death		Hospital admission		ICU admission		Death	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Active statin prescription at enrollment	0.79	0.77 — 0.80	0.98	0.95 — 1.01	0.86	0.81 — 0.90	0.94	0.88 — 1.01	0.60	0.58 — 0.62	0.81	0.77 — 0.85
Statin prescription six months prior to enrollment	0.91	0.89 — 0.93	0.93	0.90 — 0.96	0.88	0.83 — 0.93	0.97	0.91 — 1.04	0.93	0.90 — 0.97	0.94	0.89 — 0.99
Sex at birth, female	0.73	0.71 — 0.75	0.75	0.71 — 0.79	0.73	0.67 — 0.80	0.74	0.65 — 0.84	0.63	0.58 — 0.69	0.56	0.50 — 0.64
Age category, years												
19-39	1.16	1.12 — 1.19	0.61	0.57 — 0.65	0.61	0.54 — 0.69	0.60	0.51 — 0.71	0.26	0.22 — 0.30	0.15	0.11 — 0.21
40-49	0.97	0.94 — 1.01	0.75	0.70 — 0.80	0.81	0.73 — 0.91	0.68	0.59 — 0.79	0.46	0.40 — 0.54	0.38	0.30 — 0.48
50-59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-69	1.01	0.99 — 1.03	1.29	1.23 — 1.34	1.16	1.08 — 1.25	1.32	1.21 — 1.46	1.95	1.81 — 2.10	2.86	2.55 — 3.20
70-79	0.81	0.79 — 0.83	1.43	1.37 — 1.49	1.00	0.92 — 1.08	1.49	1.36 — 1.64	2.60	2.41 — 2.79	5.93	5.32 — 6.61
≥80	0.96	0.93 — 0.99	1.81	1.71 — 1.91	0.95	0.87 — 1.04	1.62	1.45 — 1.82	5.06	4.68 — 5.46	13.86	12.37 — 15.53
White (vs not white)	1.21	1.14 — 1.28	0.88	0.81 — 0.97	1.23	1.02 — 1.49	0.74	0.61 — 0.91	1.10	0.95 — 1.27	0.87	0.74 — 1.04
Black vs(not Black)	1.49	1.40 — 1.58	1.36	1.24 — 1.50	1.53	1.26 — 1.85	1.10	0.89 — 1.35	1.05	0.90 — 1.22	0.78	0.66 — 0.94
Hispanic (vs not Hispanic)	1.07	1.04 — 1.10	1.16	1.10 — 1.22	1.23	1.13 — 1.35	1.03	0.92 — 1.15	1.07	0.99 — 1.14	1.13	1.04 — 1.24
Body-mass index category, kg/m²												
<18.5	1.35	1.29 — 1.42	1.14	1.01 — 1.29	1.51	1.31 — 1.73	1.35	1.06 — 1.72	2.48	2.33 — 2.65	1.81	1.59 — 2.07
18.5-24.9	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-29.9	0.75	0.73 — 0.76	0.81	0.78 — 0.85	0.70	0.65 — 0.74	0.89	0.82 — 0.97	0.54	0.52 — 0.56	0.73	0.68 — 0.79
30-34.9	0.67	0.65 — 0.68	0.76	0.73 — 0.80	0.62	0.57 — 0.66	0.88	0.81 — 0.96	0.42	0.40 — 0.44	0.69	0.64 — 0.74
35-39.9	0.63	0.61 — 0.65	0.76	0.72 — 0.80	0.57	0.52 — 0.62	0.85	0.76 — 0.94	0.37	0.35 — 0.40	0.64	0.59 — 0.70
≥40	0.65	0.63 — 0.67	0.87	0.82 — 0.93	0.59	0.53 — 0.65	1.03	0.91 — 1.16	0.43	0.39 — 0.46	0.80	0.72 — 0.88
Tobacco use												
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.23 — 1.28	1.11	1.08 — 1.15	1.12	1.06 — 1.19	1.10	1.02 — 1.17	1.09	1.04 — 1.13	1.18	1.12 — 1.24
Current	2.02	1.98 — 2.06	1.39	1.35 — 1.44	1.76	1.66 — 1.87	1.29	1.20 — 1.39	1.67	1.60 — 1.74	1.24	1.17 — 1.32
Urban/rural/highly rural residence												
Highly rural	0.68	0.64 — 0.73	0.58	0.50 — 0.66	0.98	0.82 — 1.18	0.74	0.54 — 1.00	0.92	0.81 — 1.05	1.16	0.98 — 1.38
Rural	0.74	0.73 — 0.75	0.70	0.68 — 0.72	0.74	0.70 — 0.78	0.88	0.82 — 0.93	0.89	0.87 — 0.92	1.03	0.99 — 1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18 — 0.35	0.27	0.10 — 0.75	0.35	0.13 — 0.94	0.55	0.08 — 3.99	0.80	0.51 — 1.25	1.77	0.73 — 4.30
Diabetes	1.18	1.16 — 1.20	1.30	1.27 — 1.34	1.26	1.21 — 1.32	1.26	1.19 — 1.34	1.41	1.36 — 1.45	1.37	1.31 — 1.43
Hypertension	1.22	1.19 — 1.24	1.30	1.25 — 1.35	1.30	1.22 — 1.39	1.29	1.19 — 1.41	1.09	1.04 — 1.14	0.96	0.90 — 1.02
Cardiovascular disease	2.04	2.01 — 2.08	1.84	1.79 — 1.90	2.69	2.55 — 2.84	2.08	1.95 — 2.23	1.88	1.81 — 1.95	1.24	1.18 — 1.30
Heart failure	2.13	2.09 — 2.16	1.64	1.59 — 1.70	2.34	2.22 — 2.46	1.53	1.43 — 1.63	2.51	2.42 — 2.59	1.31	1.25 — 1.38
Alcohol use disorder	1.12	1.10 — 1.14	0.75	0.72 — 0.78	1.03	0.97 — 1.09	0.86	0.79 — 0.93	0.78	0.75 — 0.82	0.68	0.64 — 0.73
Estimated glomerular filtration rate, ml/min/1.73 m²												
≥ 90	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-89	0.80	0.79 — 0.82	0.90	0.87 — 0.93	0.80	0.76 — 0.85	0.96	0.88 — 1.04	0.60	0.57 — 0.62	1.10	1.02 — 1.18
45-59	0.84	0.81 — 0.86	0.99	0.94 — 1.03	0.84	0.78 — 0.91	1.00	0.91 — 1.10	0.71	0.67 — 0.74	1.44	1.33 — 1.56
30-44	0.93	0.90 — 0.96	1.10	1.04 — 1.16	0.92	0.84 — 1.01	1.14	1.02 — 1.29	0.99	0.93 — 1.05	1.83	1.68 — 1.99
15-29	1.15	1.10 — 1.20	1.31	1.21 — 1.42	1.14	1.01 — 1.29	1.32	1.14 — 1.53	2.07	1.94 — 2.21	2.65	2.36 — 2.97
<15 or dialysis	1.60	1.52 — 1.69	1.46	1.33 — 1.60	1.77	1.56 — 2.00	1.51	1.29 — 1.77	3.07	2.85 — 3.32	2.48	2.16 — 2.85

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location

Table 2b. Odds ratios from logistic regression models testing the association of active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2, without adjustment for prior statin use

	No positive swab, n=4,568,689									≥1 positive swab, n=231,017								
	Hospital admission			ICU admission			Death			Hospital admission			ICU admission			Death		
	OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI	
Active statin prescription at enrollment	0.75	0.74 —	0.76	0.80	0.76 —	0.83	0.58	0.56 —	0.59	0.94	0.91 —	0.96	0.93	0.88 —	0.98	0.78	0.75 —	0.82
Sex at birth, female	0.73	0.71 —	0.75	0.73	0.67 —	0.81	0.63	0.58 —	0.69	0.75	0.71 —	0.79	0.74	0.65 —	0.84	0.57	0.50 —	0.65
Age category, years																		
19-39	1.16	1.13 —	1.20	0.61	0.54 —	0.69	0.26	0.22 —	0.30	0.61	0.58 —	0.66	0.60	0.51 —	0.71	0.15	0.11 —	0.21
40-49	0.98	0.95 —	1.01	0.82	0.73 —	0.92	0.47	0.40 —	0.54	0.75	0.71 —	0.80	0.68	0.59 —	0.79	0.38	0.30 —	0.48
50-59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-69	1.01	0.98 —	1.03	1.16	1.08 —	1.25	1.95	1.81 —	2.10	1.28	1.23 —	1.34	1.32	1.21 —	1.45	2.86	2.55 —	3.20
70-79	0.81	0.79 —	0.83	0.99	0.92 —	1.07	2.59	2.41 —	2.78	1.43	1.36 —	1.49	1.49	1.36 —	1.64	5.92	5.31 —	6.60
≥80	0.96	0.93 —	0.99	0.95	0.87 —	1.04	5.06	4.68 —	5.46	1.81	1.71 —	1.91	1.62	1.45 —	1.82	13.86	12.37 —	15.53
White (vs not white)	1.20	1.14 —	1.28	1.23	1.02 —	1.49	1.10	0.95 —	1.27	0.88	0.81 —	0.97	0.75	0.61 —	0.91	0.87	0.74 —	1.04
Black vs(not Black)	1.49	1.40 —	1.58	1.53	1.26 —	1.86	1.05	0.90 —	1.22	1.37	1.24 —	1.50	1.10	0.89 —	1.35	0.78	0.66 —	0.94
Hispanic (vs not Hispanic)	1.07	1.04 —	1.10	1.23	1.13 —	1.35	1.06	0.99 —	1.14	1.16	1.10 —	1.22	1.03	0.92 —	1.15	1.13	1.04 —	1.24
Body-mass index category, kg/m²																		
<18.5	1.35	1.29 —	1.42	1.51	1.32 —	1.74	2.49	2.33 —	2.65	1.14	1.02 —	1.29	1.35	1.06 —	1.72	1.82	1.59 —	2.07
18.5-24.9	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-29.9	0.75	0.73 —	0.76	0.70	0.65 —	0.74	0.54	0.52 —	0.56	0.81	0.78 —	0.85	0.89	0.82 —	0.97	0.73	0.68 —	0.79
30-34.9	0.67	0.65 —	0.68	0.61	0.57 —	0.66	0.42	0.40 —	0.44	0.76	0.73 —	0.80	0.88	0.81 —	0.96	0.68	0.64 —	0.74
35-39.9	0.63	0.61 —	0.64	0.57	0.52 —	0.62	0.37	0.35 —	0.40	0.76	0.72 —	0.80	0.85	0.76 —	0.94	0.64	0.59 —	0.70
≥40	0.65	0.63 —	0.67	0.58	0.53 —	0.65	0.43	0.39 —	0.46	0.87	0.81 —	0.92	1.03	0.91 —	1.16	0.79	0.72 —	0.88
Tobacco use																		
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.22 —	1.27	1.12	1.05 —	1.19	1.09	1.04 —	1.13	1.11	1.08 —	1.15	1.10	1.02 —	1.17	1.18	1.12 —	1.24
Current	2.02	1.98 —	2.05	1.76	1.66 —	1.87	1.66	1.60 —	1.74	1.39	1.35 —	1.44	1.29	1.20 —	1.39	1.24	1.17 —	1.32
Urban/rural/highly rural residence																		
Highly rural	0.68	0.64 —	0.73	0.98	0.82 —	1.18	0.92	0.81 —	1.05	0.57	0.50 —	0.66	0.74	0.54 —	1.00	1.16	0.98 —	1.38
Rural	0.74	0.73 —	0.75	0.74	0.70 —	0.78	0.89	0.86 —	0.92	0.70	0.68 —	0.72	0.87	0.82 —	0.93	1.03	0.99 —	1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18 —	0.35	0.35	0.13 —	0.94	0.80	0.51 —	1.25	0.27	0.10 —	0.74	0.55	0.08 —	3.98	1.75	0.72 —	4.27
Diabetes	1.17	1.15 —	1.19	1.25	1.20 —	1.31	1.40	1.36 —	1.45	1.30	1.26 —	1.33	1.26	1.19 —	1.33	1.36	1.30 —	1.42
Hypertension	1.21	1.19 —	1.24	1.29	1.21 —	1.38	1.09	1.04 —	1.13	1.30	1.25 —	1.35	1.29	1.18 —	1.41	0.96	0.90 —	1.02
Cardiovascular disease	2.03	2.00 —	2.07	2.67	2.53 —	2.82	1.87	1.80 —	1.94	1.84	1.78 —	1.89	2.08	1.94 —	2.23	1.24	1.18 —	1.30
Heart failure	2.12	2.08 —	2.16	2.33	2.21 —	2.45	2.50	2.41 —	2.59	1.64	1.59 —	1.70	1.53	1.43 —	1.63	1.31	1.25 —	1.38
Alcohol use disorder	1.12	1.10 —	1.14	1.03	0.97 —	1.09	0.78	0.75 —	0.82	0.75	0.73 —	0.78	0.86	0.79 —	0.93	0.68	0.64 —	0.73
Estimated glomerular filtration rate, ml/min/1.73 m²																		
≥ 90	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-89	0.80	0.79 —	0.82	0.80	0.75 —	0.85	0.60	0.57 —	0.62	0.90	0.86 —	0.93	0.96	0.88 —	1.04	1.09	1.02 —	1.18
45-59	0.84	0.81 —	0.86	0.84	0.78 —	0.91	0.71	0.67 —	0.74	0.98	0.94 —	1.03	1.00	0.91 —	1.09	1.44	1.33 —	1.56
30-44	0.93	0.90 —	0.96	0.92	0.84 —	1.01	0.99	0.93 —	1.05	1.10	1.04 —	1.16	1.14	1.02 —	1.29	1.83	1.68 —	1.99
15-29	1.14	1.09 —	1.20	1.14	1.01 —	1.29	2.07	1.94 —	2.21	1.31	1.21 —	1.42	1.32	1.14 —	1.53	2.65	2.36 —	2.97
<15 or dialysis	1.60	1.52 —	1.69	1.77	1.56 —	2.01	3.08	2.85 —	3.32	1.46	1.33 —	1.60	1.51	1.29 —	1.77	2.48	2.16 —	2.85

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location

Table 3. Odds ratios from logistic regression models testing the association of specific statins compared to no statin with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=231,017

	Hospital admission					ICU admission					Death				
	OR	95% CI			p value	OR	95% CI			p value	OR	95% CI			p value
No statin	ref					ref					ref				
Atorvastatin	0.98	0.95	—	1.01	0.136	0.96	0.90	—	1.02	0.194	0.80	0.76	—	0.84	<0.001
Fluvastatin	1.47	0.45	—	4.82	0.524	1.79	0.23	—	13.80	0.577	0.55	0.07	—	4.43	0.575
Lovastatin	0.73	0.57	—	0.93	0.012	0.48	0.26	—	0.90	0.022	0.64	0.45	—	0.91	0.013
Pitavastatin	0.45	0.16	—	1.26	0.128	0.66	0.09	—	4.80	0.679	0.82	0.25	—	2.68	0.738
Pravastatin	0.93	0.86	—	1.00	0.045	0.94	0.81	—	1.10	0.443	0.78	0.70	—	0.87	<0.001
Rosuvastatin	0.81	0.76	—	0.86	<0.001	0.82	0.72	—	0.93	0.002	0.72	0.65	—	0.79	<0.001
Simvastatin	0.91	0.86	—	0.97	0.001	0.91	0.80	—	1.02	0.107	0.77	0.71	—	0.84	<0.001
Sex at birth, female	0.75	0.71	—	0.80	<0.001	0.74	0.65	—	0.84	<0.001	0.57	0.50	—	0.65	<0.001
Age category, years															
19-39	0.61	0.58	—	0.66	<0.001	0.60	0.51	—	0.71	<0.001	0.15	0.11	—	0.21	<0.001
40-49	0.75	0.71	—	0.80	<0.001	0.68	0.59	—	0.79	<0.001	0.38	0.30	—	0.48	<0.001
50-59	ref					ref					ref				
60-69	1.28	1.23	—	1.34	<0.001	1.32	1.21	—	1.45	<0.001	2.85	2.55	—	3.20	<0.001
70-79	1.43	1.36	—	1.49	<0.001	1.49	1.36	—	1.64	<0.001	5.92	5.31	—	6.60	<0.001
≥80	1.81	1.71	—	1.91	<0.001	1.62	1.45	—	1.82	<0.001	13.86	12.37	—	15.54	<0.001
White (vs. not white)	0.88	0.81	—	0.97	0.007	0.75	0.61	—	0.91	0.004	0.88	0.74	—	1.04	0.121
Black (vs. not Black)	1.36	1.24	—	1.50	<0.001	1.10	0.89	—	1.35	0.390	0.78	0.66	—	0.94	0.007
Hispanic (vs. not Hispanic)	1.16	1.10	—	1.22	<0.001	1.03	0.92	—	1.15	0.633	1.13	1.04	—	1.24	0.007
Body-mass index category, kg/m²															
<18.5	1.15	1.02	—	1.29	0.025	1.35	1.06	—	1.73	0.015	1.82	1.59	—	2.08	<0.001
18.5-24.9	ref					ref					ref				
25-29.9	0.81	0.78	—	0.85	<0.001	0.89	0.82	—	0.97	0.006	0.73	0.68	—	0.79	<0.001
30-34.9	0.76	0.73	—	0.80	<0.001	0.88	0.81	—	0.97	0.006	0.68	0.64	—	0.74	<0.001
35-39.9	0.76	0.72	—	0.80	<0.001	0.85	0.76	—	0.94	0.002	0.64	0.59	—	0.70	<0.001
≥40	0.87	0.81	—	0.92	<0.001	1.03	0.91	—	1.16	0.675	0.79	0.72	—	0.88	<0.001
Tobacco use															
Never	ref														
Former	1.11	1.08	—	1.15	<0.001	1.10	1.02	—	1.17	0.010	1.18	1.12	—	1.24	<0.001
Current	1.39	1.35	—	1.44	<0.001	1.29	1.20	—	1.39	<0.001	1.24	1.17	—	1.32	<0.001
Urban/rural/highly rural residence															
Highly rural	0.57	0.50	—	0.66	<0.001	0.74	0.54	—	1.00	0.051	1.16	0.97	—	1.38	0.096
Rural	0.70	0.68	—	0.72	<0.001	0.88	0.82	—	0.93	<0.001	1.04	0.99	—	1.08	0.140
Urban	ref					ref					ref				
Unknown	0.27	0.10	—	0.74	0.011	0.55	0.08	—	3.96	0.549	1.75	0.72	—	4.25	0.220
Diabetes	1.29	1.26	—	1.33	<0.001	1.26	1.19	—	1.33	<0.001	1.36	1.30	—	1.42	<0.001
Hypertension	1.30	1.25	—	1.35	<0.001	1.29	1.18	—	1.41	<0.001	0.96	0.90	—	1.02	0.149
Cardiovascular disease	1.84	1.78	—	1.89	<0.001	2.08	1.94	—	2.23	<0.001	1.24	1.18	—	1.30	<0.001
Heart failure	1.64	1.58	—	1.69	<0.001	1.53	1.43	—	1.63	<0.001	1.31	1.25	—	1.38	<0.001
Alcohol use disorder	0.75	0.73	—	0.78	<0.001	0.86	0.79	—	0.93	<0.001	0.69	0.64	—	0.73	<0.001

Table 3 CONTINUED. Odds ratios from logistic regression models testing the association of individual statins compared to no statin with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=231,017

Estimated glomerular filtration rate, ml/min/1.73 m²															
≥ 90	ref					ref					ref				
60-89	0.90	0.87	—	0.93	<0.001	0.96	0.88	—	1.04	0.273	1.10	1.02	—	1.18	0.018
45-59	0.99	0.94	—	1.03	0.519	1.00	0.91	—	1.10	0.941	1.44	1.33	—	1.56	<0.001
30-44	1.10	1.04	—	1.16	0.001	1.15	1.02	—	1.29	0.024	1.83	1.68	—	1.99	<0.001
15-29	1.31	1.21	—	1.42	<0.001	1.32	1.14	—	1.53	<0.001	2.65	2.36	—	2.97	<0.001
<15 or dialysis	1.45	1.32	—	1.59	<0.001	1.51	1.29	—	1.77	<0.001	2.48	2.16	—	2.84	<0.001

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location; not adjusted for the presence of an active statin prescription six months prior to enrollment

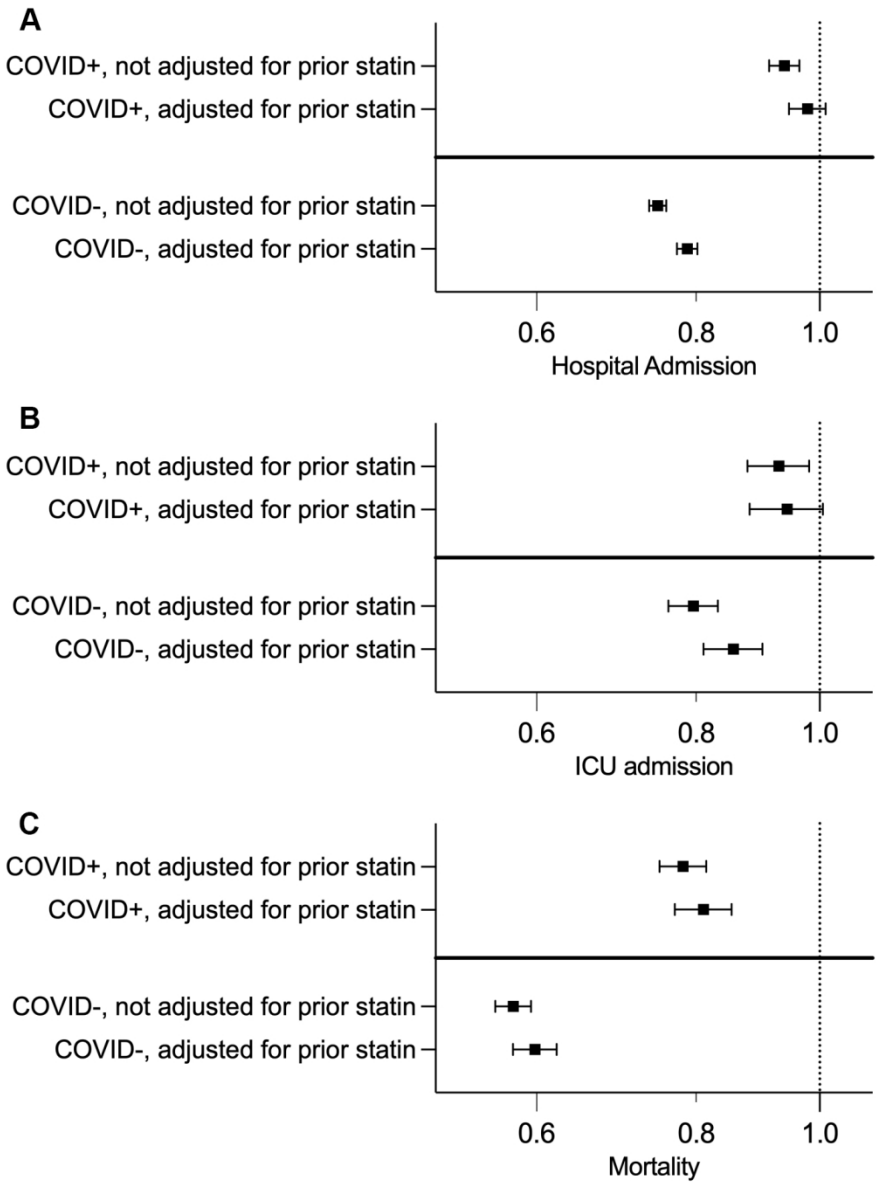
Table 4. Odds ratios from logistic regression models testing the association of low- or moderate- vs. high-potency active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=69,263

	Hospital admission					ICU admission					Death				
	OR	95% CI			p value	OR	95% CI			p value	OR	95% CI			p value
High-potency statin	1.06	1.01	—	1.10	0.011	1.05	0.96	—	1.15	0.258	0.97	0.91	—	1.04	0.407
Sex at birth, female	0.89	0.80	—	1.00	0.041	0.95	0.75	—	1.19	0.634	0.52	0.40	—	0.68	<0.001
Age category, years															
19-39	0.82	0.63	—	1.06	0.123	0.46	0.22	—	0.98	0.045	0.10	0.01	—	0.73	0.023
40-49	0.74	0.64	—	0.86	<0.001	0.55	0.38	—	0.79	0.001	0.45	0.27	—	0.75	0.002
50-59	ref					ref					ref				
60-69	1.30	1.20	—	1.40	<0.001	1.24	1.06	—	1.45	0.009	2.45	2.02	—	2.96	<0.001
70-79	1.47	1.36	—	1.58	<0.001	1.47	1.25	—	1.72	<0.001	4.42	3.67	—	5.32	<0.001
≥80	1.95	1.78	—	2.15	<0.001	1.69	1.40	—	2.04	<0.001	9.54	7.84	—	11.60	<0.001
White (vs not white)	0.81	0.69	—	0.96	0.012	0.75	0.52	—	1.08	0.118	0.85	0.64	—	1.11	0.221
Black vs(not Black)	1.31	1.10	—	1.55	0.002	1.12	0.77	—	1.63	0.545	0.80	0.60	—	1.06	0.125
Hispanic (vs not Hispanic)	1.12	1.02	—	1.22	0.013	0.91	0.75	—	1.10	0.330	1.20	1.04	—	1.38	0.014
Body-mass index category, kg/m²															
<18.5	1.04	0.79	—	1.38	0.766	1.19	0.71	—	1.98	0.511	1.45	1.02	—	2.05	0.039
18.5-24.9	ref					ref					ref				
25-29.9	0.81	0.75	—	0.86	<0.001	0.89	0.77	—	1.02	0.095	0.78	0.70	—	0.87	<0.001
30-34.9	0.78	0.73	—	0.84	<0.001	0.92	0.80	—	1.07	0.272	0.78	0.70	—	0.87	<0.001
35-39.9	0.78	0.71	—	0.85	<0.001	0.90	0.76	—	1.06	0.188	0.75	0.67	—	0.85	<0.001
≥40	0.86	0.77	—	0.95	0.002	1.08	0.89	—	1.30	0.452	0.91	0.78	—	1.06	0.221
Tobacco use															
Never	ref					ref					ref				
Former	1.18	1.12	—	1.25	<0.001	1.16	1.03	—	1.30	0.013	1.29	1.18	—	1.40	<0.001
Current	1.36	1.28	—	1.44	<0.001	1.36	1.19	—	1.55	<0.001	1.21	1.09	—	1.34	<0.001
Urban/rural/highly rural residence															
Highly rural	0.59	0.47	—	0.73	<0.001	0.93	0.61	—	1.42	0.728	1.40	1.08	—	1.82	0.011
Rural	0.68	0.65	—	0.72	<0.001	0.87	0.79	—	0.96	0.006	1.05	0.97	—	1.12	0.233
Urban	ref					ref					ref				
Unknown	0.17	0.02	—	1.26	0.083	1.69	0.22	—	12.83	0.612	1.41	0.31	—	6.48	0.662
Diabetes	1.29	1.23	—	1.35	<0.001	1.16	1.05	—	1.27	0.003	1.31	1.22	—	1.41	<0.001
Hypertension	1.28	1.18	—	1.39	<0.001	1.38	1.14	—	1.67	0.001	0.98	0.85	—	1.11	0.704
Cardiovascular disease	1.71	1.62	—	1.80	<0.001	1.96	1.75	—	2.21	<0.001	1.25	1.14	—	1.36	<0.001
Heart failure	1.68	1.60	—	1.77	<0.001	1.58	1.44	—	1.74	<0.001	1.33	1.23	—	1.43	<0.001
Alcohol use disorder	0.66	0.62	—	0.71	<0.001	0.81	0.71	—	0.94	0.004	0.69	0.61	—	0.77	<0.001
Estimated glomerular filtration rate, ml/min/1.73 m²															
≥ 90	ref					ref					ref				
60-89	0.98	0.92	—	1.05	0.625	1.05	0.91	—	1.20	0.538	1.14	1.01	—	1.29	0.041
45-59	1.08	1.00	—	1.16	0.050	1.05	0.90	—	1.24	0.530	1.58	1.37	—	1.82	<0.001
30-44	1.21	1.10	—	1.32	<0.001	1.20	1.00	—	1.44	0.055	2.00	1.72	—	2.33	<0.001
15-29	1.53	1.35	—	1.72	<0.001	1.37	1.09	—	1.72	0.007	3.19	2.69	—	3.78	<0.001
<15 or dialysis	1.64	1.42	—	1.90	<0.001	1.95	1.52	—	2.50	<0.001	3.01	2.44	—	3.73	<0.001

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location; not adjusted for the presence of an active statin prescription six months prior to enrollment

Figure Legend

Fig. 1. ORs and 95% confidence intervals for associations of statin use at study enrollment with A) hospitalization, B) ICU admission, and C) death at 30 days before and after adjustment for statin use six months prior to diagnosis among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2. All analyses are adjusted for sex, age, race/ethnicity, BMI, tobacco use, facility location, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder.



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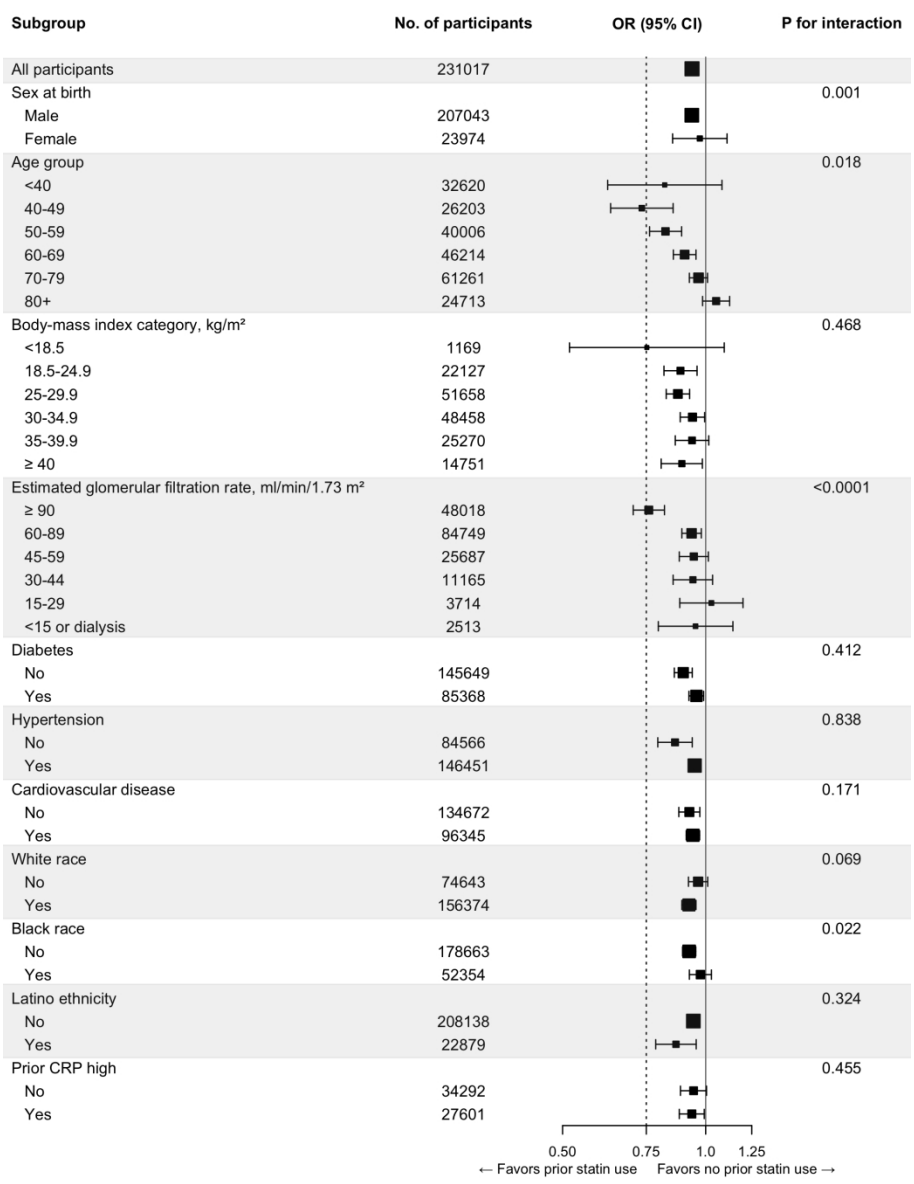

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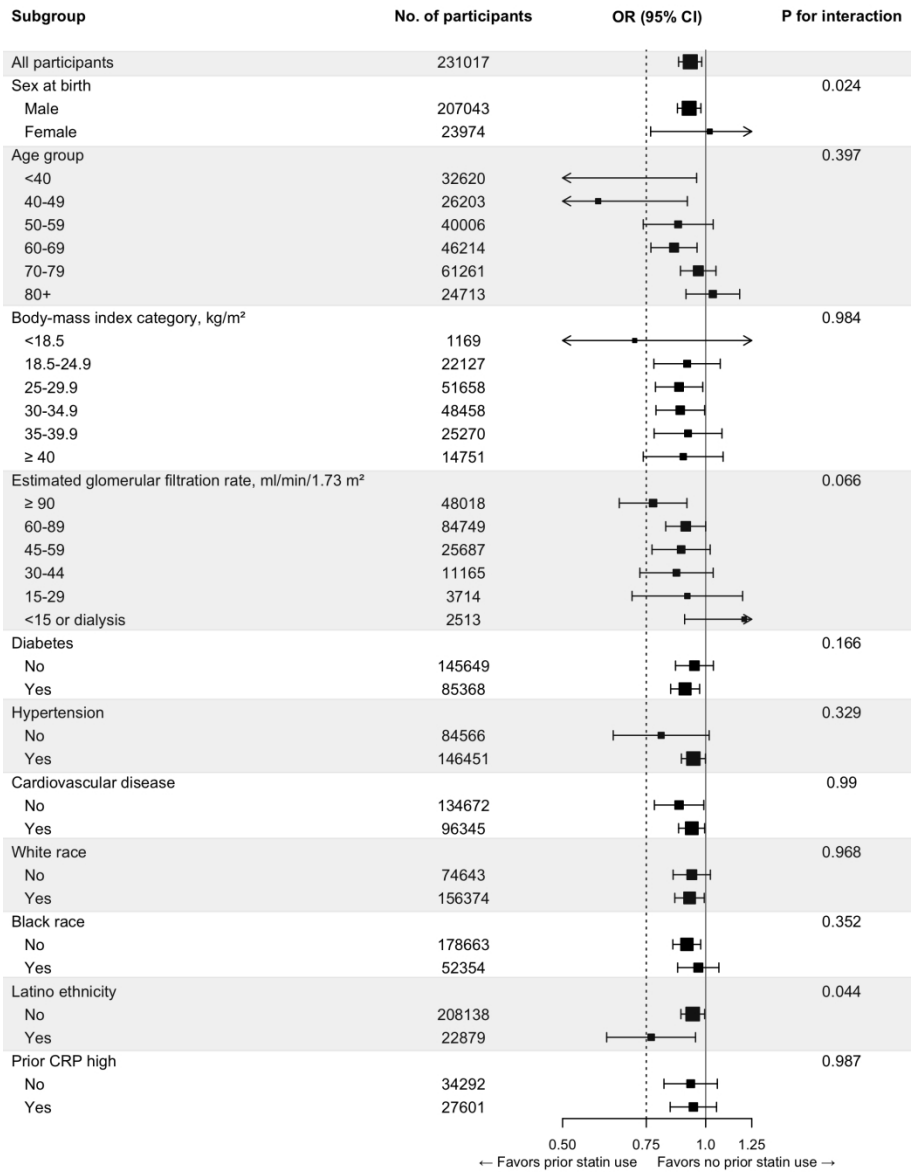

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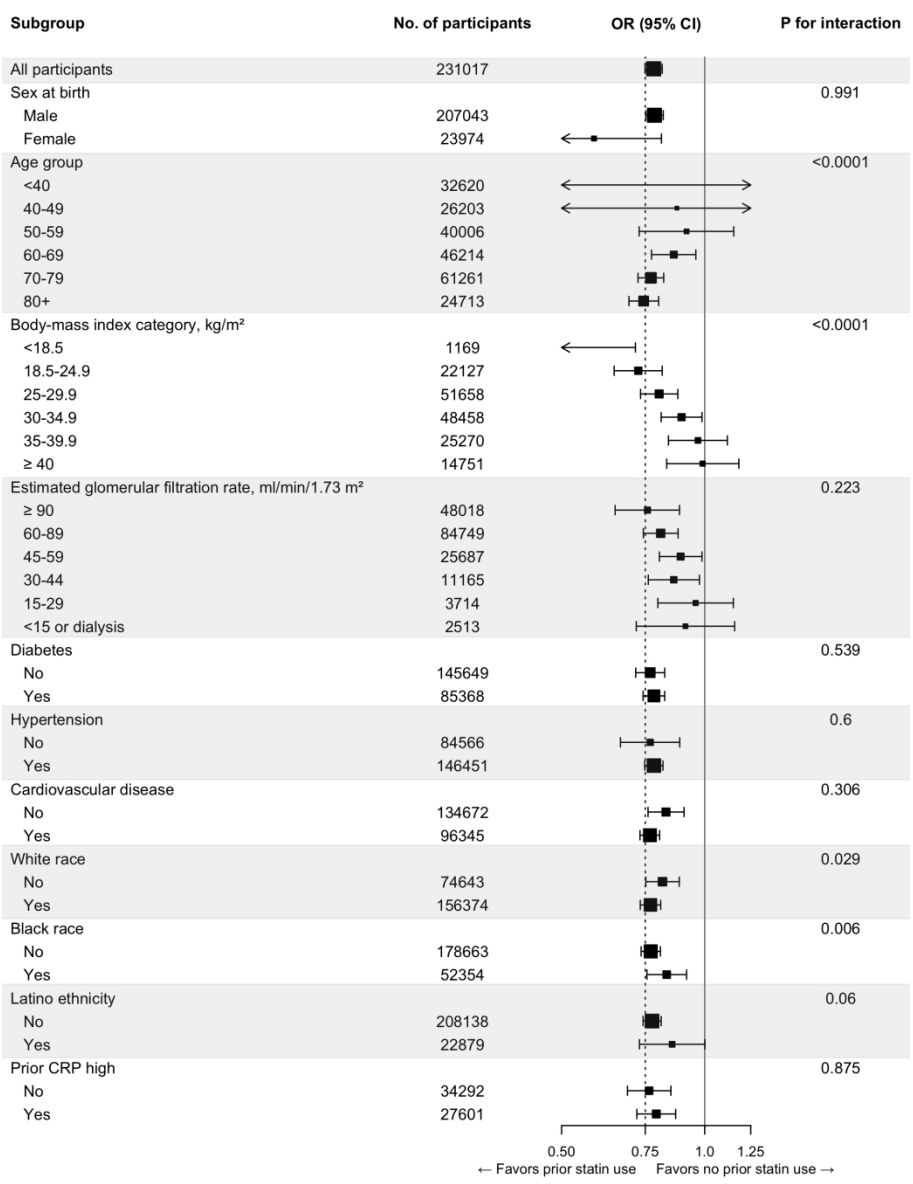

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Associations of statin use with 30-day adverse outcomes among 4,801,406 U.S. Veterans with and without SARS-CoV-2: An observational cohort study

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Associations of statin use with 30-day adverse outcomes among 4,801,406 U.S. Veterans with and without SARS-CoV-2: An observational cohort study

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ABSTRACT

Objective: To estimate associations of statin use with hospitalization, intensive care unit (ICU) admission, and mortality at 30 days among individuals with and without a positive test for SARS-CoV-2

Design: Retrospective cohort study

Setting: U.S. Veterans Health Administration (VHA)

Participants: All Veterans receiving VHA health care with ≥1 positive nasal swab for SARS-CoV-2 between March 1, 2020 and March 10, 2021 (cases; n=231,154) and a comparator group of controls comprising all Veterans who did not have a positive nasal swab for SARS-CoV-2 but who did have ≥1 clinical lab test performed during the same time period (n=4,570,252).

Main outcomes: Associations of (1) Any statin use, (2) use of specific statins, or (3) low-/moderate- vs. high-intensity statin use at the time of positive nasal swab for SARS-CoV-2 (cases) or result of clinical lab test (controls) assessed from pharmacy records with hospitalization, ICU admission, and death at 30 days. We also examined whether associations differed between individuals with and without a positive test for SARS-CoV-2.

Results: Among individuals who tested positive for SARS-CoV-2, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]) but not with hospitalization or ICU admission. Associations were similar comparing use of each specific statin to no statin. Compared to low-/moderate-intensity statin use, high-intensity statin use was not associated with lower odds of ICU admission or death. Over the same time period, associations of statin use with 30-day outcomes were significantly stronger among individuals without a positive test for SARS-CoV-2: hospitalization OR 0.79 (95%CI 0.77–0.80), ICU admission OR 0.86 (95%CI 0.81–0.90), and death 0.60 (95%CI 0.58–0.62), p for interaction all <0.001.

Conclusions: Associations of statin use with lower adverse 30-day outcomes are weaker among individuals who tested positive for SARS-CoV-2 compared to individuals without a positive test, indicating that statins do not exert SARS-CoV-2–specific effects.

Strengths and limitations of this study

- Large, well characterized national (U.S.) sample
- First study to formally assess and compare statin effects seen in SARS-CoV-2 infection using a negative control
- Observational design cannot exclude the possibility of residual confounding
- Did not capture hospitalizations or diagnoses occurring outside VHA

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INTRODUCTION

New cases of COVID-19/SARS-CoV-2 infection continue to occur at high rates in the United States and worldwide with few treatments available to decrease mortality. Statin use at the time of COVID-19 diagnosis has been associated with a lower risk of short-term mortality in observational studies[1] and systematic reviews[2]. Based on these early findings and their demonstrated effects on inflammation, oxidative stress, and immune responses, statins have been proposed as a low-cost, accessible, and effective treatment for COVID-19[3]. However, an inverse association of statin use with mortality is not uniformly seen across observational studies of persons with COVID-19[4 5]. Further, preliminary findings from a randomized placebo-controlled trial of patients admitted to the ICU did not show a protective effect of atorvastatin 20 mg/day on 30-day mortality after COVID-19 diagnosis, among patients not taking statins prior to admission[6]. These paradoxical findings may reflect the presence of residual confounding in observational studies. In addition, effects of statins on mortality after COVID-19 may differ across populations, for example, among individuals with or without cardiovascular disease (CVD), or specific to certain statins but not all medications in this class. Therefore, observational studies with comprehensive strategies to examine potential bias from unmeasured confounding—such as the use of negative control populations[2]—are needed to improve estimates of the potential causal effect of statin use at diagnosis on mortality after COVID-19.

To address these gaps, we used national data from the Veterans Health Administration (VHA) to quantify the independent association of statin use at diagnosis with adverse outcomes from COVID-19 at 30 days, including hospitalization, intensive-care unit (ICU) admission, and mortality. We used the following strategies to mitigate or estimate bias: 1) directed-acyclic graphs to guide the choice of potential confounders; 2) comparison of associations among SARS-CoV-2 infected individuals (n=231,154) with associations among an uninfected comparator sample (n=4,570,252); and 3) a dose-response analysis comparing low- or moderate-intensity statin use to high-intensity use. In additional analyses, we investigated associations of individual statins with 30-day outcomes after COVID-19 and evaluated the magnitude of the statin-mortality association in strata of sex, age, race, BMI, clinical comorbidities, and C-reactive protein (CRP) level prior to diagnosis.

METHODS

Study setting and population

The Veterans Health Administration (VHA)—the largest integrated healthcare system in the United States—provides care to more than 7 million Veterans at 170 medical centers and 1,074 outpatient sites[7]. We used data from the Corporate Data Warehouse (CDW), a data repository derived from VHA's integrated electronic medical record, including a COVID-19 Shared Data Resource, which contains analytic variables for all enrollees tested for SARS-CoV-2[8]. The study was approved by the institutional review board at VA Puget Sound Health Care System. The requirement for informed consent was waived.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

Selection of the SARS-CoV-2–positive cohort

We identified all enrollees with one or more positive nasal swabs for SARS-CoV-2 between March 1, 2020, and March 10, 2021. The index date was defined as the date the first positive test was performed. Most tests were performed in VA laboratories using US Food and Drug Administration (FDA)–approved RealTime (Abbott Laboratories) or Xpert-Xpress (Cepheid) SARS-CoV-2 assays. A small number were sent to outside laboratories.

Selection of the SARS-CoV-2–negative cohort

Individuals without a positive nasal swab for SARS-CoV-2 and with any clinical lab test available in the medical record between March 1, 2020, and March 31, 2021, were chosen as a comparison group. A negative nasal swab for SARS-CoV-2 was not required for inclusion. Participants without a positive nasal swab for SARS-CoV-2 were assigned an index month during the study period for which they had a lab result, and a random index date during the index month which was used as the start of follow-up.

Exposure

Current statin use was defined as receipt of a statin prescription with a fill date prior to the index date and a quantity prescribed that would extend past the index date. Statin intensity was defined as low, moderate, or high using definitions from the American Heart Association/American College of Cardiology guidelines on management of cholesterol[9] and was calculated based on the specific statin and dosage prescribed. Prescribing data were available for the following specific statins: Atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin. We defined prior statin use as receipt of a statin prescription with a fill date that included the time period six months prior to the index date.

Covariates

We collected data on age, sex, race/ethnicity, VHA facility location, and urban, rural, or highly rural residence using a validated classification scheme that has been previously described[10]. Body mass index (BMI) was defined as weight in kg divided by (height in meters)^2. Smoking status was classified as current, former, or never based on VHA health factors data. If no smoking code was entered, the participant was classified as never smoked. At-risk drinking was defined using a score ≥3 for men and ≥4 for women on the Alcohol Use Disorders Identification Test consumption questions (AUDIT-C)[11]. Comorbidities (hypertension (HTN), CVD, and heart failure) were identified using ICD-9-CM and -10 codes entered after October 1, 1999, the date when VHA began using a universal electronic health record[12]. We defined chronic kidney disease (CKD) by categories of estimated glomerular filtration rate[13] using the most recent creatinine at least 3 days, but not more than 1 year, before the index date. For individuals with data available on CRP at least 14 days but not more than six months before the index date (n=27,630), we dichotomized CRP values as normal or elevated based on cut points provided for each assay at the testing site because a variety of assays for these biomarkers are used across the VA system.

Outcomes

In both groups, we collected data on 30-day hospitalizations, ICU admissions, and deaths occurring through March 10, 2021. Deaths were verified by official sources including VHA Patient Treatment File, the Beneficiary Identification Records Locator Subsystem (BIRLS), and VA/CMS Medicare Vital Status File; Social Security Administration (SSA) Death Master File; death certificates, and VHA National Cemetery Administration[14].

Statistical analyses

We summarized baseline characteristics for SARS-CoV-2 infected and uninfected participants, stratified by statin use at the index date. We used multiple imputation with 10 sets of imputations for analyses that included BMI or CKD due to approximately 20% missing values for each of these variables. We used DAGitty[15] to generate a directed acyclic graph (DAG) to assist in variable selection. We fit separate logistic regression models for individuals with and without a positive swab for SARS-CoV-2, testing the association of statin use at index date with occurrence of hospitalization, ICU admission, and death, adjusting for the minimal sufficient covariate set to estimate the total effect of statin use according to our DAG (statin use ≥ six months prior to diagnosis, sex, age, race/ethnicity, BMI, tobacco use, facility location, index month, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder) separately. Index month was included as a precision variable. Facility location was included because both patterns of statin use and COVID-19 outcomes are expected to differ by region in the US. In combined models, we tested for the presence of multiplicative first-order interactions to determine whether the association between statins and odds of hospitalization, ICU admission, and death at 30 days differed between persons with and without a positive swab for SARS-CoV-2. We also controlled for prior statin use to approximate a comparison of incident users and non-users. In a sensitivity analysis, we examined associations of statin use at diagnosis with occurrence of hospitalization, ICU admission, and death in models that were not adjusted for statin use six months prior to diagnosis.

Among individuals with a positive swab for SARS-CoV-2, we fit logistic regression models examining associations of specific statins compared to no statin use with outcomes adjusted for sex, age, race/ethnicity, BMI, tobacco use, facility location, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder, as well as models comparing low-intensity to moderate- or high-intensity statin use. We evaluated the magnitude of the statin-mortality association in strata of sex, age, race, BMI, clinical comorbidities, and prior CRP concentration and tested for first-order multiplicative interactions by using interaction terms in combined models.

Role of the funding source

The analysis was funded by VA Clinical Science Research & Development, which had no role in its design, conduct, analysis, or reporting.

RESULTS

SARS-CoV-2 infected participants were 60.9 years old (±16.5) on average, and 10% percent (n= 23,974) were female. Thirty percent (69,263) had an active statin prescription at enrollment. During the 30 days after diagnosis, 14% (32,490) of SARS-CoV-2 infected participants were hospitalized, 3% (6,140) were admitted to the ICU, and 5% (12,111) died. SARS-COV-2 uninfected participants were 61.6 years old (±16.7) on average, and 13% (577,718) were female. Thirty percent (1,389,364) had an active statin prescription at enrollment. During the 30 days after the index date, 2% (91,604) were hospitalized, 0.2% (9,298) were admitted to the ICU, and 0.4% died (n=19,298). Statin users were more likely to be of white race/ethnicity, have BMI of 30 kg/m2 or greater, be former smokers, and reside in a rural zip code regardless of SARS-CoV-2 test result. Not surprisingly, statin use was higher among cardiometabolic conditions but lower in alcohol use disorder. A higher proportion of statin users were receiving hi potency therapy among participants testing positive for SARS-CoV-2 (**Table 1**).

Among SARS-COV-2 positive individuals, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]), but not with hospitalization or ICU admission. Adjustment for receipt of statin six months prior to baseline attenuated the magnitude of the association of statin use at diagnosis with all outcomes (**Fig. 1, Table 2b**) Associations with outcomes were similar for individual statins (**Table 3**). Compared to low-/moderate-intensity, high-intensity statin use was associated with higher odds of hospitalization (1.06 [95%CI 1.01–1.10]) but not with ICU admission or death (**Table 4**). Associations of statin use with hospitalization differed across strata of sex, age, race (Black vs. non-Black), and eGFR (e.g., OR for hospitalization in Black participants 0.98 [95%CI 0.92–1.03], OR for hospitalization in non-Black participants 0.92 [95%CI 0.89–0.95], p for interaction = 0.022). Associations of statin use with ICU admission differed across strata of sex and ethnicity (Latinx vs. not Latinx) (e.g., OR for ICU admission in Latinx participants 0.77 [95%CI 0.62–0.95], OR for ICU admissioni in non-Latinx participants 0.94 [95%CI 0.89–1.00], p for interaction

= 0.044). Associations of statin use with mortality differed across strata of age, race/ethnicity (white vs. non-white and Black vs. non-Black), and BMI (e.g., OR for mortality in Black participants 0.83 [95%CI 0.76–0.92], OR for mortality in non-Black participants 0.77 [95%CI 0.74–0.81], p for interaction = 0.006). Associations did not differ across strata of prevalent diabetes, hypertension, or CVD (**Supplementary Fig. 1–3**).

Compared to persons with SARS-CoV-2 infection, OR for all three outcomes were significantly lower in persons without SARS-CoV-2 infection, as reflected by p<0.001 for the interaction term of SARS-CoV-2*statin use in all three models. Among SARS-COV-2 negative individuals, statin use was associated with lower odds of hospitalization (OR 0.79 [95%CI 0.77–0.80]), ICU admission (OR 0.86 [95%CI 0.81–0.90]), and death at 30 days (OR 0.60 [95%CI 0.58–0.62]). (**Table 2a**).

DISCUSSION

In this cohort of U.S. Veterans with (n=231,154) and without (n=4,570,252) a positive respiratory swab for SARS-CoV-2, statin use was independently associated with lower odds of death at 30 days compared to no statin use, but this association over a similar time period was significantly stronger among Veterans without a positive respiratory swab for SARS-CoV-2. Among individuals with and without a positive respiratory swab for SARS-CoV-2, adjusting for prior statin use attenuated the association of statin use with all outcomes; however, in every case the magnitude of the association remained substantially greater among individuals without a diagnosis of COVID-19. Associations were similar for specific statins, and receipt of high-potency statin was not associated with lower odds of any outcome compared to moderate and low potency, except for a small difference in the odds of hospitalization. Associations were not significantly different in strata of prevalent diabetes, hypertension, or cardiovascular disease. Furthermore, the lack of a gradient of effect with statin potency also does not support a potential causal benefit of statin use. Taken together, these results suggest that while statin use is associated with lower mortality among individuals with a positive swab for SARS-CoV-2, the benefit is actually smaller for than it is for those without evidence of SARS-CoV-2 infection and does not support a possible anti-COVID effect of statin treatment. It is important to note, however, that the current study does not demonstrate a harmful effect of statin use among individuals with COVID-19, only that statins may not exert a SARS-CoV-2–specific protective effect and/or that positive findings in previous observational studies

may be due to residual confounding. Current findings therefore do not support statin cessation among individuals with COVID-19.

Use of negative controls is an important technique to detect confounding or other sources of bias in epidemiological studies[16] that has gone underutilized in the era of COVID-19 research. An instructive example is the association of pneumonia or influenza vaccination with all-cause mortality seen in elderly individuals despite rigorous control for confounding by factors related to overall health status[17]. Using negative controls, Jackson et al. examined the association of vaccination with a negative control outcome: mortality prior to influenza season[18]. They found a stronger association with mortality during the period prior to influenza season compared to during or after, a biologically implausible result that was attributed by the authors to preferential receipt of vaccines by healthy individuals. This source of bias is now recognized in studies of this topic[19]. While the use of a negative control outcome is not precisely analogous to the methods used in the current study, the example can inform interpretation of the current findings.

Several recent systematic reviews and meta-analyses have examined the association of prior statin use with short-term outcomes after COVID-19[2 20-25]. Many of these reported an inverse association of statin use at diagnosis with mortality. For example, statin use was associated with a lower hazard of death (HR 0.72 [95%CI 0.69–0.75]) in a large population-based study of English patients with diabetes independent of age and co-morbid CVD[26]. In a recent nationwide U.S. study of hospitalized individuals (n=10,541), outpatient statin, either alone or with blood pressure-lowering medications, was associated with lower odds of in-hospital death (OR 0.59 [95%CI 0.50–0.69]). The magnitude of the association of statin use at diagnosis with mortality reported in these and other analyses is quite similar to the OR in the current report among individuals with COVID-19 in models that were not adjusted for prior statin use (OR for death at 30 days 0.78 [95% CI 0.75–0.82]), likely reflecting similar strategies for confounder adjustment. The lower COVID-19 mortality risk among statin users, however, is not a universal finding. In fact, among French hospitalized patients with diabetes, statin use at diagnosis was associated with higher odds of death at 28 days (OR 1.46 [95% CI 1.08–1.95])[27]. Reasons for these disparate findings are unclear but may be due in part to differences in timing, as early in the pandemic, treatments such as dexamethasone and remdesivir were not widely used. Consistent with this, in the French

cohort mortality was about 21% at 28 days, considerably higher than our overall 30-day mortality rate of about 7%. No prior study to our knowledge has examined outcomes following statin use comparing SARS-CoV-2 infected and uninfected statin users.

We noted several differences in outcomes associated with statin use by certain characteristics such as sex, age, and race (Supplementary Fig. 1-3). As our main analysis did not show evidence of a lower risk of outcomes associated with statin use confined to COVID-19 infected participants, these interactions likely reflect associations independent of presence of this infection and therefore reflecting effect modification between statin use, stratum variables, and outcomes of interest.

Our study has several strengths, most importantly a large, well characterized national sample. To our knowledge, this is the largest observational study of prior statin use and adverse outcomes from SARS-CoV-2 in the United States (n=4,801,406) as well as the first to formally assess and compare statin effects seen in SARS-CoV-2 infection using a negative control (non-infected statin users). Second, we used several methods designed to mitigate or quantify bias due to unmeasured confounding. We: 1) constructed a DAG to estimate the minimal sufficient adjustment set to estimate the total effect of statin use on 30-day outcomes; 2) compared associations in SARS-CoV-2 infected individuals and an uninfected comparator sample; and 3) conducted dose-response analyses using statin potency to reflect dose. In addition, most VHA enrollees receive medical care and medications without cost, which likely decreases the contribution of unmeasured financial factors to differences in the quality of care received and most importantly to receipt of statin medications. Our results should be considered within the context of several limitations. The VHA population is generally older, with lower income and socioeconomic status[28] than the U.S. population as a whole, and our findings may not be generalizable to non-VHA populations. Additionally, the proportion of women was low (13%); however, although women comprised only a small proportion of the sample, the number of female participants (n=601,765) is adequate for robust statistical inference. We were also unable to capture hospitalizations or some outpatient prescriptions that occurred outside VHA. This is an important source of potential bias should propensity to seek outside care be associated with likelihood of receiving a statin, although VHA users are asked to provide notification within 72 hours of an outside hospital admission, and when possible are

transferred to a VHA facility, which would then be captured in the VHA electronic health record. Given the timing of this study, we were unable to evaluate mediating or moderating effects of vaccination use due to very limited vaccination coverage of our population by the index date. No data were available on prescription adherence; however, statin discontinuation rates have previously shown to be low in VHA patients relative to discontinuation of other lipid-lowering medications[29]. The comparison of all-cause mortality is in our opinion the best outcome by which to assess whether statin use benefitted patients with versus without SARS-CoV-2 infection. The comparison of admission to hospital or ICU is of less value given that the reasons for hospitalization likely differed greatly by presence of infection, but, nevertheless, are of value in demonstrating that no apparent benefit is seen that might not be reflected in overall mortality. Finally, not all individuals in the comparator group were tested for SARS-CoV-2, so we were unable to exclude the possibility that some SARS-CoV-2–positive participants with asymptomatic or mild disease were misclassified as SARS-CoV-2–negative. We elected to include individuals without SARS-CoV-2 tests because individuals with indications for SARS-CoV-2 testing may represent a particular (and sicker) population than the general group of VA enrollees as a whole. Further, based on the current results, inclusion of individuals with undiagnosed COVID-19 in the SARS-CoV-2–negative comparator group would be expected to attenuate observed differences in the associations of statin use with adverse outcomes between the SARS-CoV-2 infected and negative comparator groups. It is unlikely that exclusion of participants with undiagnosed COVID-19 from the comparator group would have resulted in a reduction in the observed negative association between statin use and mortality, as this would have required an opposite association to be present between undiagnosed COVID-19 infection and mortality, a possibility for which there is little reason or evidence to support.

CONCLUSIONS

In conclusion, statin use is associated with lower odds of 30-day mortality both among U.S. Veterans with or without a positive respiratory swab for SARS-CoV-2 indicating that statins may not exert COVID-19-specific beneficial effects.

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COMPETING INTERESTS. There are no relevant conflicts of interest to disclose.

DATA AVAILABILITY. Access to VA electronic health records data is limited to researchers with active, VA appointments and an IRB-approved protocol.

CONTRIBUTORSHIP. PLW conceived the project, designed the overall research plan, and wrote the first draft of the manuscript. EL analyzed the data and reviewed/edited the manuscript, LB contributed to the conception of the work and reviewed/edited the manuscript, LTP contributed to the conception of the work and reviewed/edited the manuscript, AK contributed to design/interpretation of the analyses and reviewed/edited the manuscript, AP contributed to the design/interpretation of the analyses and reviewed/edited the manuscript. SEK contributed to the conception of the work and reviewed/edited the manuscript. GD contributed to the design/interpretation of the analyses and reviewed/edited the manuscript. EJB conceived the project, designed the overall research plan, and reviewed/edited the manuscript.

ETHICS STATEMENT. The study was approved by the institutional review board at VA Puget Sound Health Care System, Seattle, WA, USA (#01897). The requirement for informed consent was waived.

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Table 1. Characteristics of VHA Veterans with and without a positive respiratory swab for SARS-CoV-2 (March 1, 2020–March 10, 2021), stratified by presence of an active statin prescription at enrollment

	Overall		No positive respiratory swab for SARS-CoV-2				≥1 positive respiratory swab for SARS-CoV-2			
	n=4,801,406		No statin prescription n=3,180,888		Active statin prescription n=1,389,364		No statin prescription n=161,891		Active statin prescription n=69,263	
Age, years	61.6	±16.7	58.3	±17.7	69.3	±10.8	57.8	±17.5	68.0	±11.4
Age category, years										
19-39	661,777	14%	613,885	19%	15,272	1%	31,645	20%	975	1%
40-49	482,871	10%	402,201	13%	54,467	4%	22,718	14%	3,485	5%
50-59	728,340	15%	516,328	16%	172,006	12%	29,099	18%	10,907	16%
60-69	993,105	21%	600,530	19%	346,361	25%	28,785	18%	17,429	25%
70-79	1,408,065	29%	735,949	23%	610,855	44%	33,303	21%	27,958	40%
80+	525,548	11%	311,010	10%	189,825	14%	16,204	10%	8,509	12%
Sex at birth, female	601,692	13%	509,443	16%	68,275	5%	20,598	13%	3,376	5%
Race/ethnicity										
White	3,335,105	69%	2,122,989	67%	1,055,742	76%	106,448	66%	49,926	72%
Black	860,829	18%	582,091	18%	226,384	16%	38,080	24%	14,274	21%
Hispanic	333,593	7%	230,848	7%	79,866	6%	17,770	11%	5,109	7%
Other	542,562	11%	430,377	14%	94,575	7%	13,410	8%	4,200	6%
Body-mass index, kg/m²	30.2	±6.09	29.8	±6.04	30.8	±6.06	30.9	±6.35	31.9	±6.26
Body-mass index category, kg/m²										
<18.5	28,116	1%	20,717	1%	6,230	1%	951	1%	218	0%
18.5-24.9	553,988	17%	379,204	20%	152,657	14%	16,249	15%	5,878	11%
25-29.9	1,107,238	35%	687,781	36%	367,799	34%	34,949	32%	16,709	30%
30-34.9	869,628	27%	507,893	26%	313,277	29%	30,944	29%	17,514	32%
35-39.9	399,754	13%	224,651	12%	149,833	14%	15,734	15%	9,536	17%
≥ 40	208,950	7%	113,491	6%	80,708	8%	9,077	8%	5,674	10%
Active statin prescription six months prior to enrollment	1,375,009	29%	259,070	8%	1,046,850	75%	17,020	11%	52,069	75%
Never	1,747,387	36%	1,338,452	42%	328,440	24%	62,782	39%	17,713	26%
Former	1,729,275	36%	984,318	31%	651,438	47%	58,321	36%	35,198	51%
Current	1,323,044	28%	857,133	27%	408,908	29%	40,651	25%	16,352	24%
Urban/rural/highly rural ZIP code										
Highly rural	57,047	1%	34,211	1%	20,620	1%	1,360	1%	856	1%
Rural	1,561,076	33%	975,607	31%	518,394	37%	43,690	27%	23,385	34%
Urban	3,172,176	66%	2,163,063	68%	847,474	61%	116,643	72%	44,996	65%
Unknown	9,407	0%	7,022	0%	2,298	0%	61	0%	26	0%
Estimated glomerular filtration rate, ml/min/1.73 m²										
≥ 90	938,310	27%	654,399	31%	235,893	20%	36,230	32%	11,788	19%
60-89	1,718,393	49%	1,034,287	49%	599,357	50%	54,598	48%	30,151	48%
45-59	520,635	15%	268,392	13%	226,556	19%	13,799	12%	11,888	19%
30-44	212,116	6%	100,776	5%	100,175	8%	5,626	5%	5,539	9%
15-29	58,464	2%	27,223	1%	27,527	2%	1,906	2%	1,808	3%
<15 or dialysis	25,765	1%	12,803	1%	10,449	1%	1,503	1%	1,010	2%

Table 1 CONTINUED. Characteristics of VHA Veterans with and without a positive respiratory swab for SARS-CoV-2 (March 1, 2020–March 10, 2021), stratified by presence of an active statin prescription at enrollment

Diabetes	1,482,197	31%	679,909	21%	716,920	52%	44,364	27%	41,004	59%
Hypertension	2,874,378	60%	1,551,529	49%	1,176,398	85%	86,382	53%	60,069	87%
Cardiovascular disease	1,749,197	36%	857,912	27%	794,940	57%	53,635	33%	42,710	62%
Heart failure	352,710	7%	144,971	5%	183,128	13%	12,388	8%	12,223	18%
Alcohol use disorder	909,010	19%	629,005	20%	238,333	17%	31,212	19%	10,460	15%
Statin prescribed										
None	3,341,657	70%	3,179,903	100%	0	0%	161,754	100%	0	0%
Atorvastatin	872,981	18%			829,795	60%			43,186	62%
Fluvastatin	364	<1%			348	0%			16	0%
Lovastatin	15,375	<1%			14,751	1%			624	1%
Pitavastatin	801	<1%			748	<1%			53	<1%
Pravastatin	123,779	3%			118,039	8%			5,740	8%
Rosuvastatin	173,943	4%			165,066	12%			8,877	13%
Simvastatin	270,806	6%			260,039	19%			10,767	16%
High-potency statin (vs. low- or moderate-potency)*	616,824	42%	0	<1%	585,224	42%	0	<1%	31,600	46%
Mean hsCRP in the prior six months, mg/L**	17.3	±136	16.4	±151	18.2	±120	19.9	±49.6	21.0	±52.9
hsCRP in the prior six months ≥2 mg/L**	390,796	41%	217,408	40%	145,787	42%	17,407	44%	10,194	45%
Mean hsCRP at or after the index date, mg/L***	29.3	±54.1	22.2	±46.6	25.6	±50.8	57.8	±70.8	65.2	±71.1
hsCRP at or after the index date ≤2 mg/L***	125,178	52%	61,501	46%	34,630	49%	18,260	75%	10,787	79%
OUTCOMES										
Hospital admission within 30 days	124,094	3%	61,651	2%	29,953	2%	20,280	13%	12,210	18%
ICU admission within 30 days	15,438	<1%	5,710	<1%	3,588	<1%	3,754	2%	2,386	3%
Death w/in 30 days	31,409	1%	13,074	<1%	6,224	<1%	7,815	5%	4,296	6%

Data are presented as mean ± standard deviation (SD) for continuous variables and n (%) for categorical variables

p-values for global differences in participant characteristics across categories of COVID diagnosis and prior statin use all <0.001

* based on estimated % LDL-c reduction

** up to 14 days prior to index date (Overall n=958,343)

*** Overall n=224,930

Table 2a. Odds ratios from logistic regression models testing the association of active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2, including adjustment for prior statin use

	No positive swab, n=4,568,689						≥1 positive swab, n=231,017					
	Hospital admission		ICU admission		Death		Hospital admission		ICU admission		Death	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Active statin prescription at enrollment	0.79	0.77 — 0.80	0.98	0.95 — 1.01	0.86	0.81 — 0.90	0.94	0.88 — 1.01	0.60	0.58 — 0.62	0.81	0.77 — 0.85
Statin prescription six months prior to enrollment	0.91	0.89 — 0.93	0.93	0.90 — 0.96	0.88	0.83 — 0.93	0.97	0.91 — 1.04	0.93	0.90 — 0.97	0.94	0.89 — 0.99
Sex at birth, female	0.73	0.71 — 0.75	0.75	0.71 — 0.79	0.73	0.67 — 0.80	0.74	0.65 — 0.84	0.63	0.58 — 0.69	0.56	0.50 — 0.64
Age category, years												
19-39	1.16	1.12 — 1.19	0.61	0.57 — 0.65	0.61	0.54 — 0.69	0.60	0.51 — 0.71	0.26	0.22 — 0.30	0.15	0.11 — 0.21
40-49	0.97	0.94 — 1.01	0.75	0.70 — 0.80	0.81	0.73 — 0.91	0.68	0.59 — 0.79	0.46	0.40 — 0.54	0.38	0.30 — 0.48
50-59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-69	1.01	0.99 — 1.03	1.29	1.23 — 1.34	1.16	1.08 — 1.25	1.32	1.21 — 1.46	1.95	1.81 — 2.10	2.86	2.55 — 3.20
70-79	0.81	0.79 — 0.83	1.43	1.37 — 1.49	1.00	0.92 — 1.08	1.49	1.36 — 1.64	2.60	2.41 — 2.79	5.93	5.32 — 6.61
≥80	0.96	0.93 — 0.99	1.81	1.71 — 1.91	0.95	0.87 — 1.04	1.62	1.45 — 1.82	5.06	4.68 — 5.46	13.86	12.37 — 15.53
White (vs not white)	1.21	1.14 — 1.28	0.88	0.81 — 0.97	1.23	1.02 — 1.49	0.74	0.61 — 0.91	1.10	0.95 — 1.27	0.87	0.74 — 1.04
Black vs(not Black)	1.49	1.40 — 1.58	1.36	1.24 — 1.50	1.53	1.26 — 1.85	1.10	0.89 — 1.35	1.05	0.90 — 1.22	0.78	0.66 — 0.94
Hispanic (vs not Hispanic)	1.07	1.04 — 1.10	1.16	1.10 — 1.22	1.23	1.13 — 1.35	1.03	0.92 — 1.15	1.07	0.99 — 1.14	1.13	1.04 — 1.24
Body-mass index category, kg/m²												
<18.5	1.35	1.29 — 1.42	1.14	1.01 — 1.29	1.51	1.31 — 1.73	1.35	1.06 — 1.72	2.48	2.33 — 2.65	1.81	1.59 — 2.07
18.5-24.9	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-29.9	0.75	0.73 — 0.76	0.81	0.78 — 0.85	0.70	0.65 — 0.74	0.89	0.82 — 0.97	0.54	0.52 — 0.56	0.73	0.68 — 0.79
30-34.9	0.67	0.65 — 0.68	0.76	0.73 — 0.80	0.62	0.57 — 0.66	0.88	0.81 — 0.96	0.42	0.40 — 0.44	0.69	0.64 — 0.74
35-39.9	0.63	0.61 — 0.65	0.76	0.72 — 0.80	0.57	0.52 — 0.62	0.85	0.76 — 0.94	0.37	0.35 — 0.40	0.64	0.59 — 0.70
≥40	0.65	0.63 — 0.67	0.87	0.82 — 0.93	0.59	0.53 — 0.65	1.03	0.91 — 1.16	0.43	0.39 — 0.46	0.80	0.72 — 0.88
Tobacco use												
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.23 — 1.28	1.11	1.08 — 1.15	1.12	1.06 — 1.19	1.10	1.02 — 1.17	1.09	1.04 — 1.13	1.18	1.12 — 1.24
Current	2.02	1.98 — 2.06	1.39	1.35 — 1.44	1.76	1.66 — 1.87	1.29	1.20 — 1.39	1.67	1.60 — 1.74	1.24	1.17 — 1.32
Urban/rural/highly rural residence												
Highly rural	0.68	0.64 — 0.73	0.58	0.50 — 0.66	0.98	0.82 — 1.18	0.74	0.54 — 1.00	0.92	0.81 — 1.05	1.16	0.98 — 1.38
Rural	0.74	0.73 — 0.75	0.70	0.68 — 0.72	0.74	0.70 — 0.78	0.88	0.82 — 0.93	0.89	0.87 — 0.92	1.03	0.99 — 1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18 — 0.35	0.27	0.10 — 0.75	0.35	0.13 — 0.94	0.55	0.08 — 3.99	0.80	0.51 — 1.25	1.77	0.73 — 4.30
Diabetes	1.18	1.16 — 1.20	1.30	1.27 — 1.34	1.26	1.21 — 1.32	1.26	1.19 — 1.34	1.41	1.36 — 1.45	1.37	1.31 — 1.43
Hypertension	1.22	1.19 — 1.24	1.30	1.25 — 1.35	1.30	1.22 — 1.39	1.29	1.19 — 1.41	1.09	1.04 — 1.14	0.96	0.90 — 1.02
Cardiovascular disease	2.04	2.01 — 2.08	1.84	1.79 — 1.90	2.69	2.55 — 2.84	2.08	1.95 — 2.23	1.88	1.81 — 1.95	1.24	1.18 — 1.30
Heart failure	2.13	2.09 — 2.16	1.64	1.59 — 1.70	2.34	2.22 — 2.46	1.53	1.43 — 1.63	2.51	2.42 — 2.59	1.31	1.25 — 1.38
Alcohol use disorder	1.12	1.10 — 1.14	0.75	0.72 — 0.78	1.03	0.97 — 1.09	0.86	0.79 — 0.93	0.78	0.75 — 0.82	0.68	0.64 — 0.73
Estimated glomerular filtration rate, ml/min/1.73 m²												
≥ 90	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-89	0.80	0.79 — 0.82	0.90	0.87 — 0.93	0.80	0.76 — 0.85	0.96	0.88 — 1.04	0.60	0.57 — 0.62	1.10	1.02 — 1.18
45-59	0.84	0.81 — 0.86	0.99	0.94 — 1.03	0.84	0.78 — 0.91	1.00	0.91 — 1.10	0.71	0.67 — 0.74	1.44	1.33 — 1.56
30-44	0.93	0.90 — 0.96	1.10	1.04 — 1.16	0.92	0.84 — 1.01	1.14	1.02 — 1.29	0.99	0.93 — 1.05	1.83	1.68 — 1.99
15-29	1.15	1.10 — 1.20	1.31	1.21 — 1.42	1.14	1.01 — 1.29	1.32	1.14 — 1.53	2.07	1.94 — 2.21	2.65	2.36 — 2.97
<15 or dialysis	1.60	1.52 — 1.69	1.46	1.33 — 1.60	1.77	1.56 — 2.00	1.51	1.29 — 1.77	3.07	2.85 — 3.32	2.48	2.16 — 2.85

Models additionally adjusted for index month and geographic location by Veterans Integrated Service Network location

Table 2b. Odds ratios from logistic regression models testing the association of active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2, without adjustment for prior statin use

	No positive swab, n=4,568,689									≥1 positive swab, n=231,017								
	Hospital admission			ICU admission			Death			Hospital admission			ICU admission			Death		
	OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI	
Active statin prescription at enrollment	0.75	0.74	0.76	0.80	0.76	0.83	0.58	0.56	0.59	0.94	0.91	0.96	0.93	0.88	0.98	0.78	0.75	0.82
Sex at birth, female	0.73	0.71	0.75	0.73	0.67	0.81	0.63	0.58	0.69	0.75	0.71	0.79	0.74	0.65	0.84	0.57	0.50	0.65
Age category, years																		
19-39	1.16	1.13	1.20	0.61	0.54	0.69	0.26	0.22	0.30	0.61	0.58	0.66	0.60	0.51	0.71	0.15	0.11	0.21
40-49	0.98	0.95	1.01	0.82	0.73	0.92	0.47	0.40	0.54	0.75	0.71	0.80	0.68	0.59	0.79	0.38	0.30	0.48
50-59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-69	1.01	0.98	1.03	1.16	1.08	1.25	1.95	1.81	2.10	1.28	1.23	1.34	1.32	1.21	1.45	2.86	2.55	3.20
70-79	0.81	0.79	0.83	0.99	0.92	1.07	2.59	2.41	2.78	1.43	1.36	1.49	1.49	1.36	1.64	5.92	5.31	6.60
≥80	0.96	0.93	0.99	0.95	0.87	1.04	5.06	4.68	5.46	1.81	1.71	1.91	1.62	1.45	1.82	13.86	12.37	15.53
White (vs not white)	1.20	1.14	1.28	1.23	1.02	1.49	1.10	0.95	1.27	0.88	0.81	0.97	0.75	0.61	0.91	0.87	0.74	1.04
Black vs(not Black)	1.49	1.40	1.58	1.53	1.26	1.86	1.05	0.90	1.22	1.37	1.24	1.50	1.10	0.89	1.35	0.78	0.66	0.94
Hispanic (vs not Hispanic)	1.07	1.04	1.10	1.23	1.13	1.35	1.06	0.99	1.14	1.16	1.10	1.22	1.03	0.92	1.15	1.13	1.04	1.24
Body-mass index category, kg/m²																		
<18.5	1.35	1.29	1.42	1.51	1.32	1.74	2.49	2.33	2.65	1.14	1.02	1.29	1.35	1.06	1.72	1.82	1.59	2.07
18.5-24.9	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-29.9	0.75	0.73	0.76	0.70	0.65	0.74	0.54	0.52	0.56	0.81	0.78	0.85	0.89	0.82	0.97	0.73	0.68	0.79
30-34.9	0.67	0.65	0.68	0.61	0.57	0.66	0.42	0.40	0.44	0.76	0.73	0.80	0.88	0.81	0.96	0.68	0.64	0.74
35-39.9	0.63	0.61	0.64	0.57	0.52	0.62	0.37	0.35	0.40	0.76	0.72	0.80	0.85	0.76	0.94	0.64	0.59	0.70
≥40	0.65	0.63	0.67	0.58	0.53	0.65	0.43	0.39	0.46	0.87	0.81	0.92	1.03	0.91	1.16	0.79	0.72	0.88
Tobacco use																		
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.22	1.27	1.12	1.05	1.19	1.09	1.04	1.13	1.11	1.08	1.15	1.10	1.02	1.17	1.18	1.12	1.24
Current	2.02	1.98	2.05	1.76	1.66	1.87	1.66	1.60	1.74	1.39	1.35	1.44	1.29	1.20	1.39	1.24	1.17	1.32
Urban/rural/highly rural residence																		
Highly rural	0.68	0.64	0.73	0.98	0.82	1.18	0.92	0.81	1.05	0.57	0.50	0.66	0.74	0.54	1.00	1.16	0.98	1.38
Rural	0.74	0.73	0.75	0.74	0.70	0.78	0.89	0.86	0.92	0.70	0.68	0.72	0.87	0.82	0.93	1.03	0.99	1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18	0.35	0.35	0.13	0.94	0.80	0.51	1.25	0.27	0.10	0.74	0.55	0.08	3.98	1.75	0.72	4.27
Diabetes	1.17	1.15	1.19	1.25	1.20	1.31	1.40	1.36	1.45	1.30	1.26	1.33	1.26	1.19	1.33	1.36	1.30	1.42
Hypertension	1.21	1.19	1.24	1.29	1.21	1.38	1.09	1.04	1.13	1.30	1.25	1.35	1.29	1.18	1.41	0.96	0.90	1.02
Cardiovascular disease	2.03	2.00	2.07	2.67	2.53	2.82	1.87	1.80	1.94	1.84	1.78	1.89	2.08	1.94	2.23	1.24	1.18	1.30
Heart failure	2.12	2.08	2.16	2.33	2.21	2.45	2.50	2.41	2.59	1.64	1.59	1.70	1.53	1.43	1.63	1.31	1.25	1.38
Alcohol use disorder	1.12	1.10	1.14	1.03	0.97	1.09	0.78	0.75	0.82	0.75	0.73	0.78	0.86	0.79	0.93	0.68	0.64	0.73
Estimated glomerular filtration rate, ml/min/1.73 m²																		
≥ 90	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-89	0.80	0.79	0.82	0.80	0.75	0.85	0.60	0.57	0.62	0.90	0.86	0.93	0.96	0.88	1.04	1.09	1.02	1.18
45-59	0.84	0.81	0.86	0.84	0.78	0.91	0.71	0.67	0.74	0.98	0.94	1.03	1.00	0.91	1.09	1.44	1.33	1.56
30-44	0.93	0.90	0.96	0.92	0.84	1.01	0.99	0.93	1.05	1.10	1.04	1.16	1.14	1.02	1.29	1.83	1.68	1.99
15-29	1.14	1.09	1.20	1.14	1.01	1.29	2.07	1.94	2.21	1.31	1.21	1.42	1.32	1.14	1.53	2.65	2.36	2.97
<15 or dialysis	1.60	1.52	1.69	1.77	1.56	2.01	3.08	2.85	3.32	1.46	1.33	1.60	1.51	1.29	1.77	2.48	2.16	2.85

Models additionally adjusted for index month and geographic location by Veterans Integrated Service Network location

Table 3. Odds ratios from logistic regression models testing the association of specific statins compared to no statin with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=231,017

	Hospital admission					ICU admission					Death				
	OR	95% CI			p value	OR	95% CI			p value	OR	95% CI			p value
No statin	ref					ref					ref				
Atorvastatin	0.98	0.95	—	1.01	0.136	0.96	0.90	—	1.02	0.194	0.80	0.76	—	0.84	<0.001
Fluvastatin	1.47	0.45	—	4.82	0.524	1.79	0.23	—	13.80	0.577	0.55	0.07	—	4.43	0.575
Lovastatin	0.73	0.57	—	0.93	0.012	0.48	0.26	—	0.90	0.022	0.64	0.45	—	0.91	0.013
Pitavastatin	0.45	0.16	—	1.26	0.128	0.66	0.09	—	4.80	0.679	0.82	0.25	—	2.68	0.738
Pravastatin	0.93	0.86	—	1.00	0.045	0.94	0.81	—	1.10	0.443	0.78	0.70	—	0.87	<0.001
Rosuvastatin	0.81	0.76	—	0.86	<0.001	0.82	0.72	—	0.93	0.002	0.72	0.65	—	0.79	<0.001
Simvastatin	0.91	0.86	—	0.97	0.001	0.91	0.80	—	1.02	0.107	0.77	0.71	—	0.84	<0.001
Sex at birth, female	0.75	0.71	—	0.80	<0.001	0.74	0.65	—	0.84	<0.001	0.57	0.50	—	0.65	<0.001
Age category, years															
19-39	0.61	0.58	—	0.66	<0.001	0.60	0.51	—	0.71	<0.001	0.15	0.11	—	0.21	<0.001
40-49	0.75	0.71	—	0.80	<0.001	0.68	0.59	—	0.79	<0.001	0.38	0.30	—	0.48	<0.001
50-59	ref					ref					ref				
60-69	1.28	1.23	—	1.34	<0.001	1.32	1.21	—	1.45	<0.001	2.85	2.55	—	3.20	<0.001
70-79	1.43	1.36	—	1.49	<0.001	1.49	1.36	—	1.64	<0.001	5.92	5.31	—	6.60	<0.001
≥80	1.81	1.71	—	1.91	<0.001	1.62	1.45	—	1.82	<0.001	13.86	12.37	—	15.54	<0.001
White (vs. not white)	0.88	0.81	—	0.97	0.007	0.75	0.61	—	0.91	0.004	0.88	0.74	—	1.04	0.121
Black (vs. not Black)	1.36	1.24	—	1.50	<0.001	1.10	0.89	—	1.35	0.390	0.78	0.66	—	0.94	0.007
Hispanic (vs. not Hispanic)	1.16	1.10	—	1.22	<0.001	1.03	0.92	—	1.15	0.633	1.13	1.04	—	1.24	0.007
Body-mass index category, kg/m²															
<18.5	1.15	1.02	—	1.29	0.025	1.35	1.06	—	1.73	0.015	1.82	1.59	—	2.08	<0.001
18.5-24.9	ref					ref					ref				
25-29.9	0.81	0.78	—	0.85	<0.001	0.89	0.82	—	0.97	0.006	0.73	0.68	—	0.79	<0.001
30-34.9	0.76	0.73	—	0.80	<0.001	0.88	0.81	—	0.97	0.006	0.68	0.64	—	0.74	<0.001
35-39.9	0.76	0.72	—	0.80	<0.001	0.85	0.76	—	0.94	0.002	0.64	0.59	—	0.70	<0.001
≥40	0.87	0.81	—	0.92	<0.001	1.03	0.91	—	1.16	0.675	0.79	0.72	—	0.88	<0.001
Tobacco use															
Never	ref														
Former	1.11	1.08	—	1.15	<0.001	1.10	1.02	—	1.17	0.010	1.18	1.12	—	1.24	<0.001
Current	1.39	1.35	—	1.44	<0.001	1.29	1.20	—	1.39	<0.001	1.24	1.17	—	1.32	<0.001
Urban/rural/highly rural residence															
Highly rural	0.57	0.50	—	0.66	<0.001	0.74	0.54	—	1.00	0.051	1.16	0.97	—	1.38	0.096
Rural	0.70	0.68	—	0.72	<0.001	0.88	0.82	—	0.93	<0.001	1.04	0.99	—	1.08	0.140
Urban	ref					ref					ref				
Unknown	0.27	0.10	—	0.74	0.011	0.55	0.08	—	3.96	0.549	1.75	0.72	—	4.25	0.220
Diabetes	1.29	1.26	—	1.33	<0.001	1.26	1.19	—	1.33	<0.001	1.36	1.30	—	1.42	<0.001
Hypertension	1.30	1.25	—	1.35	<0.001	1.29	1.18	—	1.41	<0.001	0.96	0.90	—	1.02	0.149
Cardiovascular disease	1.84	1.78	—	1.89	<0.001	2.08	1.94	—	2.23	<0.001	1.24	1.18	—	1.30	<0.001
Heart failure	1.64	1.58	—	1.69	<0.001	1.53	1.43	—	1.63	<0.001	1.31	1.25	—	1.38	<0.001
Alcohol use disorder	0.75	0.73	—	0.78	<0.001	0.86	0.79	—	0.93	<0.001	0.69	0.64	—	0.73	<0.001

Table 3 CONTINUED. Odds ratios from logistic regression models testing the association of individual statins compared to no statin with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=231,017

Estimated glomerular filtration rate, ml/min/1.73 m²															
≥ 90	ref					ref					ref				
60-89	0.90	0.87	—	0.93	<0.001	0.96	0.88	—	1.04	0.273	1.10	1.02	—	1.18	0.018
45-59	0.99	0.94	—	1.03	0.519	1.00	0.91	—	1.10	0.941	1.44	1.33	—	1.56	<0.001
30-44	1.10	1.04	—	1.16	0.001	1.15	1.02	—	1.29	0.024	1.83	1.68	—	1.99	<0.001
15-29	1.31	1.21	—	1.42	<0.001	1.32	1.14	—	1.53	<0.001	2.65	2.36	—	2.97	<0.001
<15 or dialysis	1.45	1.32	—	1.59	<0.001	1.51	1.29	—	1.77	<0.001	2.48	2.16	—	2.84	<0.001

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location; not adjusted for the presence of an active statin prescription six months prior to enrollment

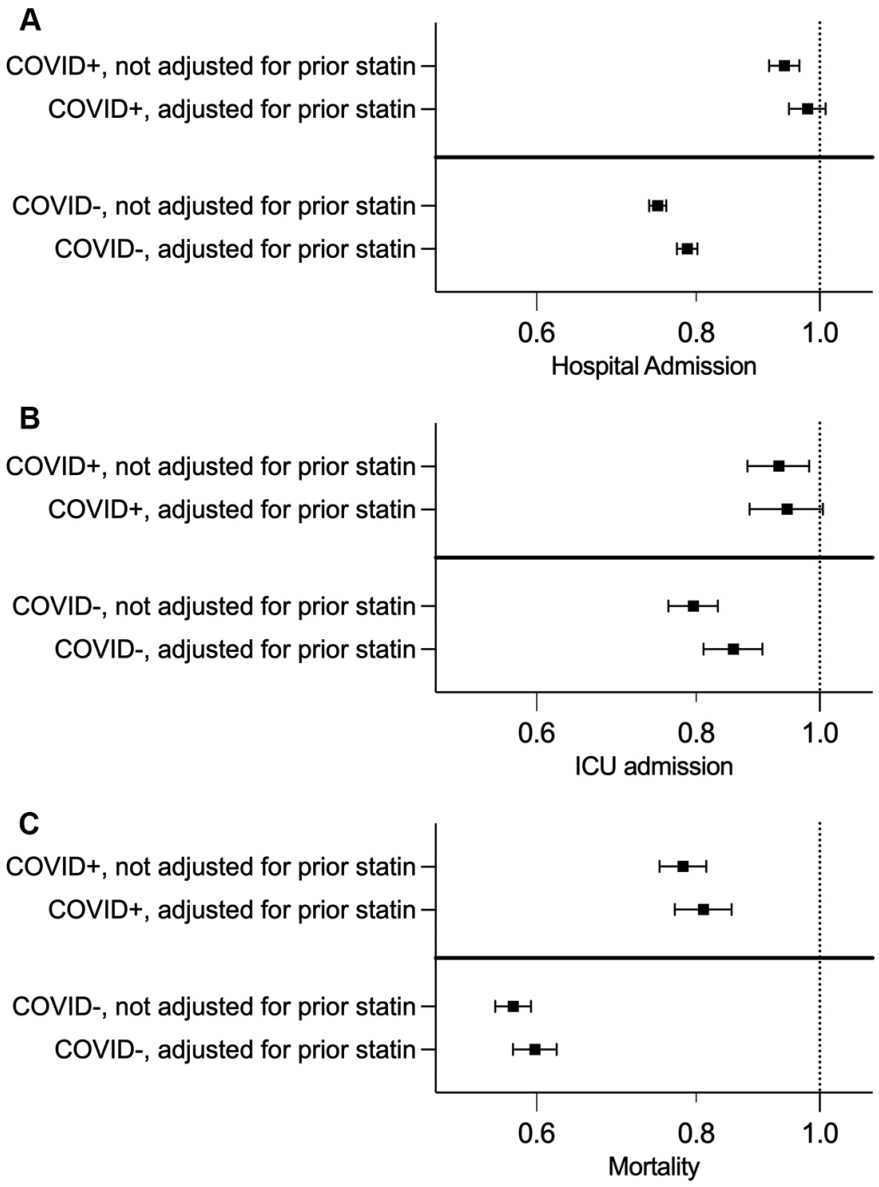
Table 4. Odds ratios from logistic regression models testing the association of low- or moderate- vs. high-potency active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=69,263

	Hospital admission					ICU admission					Death				
	OR	95% CI			p value	OR	95% CI			p value	OR	95% CI			p value
High-potency statin	1.06	1.01	—	1.10	0.011	1.05	0.96	—	1.15	0.258	0.97	0.91	—	1.04	0.407
Sex at birth, female	0.89	0.80	—	1.00	0.041	0.95	0.75	—	1.19	0.634	0.52	0.40	—	0.68	<0.001
Age category, years															
19-39	0.82	0.63	—	1.06	0.123	0.46	0.22	—	0.98	0.045	0.10	0.01	—	0.73	0.023
40-49	0.74	0.64	—	0.86	<0.001	0.55	0.38	—	0.79	0.001	0.45	0.27	—	0.75	0.002
50-59	ref					ref					ref				
60-69	1.30	1.20	—	1.40	<0.001	1.24	1.06	—	1.45	0.009	2.45	2.02	—	2.96	<0.001
70-79	1.47	1.36	—	1.58	<0.001	1.47	1.25	—	1.72	<0.001	4.42	3.67	—	5.32	<0.001
≥80	1.95	1.78	—	2.15	<0.001	1.69	1.40	—	2.04	<0.001	9.54	7.84	—	11.60	<0.001
White (vs not white)	0.81	0.69	—	0.96	0.012	0.75	0.52	—	1.08	0.118	0.85	0.64	—	1.11	0.221
Black vs(not Black)	1.31	1.10	—	1.55	0.002	1.12	0.77	—	1.63	0.545	0.80	0.60	—	1.06	0.125
Hispanic (vs not Hispanic)	1.12	1.02	—	1.22	0.013	0.91	0.75	—	1.10	0.330	1.20	1.04	—	1.38	0.014
Body-mass index category, kg/m²															
<18.5	1.04	0.79	—	1.38	0.766	1.19	0.71	—	1.98	0.511	1.45	1.02	—	2.05	0.039
18.5-24.9	ref					ref					ref				
25-29.9	0.81	0.75	—	0.86	<0.001	0.89	0.77	—	1.02	0.095	0.78	0.70	—	0.87	<0.001
30-34.9	0.78	0.73	—	0.84	<0.001	0.92	0.80	—	1.07	0.272	0.78	0.70	—	0.87	<0.001
35-39.9	0.78	0.71	—	0.85	<0.001	0.90	0.76	—	1.06	0.188	0.75	0.67	—	0.85	<0.001
≥40	0.86	0.77	—	0.95	0.002	1.08	0.89	—	1.30	0.452	0.91	0.78	—	1.06	0.221
Tobacco use															
Never	ref					ref					ref				
Former	1.18	1.12	—	1.25	<0.001	1.16	1.03	—	1.30	0.013	1.29	1.18	—	1.40	<0.001
Current	1.36	1.28	—	1.44	<0.001	1.36	1.19	—	1.55	<0.001	1.21	1.09	—	1.34	<0.001
Urban/rural/highly rural residence															
Highly rural	0.59	0.47	—	0.73	<0.001	0.93	0.61	—	1.42	0.728	1.40	1.08	—	1.82	0.011
Rural	0.68	0.65	—	0.72	<0.001	0.87	0.79	—	0.96	0.006	1.05	0.97	—	1.12	0.233
Urban	ref					ref					ref				
Unknown	0.17	0.02	—	1.26	0.083	1.69	0.22	—	12.83	0.612	1.41	0.31	—	6.48	0.662
Diabetes	1.29	1.23	—	1.35	<0.001	1.16	1.05	—	1.27	0.003	1.31	1.22	—	1.41	<0.001
Hypertension	1.28	1.18	—	1.39	<0.001	1.38	1.14	—	1.67	0.001	0.98	0.85	—	1.11	0.704
Cardiovascular disease	1.71	1.62	—	1.80	<0.001	1.96	1.75	—	2.21	<0.001	1.25	1.14	—	1.36	<0.001
Heart failure	1.68	1.60	—	1.77	<0.001	1.58	1.44	—	1.74	<0.001	1.33	1.23	—	1.43	<0.001
Alcohol use disorder	0.66	0.62	—	0.71	<0.001	0.81	0.71	—	0.94	0.004	0.69	0.61	—	0.77	<0.001
Estimated glomerular filtration rate, ml/min/1.73 m²															
≥ 90	ref					ref					ref				
60-89	0.98	0.92	—	1.05	0.625	1.05	0.91	—	1.20	0.538	1.14	1.01	—	1.29	0.041
45-59	1.08	1.00	—	1.16	0.050	1.05	0.90	—	1.24	0.530	1.58	1.37	—	1.82	<0.001
30-44	1.21	1.10	—	1.32	<0.001	1.20	1.00	—	1.44	0.055	2.00	1.72	—	2.33	<0.001
15-29	1.53	1.35	—	1.72	<0.001	1.37	1.09	—	1.72	0.007	3.19	2.69	—	3.78	<0.001
<15 or dialysis	1.64	1.42	—	1.90	<0.001	1.95	1.52	—	2.50	<0.001	3.01	2.44	—	3.73	<0.001

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location; not adjusted for the presence of an active statin prescription six months prior to enrollment

Figure Legend

Fig. 1. ORs and 95% confidence intervals for associations of statin use at study enrollment with A) hospitalization, B) ICU admission, and C) death at 30 days before and after adjustment for statin use six months prior to diagnosis among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2. All analyses are adjusted for sex, age, race/ethnicity, BMI, tobacco use, facility location, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder.



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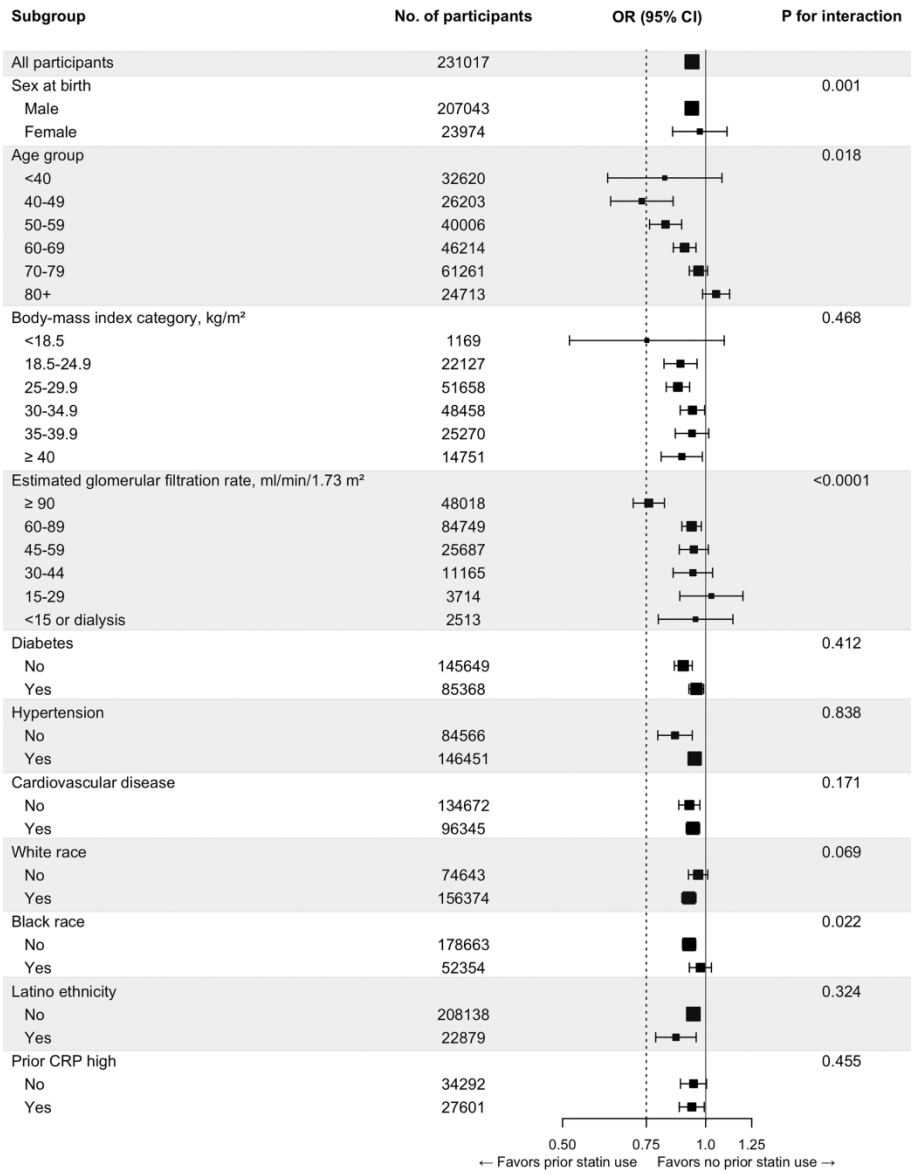

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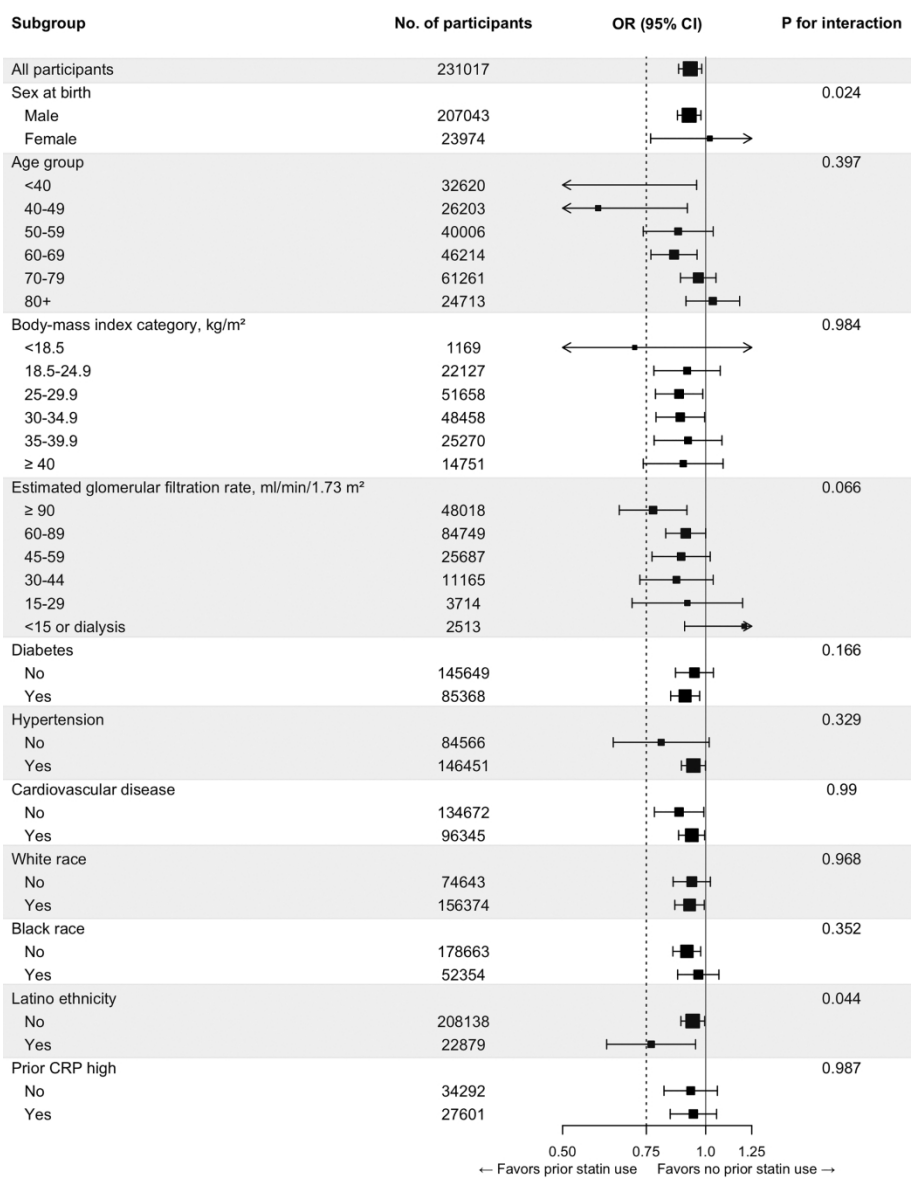

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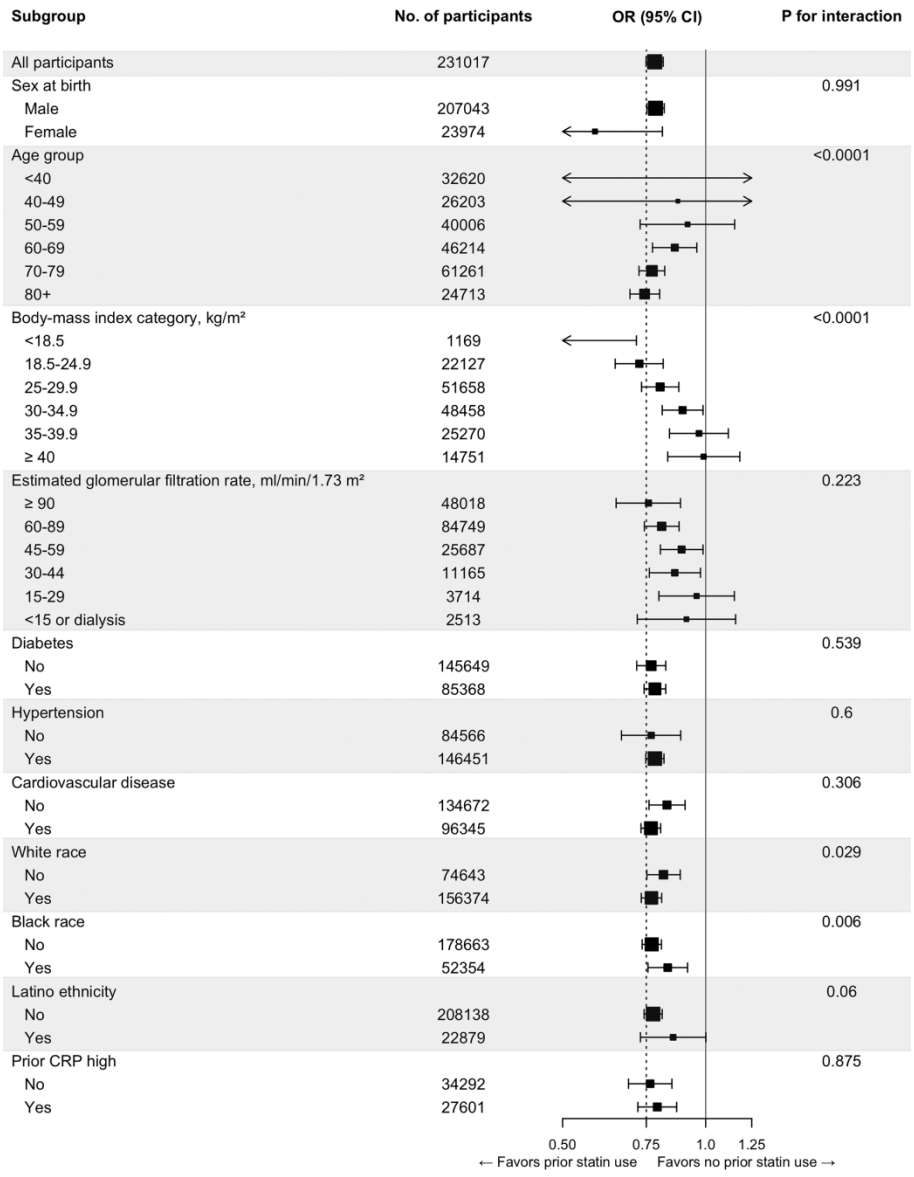

293x387mm (236 x 236 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

Associations of statin use with 30-day adverse outcomes among 4,801,406 U.S. Veterans with and without SARS-CoV-2: An observational cohort study

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Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.

app fig 1. forest_adm_7-20-21.jpf
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Associations of statin use with 30-day adverse outcomes among 4,801,406 US Veterans with and without SARS-CoV-2: an observational cohort study

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Word count (not including title, abstract, acknowledgment, references, tables, and figure legends): 2,900

ABSTRACT

Objective: To estimate associations of statin use with hospitalization, intensive care unit (ICU) admission, and mortality at 30 days among individuals with and without a positive test for SARS-CoV-2.

Design: Retrospective cohort study.

Setting: U.S. Veterans Health Administration (VHA).

Participants: All Veterans receiving VHA health care with ≥1 positive nasal swab for SARS-CoV-2 between March 1, 2020 and March 10, 2021 (cases; n=231,154) and a comparator group of controls comprising all Veterans who did not have a positive nasal swab for SARS-CoV-2 but who did have ≥1 clinical lab test performed during the same time period (n=4,570,252).

Main outcomes: Associations of (1) Any statin use, (2) use of specific statins, or (3) low-/moderate- vs. high-intensity statin use at the time of positive nasal swab for SARS-CoV-2 (cases) or result of clinical lab test (controls) assessed from pharmacy records with hospitalization, ICU admission, and death at 30 days. We also examined whether associations differed between individuals with and without a positive test for SARS-CoV-2.

Results: Among individuals who tested positive for SARS-CoV-2, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]) but not with hospitalization or ICU admission. Associations were similar comparing use of each specific statin to no statin. Compared to low-/moderate-intensity statin use, high-intensity statin use was not associated with lower odds of ICU admission or death. Over the same period, associations of statin use with 30-day outcomes were significantly stronger among individuals without a positive test for SARS-CoV-2: hospitalization OR 0.79 (95%CI 0.77–0.80), ICU admission OR 0.86 (95%CI 0.81–0.90), and death 0.60 (95%CI 0.58–0.62; p for interaction all <0.001).

Conclusions: Associations of statin use with lower adverse 30-day outcomes are weaker among individuals who tested positive for SARS-CoV-2 compared to individuals without a positive test, indicating that statins do not exert SARS-CoV-2-specific effects.

Strengths and limitations of this study

- Large, well characterized national (U.S.) sample.
- First study to formally assess and compare statin effects seen in SARS-CoV-2 infection using a negative control.

- Observational design cannot exclude the possibility of residual confounding.
- Did not capture hospitalizations or diagnoses occurring outside Veterans Health Administration.

INTRODUCTION

New cases of COVID-19/SARS-CoV-2 infection continue to occur at high rates in the United States and worldwide with few treatments available to decrease mortality. Statin use at the time of COVID-19 diagnosis has been associated with a lower risk of short-term mortality in observational studies[1] and systematic reviews[2]. Based on these early findings and their demonstrated effects on inflammation, oxidative stress, and immune responses, statins have been proposed as a low-cost, accessible, and effective treatment for COVID-19[3]. However, an inverse association of statin use with mortality is not uniformly seen across observational studies of persons with COVID-19[4 5]. Further, preliminary findings from a randomized placebo-controlled trial of patients admitted to the ICU did not show a protective effect of atorvastatin 20 mg/day on 30-day mortality after COVID-19 diagnosis, among patients not taking statins prior to admission[6]. These paradoxical findings may reflect the presence of residual confounding in observational studies. In addition, effects of statins on mortality after COVID-19 may differ across populations, for example, among individuals with or without cardiovascular disease (CVD), or specific to certain statins but not all medications in this class. Therefore, observational studies with comprehensive strategies to examine potential bias from unmeasured confounding—such as the use of negative control populations[2]—are needed to improve estimates of the potential causal effect of statin use at diagnosis on mortality after COVID-19.

To address these gaps, we used national data from the Veterans Health Administration (VHA) to quantify the independent association of statin use at diagnosis with adverse outcomes from COVID-19 at 30 days, including hospitalization, intensive-care unit (ICU) admission, and mortality. We used the following strategies to mitigate or estimate bias: 1) directed-acyclic graphs to guide the choice of potential confounders; 2) comparison of associations among SARS-CoV-2 infected individuals (n=231,154) with associations among an uninfected comparator sample (n=4,570,252); and 3) a dose-response analysis comparing low- or moderate-intensity statin use to high-intensity use. In additional analyses, we investigated associations of individual statins with 30-day outcomes after COVID-19 and evaluated the magnitude of the statin-mortality association in strata of sex, age, race, BMI, clinical comorbidities, and C-reactive protein (CRP) level prior to diagnosis.

METHODS

Study setting and population

The Veterans Health Administration (VHA)—the largest integrated healthcare system in the United States—provides care to more than 7 million Veterans at 170 medical centers and 1,074 outpatient sites[7]. We used data from the Corporate Data Warehouse (CDW), a data repository derived from VHA's integrated electronic medical record, including a COVID-19 Shared Data Resource, which contains analytic variables for all enrollees tested for SARS-CoV-2[8]. The study was approved by the institutional review board at VA Puget Sound Health Care System. The requirement for informed consent was waived.

Selection of the SARS-CoV-2–positive cohort

We identified all enrollees with one or more positive nasal swabs for SARS-CoV-2 between March 1, 2020, and March 10, 2021. The index date was defined as the date the first positive test was performed. Most tests were performed in VA laboratories using US Food and Drug Administration (FDA)–approved RealTime (Abbott Laboratories) or Xpert-Xpress (Cepheid) SARS-CoV-2 assays. A small number were sent to outside laboratories.

Selection of the SARS-CoV-2–negative cohort

Individuals without a positive nasal swab for SARS-CoV-2 and with any clinical lab test available in the medical record between March 1, 2020, and March 31, 2021, were chosen as a comparison group. A negative nasal swab for SARS-CoV-2 was not required for inclusion. Participants without a positive nasal swab for SARS-CoV-2 were assigned an index month during the study period for which they had a lab result, and a random index date during the index month which was used as the start of follow-up.

Exposure

Current statin use was defined as receipt of a statin prescription with a fill date prior to the index date and a quantity prescribed that would extend past the index date. Statin intensity was defined as low, moderate, or high using definitions from the American Heart Association/American College of Cardiology guidelines on management of cholesterol[9] and was calculated based on the specific statin and dosage prescribed. Prescribing data were available for the following specific statins: Atorvastatin, fluvastatin, lovastatin,

pitavastatin, pravastatin, rosuvastatin, simvastatin. We defined prior statin use as receipt of a statin prescription with a fill date that included the time period six months prior to the index date.

Covariates

We collected data on age, sex, race/ethnicity, VHA facility location, and urban, rural, or highly rural residence using a validated classification scheme that has been previously described[10]. Body mass index (BMI) was defined as weight in kg divided by (height in meters)^2. Smoking status was classified as current, former, or never based on VHA health factors data. If no smoking code was entered, the participant was classified as never smoked. At-risk drinking was defined using a score ≥3 for men and ≥4 for women on the Alcohol Use Disorders Identification Test consumption questions (AUDIT-C)[11]. Comorbidities (hypertension (HTN), CVD, and heart failure) were identified using ICD-9-CM and -10 codes entered after October 1, 1999, the date when VHA began using a universal electronic health record[12]. We defined chronic kidney disease (CKD) by categories of estimated glomerular filtration rate[13] using the most recent creatinine at least 3 days, but not more than 1 year, before the index date. For individuals with data available on CRP at least 14 days but not more than six months before the index date (n=27,630), we dichotomized CRP values as normal or elevated based on cut points provided for each assay at the testing site because a variety of assays for these biomarkers are used across the VA system.

Outcomes

In both groups, we collected data on 30-day hospitalizations, ICU admissions, and deaths occurring through March 10, 2021. Deaths were verified by official sources including VHA Patient Treatment File, the Beneficiary Identification Records Locator Subsystem (BIRLS), and VA/CMS Medicare Vital Status File; Social Security Administration (SSA) Death Master File; death certificates, and VHA National Cemetery Administration[14].

Statistical analyses

We summarized baseline characteristics for SARS-CoV-2 infected and uninfected participants, stratified by statin use at the index date. We used multiple imputation with 10 sets of imputations for analyses that included BMI or CKD due to approximately 20% missing values for each of these variables. We used DAGitty[15] to

generate a directed acyclic graph (DAG) to assist in variable selection. We fit separate logistic regression models for individuals with and without a positive swab for SARS-CoV-2, testing the association of statin use at index date with occurrence of hospitalization, ICU admission, and death, adjusting for the minimal sufficient covariate set to estimate the total effect of statin use according to our DAG (statin use ≥ six months prior to diagnosis, sex, age, race/ethnicity, BMI, tobacco use, facility location, index month, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder) separately. Index month was included as a precision variable. Facility location was included because both patterns of statin use and COVID-19 outcomes are expected to differ by region in the US. In combined models, we tested for the presence of multiplicative first-order interactions to determine whether the association between statins and odds of hospitalization, ICU admission, and death at 30 days differed between persons with and without a positive swab for SARS-CoV-2. We also controlled for prior statin use to approximate a comparison of incident users and non-users. In a sensitivity analysis, we examined associations of statin use at diagnosis with occurrence of hospitalization, ICU admission, and death in models that were not adjusted for statin use six months prior to diagnosis.

Among individuals with a positive swab for SARS-CoV-2, we fit logistic regression models examining associations of specific statins compared to no statin use with outcomes adjusted for sex, age, race/ethnicity, BMI, tobacco use, facility location, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder, as well as models comparing low-intensity to moderate- or high-intensity statin use. We evaluated the magnitude of the statin-mortality association in strata of sex, age, race, BMI, clinical comorbidities, and prior CRP concentration and tested for first-order multiplicative interactions by using interaction terms in combined models.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

SARS-CoV-2 infected participants were 60.9 years old (±16.5) on average, and 10% percent (n= 23,974) were female. Thirty percent (69,263) had an active statin prescription at enrollment. During the 30 days after diagnosis, 14% (32,490) of SARS-CoV-2 infected participants were hospitalized, 3% (6,140) were admitted to the ICU, and 5% (12,111) died. SARS-COV-2 uninfected participants were 61.6 years old (±16.7) on average, and 13% (577,718) were female. Thirty percent (1,389,364) had an active statin prescription at enrollment. During the 30 days after the index date, 2% (91,604) were hospitalized, 0.2% (9,298) were admitted to the ICU, and 0.4% died (n=19,298). Statin users were more likely to be of white race/ethnicity, have BMI of 30 kg/m2 or greater, be former smokers, and reside in a rural zip code regardless of SARS-CoV-2 test result. Not surprisingly, statin use was higher among cardiometabolic conditions but lower in alcohol use disorder. A higher proportion of statin users were receiving hi potency therapy among participants testing positive for SARS-CoV-2 (**Table 1**).

Among SARS-COV-2 positive individuals, statin use was associated with lower odds of death at 30 days (OR 0.81 [95%CI 0.77–0.85]), but not with hospitalization or ICU admission. Adjustment for receipt of statin six months prior to baseline attenuated the magnitude of the association of statin use at diagnosis with all outcomes (**Fig. 1, Tables 2a and 2b**) Associations with outcomes were similar for individual statins (**Table 3**). Compared to low-/moderate-intensity, high-intensity statin use was associated with higher odds of hospitalization (1.06 [95%CI 1.01–1.10]) but not with ICU admission or death (**Table 4**). Associations of statin use with hospitalization differed across strata of sex, age, race (Black vs. non-Black), and eGFR (e.g., OR for hospitalization in Black participants 0.98 [95%CI 0.92–1.03], OR for hospitalization in non-Black participants 0.92 [95%CI 0.89–0.95], p for interaction = 0.022). Associations of statin use with ICU admission differed across strata of sex and ethnicity (Latinx vs. not Latinx) (e.g., OR for ICU admission in Latinx participants 0.77 [95%CI 0.62–0.95], OR for ICU admissioni in non-Latinx participants 0.94 [95%CI 0.89–1.00], p for interaction = 0.044). Associations of statin use with mortality differed across strata of age, race/ethnicity (white vs. non-white and Black vs. non-Black), and BMI (e.g., OR for mortality in Black participants 0.83 [95%CI 0.76–0.92], OR for mortality in non-Black participants 0.77 [95%CI 0.74–0.81], p for interaction = 0.006). Associations did not differ across strata of prevalent diabetes, hypertension, or CVD (**Supplementary Fig. 1–3**).

Compared to persons with SARS-CoV-2 infection, OR for all three outcomes were significantly lower in persons without SARS-CoV-2 infection, as reflected by p<0.001 for the interaction term of SARS-CoV-2*statin use in all three models. Among SARS-COV-2 negative individuals, statin use was associated with lower odds of hospitalization (OR 0.79 [95%CI 0.77–0.80]), ICU admission (OR 0.86 [95%CI 0.81–0.90]), and death at 30 days (OR 0.60 [95%CI 0.58–0.62]). (**Table 2a**).

DISCUSSION

In this cohort of U.S. Veterans with (n=231,154) and without (n=4,570,252) a positive respiratory swab for SARS-CoV-2, statin use was independently associated with lower odds of death at 30 days compared to no statin use, but this association over a similar time period was significantly stronger among Veterans without a positive respiratory swab for SARS-CoV-2. Among individuals with and without a positive respiratory swab for SARS-CoV-2, adjusting for prior statin use attenuated the association of statin use with all outcomes; however, in every case the magnitude of the association remained substantially greater among individuals without a diagnosis of COVID-19. Associations were similar for specific statins, and receipt of high-potency statin was not associated with lower odds of any outcome compared to moderate and low potency, except for a small difference in the odds of hospitalization. Associations were not significantly different in strata of prevalent diabetes, hypertension, or cardiovascular disease. Furthermore, the lack of a gradient of effect with statin potency also does not support a potential causal benefit of statin use. Taken together, these results suggest that while statin use is associated with lower mortality among individuals with a positive swab for SARS-CoV-2, the benefit is actually smaller for than it is for those without evidence of SARS-CoV-2 infection and does not support a possible anti-COVID effect of statin treatment. It is important to note, however, that the current study does not demonstrate a harmful effect of statin use among individuals with COVID-19, only that statins may not exert a SARS-CoV-2-specific protective effect and/or that positive findings in previous observational studies may be due to residual confounding. Current findings therefore do not support statin cessation among individuals with COVID-19.

Use of negative controls is an important technique to detect confounding or other sources of bias in epidemiological studies[16] that has gone underutilized in the era of COVID-19 research. An instructive example

is the association of pneumonia or influenza vaccination with all-cause mortality seen in elderly individuals despite rigorous control for confounding by factors related to overall health status[17]. Using negative controls, Jackson et al. examined the association of vaccination with a negative control outcome: mortality prior to influenza season[18]. They found a stronger association with mortality during the period prior to influenza season compared to during or after, a biologically implausible result that was attributed by the authors to preferential receipt of vaccines by healthy individuals. This source of bias is now recognized in studies of this topic[19]. While the use of a negative control outcome is not precisely analogous to the methods used in the current study, the example can inform interpretation of the current findings.

Several recent systematic reviews and meta-analyses have examined the association of prior statin use with short-term outcomes after COVID-19[2 20-25]. Many of these reported an inverse association of statin use at diagnosis with mortality. For example, statin use was associated with a lower hazard of death (HR 0.72 [95%CI 0.69–0.75]) in a large population-based study of English patients with diabetes independent of age and co-morbid CVD[26]. In a recent nationwide U.S. study of hospitalized individuals (n=10,541), outpatient statin, either alone or with blood pressure-lowering medications, was associated with lower odds of in-hospital death (OR 0.59 [95%CI 0.50–0.69]). The magnitude of the association of statin use at diagnosis with mortality reported in these and other analyses is quite similar to the OR in the current report among individuals with COVID-19 in models that were not adjusted for prior statin use (OR for death at 30 days 0.78 [95% CI 0.75–0.82]), likely reflecting similar strategies for confounder adjustment. The lower COVID-19 mortality risk among statin users, however, is not a universal finding. In fact, among French hospitalized patients with diabetes, statin use at diagnosis was associated with higher odds of death at 28 days (OR 1.46 [95% CI 1.08–1.95])[27]. Reasons for these disparate findings are unclear but may be due in part to differences in timing, as early in the pandemic, treatments such as dexamethasone and remdesivir were not widely used. Consistent with this, in the French cohort mortality was about 21% at 28 days, considerably higher than our overall 30-day mortality rate of about 7%. No prior study to our knowledge has examined outcomes following statin use comparing SARS-CoV-2 infected and uninfected statin users.

We did not examine in-hospital statin continuation in the current analysis—a question which remains unaddressed—but instead focused on the association between statin use prior to COVID diagnosis and outcomes, where use of this medication would not have been confounded by the onset of COVID. Methodological issues (most importantly residual confounding by indication and heterogeneity of the populations studied) limit the conclusions that can be drawn from earlier observational studies of statin continuation at hospitalization. Masana et al. examined associations of statin use with in-hospital mortality in a cohort of hospitalized Spanish patients with a positive test for SARS-CoV-2[28] comparing statin non-users, users who continued statins during hospitalization, and users who stopped statins during hospitalization. Overall, 25.7% of non-users died, while 19.8% of continued users died, and 17.4% of stoppers died. In that analysis, matching was used to account for differences in pre-admission characteristics; however, the authors were not able to account for characteristics (e.g., severity of COVID-19 illness, perceived prognosis, goals of care, etc.) that might impact the decision to stop statin therapy at the time of admission. In a meta-analysis, Permana et al. examined associations of pre-admission statin use and in-hospital statin use among patients hospitalized after a positive test for SARS-CoV-2[21], which is a related question. In-hospital but not pre-admission statin use was associated with a lower risk of mortality; however, these pre-admission and in-hospital study populations differed in characteristics such as age and sex that are strongly associated with adverse COVID-19 outcomes, limiting direct comparisons between the groups. Given the many possible determinants of statin cessation or continuation following the diagnosis of COVID-19 potentially related to adverse outcomes that would be difficult to extract from medical records (electronic or otherwise), the question of whether to cease or initiate statins following COVID diagnosis will be best determined by a clinical trial.

We noted several differences in outcomes associated with statin use by certain characteristics such as sex, age, and race (Supplementary Fig. 1-3). As our main analysis did not show evidence of a lower risk of outcomes associated with statin use confined to COVID-19 infected participants, these interactions likely reflect associations independent of presence of this infection and therefore reflecting effect modification between statin use, stratum variables, and outcomes of interest.

Our study has several strengths, most importantly a large, well characterized national sample. To our knowledge, this is the largest observational study of prior statin use and adverse outcomes from SARS-CoV-2 in the United States (n=4,801,406) as well as the first to formally assess and compare statin effects seen in SARS-CoV-2 infection using a negative control (non-infected statin users). Second, we used several methods designed to mitigate or quantify bias due to unmeasured confounding. We: 1) constructed a DAG to estimate the minimal sufficient adjustment set to estimate the total effect of statin use on 30-day outcomes; 2) compared associations in SARS-CoV-2 infected individuals and an uninfected comparator sample; and 3) conducted dose-response analyses using statin potency to reflect dose. In addition, most VHA enrollees receive medical care and medications without cost, which likely decreases the contribution of unmeasured financial factors to differences in the quality of care received and most importantly to receipt of statin medications. Our results should be considered within the context of several limitations. The VHA population is generally older, with lower income and socioeconomic status[29] than the U.S. population as a whole, and our findings may not be generalizable to non-VHA populations. Additionally, the proportion of women was low (13%); however, although women comprised only a small proportion of the sample, the number of female participants (n=601,765) is adequate for robust statistical inference. We were also unable to capture hospitalizations or some outpatient prescriptions that occurred outside VHA. This is an important source of potential bias should propensity to seek outside care be associated with likelihood of receiving a statin, although VHA users are asked to provide notification within 72 hours of an outside hospital admission, and when possible are transferred to a VHA facility, which would then be captured in the VHA electronic health record. Given the timing of this study, we were unable to evaluate mediating or moderating effects of vaccination use due to very limited vaccination coverage of our population by the index date. No data were available on prescription adherence; however, statin discontinuation rates have previously shown to be low in VHA patients relative to discontinuation of other lipid-lowering medications[30]. The comparison of all-cause mortality is in our opinion the best outcome by which to assess whether statin use benefitted patients with versus without SARS-CoV-2 infection. The comparison of admission to hospital or ICU is of less value given that the reasons for hospitalization likely differed greatly by presence of infection, but, nevertheless, are of value in demonstrating that no apparent benefit is seen that might not be reflected in overall mortality. Finally, not all individuals in the comparator group were tested for SARS-CoV-2, so we were unable to exclude the possibility that some SARS-

CoV-2–positive participants with asymptomatic or mild disease were misclassified as SARS-CoV-2–negative. We elected to include individuals without SARS-CoV-2 tests because individuals with indications for SARS-CoV-2 testing may represent a particular (and sicker) population than the general group of VA enrollees as a whole. Further, based on the current results, inclusion of individuals with undiagnosed COVID-19 in the SARS-CoV-2–negative comparator group would be expected to attenuate observed differences in the associations of statin use with adverse outcomes between the SARS-CoV-2 infected and negative comparator groups. It is unlikely that exclusion of participants with undiagnosed COVID-19 from the comparator group would have resulted in a reduction in the observed negative association between statin use and mortality, as this would have required an opposite association to be present between undiagnosed COVID-19 infection and mortality, a possibility for which there is little reason or evidence to support.

CONCLUSIONS

In conclusion, statin use is associated with lower odds of 30-day mortality both among U.S. Veterans with or without a positive respiratory swab for SARS-CoV-2 indicating that statins may not exert COVID-19-specific beneficial effects.

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DATA AVAILABILITY STATEMENT. Access to VA electronic health records data is limited to researchers with active, VA appointments and an IRB-approved protocol.

CONTRIBUTORSHIP. PLW conceived the project, designed the overall research plan, and wrote the first draft of the manuscript. EL analyzed the data and reviewed/edited the manuscript, LB contributed to the conception of the work and reviewed/edited the manuscript, LTP contributed to the conception of the work and reviewed/edited the manuscript, AK contributed to design/interpretation of the analyses and reviewed/edited

the manuscript, AP contributed to the design/interpretation of the analyses and reviewed/edited the manuscript. SEK contributed to the conception of the work and reviewed/edited the manuscript. GD contributed to the design/interpretation of the analyses and reviewed/edited the manuscript. EJB conceived the project, designed the overall research plan, and reviewed/edited the manuscript.

ETHICS STATEMENT. The study was approved by the institutional review board at VA Puget Sound Health Care System, Seattle, WA, USA (#01897). The requirement for informed consent was waived.

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Table 1. Characteristics of VHA Veterans with and without a positive respiratory swab for SARS-CoV-2 (March 1, 2020–March 10, 2021), stratified by presence of an active statin prescription at enrollment

	Overall		No positive respiratory swab for SARS-CoV-2				≥1 positive respiratory swab for SARS-CoV-2			
	n=4,801,406		No statin prescription n=3,180,888		Active statin prescription n=1,389,364		No statin prescription n=161,891		Active statin prescription n=69,263	
Age, years	61.6	±16.7	58.3	±17.7	69.3	±10.8	57.8	±17.5	68.0	±11.4
Age category, years										
19-39	661,777	14%	613,885	19%	15,272	1%	31,645	20%	975	1%
40-49	482,871	10%	402,201	13%	54,467	4%	22,718	14%	3,485	5%
50-59	728,340	15%	516,328	16%	172,006	12%	29,099	18%	10,907	16%
60-69	993,105	21%	600,530	19%	346,361	25%	28,785	18%	17,429	25%
70-79	1,408,065	29%	735,949	23%	610,855	44%	33,303	21%	27,958	40%
80+	525,548	11%	311,010	10%	189,825	14%	16,204	10%	8,509	12%
Sex at birth, female	601,692	13%	509,443	16%	68,275	5%	20,598	13%	3,376	5%
Race/ethnicity										
White	3,335,105	69%	2,122,989	67%	1,055,742	76%	106,448	66%	49,926	72%
Black	860,829	18%	582,091	18%	226,384	16%	38,080	24%	14,274	21%
Hispanic	333,593	7%	230,848	7%	79,866	6%	17,770	11%	5,109	7%
Other	542,562	11%	430,377	14%	94,575	7%	13,410	8%	4,200	6%
Body-mass index, kg/m²	30.2	±6.09	29.8	±6.04	30.8	±6.06	30.9	±6.35	31.9	±6.26
Body-mass index category, kg/m²										
<18.5	28,116	1%	20,717	1%	6,230	1%	951	1%	218	0%
18.5-24.9	553,988	17%	379,204	20%	152,657	14%	16,249	15%	5,878	11%
25-29.9	1,107,238	35%	687,781	36%	367,799	34%	34,949	32%	16,709	30%
30-34.9	869,628	27%	507,893	26%	313,277	29%	30,944	29%	17,514	32%
35-39.9	399,754	13%	224,651	12%	149,833	14%	15,734	15%	9,536	17%
≥ 40	208,950	7%	113,491	6%	80,708	8%	9,077	8%	5,674	10%
Active statin prescription six months prior to enrollment	1,375,009	29%	259,070	8%	1,046,850	75%	17,020	11%	52,069	75%
Never	1,747,387	36%	1,338,452	42%	328,440	24%	62,782	39%	17,713	26%
Former	1,729,275	36%	984,318	31%	651,438	47%	58,321	36%	35,198	51%
Current	1,323,044	28%	857,133	27%	408,908	29%	40,651	25%	16,352	24%
Urban/rural/highly rural ZIP code										
Highly rural	57,047	1%	34,211	1%	20,620	1%	1,360	1%	856	1%
Rural	1,561,076	33%	975,607	31%	518,394	37%	43,690	27%	23,385	34%
Urban	3,172,176	66%	2,163,063	68%	847,474	61%	116,643	72%	44,996	65%
Unknown	9,407	0%	7,022	0%	2,298	0%	61	0%	26	0%
Estimated glomerular filtration rate, ml/min/1.73 m²										
≥ 90	938,310	27%	654,399	31%	235,893	20%	36,230	32%	11,788	19%
60-89	1,718,393	49%	1,034,287	49%	599,357	50%	54,598	48%	30,151	48%
45-59	520,635	15%	268,392	13%	226,556	19%	13,799	12%	11,888	19%
30-44	212,116	6%	100,776	5%	100,175	8%	5,626	5%	5,539	9%
15-29	58,464	2%	27,223	1%	27,527	2%	1,906	2%	1,808	3%
<15 or dialysis	25,765	1%	12,803	1%	10,449	1%	1,503	1%	1,010	2%

Table 1 CONTINUED. Characteristics of VHA Veterans with and without a positive respiratory swab for SARS-CoV-2 (March 1, 2020–March 10, 2021), stratified by presence of an active statin prescription at enrollment

Diabetes	1,482,197	31%	679,909	21%	716,920	52%	44,364	27%	41,004	59%
Hypertension	2,874,378	60%	1,551,529	49%	1,176,398	85%	86,382	53%	60,069	87%
Cardiovascular disease	1,749,197	36%	857,912	27%	794,940	57%	53,635	33%	42,710	62%
Heart failure	352,710	7%	144,971	5%	183,128	13%	12,388	8%	12,223	18%
Alcohol use disorder	909,010	19%	629,005	20%	238,333	17%	31,212	19%	10,460	15%
Statin prescribed										
None	3,341,657	70%	3,179,903	100%	0	0%	161,754	100%	0	0%
Atorvastatin	872,981	18%			829,795	60%			43,186	62%
Fluvastatin	364	<1%			348	0%			16	0%
Lovastatin	15,375	<1%			14,751	1%			624	1%
Pitavastatin	801	<1%			748	<1%			53	<1%
Pravastatin	123,779	3%			118,039	8%			5,740	8%
Rosuvastatin	173,943	4%			165,066	12%			8,877	13%
Simvastatin	270,806	6%			260,039	19%			10,767	16%
High-potency statin (vs. low- or moderate-potency)*	616,824	42%	0	<1%	585,224	42%	0	<1%	31,600	46%
Mean hsCRP in the prior six months, mg/L**	17.3	±136	16.4	±151	18.2	±120	19.9	±49.6	21.0	±52.9
hsCRP in the prior six months ≥2 mg/L**	390,796	41%	217,408	40%	145,787	42%	17,407	44%	10,194	45%
Mean hsCRP at or after the index date, mg/L***	29.3	±54.1	22.2	±46.6	25.6	±50.8	57.8	±70.8	65.2	±71.1
hsCRP at or after the index date ≤2 mg/L***	125,178	52%	61,501	46%	34,630	49%	18,260	75%	10,787	79%
OUTCOMES										
Hospital admission within 30 days	124,094	3%	61,651	2%	29,953	2%	20,280	13%	12,210	18%
ICU admission within 30 days	15,438	<1%	5,710	<1%	3,588	<1%	3,754	2%	2,386	3%
Death w/in 30 days	31,409	1%	13,074	<1%	6,224	<1%	7,815	5%	4,296	6%

Data are presented as mean ± standard deviation (SD) for continuous variables and n (%) for categorical variables

p-values for global differences in participant characteristics across categories of COVID diagnosis and prior statin use all <0.001

* based on estimated % LDL-c reduction

** up to 14 days prior to index date (Overall n=958,343)

*** Overall n=224,930

Table 2a. Odds ratios from logistic regression models testing the association of active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2, including adjustment for prior statin use

	No positive swab, n=4,568,689						≥1 positive swab, n=231,017					
	Hospital admission		ICU admission		Death		Hospital admission		ICU admission		Death	
	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI	OR	95%CI
Active statin prescription at enrollment	0.79	0.77 — 0.80	0.98	0.95 — 1.01	0.86	0.81 — 0.90	0.94	0.88 — 1.01	0.60	0.58 — 0.62	0.81	0.77 — 0.85
Statin prescription six months prior to enrollment	0.91	0.89 — 0.93	0.93	0.90 — 0.96	0.88	0.83 — 0.93	0.97	0.91 — 1.04	0.93	0.90 — 0.97	0.94	0.89 — 0.99
Sex at birth, female	0.73	0.71 — 0.75	0.75	0.71 — 0.79	0.73	0.67 — 0.80	0.74	0.65 — 0.84	0.63	0.58 — 0.69	0.56	0.50 — 0.64
Age category, years												
19-39	1.16	1.12 — 1.19	0.61	0.57 — 0.65	0.61	0.54 — 0.69	0.60	0.51 — 0.71	0.26	0.22 — 0.30	0.15	0.11 — 0.21
40-49	0.97	0.94 — 1.01	0.75	0.70 — 0.80	0.81	0.73 — 0.91	0.68	0.59 — 0.79	0.46	0.40 — 0.54	0.38	0.30 — 0.48
50-59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-69	1.01	0.99 — 1.03	1.29	1.23 — 1.34	1.16	1.08 — 1.25	1.32	1.21 — 1.46	1.95	1.81 — 2.10	2.86	2.55 — 3.20
70-79	0.81	0.79 — 0.83	1.43	1.37 — 1.49	1.00	0.92 — 1.08	1.49	1.36 — 1.64	2.60	2.41 — 2.79	5.93	5.32 — 6.61
≥80	0.96	0.93 — 0.99	1.81	1.71 — 1.91	0.95	0.87 — 1.04	1.62	1.45 — 1.82	5.06	4.68 — 5.46	13.86	12.37 — 15.53
White (vs not white)	1.21	1.14 — 1.28	0.88	0.81 — 0.97	1.23	1.02 — 1.49	0.74	0.61 — 0.91	1.10	0.95 — 1.27	0.87	0.74 — 1.04
Black vs(not Black)	1.49	1.40 — 1.58	1.36	1.24 — 1.50	1.53	1.26 — 1.85	1.10	0.89 — 1.35	1.05	0.90 — 1.22	0.78	0.66 — 0.94
Hispanic (vs not Hispanic)	1.07	1.04 — 1.10	1.16	1.10 — 1.22	1.23	1.13 — 1.35	1.03	0.92 — 1.15	1.07	0.99 — 1.14	1.13	1.04 — 1.24
Body-mass index category, kg/m²												
<18.5	1.35	1.29 — 1.42	1.14	1.01 — 1.29	1.51	1.31 — 1.73	1.35	1.06 — 1.72	2.48	2.33 — 2.65	1.81	1.59 — 2.07
18.5-24.9	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-29.9	0.75	0.73 — 0.76	0.81	0.78 — 0.85	0.70	0.65 — 0.74	0.89	0.82 — 0.97	0.54	0.52 — 0.56	0.73	0.68 — 0.79
30-34.9	0.67	0.65 — 0.68	0.76	0.73 — 0.80	0.62	0.57 — 0.66	0.88	0.81 — 0.96	0.42	0.40 — 0.44	0.69	0.64 — 0.74
35-39.9	0.63	0.61 — 0.65	0.76	0.72 — 0.80	0.57	0.52 — 0.62	0.85	0.76 — 0.94	0.37	0.35 — 0.40	0.64	0.59 — 0.70
≥40	0.65	0.63 — 0.67	0.87	0.82 — 0.93	0.59	0.53 — 0.65	1.03	0.91 — 1.16	0.43	0.39 — 0.46	0.80	0.72 — 0.88
Tobacco use												
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.23 — 1.28	1.11	1.08 — 1.15	1.12	1.06 — 1.19	1.10	1.02 — 1.17	1.09	1.04 — 1.13	1.18	1.12 — 1.24
Current	2.02	1.98 — 2.06	1.39	1.35 — 1.44	1.76	1.66 — 1.87	1.29	1.20 — 1.39	1.67	1.60 — 1.74	1.24	1.17 — 1.32
Urban/rural/highly rural residence												
Highly rural	0.68	0.64 — 0.73	0.58	0.50 — 0.66	0.98	0.82 — 1.18	0.74	0.54 — 1.00	0.92	0.81 — 1.05	1.16	0.98 — 1.38
Rural	0.74	0.73 — 0.75	0.70	0.68 — 0.72	0.74	0.70 — 0.78	0.88	0.82 — 0.93	0.89	0.87 — 0.92	1.03	0.99 — 1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18 — 0.35	0.27	0.10 — 0.75	0.35	0.13 — 0.94	0.55	0.08 — 3.99	0.80	0.51 — 1.25	1.77	0.73 — 4.30
Diabetes	1.18	1.16 — 1.20	1.30	1.27 — 1.34	1.26	1.21 — 1.32	1.26	1.19 — 1.34	1.41	1.36 — 1.45	1.37	1.31 — 1.43
Hypertension	1.22	1.19 — 1.24	1.30	1.25 — 1.35	1.30	1.22 — 1.39	1.29	1.19 — 1.41	1.09	1.04 — 1.14	0.96	0.90 — 1.02
Cardiovascular disease	2.04	2.01 — 2.08	1.84	1.79 — 1.90	2.69	2.55 — 2.84	2.08	1.95 — 2.23	1.88	1.81 — 1.95	1.24	1.18 — 1.30
Heart failure	2.13	2.09 — 2.16	1.64	1.59 — 1.70	2.34	2.22 — 2.46	1.53	1.43 — 1.63	2.51	2.42 — 2.59	1.31	1.25 — 1.38
Alcohol use disorder	1.12	1.10 — 1.14	0.75	0.72 — 0.78	1.03	0.97 — 1.09	0.86	0.79 — 0.93	0.78	0.75 — 0.82	0.68	0.64 — 0.73
Estimated glomerular filtration rate, ml/min/1.73 m²												
≥ 90	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-89	0.80	0.79 — 0.82	0.90	0.87 — 0.93	0.80	0.76 — 0.85	0.96	0.88 — 1.04	0.60	0.57 — 0.62	1.10	1.02 — 1.18
45-59	0.84	0.81 — 0.86	0.99	0.94 — 1.03	0.84	0.78 — 0.91	1.00	0.91 — 1.10	0.71	0.67 — 0.74	1.44	1.33 — 1.56
30-44	0.93	0.90 — 0.96	1.10	1.04 — 1.16	0.92	0.84 — 1.01	1.14	1.02 — 1.29	0.99	0.93 — 1.05	1.83	1.68 — 1.99
15-29	1.15	1.10 — 1.20	1.31	1.21 — 1.42	1.14	1.01 — 1.29	1.32	1.14 — 1.53	2.07	1.94 — 2.21	2.65	2.36 — 2.97
<15 or dialysis	1.60	1.52 — 1.69	1.46	1.33 — 1.60	1.77	1.56 — 2.00	1.51	1.29 — 1.77	3.07	2.85 — 3.32	2.48	2.16 — 2.85

Models additionally adjusted for index month and geographic location by Veterans Integrated Service Network location

Table 2b. Odds ratios from logistic regression models testing the association of active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2, without adjustment for prior statin use

	No positive swab, n=4,568,689									≥1 positive swab, n=231,017								
	Hospital admission			ICU admission			Death			Hospital admission			ICU admission			Death		
	OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI		OR	95%CI	
Active statin prescription at enrollment	0.75	0.74 —	0.76	0.80	0.76 —	0.83	0.58	0.56 —	0.59	0.94	0.91 —	0.96	0.93	0.88 —	0.98	0.78	0.75 —	0.82
Sex at birth, female	0.73	0.71 —	0.75	0.73	0.67 —	0.81	0.63	0.58 —	0.69	0.75	0.71 —	0.79	0.74	0.65 —	0.84	0.57	0.50 —	0.65
Age category, years																		
19-39	1.16	1.13 —	1.20	0.61	0.54 —	0.69	0.26	0.22 —	0.30	0.61	0.58 —	0.66	0.60	0.51 —	0.71	0.15	0.11 —	0.21
40-49	0.98	0.95 —	1.01	0.82	0.73 —	0.92	0.47	0.40 —	0.54	0.75	0.71 —	0.80	0.68	0.59 —	0.79	0.38	0.30 —	0.48
50-59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-69	1.01	0.98 —	1.03	1.16	1.08 —	1.25	1.95	1.81 —	2.10	1.28	1.23 —	1.34	1.32	1.21 —	1.45	2.86	2.55 —	3.20
70-79	0.81	0.79 —	0.83	0.99	0.92 —	1.07	2.59	2.41 —	2.78	1.43	1.36 —	1.49	1.49	1.36 —	1.64	5.92	5.31 —	6.60
≥80	0.96	0.93 —	0.99	0.95	0.87 —	1.04	5.06	4.68 —	5.46	1.81	1.71 —	1.91	1.62	1.45 —	1.82	13.86	12.37 —	15.53
White (vs not white)	1.20	1.14 —	1.28	1.23	1.02 —	1.49	1.10	0.95 —	1.27	0.88	0.81 —	0.97	0.75	0.61 —	0.91	0.87	0.74 —	1.04
Black vs(not Black)	1.49	1.40 —	1.58	1.53	1.26 —	1.86	1.05	0.90 —	1.22	1.37	1.24 —	1.50	1.10	0.89 —	1.35	0.78	0.66 —	0.94
Hispanic (vs not Hispanic)	1.07	1.04 —	1.10	1.23	1.13 —	1.35	1.06	0.99 —	1.14	1.16	1.10 —	1.22	1.03	0.92 —	1.15	1.13	1.04 —	1.24
Body-mass index category, kg/m²																		
<18.5	1.35	1.29 —	1.42	1.51	1.32 —	1.74	2.49	2.33 —	2.65	1.14	1.02 —	1.29	1.35	1.06 —	1.72	1.82	1.59 —	2.07
18.5-24.9	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
25-29.9	0.75	0.73 —	0.76	0.70	0.65 —	0.74	0.54	0.52 —	0.56	0.81	0.78 —	0.85	0.89	0.82 —	0.97	0.73	0.68 —	0.79
30-34.9	0.67	0.65 —	0.68	0.61	0.57 —	0.66	0.42	0.40 —	0.44	0.76	0.73 —	0.80	0.88	0.81 —	0.96	0.68	0.64 —	0.74
35-39.9	0.63	0.61 —	0.64	0.57	0.52 —	0.62	0.37	0.35 —	0.40	0.76	0.72 —	0.80	0.85	0.76 —	0.94	0.64	0.59 —	0.70
≥40	0.65	0.63 —	0.67	0.58	0.53 —	0.65	0.43	0.39 —	0.46	0.87	0.81 —	0.92	1.03	0.91 —	1.16	0.79	0.72 —	0.88
Tobacco use																		
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.22 —	1.27	1.12	1.05 —	1.19	1.09	1.04 —	1.13	1.11	1.08 —	1.15	1.10	1.02 —	1.17	1.18	1.12 —	1.24
Current	2.02	1.98 —	2.05	1.76	1.66 —	1.87	1.66	1.60 —	1.74	1.39	1.35 —	1.44	1.29	1.20 —	1.39	1.24	1.17 —	1.32
Urban/rural/highly rural residence																		
Highly rural	0.68	0.64 —	0.73	0.98	0.82 —	1.18	0.92	0.81 —	1.05	0.57	0.50 —	0.66	0.74	0.54 —	1.00	1.16	0.98 —	1.38
Rural	0.74	0.73 —	0.75	0.74	0.70 —	0.78	0.89	0.86 —	0.92	0.70	0.68 —	0.72	0.87	0.82 —	0.93	1.03	0.99 —	1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18 —	0.35	0.35	0.13 —	0.94	0.80	0.51 —	1.25	0.27	0.10 —	0.74	0.55	0.08 —	3.98	1.75	0.72 —	4.27
Diabetes	1.17	1.15 —	1.19	1.25	1.20 —	1.31	1.40	1.36 —	1.45	1.30	1.26 —	1.33	1.26	1.19 —	1.33	1.36	1.30 —	1.42
Hypertension	1.21	1.19 —	1.24	1.29	1.21 —	1.38	1.09	1.04 —	1.13	1.30	1.25 —	1.35	1.29	1.18 —	1.41	0.96	0.90 —	1.02
Cardiovascular disease	2.03	2.00 —	2.07	2.67	2.53 —	2.82	1.87	1.80 —	1.94	1.84	1.78 —	1.89	2.08	1.94 —	2.23	1.24	1.18 —	1.30
Heart failure	2.12	2.08 —	2.16	2.33	2.21 —	2.45	2.50	2.41 —	2.59	1.64	1.59 —	1.70	1.53	1.43 —	1.63	1.31	1.25 —	1.38
Alcohol use disorder	1.12	1.10 —	1.14	1.03	0.97 —	1.09	0.78	0.75 —	0.82	0.75	0.73 —	0.78	0.86	0.79 —	0.93	0.68	0.64 —	0.73
Estimated glomerular filtration rate, ml/min/1.73 m²																		
≥ 90	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60-89	0.80	0.79 —	0.82	0.80	0.75 —	0.85	0.60	0.57 —	0.62	0.90	0.86 —	0.93	0.96	0.88 —	1.04	1.09	1.02 —	1.18
45-59	0.84	0.81 —	0.86	0.84	0.78 —	0.91	0.71	0.67 —	0.74	0.98	0.94 —	1.03	1.00	0.91 —	1.09	1.44	1.33 —	1.56
30-44	0.93	0.90 —	0.96	0.92	0.84 —	1.01	0.99	0.93 —	1.05	1.10	1.04 —	1.16	1.14	1.02 —	1.29	1.83	1.68 —	1.99
15-29	1.14	1.09 —	1.20	1.14	1.01 —	1.29	2.07	1.94 —	2.21	1.31	1.21 —	1.42	1.32	1.14 —	1.53	2.65	2.36 —	2.97
<15 or dialysis	1.60	1.52 —	1.69	1.77	1.56 —	2.01	3.08	2.85 —	3.32	1.46	1.33 —	1.60	1.51	1.29 —	1.77	2.48	2.16 —	2.85

Models additionally adjusted for index month and geographic location by Veterans Integrated Service Network location

Table 3. Odds ratios from logistic regression models testing the association of specific statins compared to no statin with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=231,017

	Hospital admission					ICU admission					Death				
	OR	95% CI			p value	OR	95% CI			p value	OR	95% CI			p value
No statin	ref					ref					ref				
Atorvastatin	0.98	0.95	—	1.01	0.136	0.96	0.90	—	1.02	0.194	0.80	0.76	—	0.84	<0.001
Fluvastatin	1.47	0.45	—	4.82	0.524	1.79	0.23	—	13.80	0.577	0.55	0.07	—	4.43	0.575
Lovastatin	0.73	0.57	—	0.93	0.012	0.48	0.26	—	0.90	0.022	0.64	0.45	—	0.91	0.013
Pitavastatin	0.45	0.16	—	1.26	0.128	0.66	0.09	—	4.80	0.679	0.82	0.25	—	2.68	0.738
Pravastatin	0.93	0.86	—	1.00	0.045	0.94	0.81	—	1.10	0.443	0.78	0.70	—	0.87	<0.001
Rosuvastatin	0.81	0.76	—	0.86	<0.001	0.82	0.72	—	0.93	0.002	0.72	0.65	—	0.79	<0.001
Simvastatin	0.91	0.86	—	0.97	0.001	0.91	0.80	—	1.02	0.107	0.77	0.71	—	0.84	<0.001
Sex at birth, female	0.75	0.71	—	0.80	<0.001	0.74	0.65	—	0.84	<0.001	0.57	0.50	—	0.65	<0.001
Age category, years															
19-39	0.61	0.58	—	0.66	<0.001	0.60	0.51	—	0.71	<0.001	0.15	0.11	—	0.21	<0.001
40-49	0.75	0.71	—	0.80	<0.001	0.68	0.59	—	0.79	<0.001	0.38	0.30	—	0.48	<0.001
50-59	ref					ref					ref				
60-69	1.28	1.23	—	1.34	<0.001	1.32	1.21	—	1.45	<0.001	2.85	2.55	—	3.20	<0.001
70-79	1.43	1.36	—	1.49	<0.001	1.49	1.36	—	1.64	<0.001	5.92	5.31	—	6.60	<0.001
≥80	1.81	1.71	—	1.91	<0.001	1.62	1.45	—	1.82	<0.001	13.86	12.37	—	15.54	<0.001
White (vs. not white)	0.88	0.81	—	0.97	0.007	0.75	0.61	—	0.91	0.004	0.88	0.74	—	1.04	0.121
Black (vs. not Black)	1.36	1.24	—	1.50	<0.001	1.10	0.89	—	1.35	0.390	0.78	0.66	—	0.94	0.007
Hispanic (vs. not Hispanic)	1.16	1.10	—	1.22	<0.001	1.03	0.92	—	1.15	0.633	1.13	1.04	—	1.24	0.007
Body-mass index category, kg/m²															
<18.5	1.15	1.02	—	1.29	0.025	1.35	1.06	—	1.73	0.015	1.82	1.59	—	2.08	<0.001
18.5-24.9	ref					ref					ref				
25-29.9	0.81	0.78	—	0.85	<0.001	0.89	0.82	—	0.97	0.006	0.73	0.68	—	0.79	<0.001
30-34.9	0.76	0.73	—	0.80	<0.001	0.88	0.81	—	0.97	0.006	0.68	0.64	—	0.74	<0.001
35-39.9	0.76	0.72	—	0.80	<0.001	0.85	0.76	—	0.94	0.002	0.64	0.59	—	0.70	<0.001
≥40	0.87	0.81	—	0.92	<0.001	1.03	0.91	—	1.16	0.675	0.79	0.72	—	0.88	<0.001
Tobacco use															
Never	ref														
Former	1.11	1.08	—	1.15	<0.001	1.10	1.02	—	1.17	0.010	1.18	1.12	—	1.24	<0.001
Current	1.39	1.35	—	1.44	<0.001	1.29	1.20	—	1.39	<0.001	1.24	1.17	—	1.32	<0.001
Urban/rural/highly rural residence															
Highly rural	0.57	0.50	—	0.66	<0.001	0.74	0.54	—	1.00	0.051	1.16	0.97	—	1.38	0.096
Rural	0.70	0.68	—	0.72	<0.001	0.88	0.82	—	0.93	<0.001	1.04	0.99	—	1.08	0.140
Urban	ref					ref					ref				
Unknown	0.27	0.10	—	0.74	0.011	0.55	0.08	—	3.96	0.549	1.75	0.72	—	4.25	0.220
Diabetes	1.29	1.26	—	1.33	<0.001	1.26	1.19	—	1.33	<0.001	1.36	1.30	—	1.42	<0.001
Hypertension	1.30	1.25	—	1.35	<0.001	1.29	1.18	—	1.41	<0.001	0.96	0.90	—	1.02	0.149
Cardiovascular disease	1.84	1.78	—	1.89	<0.001	2.08	1.94	—	2.23	<0.001	1.24	1.18	—	1.30	<0.001
Heart failure	1.64	1.58	—	1.69	<0.001	1.53	1.43	—	1.63	<0.001	1.31	1.25	—	1.38	<0.001
Alcohol use disorder	0.75	0.73	—	0.78	<0.001	0.86	0.79	—	0.93	<0.001	0.69	0.64	—	0.73	<0.001

Table 3 CONTINUED. Odds ratios from logistic regression models testing the association of individual statins compared to no statin with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=231,017

Estimated glomerular filtration rate, ml/min/1.73 m²															
≥ 90	ref					ref					ref				
60-89	0.90	0.87	—	0.93	<0.001	0.96	0.88	—	1.04	0.273	1.10	1.02	—	1.18	0.018
45-59	0.99	0.94	—	1.03	0.519	1.00	0.91	—	1.10	0.941	1.44	1.33	—	1.56	<0.001
30-44	1.10	1.04	—	1.16	0.001	1.15	1.02	—	1.29	0.024	1.83	1.68	—	1.99	<0.001
15-29	1.31	1.21	—	1.42	<0.001	1.32	1.14	—	1.53	<0.001	2.65	2.36	—	2.97	<0.001
<15 or dialysis	1.45	1.32	—	1.59	<0.001	1.51	1.29	—	1.77	<0.001	2.48	2.16	—	2.84	<0.001

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location; not adjusted for the presence of an active statin prescription six months prior to enrollment

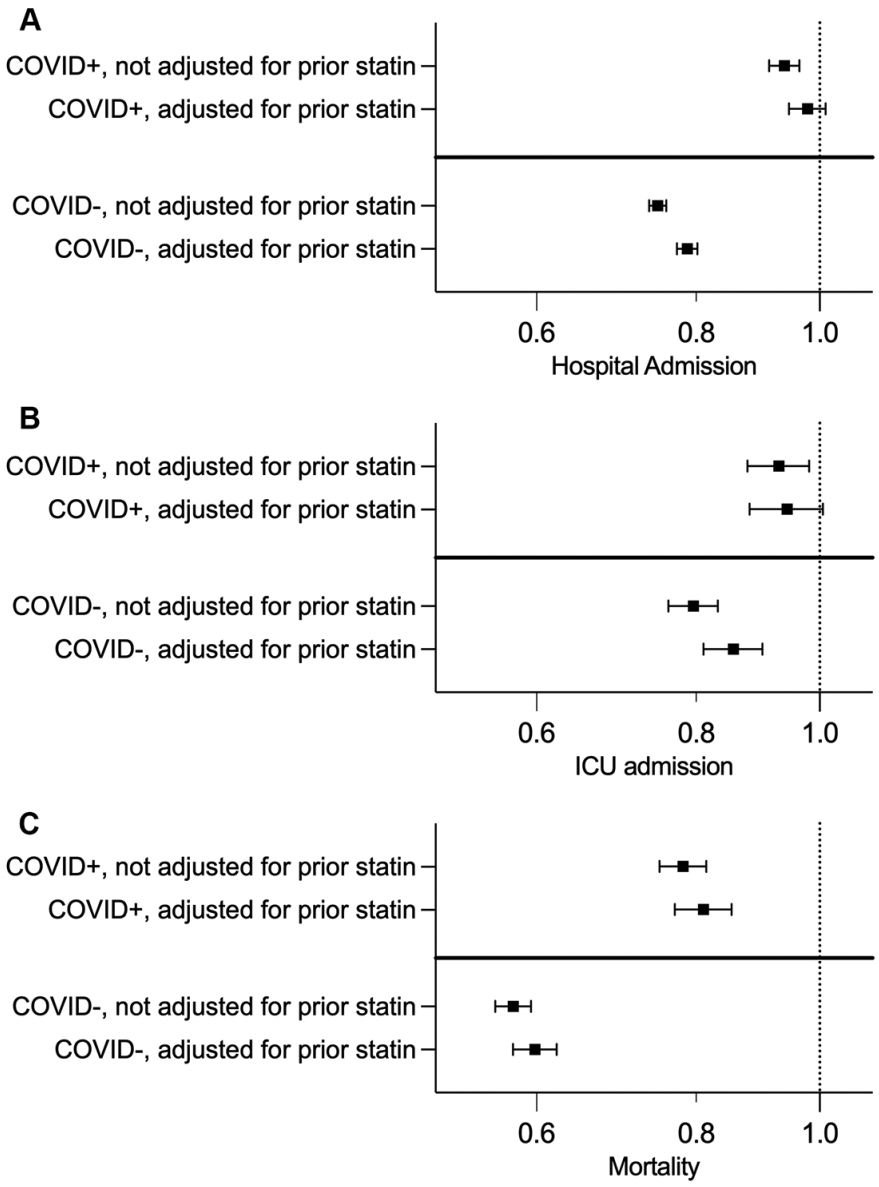
Table 4. Odds ratios from logistic regression models testing the association of low- or moderate- vs. high-potency active statin prescription at enrollment with adverse 30-day outcomes among VHA Veterans with a positive respiratory swab for SARS-CoV-2, n=69,263

	Hospital admission					ICU admission					Death				
	OR	95% CI			p value	OR	95% CI			p value	OR	95% CI			p value
High-potency statin	1.06	1.01	—	1.10	0.011	1.05	0.96	—	1.15	0.258	0.97	0.91	—	1.04	0.407
Sex at birth, female	0.89	0.80	—	1.00	0.041	0.95	0.75	—	1.19	0.634	0.52	0.40	—	0.68	<0.001
Age category, years															
19-39	0.82	0.63	—	1.06	0.123	0.46	0.22	—	0.98	0.045	0.10	0.01	—	0.73	0.023
40-49	0.74	0.64	—	0.86	<0.001	0.55	0.38	—	0.79	0.001	0.45	0.27	—	0.75	0.002
50-59	ref					ref					ref				
60-69	1.30	1.20	—	1.40	<0.001	1.24	1.06	—	1.45	0.009	2.45	2.02	—	2.96	<0.001
70-79	1.47	1.36	—	1.58	<0.001	1.47	1.25	—	1.72	<0.001	4.42	3.67	—	5.32	<0.001
≥80	1.95	1.78	—	2.15	<0.001	1.69	1.40	—	2.04	<0.001	9.54	7.84	—	11.60	<0.001
White (vs not white)	0.81	0.69	—	0.96	0.012	0.75	0.52	—	1.08	0.118	0.85	0.64	—	1.11	0.221
Black vs(not Black)	1.31	1.10	—	1.55	0.002	1.12	0.77	—	1.63	0.545	0.80	0.60	—	1.06	0.125
Hispanic (vs not Hispanic)	1.12	1.02	—	1.22	0.013	0.91	0.75	—	1.10	0.330	1.20	1.04	—	1.38	0.014
Body-mass index category, kg/m²															
<18.5	1.04	0.79	—	1.38	0.766	1.19	0.71	—	1.98	0.511	1.45	1.02	—	2.05	0.039
18.5-24.9	ref					ref					ref				
25-29.9	0.81	0.75	—	0.86	<0.001	0.89	0.77	—	1.02	0.095	0.78	0.70	—	0.87	<0.001
30-34.9	0.78	0.73	—	0.84	<0.001	0.92	0.80	—	1.07	0.272	0.78	0.70	—	0.87	<0.001
35-39.9	0.78	0.71	—	0.85	<0.001	0.90	0.76	—	1.06	0.188	0.75	0.67	—	0.85	<0.001
≥40	0.86	0.77	—	0.95	0.002	1.08	0.89	—	1.30	0.452	0.91	0.78	—	1.06	0.221
Tobacco use															
Never	ref					ref					ref				
Former	1.18	1.12	—	1.25	<0.001	1.16	1.03	—	1.30	0.013	1.29	1.18	—	1.40	<0.001
Current	1.36	1.28	—	1.44	<0.001	1.36	1.19	—	1.55	<0.001	1.21	1.09	—	1.34	<0.001
Urban/rural/highly rural residence															
Highly rural	0.59	0.47	—	0.73	<0.001	0.93	0.61	—	1.42	0.728	1.40	1.08	—	1.82	0.011
Rural	0.68	0.65	—	0.72	<0.001	0.87	0.79	—	0.96	0.006	1.05	0.97	—	1.12	0.233
Urban	ref					ref					ref				
Unknown	0.17	0.02	—	1.26	0.083	1.69	0.22	—	12.83	0.612	1.41	0.31	—	6.48	0.662
Diabetes	1.29	1.23	—	1.35	<0.001	1.16	1.05	—	1.27	0.003	1.31	1.22	—	1.41	<0.001
Hypertension	1.28	1.18	—	1.39	<0.001	1.38	1.14	—	1.67	0.001	0.98	0.85	—	1.11	0.704
Cardiovascular disease	1.71	1.62	—	1.80	<0.001	1.96	1.75	—	2.21	<0.001	1.25	1.14	—	1.36	<0.001
Heart failure	1.68	1.60	—	1.77	<0.001	1.58	1.44	—	1.74	<0.001	1.33	1.23	—	1.43	<0.001
Alcohol use disorder	0.66	0.62	—	0.71	<0.001	0.81	0.71	—	0.94	0.004	0.69	0.61	—	0.77	<0.001
Estimated glomerular filtration rate, ml/min/1.73 m²															
≥ 90	ref					ref					ref				
60-89	0.98	0.92	—	1.05	0.625	1.05	0.91	—	1.20	0.538	1.14	1.01	—	1.29	0.041
45-59	1.08	1.00	—	1.16	0.050	1.05	0.90	—	1.24	0.530	1.58	1.37	—	1.82	<0.001
30-44	1.21	1.10	—	1.32	<0.001	1.20	1.00	—	1.44	0.055	2.00	1.72	—	2.33	<0.001
15-29	1.53	1.35	—	1.72	<0.001	1.37	1.09	—	1.72	0.007	3.19	2.69	—	3.78	<0.001
<15 or dialysis	1.64	1.42	—	1.90	<0.001	1.95	1.52	—	2.50	<0.001	3.01	2.44	—	3.73	<0.001

Models additionally adjusted for month of diagnosis and geographic location by Veterans Integrated Service Network location; not adjusted for the presence of an active statin prescription six months prior to enrollment

Figure Legend

Fig. 1. ORs and 95% confidence intervals for associations of statin use at study enrollment with A) hospitalization, B) ICU admission, and C) death at 30 days before and after adjustment for statin use six months prior to diagnosis among VHA Veterans with and without a positive respiratory swab for SARS-CoV-2. All analyses are adjusted for sex, age, race/ethnicity, BMI, tobacco use, facility location, urban/rural status, eGFR, and history of diabetes, hypertension, cardiovascular disease, heart failure, and alcohol use disorder.



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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	7
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	7

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	3

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.