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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

Pandora L Wander ,[1,2] Elliott Lowy,[1,3] Lauren A Beste,[1,2] Luis Tulloch-Palomino,[1,2] Anna Korpak,[1] Alexander C Peterson ,[1] Steven E Kahn,[1,2] Goodarz Danaei,[4] Edward J Boyko[1,2]

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[1]Veterans Affairs Puget Sound Health Care System Seattle Division, Seattle, Washington, USA
[2]Department of Medicine, University of Washington, Seattle, Washington, USA
[3]Department of Health Systems and Population Health, University of Washington, Seattle, Washington, USA
[4]Department of Global Health and Population, Harvard School of Public Health, Boston, Massachusetts, USA

Correspondence to
Dr Pandora L Wander; lwander@u.washington.edu

ABSTRACT

Objective To estimate associations of statin use with hospitalisation, 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 US Veterans Health Administration (VHA).

Participants All veterans receiving VHA healthcare with ≥1 positive nasal swab for SARS-CoV-2 between 1 March 2020 and 10 March 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-intensity/moderate-intensity versus 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 hospitalisation, 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 to 0.85)) but not with hospitalisation or ICU admission. Associations were similar comparing use of each specific statin to no statin. Compared with 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: hospitalisation OR 0.79 (95% CI 0.77 to 0.80), ICU admission OR 0.86 (95% CI 0.81 to 0.90) and death 0.60 (95% CI 0.58 to 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 with individuals without a positive test, indicating that statins do not exert SARS-CoV-2 specific effects.

Strengths and limitations of this study

- Large, well-characterised national (US) 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 hospitalisations 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 USA 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] Furthermore, preliminary findings from a randomised 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 hospitalisation, 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-intensity 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, body mass index (BMI), clinical comorbidities and C reactive protein (CRP) level prior to diagnosis.

METHODS

Study setting and population

The VHA—the largest integrated healthcare system in the USA—provides care to more than 7 million veterans at 170 medical centres and 1074 outpatient sites.[7] We used data from the Corporate Data Warehouse, 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]

Selection of the SARS-CoV-2 positive cohort

We identified all enrollees with one or more positive nasal swabs for SARS-CoV-2 between 1 March 2020 and 10 March 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 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 1 March 2020 and 31 March 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 and simvastatin. We defined prior statin use as receipt of a statin prescription with a fill date that included the time period 6 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] BMI was defined as weight in kg divided by (height in metres).[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.[11] Comorbidities (hypertension, CVD and heart failure) were identified using International Classification of Diseases (ICD)-9-Clinical Modification (CM) and ICD-10 codes entered after 1 October 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 6 months before the index date (n=27 630), we dichotomised 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 hospitalisations, ICU admissions and deaths occurring through 10 March 2021. Deaths were verified by official sources including VHA Patient Treatment File, the Beneficiary Identification Records Locator Subsystem and VA/CMS Medicare Vital Status File; Social Security Administration Death Master File; death certificates; and VHA National Cemetery Administration.[14]

Statistical analyses

We summarised 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

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

	Overall		No positive respiratory swab for SARS-CoV-2				≥1 positive respiratory swab for SARS-CoV-2			
			No statin prescription		Active statin prescription		No statin prescription		Active statin prescription	
	n=4 801 406		n=3 180 888		n=1 389 364		n=161 891		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)	19%	15 272 (1)	1%	31 645 (20)	20%	975 (1)	1%
40–49	482 871	10%	402 201	13%	54 467	4%	22 718	14%	3485	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%	8509	12%
Sex at birth, female	601 692	13%	509 443	16%	68 275	5%	20 598	13%	3376	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%	5109	7%
Other	542 562	11%	430 377	14%	94 575	7%	13 410	8%	4200	6%
Body mass index, kg/m^2	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/m^2										
<18.5	28 116	1%	20 717	1%	6230	1%	951	1%	218	0%
18.5–24.9	553 988	17%	379 204	20%	152 657	14%	16 249	15%	5878	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%	9536	17%
≥40	208 950	7%	113 491	6%	80 708	8%	9077	8%	5674	10%
Active statin prescription 6 months prior to enrolment	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%	1360	1%	856	1%

Continued

Table 1 Continued

	Overall		No positive respiratory swab for SARS-CoV-2				≥1 positive respiratory swab for SARS-CoV-2			
			No statin prescription		Active statin prescription		No statin prescription		Active statin prescription	
	n=4 801 406		n=3 180 888		n=1 389 364		n=161 891		n=69 263	
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	9407	0%	7022	0%	2298	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%	5626	5%	5539	9%
15–29	58 464	2%	27 223	1%	27 527	2%	1906	2%	1808	3%
<15 or dialysis	25 765	1%	12 803	1%	10 449	1%	1503	1%	1010	2%
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%			5740	8%
Rosuvastatin	173 943	4%			165 066	12%			8877	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 6 months, mg/L†	17.3	±136	16.4	±151	18.2	±120	19.9	±49.6	21.0	±52.9
hsCRP in the prior 6 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

Continued

Table 1 Continued

	Overall		No positive respiratory swab for SARS-CoV-2			≥1 positive respiratory swab for SARS-CoV-2		
			No statin prescription	Active statin prescription		No statin prescription	Active statin prescription	
	n=4 801 406		n=3 180 888	n=1 389 364		n=161 891	n=69 263	
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%	5710	<1%	3588	<1%	3754	2%	2386	3%
Death within 30 days	31 409	1%	13 074	<1%	6224	<1%	7815	5%	4296	6%

Data are presented as mean±SD for continuous variables and n (%) for categorical variables.
P values for global differences in participant characteristics across categories of COVID-19 diagnosis and prior statin use all <0.001.
*Based on estimated % low-density lipoprotein-cholesterol reduction.
†Up to 14 days prior to index date (overall n=958 343).
‡Overall n=224 930.
VHA, Veterans Health Administration.

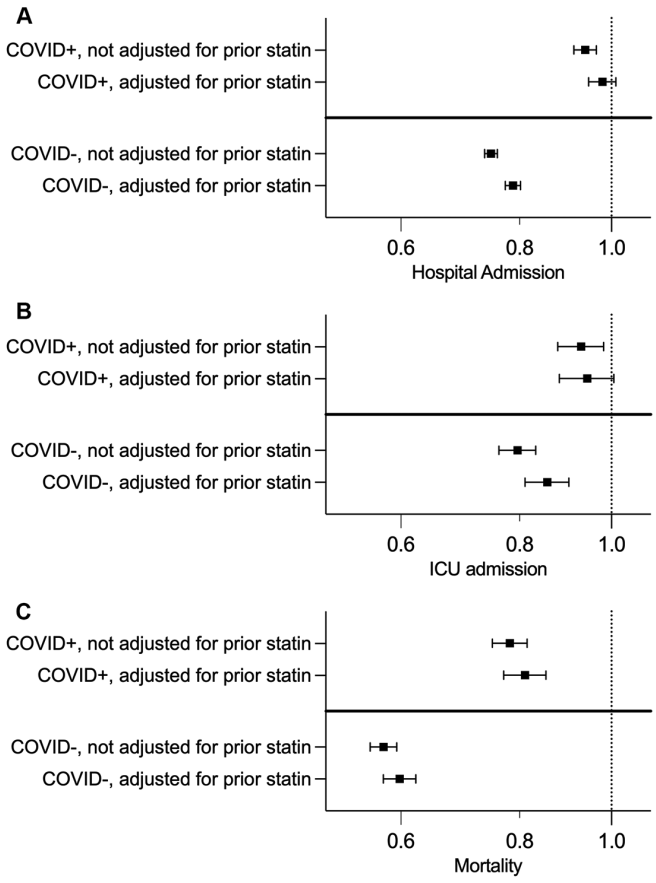

Figure 1 ORs and 95% CIs for associations of statin use at study enrolment with: (A) hospitalisation, (B) ICU admission and (C) death at 30 days before and after adjustment for statin use 6 months prior to diagnosis among VHA veterans with and without a positive respiratory swab for SARS-CoV-2. All analyses 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. BMI, body mass index; ICU, intensive care unit; VHA, Veterans Health Administration.

and without a positive swab for SARS-CoV-2, testing the association of statin use at index date with occurrence of hospitalisation, 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 ≥6 months prior to diagnosis, sex, age, race/ethnicity, BMI, tobacco use, facility location, index month, urban/rural status, eGFR and history of diabetes, hypertension, CVD, 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 USA. In combined models, we tested for the presence of multiplicative first-order interactions to determine whether the association between statins and odds of hospitalisation, 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

Table 2 ORs from logistic regression models testing the association of active statin prescription at enrolment 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 enrolment	0.79	0.77 to 0.80	0.86	0.81 to 0.90	0.60	0.58 to 0.62	0.98	0.95 to 1.01	0.94	0.88 to 1.01	0.81	0.77 to 0.85
Statin prescription 6 months prior to enrolment	0.91	0.89 to 0.93	0.88	0.83 to 0.93	0.93	0.9 to 0.97	0.93	0.9 to 0.96	0.97	0.91 to 1.04	0.94	0.89 to 0.99
Sex at birth, female	0.73	0.71 to 0.75	0.73	0.67 to 0.8	0.63	0.58 to 0.69	0.75	0.71 to 0.79	0.74	0.65 to 0.84	0.56	0.50 to 0.64
Age category, years												
19–39	1.16	1.12 to 1.19	0.61	0.54 to 0.69	0.26	0.22 to 0.30	0.61	0.57 to 0.65	0.6	0.51 to 0.71	0.15	0.11 to 0.21
40–49	0.97	0.94 to 1.01	0.81	0.73 to 0.91	0.46	0.40 to 0.54	0.75	0.70 to 0.80	0.68	0.59 to 0.79	0.38	0.30 to 0.48
50–59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60–69	1.01	0.99 to 1.03	1.16	1.08 to 1.25	1.95	1.81 to 2.10	1.29	1.23 to 1.34	1.32	1.21 to 1.46	2.86	2.55 to 3.20
70–79	0.81	0.79 to 0.83	1.00	0.92 to 1.08	2.6	2.41 to 2.79	1.43	1.37 to 1.49	1.49	1.36 to 1.64	5.93	5.32 to 6.61
≥80	0.96	0.93 to 0.99	0.95	0.87 to 1.04	5.06	4.68 to 5.46	1.81	1.71 to 1.91	1.62	1.45 to 1.82	13.86	12.37 to 15.53
White (vs not white)	1.21	1.14 to 1.28	1.23	1.02 to 1.49	1.1	0.95 to 1.27	0.88	0.81 to 0.97	0.74	0.61 to 0.91	0.87	0.74 to 1.04
Black vs(not Black)	1.49	1.40 to 1.58	1.53	1.26 to 1.85	1.05	0.90 to 1.22	1.36	1.24 to 1.50	1.10	0.89 to 1.35	0.78	0.66 to 0.94
Hispanic (vs not Hispanic)	1.07	1.04 to 1.10	1.23	1.13 to 1.35	1.07	0.99 to 1.14	1.16	1.10 to 1.22	1.03	0.92 to 1.15	1.13	1.04 to 1.24
Body mass index category, kg/m^2												
<18.5	1.35	1.29 to 1.42	1.51	1.31 to 1.73	2.48	2.33 to 2.65	1.14	1.01 to 1.29	1.35	1.06 to 1.72	1.81	1.59 to 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 to 0.76	0.70	0.65 to 0.74	0.54	0.52 to 0.56	0.81	0.78 to 0.85	0.89	0.82 to 0.97	0.73	0.68 to 0.79
30–34.9	0.67	0.65 to 0.68	0.62	0.57 to 0.66	0.42	0.40 to 0.44	0.76	0.73 to 0.80	0.88	0.81 to 0.96	0.69	0.64 to 0.74
35–39.9	0.63	0.61 to 0.65	0.57	0.52 to 0.62	0.37	0.35 to 0.40	0.76	0.72 to 0.80	0.85	0.76 to 0.94	0.64	0.59 to 0.70
≥40	0.65	0.63 to 0.67	0.59	0.53 to 0.65	0.43	0.39 to 0.46	0.87	0.82 to 0.93	1.03	0.91 to 1.16	0.80	0.72 to 0.88
Tobacco use												
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.23 to 1.28	1.12	1.06 to 1.19	1.09	1.04 to 1.13	1.11	1.08 to 1.15	1.10	1.02 to 1.17	1.18	1.12 to 1.24
Current	2.02	1.98 to 2.06	1.76	1.66 to 1.87	1.67	1.60 to 1.74	1.39	1.35 to 1.44	1.29	1.20 to 1.39	1.24	1.17 to 1.32
Urban/rural/highly rural residence												
Highly rural	0.68	0.64 to 0.73	0.98	0.82 to 1.18	0.92	0.81 to 1.05	0.58	0.50 to 0.66	0.74	0.54 to 1.00	1.16	0.98 to 1.38

Continued

Table 2 Continued

	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
Rural	0.74	0.73 to 0.75	0.74	0.70 to 0.78	0.89	0.87 to 0.92	0.70	0.68 to 0.72	0.88	0.82 to 0.93	1.03	0.99 to 1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18 to 0.35	0.35	0.13 to 0.94	0.80	0.51 to 1.25	0.27	0.10 to 0.75	0.55	0.08 to 3.99	1.77	0.73 to 4.30
Diabetes	1.18	1.16 to 1.20	1.26	1.21 to 1.32	1.41	1.36 to 1.45	1.30	1.27 to 1.34	1.26	1.19 to 1.34	1.37	1.31 to 1.43
Hypertension	1.22	1.19 to 1.24	1.30	1.22 to 1.39	1.09	1.04 to 1.14	1.30	1.25 to 1.35	1.29	1.19 to 1.41	0.96	0.90 to 1.02
Cardiovascular disease	2.04	2.01 to 2.08	2.69	2.55 to 2.84	1.88	1.81 to 1.95	1.84	1.79 to 1.90	2.08	1.95 to 2.23	1.24	1.18 to 1.30
Heart failure	2.13	2.09 to 2.16	2.34	2.22 to 2.46	2.51	2.42 to 2.59	1.64	1.59 to 1.70	1.53	1.43 to 1.63	1.31	1.25 to 1.38
Alcohol use disorder	1.12	1.10 to 1.14	1.03	0.97 to 1.09	0.78	0.75 to 0.82	0.75	0.72 to 0.78	0.86	0.79 to 0.93	0.68	0.64 to 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 to 0.82	0.80	0.76 to 0.85	0.60	0.57 to 0.62	0.90	0.87 to 0.93	0.96	0.88 to 1.04	1.10	1.02 to 1.18
45–59	0.84	0.81 to 0.86	0.84	0.78 to 0.91	0.71	0.67 to 0.74	0.99	0.94 to 1.03	1.00	0.91 to 1.10	1.44	1.33 to 1.56
30–44	0.93	0.90 to 0.96	0.92	0.84 to 1.01	0.99	0.93 to 1.05	1.10	1.04 to 1.16	1.14	1.02 to 1.29	1.83	1.68 to 1.99
15–29	1.15	1.10 to 1.20	1.14	1.01 to 1.29	2.07	1.94 to 2.21	1.31	1.21 to 1.42	1.32	1.14 to 1.53	2.65	2.36 to 2.97
<15 or dialysis	1.60	1.52 to 1.69	1.77	1.56 to 2.00	3.07	2.85 to 3.32	1.46	1.33 to 1.60	1.51	1.29 to 1.77	2.48	2.16 to 2.85

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

Table 3 ORs from logistic regression models testing the association of active statin prescription at enrolment 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 enrolment	0.75	0.74 to 0.76	0.8	0.76 to 0.83	0.58	0.56 to 0.59	0.94	0.91 to 0.96	0.93	0.88 to 0.98	0.78	0.75 to 0.82
Sex at birth, female	0.73	0.71 to 0.75	0.73	0.67 to 0.81	0.63	0.58 to 0.69	0.75	0.71 to 0.79	0.74	0.65 to 0.84	0.57	0.5 to 0.65
Age category, years												
19–39	1.16	1.13 to 1.2	0.61	0.54 to 0.69	0.26	0.22 to 0.3	0.61	0.58 to 0.66	0.6	0.51 to 0.71	0.15	0.11 to 0.21
40–49	0.98	0.95 to 1.01	0.82	0.73 to 0.92	0.47	0.4 to 0.54	0.75	0.71 to 0.8	0.68	0.59 to 0.79	0.38	0.3 to 0.48
50–59	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
60–69	1.01	0.98 to 1.03	1.16	1.08 to 1.25	1.95	1.81 to 2.1	1.28	1.23 to 1.34	1.32	1.21 to 1.45	2.86	2.55 to 3.2
70–79	0.81	0.79 to 0.83	0.99	0.92 to 1.07	2.59	2.41 to 2.78	1.43	1.36 to 1.49	1.49	1.36 to 1.64	5.92	5.31 to 6.6
≥80	0.96	0.93 to 0.99	0.95	0.87 to 1.04	5.06	4.68 to 5.46	1.81	1.71 to 1.91	1.62	1.45 to 1.82	13.86	12.37 to 15.53
White (vs not white)	1.2	1.14 to 1.28	1.23	1.02 to 1.49	1.1	0.95 to 1.27	0.88	0.81 to 0.97	0.75	0.61 to 0.91	0.87	0.74 to 1.04
Black vs (not Black)	1.49	1.4 to 1.58	1.53	1.26 to 1.86	1.05	0.9 to 1.22	1.37	1.24 to 1.5	1.1	0.89 to 1.35	0.78	0.66 to 0.94
Hispanic (vs not Hispanic)	1.07	1.04 to 1.1	1.23	1.13 to 1.35	1.06	0.99 to 1.14	1.16	1.1 to 1.22	1.03	0.92 to 1.15	1.13	1.04 to 1.24
Body mass index category, kg/m^2												
<18.5	1.35	1.29 to 1.42	1.51	1.32 to 1.74	2.49	2.33 to 2.65	1.14	1.02 to 1.29	1.35	1.06 to 1.72	1.82	1.59 to 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 to 0.76	0.7	0.65 to 0.74	0.54	0.52 to 0.56	0.81	0.78 to 0.85	0.89	0.82 to 0.97	0.73	0.68 to 0.79
30–34.9	0.67	0.65 to 0.68	0.61	0.57 to 0.66	0.42	0.4 to 0.44	0.76	0.73 to 0.8	0.88	0.81 to 0.96	0.68	0.64 to 0.74
35–39.9	0.63	0.61 to 0.64	0.57	0.52 to 0.62	0.37	0.35 to 0.4	0.76	0.72 to 0.8	0.85	0.76 to 0.94	0.64	0.59 to 0.7
≥40	0.65	0.63 to 0.67	0.58	0.53 to 0.65	0.43	0.39 to 0.46	0.87	0.81 to 0.92	1.03	0.91 to 1.16	0.79	0.72 to 0.88
Tobacco use												
Never	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Former	1.25	1.22 to 1.27	1.12	1.05 to 1.19	1.09	1.04 to 1.13	1.11	1.08 to 1.15	1.1	1.02 to 1.17	1.18	1.12 to 1.24
Current	2.02	1.98 to 2.05	1.76	1.66 to 1.87	1.66	1.6 to 1.74	1.39	1.35 to 1.44	1.29	1.2 to 1.39	1.24	1.17 to 1.32
Urban/rural/highly rural residence												
Highly rural	0.68	0.64 to 0.73	0.98	0.82 to 1.18	0.92	0.81 to 1.05	0.57	0.5 to 0.66	0.74	0.54 to 1	1.16	0.98 to 1.38
Rural	0.74	0.73 to 0.75	0.74	0.7 to 0.78	0.89	0.86 to 0.92	0.7	0.68 to 0.72	0.87	0.82 to 0.93	1.03	0.99 to 1.08
Urban	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Unknown	0.25	0.18 to 0.35	0.35	0.13 to 0.94	0.8	0.51 to 1.25	0.27	0.1 to 0.74	0.55	0.08 to 3.98	1.75	0.72 to 4.27
Diabetes	1.17	1.15 to 1.19	1.25	1.2 to 1.31	1.4	1.36 to 1.45	1.3	1.26 to 1.33	1.26	1.19 to 1.33	1.36	1.3 to 1.42
Hypertension	1.21	1.19 to 1.24	1.29	1.21 to 1.38	1.09	1.04 to 1.13	1.3	1.25 to 1.35	1.29	1.18 to 1.41	0.96	0.9 to 1.02

Continued

Table 3 Continued

	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
Cardiovascular disease	2.03	two to 2.07	2.67	2.53 to 2.82	1.87	1.8 to 1.94	1.84	1.78 to 1.89	2.08	1.94 to 2.23	1.24	1.18 to 1.3
Heart failure	2.12	2.08 to 2.16	2.33	2.21 to 2.45	2.5	2.41 to 2.59	1.64	1.59 to 1.7	1.53	1.43 to 1.63	1.31	1.25 to 1.38
Alcohol use disorder	1.12	1.1 to 1.14	1.03	0.97 to 1.09	0.78	0.75 to 0.82	0.75	0.73 to 0.78	0.86	0.79 to 0.93	0.68	0.64 to 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	0.8	0.79 to 0.82	0.8	0.75 to 0.85	0.6	0.57 to 0.62	0.9	0.86 to 0.93	0.96	0.88 to 1.04	1.09	1.02 to 1.18
45–59	0.84	0.81 to 0.86	0.84	0.78 to 0.91	0.71	0.67 to 0.74	0.98	0.94 to 1.03	1	0.91 to 1.09	1.44	1.33 to 1.56
30–44	0.93	0.9 to 0.96	0.92	0.84 to 1.01	0.99	0.93 to 1.05	1.1	1.04 to 1.16	1.14	1.02 to 1.29	1.83	1.68 to 1.99
15–29	1.14	1.09 to 1.2	1.14	1.01 to 1.29	2.07	1.94 to 2.21	1.31	1.21 to 1.42	1.32	1.14 to 1.53	2.65	2.36 to 2.97
<15 or dialysis	1.6	1.52 to 1.69	1.77	1.56 to 2.01	3.08	2.85 to 3.32	1.46	1.33 to 1.6	1.51	1.29 to 1.77	2.48	2.16 to 2.85

ICU, intensive care unit; VHA, Veterans Health Administration.

non-users. In a sensitivity analysis, we examined associations of statin use at diagnosis with occurrence of hospitalisation, ICU admission and death in models that were not adjusted for statin use 6 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 with 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, CVD, heart failure and alcohol use disorder, as well as models comparing low-intensity to moderate-intensity 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% (n=23 974) were female. Thirty per cent (69,263) had an active statin prescription at enrolment. During the 30 days after diagnosis, 14% (32 490) of SARS-CoV-2 infected participants were hospitalised, 3% (6140) 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 per cent (1 389 364) had an active statin prescription at enrolment. During the 30 days after the index date, 2% (91 604) were hospitalised, 0.2% (9298) 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/m^2 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 high-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 to 0.85)), but not with hospitalisation or ICU admission. Adjustment for receipt of statin 6 months prior to baseline attenuated the magnitude of the association of statin use at diagnosis with all outcomes (figure 1, tables 2 and 3). Associations with outcomes were similar for individual statins (table 4). Compared with low/moderate intensity statin, high-intensity statin use was associated with higher odds of hospitalisation (1.06 (95% CI 1.01 to 1.10)) but not with ICU admission or death (table 5). Associations of statin use with hospitalisation differed across strata of sex, age, race (black vs

Table 4 ORs from logistic regression models testing the association of specific statins compared with 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 to 1.01	0.136	0.96	0.9 to 1.02	0.194	0.8	0.76 to 0.84	<0.001
Fluvastatin	1.47	0.45 to 4.82	0.524	1.79	0.23 to 13.8	0.577	0.55	0.07 to 4.43	0.575
Lovastatin	0.73	0.57 to 0.93	0.012	0.48	0.26 to 0.9	0.022	0.64	0.45 to 0.91	0.013
Pitavastatin	0.45	0.16 to 1.26	0.128	0.66	0.09 to 4.8	0.679	0.82	0.25 to 2.68	0.738
Pravastatin	0.93	0.86 to 1	0.045	0.94	0.81 to 1.1	0.443	0.78	0.7 to 0.87	<0.001
Rosuvastatin	0.81	0.76 to 0.86	<0.001	0.82	0.72 to 0.93	0.002	0.72	0.65 to 0.79	<0.001
Simvastatin	0.91	0.86 to 0.97	0.001	0.91	0.8 to 1.02	0.107	0.77	0.71 to 0.84	<0.001
Sex at birth, female	0.75	0.71 to 0.8	<0.001	0.74	0.65 to 0.84	<0.001	0.57	0.5 to 0.65	<0.001
Age category, years									
19–39	0.61	0.58 to 0.66	<0.001	0.6	0.51 to 0.71	<0.001	0.15	0.11 to 0.21	<0.001
40–49	0.75	0.71 to 0.8	<0.001	0.68	0.59 to 0.79	<0.001	0.38	0.3 to 0.48	<0.001
50–59	ref			ref			ref		
60–69	1.28	1.23 to 1.34	<0.001	1.32	1.21 to 1.45	<0.001	2.85	2.55 to 3.2	<0.001
70–79	1.43	1.36 to 1.49	<0.001	1.49	1.36 to 1.64	<0.001	5.92	5.31 to 6.6	<0.001
≥80	1.81	1.71 to 1.91	<0.001	1.62	1.45 to 1.82	<0.001	13.86	12.37 to 15.54	<0.001
White (vs not white)	0.88	0.81 to 0.97	0.007	0.75	0.61 to 0.91	0.004	0.88	0.74 to 1.04	0.121
Black (vs not black)	1.36	1.24 to 1.5	<0.001	1.1	0.89 to 1.35	0.39	0.78	0.66 to 0.94	0.007
Hispanic (vs not Hispanic)	1.16	1.1 to 1.22	<0.001	1.03	0.92 to 1.15	0.633	1.13	1.04 to 1.24	0.007
Body mass index category, kg/m²									
<18.5	1.15	1.02 to 1.29	0.025	1.35	1.06 to 1.73	0.015	1.82	1.59 to 2.08	<0.001
18.5–24.9	ref			ref			ref		
25–29.9	0.81	0.78 to 0.85	<0.001	0.89	0.82 to 0.97	0.006	0.73	0.68 to 0.79	<0.001
30–34.9	0.76	0.73 to 0.8	<0.001	0.88	0.81 to 0.97	0.006	0.68	0.64 to 0.74	<0.001
35–39.9	0.76	0.72 to 0.8	<0.001	0.85	0.76 to 0.94	0.002	0.64	0.59 to 0.7	<0.001
≥40	0.87	0.81 to 0.92	<0.001	1.03	0.91 to 1.16	0.675	0.79	0.72 to 0.88	<0.001
Tobacco use									
Never	ref								
Former	1.11	1.08 to 1.15	<0.001	1.1	1.02 to 1.17	0.01	1.18	1.12 to 1.24	<0.001
Current	1.39	1.35 to 1.44	<0.001	1.29	1.2 to 1.39	<0.001	1.24	1.17 to 1.32	<0.001
Urban/rural/highly rural residence									
Highly rural	0.57	0.5 to 0.66	<0.001	0.74	0.54 to 1	0.051	1.16	0.97 to 1.38	0.096
Rural	0.7	0.68 to 0.72	<0.001	0.88	0.82 to 0.93	<0.001	1.04	0.99 to 1.08	0.14
Urban	ref			ref			ref		
Unknown	0.27	0.1 to 0.74	0.011	0.55	0.08 to 3.96	0.549	1.75	0.72 to 4.25	0.22
Diabetes	1.29	1.26 to 1.33	<0.001	1.26	1.19 to 1.33	<0.001	1.36	1.3 to 1.42	<0.001
Hypertension	1.3	1.25 to 1.35	<0.001	1.29	1.18 to 1.41	<0.001	0.96	0.9 to 1.02	0.149
Cardiovascular disease	1.84	1.78 to 1.89	<0.001	2.08	1.94 to 2.23	<0.001	1.24	1.18 to 1.3	<0.001
Heart failure	1.64	1.58 to 1.69	<0.001	1.53	1.43 to 1.63	<0.001	1.31	1.25 to 1.38	<0.001
Alcohol use disorder	0.75	0.73 to 0.78	<0.001	0.86	0.79 to 0.93	<0.001	0.69	0.64 to 0.73	<0.001
Estimated glomerular filtration rate, mL/min/1.73 m²									
≥90	ref			ref			ref		
60–89	0.9	0.87 to 0.93	<0.001	0.96	0.88 to 1.04	0.273	1.1	1.02 to 1.18	0.018

Continued

Table 4 Continued

	Hospital admission			ICU admission			Death		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
45–59	0.99	0.94 to 1.03	0.519	1	0.91 to 1.1	0.941	1.44	1.33 to 1.56	<0.001
30–44	1.1	1.04 to 1.16	0.001	1.15	1.02 to 1.29	0.024	1.83	1.68 to 1.99	<0.001
15–29	1.31	1.21 to 1.42	<0.001	1.32	1.14 to 1.53	<0.001	2.65	2.36 to 2.97	<0.001
<15 or dialysis	1.45	1.32 to 1.59	<0.001	1.51	1.29 to 1.77	<0.001	2.48	2.16 to 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 6 months prior to enrolment.
ICU, intensive care unit; VHA, Veterans Health Administration.

non-black) and eGFR (eg, OR for hospitalisation in black participants 0.98 (95% CI 0.92 to 1.03), OR for hospitalisation in non-black participants 0.92 (95% CI 0.89 to 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) (eg, OR for ICU admission in Latinx participants 0.77 (95% CI 0.62 to 0.95), OR for ICU admissioni in non-Latinx participants 0.94 (95% CI 0.89 to 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 (eg, OR for mortality in black participants: 0.83 (95% CI 0.76 to 0.92), OR for mortality in non-black participants: 0.77 (95% CI 0.74 to 0.81), p for interaction=0.006). Associations did not differ across strata of prevalent diabetes, hypertension or CVD (online supplemental figures 1–3).

Compared with 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 hospitalisation (OR 0.79 (95% CI 0.77 to 0.80)), ICU admission (OR 0.86 (95% CI 0.81 to 0.90)) and death at 30 days (OR 0.60 (95% CI 0.58 to 0.62)) (table 2).

DISCUSSION

In this cohort of US 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 with 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 with moderate and low potency, except for a small difference in the odds of hospitalisation. Associations were not significantly different in strata of prevalent diabetes, hypertension or CVD. 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 underused 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*[18] examined the association of vaccination with a negative control outcome: mortality prior to influenza season. They found a stronger association with mortality during the period prior to influenza season compared with 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 recognised 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

Table 5 ORs from logistic regression models testing the association of low or moderate potency versus high-potency active statin prescription at enrolment 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 to 1.1	0.011	1.05	0.96 to 1.15	0.258	0.97	0.91 to 1.04	0.407
Sex at birth, female	0.89	0.8 to 1	0.041	0.95	0.75 to 1.19	0.634	0.52	0.4 to 0.68	<0.001
Age category, years									
19–39	0.82	0.63 to 1.06	0.123	0.46	0.22 to 0.98	0.045	0.1	0.01 to 0.73	0.023
40–49	0.74	0.64 to 0.86	<0.001	0.55	0.38 to 0.79	0.001	0.45	0.27 to 0.75	0.002
50–59	ref			ref			ref		
60–69	1.3	1.2 to 1.4	<0.001	1.24	1.06 to 1.45	0.009	2.45	2.02 to 2.96	<0.001
70–79	1.47	1.36 to 1.58	<0.001	1.47	1.25 to 1.72	<0.001	4.42	3.67 to 5.32	<0.001
≥80	1.95	1.78 to 2.15	<0.001	1.69	1.4 to 2.04	<0.001	9.54	7.84 to 11.6	<0.001
White (vs not white)	0.81	0.69 to 0.96	0.012	0.75	0.52 to 1.08	0.118	0.85	0.64 to 1.11	0.221
Black vs (not Black)	1.31	1.1 to 1.55	0.002	1.12	0.77 to 1.63	0.545	0.8	0.6 to 1.06	0.125
Hispanic (vs not Hispanic)	1.12	1.02 to 1.22	0.013	0.91	0.75 to 1.1	0.33	1.2	1.04 to 1.38	0.014
Body mass index category, kg/m²									
<18.5	1.04	0.79 to 1.38	0.766	1.19	0.71 to 1.98	0.511	1.45	1.02 to 2.05	0.039
18.5–24.9	ref			ref			ref		
25–29.9	0.81	0.75 to 0.86	<0.001	0.89	0.77 to 1.02	0.095	0.78	0.7 to 0.87	<0.001
30–34.9	0.78	0.73 to 0.84	<0.001	0.92	0.8 to 1.07	0.272	0.78	0.7 to 0.87	<0.001
35–39.9	0.78	0.71 to 0.85	<0.001	0.9	0.76 to 1.06	0.188	0.75	0.67 to 0.85	<0.001
≥40	0.86	0.77 to 0.95	0.002	1.08	0.89 to 1.3	0.452	0.91	0.78 to 1.06	0.221
Tobacco use									
Never	ref			ref			ref		
Former	1.18	1.12 to 1.25	<0.001	1.16	1.03 to 1.3	0.013	1.29	1.18 to 1.4	<0.001
Current	1.36	1.28 to 1.44	<0.001	1.36	1.19 to 1.55	<0.001	1.21	1.09 to 1.34	<0.001
Urban/rural/highly rural residence									
Highly rural	0.59	0.47 to 0.73	<0.001	0.93	0.61 to 1.42	0.728	1.4	1.08 to 1.82	0.011
Rural	0.68	0.65 to 0.72	<0.001	0.87	0.79 to 0.96	0.006	1.05	0.97 to 1.12	0.233
Urban	ref			ref			ref		
Unknown	0.17	0.02 to 1.26	0.083	1.69	0.22 to 12.83	0.612	1.41	0.31 to 6.48	0.662
Diabetes	1.29	1.23 to 1.35	<0.001	1.16	1.05 to 1.27	0.003	1.31	1.22 to 1.41	<0.001
Hypertension	1.28	1.18 to 1.39	<0.001	1.38	1.14 to 1.67	0.001	0.98	0.85 to 1.11	0.704
Cardiovascular disease	1.71	1.62 to 1.8	<0.001	1.96	1.75 to 2.21	<0.001	1.25	1.14 to 1.36	<0.001
Heart failure	1.68	1.6 to 1.77	<0.001	1.58	1.44 to 1.74	<0.001	1.33	1.23 to 1.43	<0.001
Alcohol use disorder	0.66	0.62 to 0.71	<0.001	0.81	0.71 to 0.94	0.004	0.69	0.61 to 0.77	<0.001
Estimated glomerular filtration rate, mL/min/1.73 m²									
≥90	ref			ref			ref		
60–89	0.98	0.92 to 1.05	0.625	1.05	0.91 to 1.2	0.538	1.14	1.01 to 1.29	0.041
45–59	1.08	one to 1.16	0.05	1.05	0.9 to 1.24	0.53	1.58	1.37 to 1.82	<0.001
30–44	1.21	1.1 to 1.32	<0.001	1.2	one to 1.44	0.055	2	1.72 to 2.33	<0.001
15–29	1.53	1.35 to 1.72	<0.001	1.37	1.09 to 1.72	0.007	3.19	2.69 to 3.78	<0.001
<15 or dialysis	1.64	1.42 to 1.9	<0.001	1.95	1.52 to 2.5	<0.001	3.01	2.44 to 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 6 months prior to enrolment.
ICU, intensive care unit; VHA, Veterans Health Administration.

a lower hazard of death (HR 0.72 (95% CI 0.69 to 0.75)) in a large population-based study of English patients with diabetes independent of age and comorbid CVD.[26] In a recent nationwide US study of hospitalised 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 to 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 to 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 hospitalised patients with diabetes, statin use at diagnosis was associated with higher odds of death at 28 days (OR 1.46 (95% CI 1.08 to 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 that remains unaddressed—but instead focused on the association between statin use prior to COVID-19 diagnosis and outcomes, where use of this medication would not have been confounded by the onset of COVID-19. 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 hospitalisation. Masana *et al*[28] examined associations of statin use with in-hospital mortality in a cohort of hospitalised Spanish patients with a positive test for SARS-CoV-2 comparing statin non-users, users who continued statins during hospitalisation and users who stopped statins during hospitalisation. 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 preadmission characteristics; however, the authors were not able to account for characteristics (eg, 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*[21] examined associations of preadmission statin use and in-hospital statin use among patients hospitalised after a positive test for SARS-CoV-2, which is a related question. In-hospital but not preadmission statin use was associated with a lower risk of mortality; however, these preadmission 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-19 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 (online supplemental figures 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-characterised national sample. To our knowledge, this is the largest observational study of prior statin use and adverse outcomes from SARS-CoV-2 in the USA (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 US population as a whole, and our findings may not be generalisable 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 hospitalisations 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 hospitalisation 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. Furthermore, 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 US Veterans with or without a positive respiratory swab for SARS-CoV-2 indicating that statins may not exert COVID-19 specific beneficial effects.

Twitter Pandora L Wander @pandoralucrezia

Contributors PLW conceived the project, designed the overall research plan and wrote the first draft of the manuscript. EL analysed the data and reviewed/edited the manuscript; LAB, LT-P and SEK 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 and 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. PLW and EJB are the guarantors of this work, as such they accept full responsibility for the finished work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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ORCID iDs
Pandora L Wander http://orcid.org/0000-0003-3671-1464
Alexander C Peterson http://orcid.org/0000-0003-1697-4259

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