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ORIGINAL RESEARCH

Association of Statins for Primary Prevention of Cardiovascular Diseases With Hospitalization for COVID-19: A Nationwide Matched Population-Based Cohort Study

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BACKGROUND: There is little evidence on the relationship between statin use and the risk of hospitalization attributable to COVID-19.

METHODS AND RESULTS: The French National Healthcare Data System database was used to conduct a matched-cohort study. For each adult aged ≥40 years receiving statins for the primary prevention of cardiovascular diseases, one nonuser was randomly selected and matched for year of birth, sex, residence area, and comorbidities. The association between statin use and hospitalization for COVID-19 was examined using conditional Cox proportional hazards models, adjusted for baseline characteristics, comorbidities, and long-term medications. Its association with in-hospital death from COVID-19 was also explored. All participants were followed up from February 15, 2020, to June 15, 2020. The matching procedure generated 2 058 249 adults in the statin group and 2 058 249 in the control group, composed of 46.6% of men with a mean age of 68.7 years. Statin users had a 16% lower risk of hospitalization for COVID-19 than nonusers (adjusted hazard ratio [HR], 0.84; 95% CI, 0.81–0.88). All types of statins were significantly associated with a lower risk of hospitalization, with the adjusted HR ranging from 0.75 for fluvastatin to 0.89 for atorvastatin. Low- and moderate-intensity statins also showed a lower risk compared with nonusers (HR, 0.78 [95% CI, 0.71–0.86] and HR, 0.84 [95% CI, 0.80–0.89], respectively), whereas high-intensity statins did not (HR, 1.01; 95% CI, 0.86–1.18). We found similar results with in-hospital death from COVID-19.

CONCLUSIONS: Our findings support that the use of statins for primary prevention is associated with lower risks of hospitalization for COVID-19 and of in-hospital death from COVID-19.

Key Words: COVID-19 ■ hospitalization ■ mortality ■ SARS-CoV-2 ■ statins

A better understanding of the determinants associated with COVID-19 helps to identify vulnerable individuals and to provide satisfactory health care management. Given the absence of a specific treatment for COVID-19, several existing drugs were thought to be beneficial, in particular those with anti-inflammatory or immunomodulatory activities such as statins.[1] Besides their well-known lipid-lowering effect, statins have been reported to have pleiotropic beneficial actions by regulating numerous biological pathways implicated in anti-inflammatory, immune-modulatory, or anticoagulant actions. These drugs were found to be effective in previous outbreaks, namely those of hemagglutinin type 1 and neuraminidase type 1 (H1N1) influenza[2,3] and the Ebola virus.[3,4] It has also been shown that they have been useful for survival in SARS-CoV and Middle

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CLINICAL PERSPECTIVE

What Is New?

- The evidence about statins and serious in-hospital COVID-19 outcomes is abundant but is scarce for initial outcomes in the disease course such as hospitalization for COVID-19. We conducted a population-based matched cohort study including 2 million adults aged ≥40 years who used statins for the primary prevention of cardiovascular diseases compared with 2 million nonusers.
- Our finding supports that statin use was associated with a lower risk of hospitalization for COVID-19, and we found similar results with all types of statins.
- Low- and moderate-intensity statins were also associated with a lower risk compared with nonuse, whereas high-intensity statins were not.

What Are the Clinical Implications?

- Statins are now known to be beneficial in primary prevention, decreasing all-cause mortality, cardiovascular diseases, coronary heart disease, and stroke without any evidence of serious harm caused by their use.
- Since the beginning of the COVID-19 pandemic, many clinicians have suggested that statins could be used as an adjunctive treatment for SARS-CoV infection.
- Our finding supports the hypothesis that low- and moderate-intensity statin use might contribute to a small risk reduction of hospitalization for COVID-19.

Nonstandard Abbreviations and Acronyms

ASD	absolute standardized difference
CCAM	French medical classification for clinical procedures (*Classification Commune des Actes Médicaux*)
CIP	French coding scheme for identifying a single drug package (*Code Identifiant de Présentation*)
CNIL	French Data Protection Office (*Commission Nationale de l'Informatique et des Libertés*)
IPTW	inverse probability of treatment weighting
MERS-CoV	Middle East respiratory syndrome coronavirus
PMSI	National Hospital Discharge Database (*Programme de Médicalisation des Systèmes d'Information*)
SNDS	French National Healthcare Data System (*Système National des Données de Santé*)
UCD	French coding scheme used for identifying hospital drugs (*Unité Commune de Dispensation*)

East respiratory syndrome coronavirus (MERS-CoV) infections.[5] Statins exert an anti-inflammatory effect by directly inhibiting the toll-like receptor MYD88-NF-kB pathway and by upregulating angiotensin-converting enzyme 2 (ACE-2) expression.[6–10]

Numerous epidemiological studies demonstrate that individuals who were previously treated with statins had a lower risk of experiencing severe COVID-19 outcomes, including admission into an intensive care unit, invasive mechanical intubation, acute respiratory distress syndrome, and in-hospital death, compared with nonexposed individuals. In total, 36 of 49 studies (73%) show a lower risk of severe COVID-19 outcomes––in particular mortality––among statin users compared with nonusers.[11–46] In 11 studies, ratio measures were close to 1.[47–57] In 2 studies, an increased risk was observed.[58,59] Most of these studies were conducted in hospitalized patients and/or patients tested for COVID-19. This could have led to a collider bias––also known as admission bias––which could have distorted the association between statin exposure and severe COVID-19 outcomes compared with that observed in the general population. That is, both the cause of using statins and the risk for COVID-19–related hospitalization may influence the likelihood of being selected for the study.[60] Furthermore, in the literature, there is little evidence on statin use with hospitalization for COVID-19.

In this context, we conducted a matched-cohort study in a general population aimed at studying the relationship between statin use before the start of the COVID-19 pandemic and symptomatic COVID-19 leading to hospitalization, using a French nationwide database. In addition, we examined its association with in-hospital death from COVID-19, frequently investigated in published studies.

METHODS

According to data protection and French regulation, the authors cannot publicly release data from the SNDS (French National Healthcare Data System [*Système National des Données de Santé*]. However, any person or structure, public or private, for-profit or nonprofit, can access SNDS data on authorization from the CNIL (French Data Protection Office [*Commission*

Nationale de l'Informatique et des Libertés]) to perform a study, research, or an evaluation of public interest (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://www.indsante.fr/).

Data Source

This cohort study used data from the SNDS, formerly known as SNIIRAM, established in 2006.[61]

SNDS covers the entire population of France (67 million residents). Each person is identified by a unique and anonymous number. Since 2006, SNDS has recorded all reimbursement data on: (1) outpatient care including drugs, imaging, and laboratory tests; (2) inpatient care (including diagnoses and procedures performed) from the national hospital discharge database (PMSI [*Programme de Médicalisation des Systèmes d'Information*]); and (3) health expenditure for patients with long-term diseases, such as cancer and diabetes, which is fully reimbursed. SNDS has been extensively used in France to conduct real-life pharmacoepidemiological studies including those on the COVID-19 pandemic.[62–73] SNDS also contains sociodemographic data and, when applicable, the date of death.

As a routine, information on hospital stays is collected monthly in the PMSI and integrated annually into the SNDS the following year. In April 2020, the French government encouraged hospitals to report all hospital stays attributable to COVID-19 once or twice a week through an exceptional fast-tracking procedure ("fast-track" PMSI). The present study was based on the fast-track PMSI database available as of September 30, 2020. A cutoff discharge date of June 15, 2020, was chosen to ensure completeness of data over the study period, which covers the first epidemic wave in France. At this date, 87 809 participants were admitted with a principal diagnosis of COVID-19, and 95% of them were linked to outpatient data using anonymized identifiers. Of these 87 809 participants, 15 661 died in hospital.

All variables used in this study were defined based on *International Statistical Classification of Diseases, Tenth Revision (ICD-10)*, codes for primary and secondary diagnosis; the French common classification of medical procedures *Classification Commune des Actes Médicaux* (CCAM) codes for procedures; and Anatomical Therapeutic Chemical, *Code Identifiant de Présentation* (CIP), or *Unité Commune de Dispensation* (UCD) codes for drugs. We used algorithms developed by the national health insurance in the Diseases and Health Expenditures Mapping,[68,74] which are detailed in Tables S1 through S4. For the *ICD-10* and CCAM codes, any occurrence in the 5 years preceding inclusion is used. For the anatomical therapeutic chemical and CIP codes, at least 3 drug dispensing (or 2 when at least one concerned the dispensing of large pack size) during 2019 are used. A small pack size usually contains a sufficient number of pills for a 1-month treatment and a large one for 3 months. For the exposure variable, statins, we added another condition: at least one dispensing in the last month (if small pack size) or 3 months (if large pack size) preceding inclusion. The inclusion or index date was defined as February 15, 2020, considered the start date of the epidemic in France.

Study Population

Individuals receiving at least 1 health care reimbursement after February 15, 2019, and aged ≥40 years were included in this study. The exposed group was composed of those using statins in monotherapy for the primary prevention of cardiovascular diseases to avoid confounding biases related to these conditions.

The statin group was further studied according to statin type (atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin) and intensity (low, moderate, high), based on information (international nonproprietary name and dose) from the most recently dispensed statin between November 15, 2019, and February 15, 2020 (index date). Statin intensity on low-density lipoprotein cholesterol reduction was defined by the American College of Cardiology/American Heart Association.[75]

For each statin user, we randomly selected one nonuser (ratio 1:1) matched for year of birth, sex, residence area (101 French departments, administrative divisions), hypertension, diabetes, and chronic respiratory condition to further control for main confounding biases.

Noninclusion Criteria

The noninclusion criteria were all individuals: (1) aged <40 years, (2) using a statin combined with another statin or a lipid-lowering drug other than a statin (eg, fibrates, ezetemib, and PCSK9 inhibitors), (3) with a history of cardiovascular diseases including coronary artery disease, heart failure, and stroke (statins used as secondary prevention), cancer, kidney condition (chronic transplant, or dialysis), and dementia.

Covariates

The following baseline characteristics were described according to statin use status: social deprivation index categorized into quintiles as a marker of socioeconomic status based on the residence area's median household income; percentage of high school graduates in the population aged ≥15 years; percentage of manual workers in the labor force; and unemployment in the individual's city of residence. Other variables

included smoking-, alcohol-, and obesity-related conditions; liver and pancreas disorder; and concomitant medications (eg, NSAID, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, and antipsychotic).

Outcomes Definition

The primary outcome was COVID-19–related hospitalization defined based on 1 of the following principals or secondary diagnosis discharge codes derived from the *ICD-10* codes: U07.10 (COVID-19, respiratory form, virus identified), U07.11 (COVID-19, respiratory form, virus not identified), U07.14 (COVID-19, other clinical forms, virus identified), U07.15 (COVID-19, other clinical forms, virus not identified), and U04.9 (severe acute respiratory syndrome). The secondary outcome was in-hospital mortality from COVID-19. The latter allowed us to compare results from our study with those of other published studies. The individuals were followed up from the index date (February 15, 2020) until the occurrence of the outcome of interest or until the closure of the study on June 15, 2020.

Statistical Analysis

Categorical variables are reported as frequencies with percentages and continuous variables as means with SDs. To report the balance in each covariate between statin users and nonusers, the difference in proportions for categorical variables and means for continuous variables is standardized.[76–78] The imbalance between the groups is defined as an absolute value >0.10.[77]

Conditional Cox proportional hazards models were used to take into account the matched design and to compare the incidence of events between the various groups: (1) statin and control groups (nonusers) for the main analysis; (2) atorvastatin, fluvastatin, pravastatin, rosuvastatin, simvastatin, and control groups; (3) low, moderate, high statin intensity, and control groups; and (4) statin intensity and type (low [fluvastatin 20/40, pravastatin 10/20, simvastatin 10], moderate [atorvastatin 10/20, fluvastatin 80, pravastatin 40, rosuvastatin 5/10, simvastatin 20/40], and high [atorvastatin 40/80, rosuvastatin 20]), and control groups.

We ran 4 types of conditional Cox proportional hazards models: (1) unadjusted (model 1); (2) adjusted for all baseline characteristics described in the Covariates section (model 2); (3) stabilized inverse probability of treatment weighting (IPTW) using the propensity score (model 3)[79]; and (4) stabilized IPTW further adjusted with all covariates (model 4). Models 3 and 4 were run after trimming the IPTWs at the first and 99th percentiles, as extremely large weights may disproportionately influence results and yield estimates with high variance.[80]

We performed a subanalysis of only patients hospitalized for COVID-19 to evaluate the association between statin use and in-hospital death using a conventional multivariable Cox model because of a small number of paired individuals in this subsample.

Two sensitivity analyses were also conducted to examine the effect of excluding participants with their matched pairs who had a highly imbalanced covariate (absolute standardized difference [ASD] >0.20) between statin users and their matched nonusers, and the robustness of the association between statins and COVID-19–related hospitalization to unmeasured confounding using E-value methodology developed by VanderWeele and Ding.[81]

All analyses were performed with SAS Enterprise Guide version 4.3 software (SAS Institute Inc). A 2-sided P value <0.05 indicated significance.

Regulatory and Ethical Considerations

SNDS is a strictly anonymous database, comprising all reimbursement data derived from mandatory health insurance. The authors had access to the SNDS database, in the application of the provisions of articles R. 1461-12 et seq. of the French Public Health Code and the French data protection authority decision CNIL-2016-316, to process personal health data in retrospective cohort studies designed to describe possible statistical associations between the use of a drug product and the development of a health outcome. Therefore, informed consent from the study participants was not required. EPI-PHARE staff, individually authorized to access SNDS, extracted and analyzed the data.

RESULTS

Of the 27 250 310 eligible individuals, 2 071 465 were identified as statin users for the primary prevention of cardiovascular diseases. The 1:1 matching procedure generated 4 116 498 participants aged ≥40 years: 2 058 249 in the statin group and 2 058 249 in the control group (Figure).

Table 1 shows that the comparison groups were well balanced according to matching variables: the participants were aged 68.7 years on average (SD, 10.4), and 46.6% were men. The participants' distribution according to residence area was similar to that of the general population (Table S5). Hypertension was present in 42% of the population, diabetes in 34%, and a chronic respiratory condition in 9%.

Statin users and nonusers were comparable regarding the most extensively studied covariates (ASD <0.10), except for low-dose aspirin (ASD, 0.40): statin users were more likely to use low-dose aspirin than nonusers (26.4% versus 11.2%, respectively). For

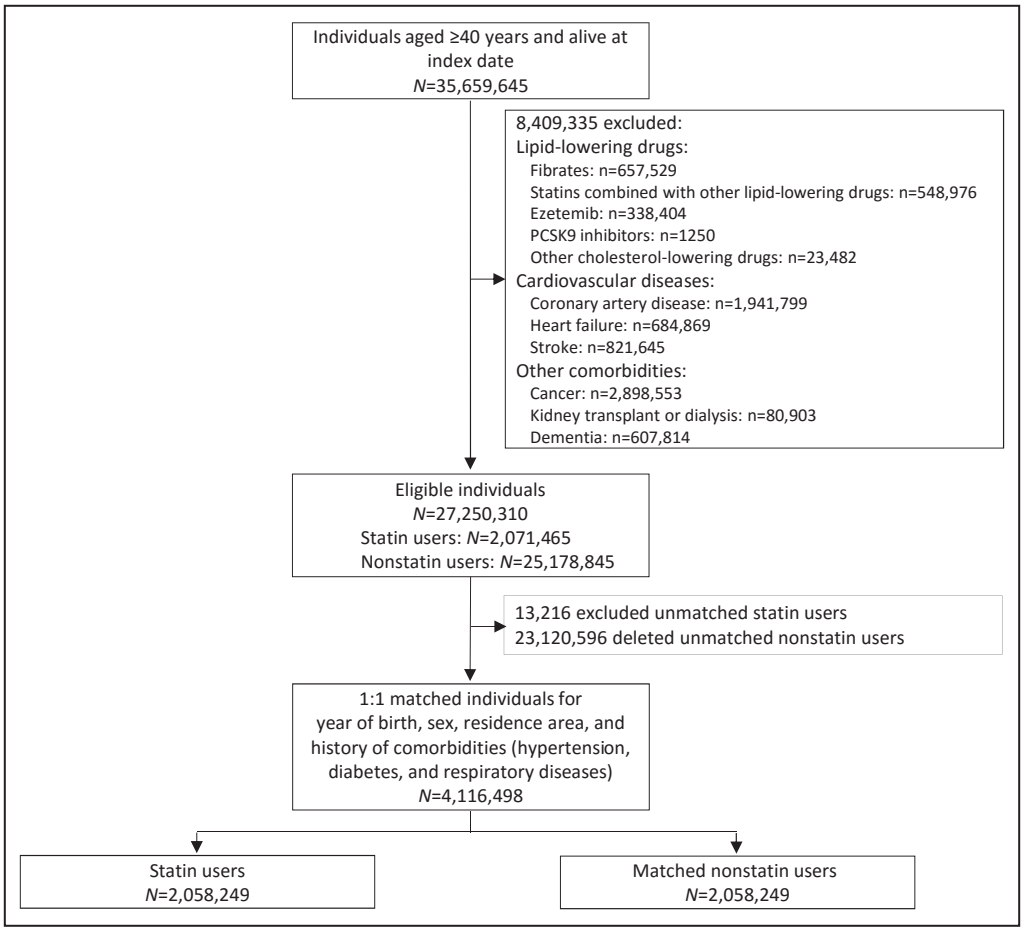

Figure. Flowchart of participants' inclusion.

antiplatelet agents, the difference was marginal in terms of ASD (2.5% versus 0.8%; ASD, 0.14) (Table 1). ASDs were close to 0 for these variables after IPTW (Figure S1).

Among statin users, atorvastin was the most frequently used (40.2%), followed by simvastatin (20.1%), rosuvastatin (18.7%), pravastatin (18.3%), and fluvastatin (2.7%). When statins were categorized according to their intensity of activity on low-density lipoprotein cholesterol reduction, moderate-intensity statins were primarily used (72.7%), followed by low-intensity (20.9%) and high-intensity (6.3%) statins. The statin group was also described according to intensity and type. The results are reported in Table 1.

Table 2 shows the association between statin use––with its 4 definitions (statin exposure [no/yes], type of statin, statin intensity, and statin intensity and its type)––and the risk of hospitalization for COVID-19. Of the total number of study participants, 9396 were hospitalized for COVID-19: 4372 statin users and 5024 nonusers. Overall, the results from crude and adjusted models show a lower risk of hospitalization among statin users compared with nonusers. The fully adjusted (model 2) and IPTW further adjusted models (model 4) provided similar results. The results from the model with IPTW are presented in Table S6. Statin users had a 16% lower risk of hospitalization for COVID-19 than nonusers (adjusted hazard ratio [HR], 0.84; 95% CI, 0.81–0.88 [P <0.0001]).

The strength of the association remained unchanged after participants taking low-dose aspirin were excluded (Table S7).

All types of statins were significantly associated with a lower risk of hospitalization, with the adjusted HR ranging from 0.75 (95% CI, 0.57–0.99) for fluvastatin to 0.89 (95% CI, 0.84–0.95) for atorvastatin. Low- and moderate-intensity statins showed a lower adjusted risk compared with nonusers (adjusted HR, 0.78 [95% CI, 0.71–0.86] and 0.84 [95% CI, 0.80–0.89], respectively); whereas high-intensity statins were not associated (adjusted HR, 1.01; 95% CI, 0.86–1.18). This subgroup, representing 6.3% of the statin group, had a different profile from those with low and moderate intensity: individuals with high-intensity statins were younger and more likely to have cardiovascular disease risks (male, diabetes, smoking, obesity) and to

Table 1. Baseline Characteristics According to Statin Exposure

	No exposure (n=2 058 249)	Statin exposure (n=2 058 249)	Standardized difference
Matching variables			
Age, y			
Mean (SD)	68.65 (10.36)	68.65 (10.36)	0.00000
Age categories, y			
40–59	395 018 (19.2)	395 018 (19.2)	
60–69	683 378 (33.2)	683 378 (33.2)	
70–79	660 264 (32.1)	660 264 (32.1)	
≥80	319 589 (15.5)	319 589 (15.5)	
Sex			
Men	958 989 (46.6)	958 989 (46.6)	0.00000
Women	1 099 260 (53.4)	1 099 260 (53.4)	
Residence area*			
Auvergne-Rhône-Alpes	213 640 (10.4)	213 640 (10.4)	0.00000
Bourgogne-Franche-Comté	98 693 (4.8)	98 693 (4.8)	
Bretagne	104 714 (5.1)	104 714 (5.1)	
Centre-Val de Loire	95 625 (4.6)	95 625 (4.6)	
Corse	8697 (0.4)	8697 (0.4)	
Grand Est	192 826 (9.4)	192 826 (9.4)	
Hauts-de-France	234 718 (11.4)	234 718 (11.4)	
Ile-de-France	317 010 (15.4)	317 010 (15.4)	
Normandie	121 260 (5.9)	121 260 (5.9)	
Nouvelle-Aquitaine	199 285 (9.7)	199 285 (9.7)	
Occitanie	164 959 (8.0)	164 959 (8.0)	
Pays de la Loire	125 184 (6.1)	125 184 (6.1)	
Provence-Alpes-Côte d'Azur	133 389 (6.5)	133 389 (6.5)	
Overseas departments	47 939 (2.3)	47 939 (2.3)	
Overseas territories	310 (0.0)	310 (0.0)	
Hypertension			
No	1 198 186 (58.2)	1 198 186 (58.2)	0.00000
Yes	860 063 (41.8)	860 063 (41.8)	
Diabetes			
No	1 364 924 (66.3)	1 364 924 (66.3)	0.00000
Yes	693 325 (33.7)	693 325 (33.7)	
Chronic respiratory condition			
No	1 872 316 (91.0)	1 872 316 (91.0)	0.00000
Yes	185 933 (9.0)	185 933 (9.0)	
Covariates			
Social deprivation index (quintiles)			
1 (least deprived)	343 795 (16.7)	330 208 (16.0)	0.05887
2	366 832 (17.8)	364 376 (17.7)	
3	393 467 (19.1)	393 311 (19.1)	
4	422 536 (20.5)	428 084 (20.8)	
5 (most deprived)	449 430 (21.8)	459 712 (22.3)	
Unknown	82 189 (4.0)	82 558 (4.0)	
Smoking-related condition			
No	2 001 677 (97.3)	1 975 967 (96.0)	0.06923
Yes	56 572 (2.7)	82 282 (4.0)	

(*Continued*)

Table 1. Continued

	No exposure (n=2 058 249)	Statin exposure (n=2 058 249)	Standardized difference
Alcohol-related condition			
No	2 025 242 (98.4)	2 027 375 (98.5)	−0.00838
Yes	33 007 (1.6)	30 874 (1.5)	
Obesity-related condition			
No	2 015 058 (97.9)	2 015 593 (97.9)	−0.00182
Yes	43 191 (2.1)	42 656 (2.1)	
Liver failure			
No	2 030 710 (98.7)	2 042 408 (99.2)	−0.05568
Yes	27 539 (1.3)	15 841 (0.8)	
NSAID			
No	1 732 982 (84.2)	1 719 946 (83.6)	0.01722
Yes	325 267 (15.8)	338 303 (16.4)	
Low-dose aspirin			
No	1 827 030 (88.8)	1 514 305 (73.6)	0.39618
Yes	231 219 (11.2)	543 944 (26.4)	
Antiplatelet agent			
No	2 042 260 (99.2)	2 005 808 (97.5)	0.13885
Yes	15 989 (0.8)	52 441 (2.5)	
Heparin			
No	2 044 349 (99.3)	2 045 508 (99.4)	−0.00702
Yes	13 900 (0.7)	12 741 (0.6)	
Anticoagulant			
No	2 010 491 (97.7)	1 999 837 (97.2)	0.03266
Yes	47 758 (2.3)	58 412 (2.8)	
Oral corticosteroid			
No	1 944 371 (94.5)	1 948 469 (94.7)	−0.00878
Yes	113 878 (5.5)	109 780 (5.3)	
Anxiolytic			
No	1 872 500 (91.0)	1 823 368 (88.6)	0.07887
Yes	185 749 (9.0)	234 881 (11.4)	
Hypnotic			
No	1 975 317 (96.0)	1 952 287 (94.9)	0.05349
Yes	82 932 (4.0)	105 962 (5.1)	
Antidepressant			
No	1 902 683 (92.4)	1 847 672 (89.8)	0.09399
Yes	155 566 (7.6)	210 577 (10.2)	
Antipsychotic			
No	2 044 795 (99.3)	2 040 905 (99.2)	0.02193
Yes	13 454 (0.7)	17 344 (0.8)	
Statin description			
Type of statin			
Atorvastatin		827 752 (40.2)	
Fluvastatin		55 585 (2.7)	
Pravastatin		375 936 (18.3)	
Rosuvastatin		384 904 (18.7)	
Simvastatin		414 072 (20.1)	

(*Continued*)

Table 1. Continued

	No exposure (n=2 058 249)	Statin exposure (n=2 058 249)	Standardized difference
Statin intensity			
Low		431 167 (20.9)	
Moderate		1 496 809 (72.7)	
High		130 273 (6.3)	
Statin intensity and its type			
Low			
Fluvastatin 20/40		34 713 (1.7)	
Pravastatin 10/20		288 465 (14.0)	
Simvastatin 10		107 989 (5.2)	
Moderate			
Atorvastatin 10/20		718 121 (34.9)	
Fluvastatin 80		20 872 (1.0)	
Pravastatin 40		87 471 (4.2)	
Rosuvastatin 5/10		364 262 (17.7)	
Simvastatin 20/40		306 083 (14.9)	
High			
Atorvastatin 40/80		109 631 (5.3)	
Rosuvastatin 20		20 642 (1.0)	

*Statin users and nonusers were matched for residence area defined at departmental level (101 French departments). For the purpose of the presentation, these departments were aggregated into 15 regions.

be treated for cardiovascular conditions other than those listed in the noninclusion criteria, necessitating a higher use of low-dose aspirin and antiplatelet agents (Table S8). The absence of a lower risk of hospitalization among high-intensity statin users persisted after participants taking low-dose aspirin were excluded (Table S7).

Similar results were observed when the exposure was categorized according to statin intensity and type. For certain groups, the strength of the association did not reach statistical significance because of the small number of events in each group. The results of the association between all covariates and hospitalization, examined in a fully adjusted model, are displayed in Table S9.

The E-values (relative risk) for the point estimate and upper confidence bound for hospitalization for COVID-19 were 1.70 and 1.56, respectively.

Similar observations can be made when the association between statin use and in-hospital deaths from COVID-19 was examined. However, the reduction of risk with statin use (adjusted HR, 0.77; 95% CI, 0.69–0.86) was higher with this outcome (Table 3 and Table S10). A subanalysis conducted only in patients hospitalized for COVID-19 also showed a lower risk of in-hospital death for COVID-19 (Table S11).

Subgroup analyses conducted using the fully adjusted model showed a lower risk with statin use in all age classes, men and women, regardless of whether the participants had comorbidities (hypertension, diabetes, and chronic respiratory condition) (Table 4).

DISCUSSION

This population-based matched cohort study was conducted in >2 million adults aged ≥40 years who used statins for the primary prevention of cardiovascular diseases compared with 2 million of those who did not use statins. Our results show that statins were associated with a lower risk of hospitalization attributable to COVID-19: statin users had a 16% lower risk than nonusers. This lower risk was observed in all age classes, men and women, regardless of whether the participants had comorbidities (hypertension, diabetes, and chronic respiratory condition). All types of statins showed a lower risk of COVID-19 outcomes. When we examined statin users according to statin intensity on low-density lipoprotein cholesterol–lowering reduction, we did not observe an association between high-intensity statin use and the risk of hospitalization. We observed similar results with in-hospital deaths from COVID-19.

Possible Underlying Mechanisms

COVID-19 is primarily a respiratory viral illness; however, it has widespread effects on the body including hypercoagulability, a hyperinflammatory state, and

Table 2. Association Between Statin Exposure and Hospitalization for COVID-19

	Hospitalization N=9396	Unadjusted model*		Fully adjusted model†		IPTW further adjusted model‡	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Statin exposure							
No	5024 (0.24)	1		1		1	
Yes	4372 (0.21)	0.87 (0.83–0.90)	<0.0001	0.84 (0.81–0.88)	<0.0001	0.84 (0.80–0.87)	<0.0001
Type of statin							
No exposure	5024 (0.24)	1		1		1	
Atorvastatin	1944 (0.23)	0.93 (0.87–0.99)	0.0152	0.89 (0.84–0.95)	0.0006	0.88 (0.83–0.94)	0.0002
Fluvastatin	92 (0.17)	0.74 (0.56–0.97)	0.0293	0.75 (0.57–0.99)	0.0401	0.71 (0.53–0.95)	0.0212
Pravastatin	730 (0.19)	0.86 (0.78–0.95)	0.0027	0.84 (0.76–0.93)	0.0006	0.84 (0.76–0.93)	0.0012
Rosuvastatin	794 (0.21)	0.83 (0.75–0.91)	<0.0001	0.80 (0.72–0.88)	<0.0001	0.80 (0.72–0.88)	<0.0001
Simvastatin	812 (0.20)	0.80 (0.73–0.88)	<0.0001	0.79 (0.72–0.87)	<0.0001	0.78 (0.71–0.87)	<0.0001
Statin intensity							
No exposure	5024 (0.24)	1		1		1	
Low	778 (0.18)	0.79 (0.72–0.87)	<0.0001	0.78 (0.71–0.86)	<0.0001	0.78 (0.71–0.87)	<0.0001
Moderate	3231 (0.22)	0.87 (0.83–0.91)	<0.0001	0.84 (0.80–0.89)	<0.0001	0.83 (0.79–0.88)	<0.0001
High	363 (0.28)	1.10 (0.95–1.28)	0.1957	1.01 (0.86–1.18)	0.9090	1.04 (0.88–1.23)	0.6193
Statin intensity and its type							
No exposure	5024 (0.24)	1		1		1	
Low							
Fluvastatin 20/40	58 (0.17)	0.75 (0.54–1.06)	0.1031	0.77 (0.54–1.08)	0.1331	0.74 (0.51–1.06)	0.0973
Pravastatin 10/20	537 (0.19)	0.83 (0.74–0.93)	0.0015	0.81 (0.72–0.91)	0.0005	0.81 (0.72–0.92)	0.0007
Moderate							
Simvastatin 10	183 (0.17)	0.72 (0.59–0.87)	0.0006	0.72 (0.59–0.87)	0.0008	0.72 (0.59–0.89)	0.0018
Atorvastatin 10/20	1638 (0.23)	0.90 (0.84–0.96)	0.0026	0.88 (0.82–0.94)	0.0002	0.86 (0.80–0.93)	<0.0001
Fluvastatin 80	34 (0.16)	0.72 (0.46–1.12)	0.1454	0.72 (0.46–1.14)	0.1599	0.67 (0.42–1.09)	0.1048
Pravastatin 40	193 (0.22)	0.95 (0.78–1.16)	0.6144	0.92 (0.75–1.13)	0.4427	0.94 (0.76–1.17)	0.5806
Rosuvastatin 5/10	737 (0.20)	0.81 (0.73–0.89)	<0.0001	0.78 (0.71–0.87)	<0.0001	0.78 (0.71–0.87)	<0.0001
Simvastatin 20/40	629 (0.21)	0.83 (0.75–0.93)	0.0007	0.82 (0.73–0.91)	0.0003	0.81 (0.72–0.90)	0.0001
High							
Atorvastatin 40/80	306 (0.28)	1.08 (0.92–1.27)	0.3426	0.99 (0.84–1.18)	0.9442	1.02 (0.85–1.22)	0.8238
Rosuvastatin 20	57 (0.28)	1.24 (0.84–1.83)	0.2793	1.11 (0.74–1.65)	0.6174	1.18 (0.78–1.80)	0.4359

HR indicates hazard ratio.

*Conditional Cox proportional hazards model.

†Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index; smoking-, alcohol-, and obesity-related conditions; liver failure; and concomitant medications (NSAID, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).

‡Conditional Cox proportional hazards model with inverse probability of treatment weighting (IPTW) and further adjustment with the same variables as those in the full adjusted model.

endothelial dysfunction. An autopsy study of COVID-19–positive patients showed that the lung was injured with diffuse alveolar damage (90%), while other effects include pulmonary emboli and microthrombi in multiple organ systems including the brain, as well as hemophagocytosis and cardiac enlargement[82]; results that are consistent with the clinical presentation of symptomatic patients with COVID-19.[83]

The lower risk of hospitalization among statin users compared with nonusers that we found in this study, if causal, would likely be attributable to the pleiotropic beneficial effects of statins as anti-inflammatory, immune-modulatory, and anticoagulant agents.[84] Indeed, several in vitro studies have supported the argument that statins may prevent individuals from being infected or having a serious COVID-19 outcome.[85–88] SARS-CoV-2 infects type II pneumocytes present in the oral mucosa and lungs of the host by docking its spike protein onto ACE-2[85] on the plasma membrane.[86] Lipid rafts––plasma membrane microdomains mainly composed of cholesterol, glycosphingolipids, and phospholipids––including ACE-2 are the sites of the initial binding, activation, internalization, and cell-to-cell transmission of SARS-CoV-2.[87] They also are key

Table 3. Association Between Statin Exposure and In-Hospital Death for COVID-19

	Death N=1648	Unadjusted model*		Fully adjusted model†		IPTW further adjusted model‡	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Statin exposure							
No exposure	914 (0.044)	1		1		1	
Statin exposure	734 (0.036)	0.80 (0.73–0.88)	<0.0001	0.77 (0.69–0.86)	<0.0001	0.76 (0.68–0.85)	<0.0001
Type of statin							
No exposure	914 (0.044)	1		1		1	
Atorvastatin	329 (0.040)	0.93 (0.80–1.08)	0.3375	0.87 (0.74–1.02)	0.0849	0.83 (0.70–0.98)	0.0280
Fluvastatin	22 (0.040)	0.88 (0.50–1.56)	0.6619	0.84 (0.46–1.54)	0.5755	0.88 (0.47–1.65)	0.6970
Pravastatin	118 (0.031)	0.70 (0.55–0.88)	0.0027	0.68 (0.53–0.87)	0.0023	0.66 (0.51–0.85)	0.0014
Rosuvastatinv	126 (0.033)	0.71 (0.57–0.89)	0.0035	0.69 (0.54-0.88)	0.0023	0.72 (0.56–0.92)	0.0084
Simvastatin	139 (0.034)	0.73 (0.58–0.91)	0.0048	0.75 (0.59–0.94)	0.0142	0.75 (0.59–0.96)	0.0212
Statin intensity							
No exposure	914 (0.044)	1		1		1	
Low	142 (0.033)	0.76 (0.61–0.94)	0.0134	0.76 (0.60–0.96)	0.0190	0.74 (0.59–0.94)	0.0116
Moderate	527 (0.035)	0.78 (0.70–0.88)	<0.0001	0.75 (0.66–0.86)	<0.0001	0.75 (0.66–0.85)	<0.0001
High	65 (0.050)	1.18 (0.83–1.69)	0.3619	1.06 (0.72–1.55)	0.7586	1.00 (0.66–1.51)	0.9977
Statin intensity and its type							
No exposure	914 (0.044)	1		1		1	
Fluvastatin 20/40	14 (0.040)	0.74 (0.37–1.47)	0.3859	0.76 (0.37–1.55)	0.4461	0.82 (0.39–1.72)	0.6016
Pravastatin 10/20	91 (0.032)	0.69 (0.53–0.91)	0.0076	0.68 (0.52–0.91)	0.0078	0.66 (0.50–0.88)	0.0041
Simvastatin 10	37 (0.034)	1.00 (0.63–1.58)	1.0000	1.04 (0.65–1.69)	0.8569	1.01 (0.62–1.64)	0.9769
Atorvastatin 10/20	273 (0.038)	0.88 (0.75–1.03)	0.1149	0.83 (0.70–0.99)	0.0368	0.80 (0.67–0.96)	0.0169
Fluvastatin 80	8 (0.038)	1.33 (0.46–3.84)	0.5943	1.10 (0.37–3.31)	0.8655	1.08 (0.33–3.55)	0.9052
Pravastatin 40	27 (0.031)	0.70 (0.43–1.16)	0.1680	0.67 (0.39–1.13)	0.1351	0.67 (0.38–1.17)	0.1628
Rosuvastatin 5/10	117 (0.032)	0.71 (0.56–0.90)	0.0045	0.68 (0.53–0.87)	0.0025	0.71 (0.55–0.91)	0.0072
Simvastatin 20/40	102 (0.033)	0.66 (0.51–0.85)	0.0014	0.67 (0.52–0.88)	0.0038	0.68 (0.52–0.91)	0.0079
Atorvastatin 40/80	56 (0.051)	1.30 (0.88–1.94)	0.1927	1.13 (0.74–1.73)	0.5633	1.02 (0.65–1.61)	0.9380
Rosuvastatin 20	9 (0.044)	0.75 (0.32–1.78)	0.5141	0.79 (0.32–1.94)	0.6052	0.93 (0.37–2.34)	0.8697

HR indicates hazard ratio.

*Conditional Cox proportional hazards model.

†Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index; smoking-, alcohol-, and obesity-related conditions; liver failure; and concomitant medications (NSAID, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).

‡Conditional Cox proportional hazards model with inverse probability of treatment weighting (IPTW) and further adjustment with the same variables as those in the full adjusted model.

regulators of immune and inflammatory responses following the infection. Depletion of cholesterol by statins is shown to disrupt lipid rafts, which, in turn, disturbs viral binding to ACE-2 cells and leads to a significant reduction in viral replication.[88]

Comparison With Other Studies

We found one study[32] that examined the association between statin use and the risk of hospitalization for COVID-19. Oh et al concluded that the risk of developing COVID-19 was 35% lower in statin users compared with nonusers (odds ratio, 0.65; 95% CI, 0.60–0.71). However, the level of evidence was not sufficient given its design: first, the authors selected eligible participants based on a case-control design–COVID-19 patients matched with the general population for age, sex, and place of residence––and performed a second matching based on propensity score between statin users and nonusers. We also identified studies that focused on risk factors and drugs associated with SARS-CoV-2 infection, conducted on patients with varied conditions (history of diabetes,[89] hypertension,[90] undergoing transcatheter aortic valve implantation,[91] or pancreas, biliary, or liver conditions[92]) or in the general population.[93–97] Results of association with statin use in these studies were heterogeneous: a significantly lower risk,[89,93,97] a lower risk but not statistically significant,[90,91,95] and an increased risk of COVID-19 diagnosis.[92,94,96] Our cohort study, specifically planned using a matched exposed/nonexposed design to examine the relationship between statin use and hospitalization

Table 4. Association Between Statin Exposure and COVID-19 Outcomes: Subgroup Analyses

	Hospitalization among nonusers n=5024	Hospitalization among statin users n=4372	Fully adjusted model*		Death among nonusers n=914	Death among statin users n=734	Fully adjusted model*	
			HR (95% CI)	*P* value			HR (95% CI)	*P* value
Age categories, y								
40–59	882/395 018 (0.22)	805/395 018 (0.20)	0.90 (0.81–1.00)	0.0494	62/395 018 (0.016)	42/395 018 (0.011)	0.64 (0.39–1.05)	0.0746
60–69	1437/683 378 (0.21)	1237/683 378 (0.18)	0.85 (0.78–0.92)	0.0001	193/683 378 (0.028)	129/683 378 (0.019)	0.71 (0.55–0.92)	0.0107
70–79	1499/660 264 (0.23)	1329/660 264 (0.20)	0.84 (0.78–0.91)	<0.0001	268/660 264 (0.041)	242/660 264 (0.037)	0.87 (0.71–1.06)	0.1625
≥80	1206/319 589 (0.38)	1001/319 589 (0.31)	0.79 (0.72–0.86)	<0.0001	391/319 589 (0.122)	321/319,589 (0.100)	0.75 (0.63–0.89)	0.0011
Sex								
Men	2,841/958,989 (0.30)	2,414/958,989 (0.25)	0.82 (0.77–0.87)	<0.0001	567/958,989 (0.059)	454/958,989 (0.047)	0.77 (0.67–0.89)	0.0003
Women	2,183/1,099,260 (0.20)	1,958/1,099,260 (0.18)	0.87 (0.81–0.93)	<0.0001	347/1,099,260 (0.032)	280/1,099,260 (0.025)	0.77 (0.64–0.92)	0.0034
Hypertension								
No	3,249/1,198,186 (0.27)	2,853/1,198,186 (0.24)	0.84 (0.80–0.89)	<0.0001	614/1,198,186 (0.051)	471/1,198 186 (0.039)	0.74 (0.65–0.85)	<0.0001
Yes	1775/860 063 (0.21)	1519/860 063 (0.18)	0.84 (0.78–0.90)	<0.0001	300/860 063 (0.035)	263/860 063 (0.031)	0.85 (0.71–1.03)	0.0985
Diabetes								
No	2522/1 364 924 (0.18)	2152/1 364 924 (0.16)	0.83 (0.78–0.88)	<0.0001	416/1 364 924 (0.030)	343/1 364 924 (0.025)	0.79 (0.67–0.92)	0.0034
Yes	2502/693 325 (0.36)	2220/693 325 (0.32)	0.85 (0.80–0.91)	<0.0001	498/693 325 (0.072)	391/693 325 (0.056)	0.77 (0.66–0.90)	0.0007
Chronic respiratory condition								
No	4279/1 872 316 (0.23)	3746/1 872 316 (0.20)	0.84 (0.80–0.88)	<0.0001	765/1 872 316 (0.041)	620/1 872 316 (0.033)	0.77 (0.69–0.87)	<0.0001
Yes	745/185 933 (0.40)	626/185 933 (0.34)	0.83 (0.74–.94)	0.0024	149/185 933 (0.080)	114/185 933 (0.061)	0.77 (0.58–1.03)	0.0754

HR indicates hazard ratio.

*Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index; smoking-, alcohol-, and obesity-related conditions; liver failure; and concomitant medications (NSAID, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).

for COVID-19, showed strong evidence of lower risk of COVID-19 outcomes associated with statins.

We also present other original findings. Our study, which was sufficiently powered to examine the risk of hospitalization for COVID-19 according to types of statins, showed that all types of statins were significantly associated with a lower risk. When we examined the exposed group according to the intensity of statins,[75] we identified a small percentage of high-intensity statin users (6.3%). This subgroup had a different profile from those with low- and moderate-intensity statin subgroups, with more risk factors for cardiovascular diseases. The absence of lower risk of COVID-19 outcomes in the high-intensity statin group compared with the unexposed group may be attributable to: (1) the lack of statistical power because of the low frequency of this group, (2) the inability to control for unmeasured confounders, or (3) a lower risk associated with statins potentially being hindered by an increased risk of hospitalization associated with cardiovascular disease risk factors.

Regarding the secondary outcome, namely in-hospital deaths from COVID-19, we found a lower risk among participants treated with statins compared with those without this treatment. This finding is consistent with that observed in numerous studies.[11–46]

Limitations and Strengths

This study has some limitations. First, our study could not assess any association between statin use and SARS-CoV-2 infection. Because databases containing this information were not available, we used a surrogate outcome: hospitalization attributable to COVID-19. In doing so, we did not include participants with asymptomatic or mild symptoms that did not lead to hospitalization.

Second, our study may have been impacted by selection bias as individuals who take statins might generally be more health conscious than nonusers and, therefore, manage their comorbidities better and seek care earlier in the course of COVID-19. To evaluate this bias, we used an indicator that may reflect health-conscious behavior such as the history of influenza vaccination within 2 years before the index date. Indeed, statin users were more likely to receive this vaccination than nonusers: 48.6% versus 40.0%, respectively (ASD, 0.17). The strength of the association between statin exposure and severe COVID-19 outcomes remained unchanged (Table S12).

Third, as in all observational studies, we cannot rule out a residual confounding effect from unmeasured covariates, in particular those of socioeconomic status such as education. However, the sensitivity analysis using E-value methodology[81] indicated that the observed HR of 0.84 for COVID-19–related hospitalization could only be explained by an unmeasured confounder that was associated with both statin use and COVID-19–related hospitalization by a relative risk association at least as large as 1.70, conditional on the measured covariates in this study (upper confidence bound, 1.56). In our study, the HRs for some of the known COVID-19–related hospitalization risk factors were 1.49 (95% CI, 1.34–2.12) for obesity-related conditions, 1.69 (95% CI, 1.34–2.12) for liver failure, and 1.55 (95% CI, 1.37–1.75) for oral corticosteroids (Table S9). It is not likely that an unmeasured or unknown confounder would have a substantially greater effect on COVID-19–related hospitalization than these known risk factors by having a relative risk exceeding 1.70.

Last, to limit selection or collider bias,[60] our matched cohort was set up from the general population––unlike other studies where hospitalized or COVID-19–positive patients were included––with the exposed group taking statins for the primary prevention of cardiovascular disease.

The SNDS, a claims database comprising the entire population of France, has allowed us to comprehensively examine the association between statins and severe COVID-19 outcomes. To avoid confounding bias as much as possible, we limited the study of the effect of statins to the context of primary prevention of cardiovascular diseases as these comorbidities are known to be strongly associated with an increased risk of hospitalization for COVID-19.[24,98] After matching for age, sex, residence area, hypertension, diabetes, and chronic respiratory condition, statin users and nonusers were comparable for 14 of 15 covariates. The only imbalanced variable was low-dose aspirin. This imbalance was taken into account by including this variable in multivariable analyses and in the calculation of IPTW, which rendered comparison groups similar among all covariates. In observational studies, adjustment for adequate covariates is the most important step. This is particularly crucial in studies examining the association between statins and COVID-19 outcomes. To illustrate this, we observed unadjusted and adjusted ratio measures (OR or HR) in published studies investigating the role of statins in in-hospital mortality by COVID-19 (Figure S2): in propensity score–matched cohort studies, unadjusted odds ratios or HRs were very close to those with adjustment.[7,12,27] In other studies where this design was not applied, adjustment systematically decreased odds ratios or HRs.[†] In certain cases, the direction of odds ratios or HRs changed drastically after adjustment: statin use was significantly associated with a higher risk in unadjusted analysis while it was associated with lower risk in adjusted analysis.[7,18] In addition, not including adjusted ratio measures in

[†]References 7,13,18,19,23,28,36,47,49.

meta-analyses, which is recommended by the Cochrane group,[99] leads to spurious results, notably the absence of association between statin use and COVID-19 outcomes.[100] Meta-analyses that did include adjusted ratio measures showed a lower risk of COVID-19 outcomes with the statin use.[101,102]

Our findings indicate that the lower risk of statins on hospitalization for COVID-19, although modest, is robust. Statins are now known to be beneficial in primary prevention, decreasing all-cause mortality, cardiovascular disease, coronary heart disease, and stroke. Furthermore, there is no evidence of any serious harm caused by their use.[103] Our study found an additional lower risk of statins against serious COVID-19 symptoms that lead to hospitalization. Since the beginning of the COVID-19 pandemic, many clinicians have suggested that statins could be used as an adjunctive treatment for the SARS-CoV-2 infection. This population-based matched cohort study conducted in 2 million adults aged ≥40 years who used statins for the primary prevention of cardiovascular diseases compared with 2 million nonusers supports the hypothesis that statin use is associated with a lower risk of hospitalization for COVID-19. All types of statins showed a similar effect.

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Supplemental Material

Tables S1-S12
Figures S1–S2

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SUPPLEMENTAL MATERIAL

Table S1. Non-inclusion criteria

Most criteria were defined based on ICD-10 and ATC codes.

ICD-10 codes: any occurrence in the 5 years preceding inclusion date (February 15, 2020) is used.

ATC codes: having 3 dispensing (or 2 when at least one concerned the dispensing of large pack size) in the year preceding inclusion date is used. For lipid lowering drugs, additional condition was required: having at least one dispensing in the last month (if small pack size) or 3 months (if large pack size) preceding inclusion.

Other codes were also detailed.

Exclusion criteria	Codes
Lipid lowering drugs	
Fibrates	
ATC	C10AB
Bile acid sequestrants	
ATC	C10AC
Nicotinic acid and derivatives	
ATC	C10AD
Other lipid lowering drugs (ezetimibe, PCSK9 inhibitors,* etc.)	
ATC	C10AX
Combinations of lipid lowering drugs	
ATC	C10B
Cardiovascular and neurovascular diseases	
Include following conditions: Acute or chronic coronary artery disease Acute stroke or aftermath Acute or chronic heart failure Peripheral vascular disease Arrhythmia or cardiac conduction disorders Valvular heart disease Acute pulmonary embolism Other cardiovascular conditions	
ICD-10	I50 J81 I11 I13 K761 I20 I21 I22 I23 I24 I25 I48 I05 I06 I07 I08 I34 I35 I36 I37 I38 I39 I44, I45, I47, I48, I49 I702, I26 I739, I74.0, I74.3, I74.4, I74.5, G46 I60 I61 I62 I63 I64 I65 I66 I67 I68 I69 G45 I26 I800 I801 I802 I803 I808 I809 I81 I82 I70, I73, I74 only for those included in the list of long-term diseases
Other comorbidities	
Cancer	
ICD-10	C0x.x-C9x.x D00.x-D09.x Z08, Z51.0, Z51.1
Kidney transplant, dialysis	
ICD-10	N18 (long-term diseases), Z940
CCAM	JAEA003, HNEA002 JVJB001, JVJF004, JVJF008, JVRP004, JVRP007, JVRP008, YYYY007
Diagnosis related group	27C06, 24M39Z, 11M17

	11K02, 28Z01-28Z04
Billing code for dialysis session conducted at home, self-care dialysis, in a dialysis unit under medical supervision	D11-D16, D20-24
Dementia	
ICD-10	F00 F01 F02 F03 F051 G30
ATC	N06DA04 N06DX01

*For PCSK9 inhibitors: any dispensing in the past year.

Table S2. Exposure of interest

Definition (ATC codes): having 3 dispensing (or 2 when at least one concerned the dispensing of large pack size) in the year preceding inclusion date and having at least one dispensing in the last month (if small pack size) or 3 months (if large pack size) preceding inclusion.

Types and statin intensity was defined based on the lastly dispensed statin between November 15, 2019 and February 15, 2020 (index date).

Types of statins

Statins (HMG CoA reductase inhibitors)	ATC codes
Atorvastatin	C10AA05
Fluvastatin	C10AA04
Pravastatin	C10AA03
Rosuvastatin	C10AA07
Simvastatin	C10AA01

Classification of statins according to their intensity

This classification is based on an article published by ACC/AHA, Circulation, 2019.

Intensity (LDL-cholesterol lowering)	Dose 1	Dose 2
Low (< 30%)		
Fluvastatin	20	40
Pravastatin	10	20
Simvastatin	10	
Moderate (30% - 49%)		
Atorvastatin	10	20
Rosuvastatin	5	10
Simvastatin	20	40
Pravastatin	40	
Fluvastatin	80	
High (≥50%)		
Atorvastatin	40	80
Rosuvastatin	20	

Table S3. Matching variables

Most criteria were defined based on ICD-10 and ATC codes.

ICD-10 codes: any occurrence in the 5 years preceding inclusion date (February 15, 2020) is used.

ATC codes: having 3 dispensing (or 2 when at least one concerned the dispensing of large pack size) in the year preceding inclusion date is used.

In addition to year of birth, sex, residence area, other matching variables were:

Covariates	Codes
Hypertension	
ATC	C02AB02, C02AC01, C02AC02, C02AC05, C02AC06, C02CA01, C02CA06, C02DC01, C02LA01, C03AA01, C03AA03, C03BA04, C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03DA01, C03DB01, C03EA, C03EA01, C03EA04, C07AA02, C07AA03, C07AA05, C07AA06, C07AA12, C07AA15, C07AA16, C07AA23, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB12, C07AG01, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C07FB02, C07FB03, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA08, C08CA09, C08CA11, C08CA13, C08CX01, C08DA01, C08DB01, C08GA02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA13, C09AA15, C09AA16, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09BB02, C09BB04, C09BB10, C09BX02, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DB01, C09DB02, C09DB04, C09XA02, C09XA52, C10BX03
Diabetes mellitus	
ICD-10	E10, E11, E12, E13, E14 G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, L97, M14.2, M14.6, N08.3
ATC	A10 excluding benfluorex (A10BX06)
Chronic respiratory condition	
ICD-10	J40, J41, J42, J43, J44, J45, J46, J47, J96 (excluding J96.0, J96.9), J98
ATC	R03 (drugs for obstructive airway diseases)

Table S4. Covariates

Most criteria were defined based on ICD-10 and ATC codes.

ICD-10 codes: any occurrence in the 5 years preceding inclusion date (February 15, 2020) is used.

ATC codes: having 3 dispensing (or 2 when at least one concerned the dispensing of large pack size) in the year preceding inclusion date is used.

Other codes were also detailed.

Covariates	Codes
Health behavior characteristics	
Smoking-related condition	
ICD-10	Z716 F17 T652 Z720
ATC	N07BA
Primary care delivery	Tobacco consultation service (9566, 9526, 9527) in the 5 years preceding index date (at least once)
Alcohol-related condition	
ICD-10	E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, R780, T51, X45, X65, Y15, Y90, Y91, Y573, Z502, Z714, or Z721
ATC	N07BB01, N07BB03, N07BB04, N07BB05 at least 2 dispensing in the 5 years preceding index date M03BX01 (baclofen) without following neurological disease (ICD-10): C70, C71, C793, C794, D32, D33, D42, D43, G04, G05,G06, G09, G12, G13, G24, G25, G26, G31, G32, G35, G36, G37, G46, G80, G81, G82, G83, G91, G93, G95
Laboratory test (NABM)	516, 517, 519 (gamma-GT)
Obesity-related condition	
ICD-10	E66 excluding E66.03, E66.13, E66.83, E66.93 (since 2006)
CCAM	HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFGC900, HFKA001, HFKA002, HFKC001, HFLC900, HFLE002, HFMA009, HFMA010, HFMA011, HFMC006, HFMC007, HFMC008, HGCA009, HGCC027 (bariatric surgery)
Comorbidities or comedications	
Liver and pancreas disorder	
ICD-10	B18, I85, K70, K71, K72, K73, K74, K75, K76 K85, K86
ATC/UCD/CIP	Treatment for chronic hepatitis B: J05AF08, J05AF10, J05AF11 9212525, 9212531 (UCD, Zeffix®) 3519671, 3519694 (CIP, Zeffix®) Treatment for chronic hepatitis B: L03AB05, L03AB09, L03AB10, L03AB11 J05AB04 J05AP08, J05AP51, J05AP55, J05AP56, J05AX (3400930108765 (CIP), 3400894287391 (UCD)), J05AX14, J05AX15, J05AX16, J05AX65, J05AX67, J05AX68
Laboratory test (NABM)	4125: hepatitis C genotype 4124: hepatitis C viral load 1000 to 1002 (Fibrotest®, Fibromètre®V, Hépascore®)
CCAM	HLQM002, HLHB001, HLHH001, HLHH005, HLHJ003 (liver biopsy, etc.)
Medications (ATC)	

Non-steroidal anti-inflammatory drugs (ATC)	M01AE09, M01AE11, M01AE01, M01AE02, M01AB01, M01AE03, M01AB05, M01AB16, M01AH01, M01AH05, M01AC01, M01AC02, M01AC06, M01AX01, M01AX17, M01AB08, M01AE16, M01AX02, M01AX22, M01AX21
Low-dose aspirin (CIP)	18 CIP codes: 3400934744198 3400933247379 3400931893639 3400932703616 3400926939939 3400938206371 3400933226558 3400934323492 3400934300141 3400930013953 3400930013984 3400930014035 3400930014066 3400935902269 3400935984814 3400926940188 3400930182543 3400930195697
Antiplatelet	B01AC04-B01AC07 B01AC22-B01AC24 B01AC30
Heparin	B01AB,B01AX
Anticoagulant	B01AA,B01AE,B01AF,B01AX
Oral corticosteroid	H02A
Anxiolytic	N05BA01, N05BA04, N05BA05, N05BA06, N05BA08, N05BA09, N05BA11, N05BA12, N05BA16, N05BA18, N05BA21, N05BA23, N05BB01, N05BB02, N05BC01, N05BE01, N05BX03
Hypnotic	N05BC51, N05CD02, N05CD03, N05CD04, N05CD05, N05CD06, N05CD07, N05CD11, N05CF01, N05CF02, N05CM11, N05CM16, N05CX
Antidepressant	N06A, N05AN01, N03AG02 3400934876233, 3400934876691, 3400935444271 (CIP)
Antipsychotic	N05A (excluding N05AN01 and N05AL06) 3400932896332 (CIP)

NABM: *nomenclature des actes de biologie médicale*.

Table S5. Population distribution by geographical region

	In metropolitan France		In the present study	
	January 1, 2021*		No exposure	Statin exposure
Auvergne-Rhône-Alpes	8,092,598	(12,4)	213,640 (10.4)	213,640 (10.4)
Bourgogne-Franche-Comté	2,786,205	(4,3)	98,693 (4.8)	98,693 (4.8)
Bretagne	3,371,297	(5,2)	104,714 (5.1)	104,714 (5.1)
Centre-Val de Loire	2,562,431	(3,9)	95,625 (4.6)	95,625 (4.6)
Corse	349,273	(0,5)	8,697 (0.4)	8,697 (0.4)
Grand Est	5,524,817	(8,5)	192,826 (9.4)	192,826 (9.4)
Hauts-de-France	5,977,46	(9,2)	234,718 (11.4)	234,718 (11.4)
Île-de-France	12,326,429	(18,9)	317,010 (15.4)	317,010 (15.4)
Normandie	3,306,092	(5,1)	121,260 (5.9)	121,260 (5.9)
Nouvelle Aquitaine	6,039,767	(9,3)	199,285 (9.7)	199,285 (9.7)
Occitanie	5,985,751	(9,2)	164,959 (8.0)	164,959 (8.0)
Pays de la Loire	3,838,060	(5,9)	125,184 (6.1)	125,184 (6.1)
Provence-Alpes-Côte d'Azur	5,089,661	(7,8)	133,389 (6.5)	133,389 (6.5)
Total	**65,249,843**		**2,058,249**	**2,058,249**

*Source: INSEE, Population census. Data available on the French Institute for Demographic Studies website (INED: https://www.ined.fr).

Table S6. Association between statin exposure and hospitalization for COVID-19

	Hospitalization N=9396	IPTW*		IPTW further adjusted model†	
		HR [95%CI]	P-value	HR [95%CI]	P-value
Statin exposure					
No exposure	5,024 (0.24)	1	.	1	.
Statin exposure	4,372 (0.21)	0.85 [0.82-0.89]	<.0001	0.84 [0.80-0.87]	<.0001
Type of statin					
No exposure	5,024 (0.24)	1	.	1	.
Atorvastatin	1,944 (0.23)	0.91 [0.85-0.97]	0.0035	0.88 [0.83-0.94]	0.0002
Fluvastatin	92 (0.17)	0.69 [0.52-0.92]	0.0114	0.71 [0.53-0.95]	0.0212
Pravastatin	730 (0.19)	0.86 [0.77-0.95]	0.0038	0.84 [0.76-0.93]	0.0012
Rosuvastatin	794 (0.21)	0.82 [0.75-0.91]	<.0001	0.80 [0.72-0.88]	<.0001
Simvastatin	812 (0.20)	0.79 [0.72-0.87]	<.0001	0.78 [0.71-0.87]	<.0001
Statin intensity					
No exposure	5,024 (0.24)	1	.	1	.
Low	778 (0.18)	0.79 [0.71-0.87]	<.0001	0.78 [0.71-0.87]	<.0001
Moderate	3,231 (0.22)	0.85 [0.81-0.89]	<.0001	0.83 [0.79-0.88]	<.0001
High	363 (0.28)	1.12 [0.95-1.31]	0.1756	1.04 [0.88-1.23]	0.6193
Statin intensity and its type					
No exposure	5,024 (0.24)	1	.	1	.
<u>Low</u>					
Fluvastatin 20/40	58 (0.17)	0.71 [0.50-1.01]	0.0595	0.74 [0.51-1.06]	0.0973
Pravastatin 10/20	537 (0.19)	0.82 [0.73-0.93]	0.0015	0.81 [0.72-0.92]	0.0007
Simvastatin 10	183 (0.17)	0.71 [0.59-0.87]	0.0009	0.72 [0.59-0.89]	0.0018
<u>Moderate</u>					
Atorvastatin 10/20	1,638 (0.23)	0.88 [0.82-0.95]	0.0004	0.86 [0.80-0.93]	<.0001
Fluvastatin 80	34 (0.16)	0.66 [0.41-1.06]	0.0886	0.67 [0.42-1.09]	0.1048
Pravastatin 40	193 (0.22)	0.97 [0.79-1.20]	0.8066	0.94 [0.76-1.17]	0.5806
Rosuvastatin 5/10	737 (0.20)	0.80 [0.72-0.88]	<.0001	0.78 [0.71-0.87]	<.0001
Simvastatin 20/40	629 (0.21)	0.82 [0.73-0.91]	0.0003	0.81 [0.72-0.90]	0.0001
<u>High</u>					
Atorvastatin 40/80	306 (0.28)	1.09 [0.91-1.29]	0.3393	1.02 [0.85-1.22]	0.8238
Rosuvastatin 20	57 (0.28)	1.29 [0.85-1.95]	0.2252	1.18 [0.78-1.80]	0.4359

HR for hazard ratio; 95%CI for 95% confidence interval; IPTW for inverse probability of treatment weighting.

*Conditional Cox proportional hazards model with IPTW.

†Conditional Cox proportional hazards model with IPTW further adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).

Table S7. Association between statin exposure and hospital outcomes after excluding participants with low-dose aspirin

	Fully adjusted model*	
	HR [95%CI]	**P-value**
Hospitalization for COVID-19		
Statin exposure		
No	1	-
Yes	0.84 [0.79-0.89]	<.0001
Statin intensity		
No exposition	1	-
Low	0.79 [0.70-0.89]	0.0002
Moderate	0.84 [0.79-0.90]	0.0000
High	1.04 [0.83-1.31]	0.7330
In-hospital deaths for COVID-19		
Statin exposure		
No	1	-
Yes	0.80 [0.68-0.92]	0.0028
Statin intensity		
No exposition	1	-
Low	0.74 [0.54-1.02]	0.0639
Moderate	0.78 [0.66-0.93]	0.0061
High	1.36 [0.73-2.54]	0.3352

HR for hazard ratio; 95%CI for 95% confidence interval.

*Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).

Table S8. Characteristics of the study population according to statin intensity

	Before IPTW				After IPTW			
	No exposure (n=2,058,249)	**Low (n=431,167)**	**Moderate (n=1,496,809)**	**High (n=130,273)**	**No exposure (n=2,059,865)**	**Low (n=430,877)**	**Moderate (n=1,497,236)**	**High (n=129,810)**
Matching variables								
Age (years)								
Mean (SD)	68.65 (10.36)	70.03 (10.39)	68.41 (10.31)	66.84 (10.40)	68.77 (10.45)	68.66 (10.43)	68.68 (10.25)	68.76 (10.25)
Age categories								
40-59	395,018 (19.2)	68,576 (15.9)	294,549 (19.7)	31,893 (24.5)	393,908 (19.1)	83,290 (19.3)	281,126 (18.8)	24,167 (18.6)
60-69	683,378 (33.2)	133,583 (31.0)	504,099 (33.7)	45,696 (35.1)	675,066 (32.8)	141,375 (32.8)	501,607 (33.5)	43,582 (33.5)
70-79	660,264 (32.1)	146,141 (33.9)	476,803 (31.9)	37,320 (28.6)	659,763 (32.1)	138,366 (32.1)	486,325 (32.5)	41,898 (32.2)
>=80	319,589 (15.5)	82,867 (19.2)	221,358 (14.8)	15,364 (11.8)	331,128 (16.1)	67,846 (15.7)	228,178 (15.2)	20,163 (15.5)
Sex								
Men	958,989 (46.6)	180,842 (41.9)	705,247 (47.1)	72,900 (56.0)	953,716 (46.3)	200,817 (46.6)	695,127 (46.4)	59,735 (45.9)
Women	1,099,260 (53.4)	250,325 (58.1)	791,562 (52.9)	57,373 (44.0)	1,106,151 (53.7)	230,062 (53.4)	802,109 (53.6)	70,076 (53.8)
Residence area								
Auvergne-Rhône-Alpes	213,640 (10.4)	46,402 (10.8)	153,759 (10.3)	13,479 (10.3)	211,820 (10.3)	46,107 (10.7)	153,836 (10.3)	13,630 (10.5)
Bourgogne-Franche-Comté	98,693 (4.8)	20,662 (4.8)	71,392 (4.8)	6,639 (5.1)	98,760 (4.8)	20,419 (4.7)	71,484 (4.8)	6,894 (5.3)
Bretagne	104,714 (5.1)	26,632 (6.2)	71,362 (4.8)	6,720 (5.2)	103,224 (5.0)	25,991 (6.0)	72,537 (4.8)	6,891 (5.3)
Centre-Val de Loire	95,625 (4.6)	21,013 (4.9)	69,118 (4.6)	5,494 (4.2)	94,986 (4.6)	20,878 (4.8)	70,104 (4.7)	5,898 (4.5)
Corse	8,697 (0.4)	1,859 (0.4)	6,499 (0.4)	339 (0.3)	9,048 (0.4)	1,789 (0.4)	6,347 (0.4)	302 (0.2)
Grand Est	192,826 (9.4)	37,524 (8.7)	144,291 (9.6)	11,011 (8.5)	196,157 (9.5)	37,416 (8.7)	142,586 (9.5)	11,074 (8.5)
Hauts-de-France	234,718 (11.4)	41,586 (9.6)	176,315 (11.8)	16,817 (12.9)	241,077 (11.7)	41,848 (9.7)	173,364 (11.6)	16,086 (12.3)
Ile-de-France	317,010 (15.4)	57,879 (13.4)	239,199 (16.0)	19,932 (15.3)	313,047 (15.2)	59,433 (13.8)	239,784 (16.0)	19,816 (15.2)
Normandie	121,260 (5.9)	27,880 (6.5)	86,616 (5.8)	6,764 (5.2)	122,824 (6.0)	27,751 (6.4)	86,127 (5.8)	6,725 (5.2)
Nouvelle-Aquitaine	199,285 (9.7)	47,489 (11.0)	139,229 (9.3)	12,567 (9.6)	198,574 (9.6)	47,079 (10.9)	141,019 (9.4)	13,143 (10.1)
Occitanie	164,959 (8.0)	37,273 (8.6)	118,545 (7.9)	9,141 (7.0)	163,733 (8.0)	37,101 (8.6)	119,146 (8.0)	9,074 (7.0)
Overseas departments	47,939 (2.3)	7,349 (1.7)	35,138 (2.3)	5,452 (4.2)	48,232 (2.3)	7,851 (1.8)	34,777 (2.3)	4,708 (3.6)
Overseas territories	310 (0.0)	65 (0.0)	207 (0.0)	38 (0.0)	315 (0.0)	74 (0.0)	206 (0.0)	36 (0.0)
Pays de la Loire	125,184 (6.1)	30,893 (7.2)	85,542 (5.7)	8,749 (6.7)	124,445 (6.0)	30,582 (7.1)	86,012 (5.7)	8,234 (6.3)
Provence-Alpes-Côte d'Azur	133,389 (6.5)	26,661 (6.2)	99,597 (6.7)	7,131 (5.5)	133,618 (6.5)	26,552 (6.2)	99,899 (6.7)	7,293 (5.6)
Covariates								
Hypertension								
No	1,198,186 (58.2)	237,112 (55.0)	878,869 (58.7)	82,205 (63.1)	1,194,456 (58.0)	249,811 (57.9)	870,240 (58.1)	78,250 (60.1)
Yes	860,063 (41.8)	194,055 (45.0)	617,940 (41.3)	48,068 (36.9)	865,410 (42.0)	181,067 (42.0)	626,997 (41.9)	51,561 (39.6)
Diabetes mellitus								

No	1,364,924 (66.3)	307,159 (71.2)	983,960 (65.7)	73,805 (56.7)	1,357,640 (66.0)	286,008 (66.3)	989,815 (66.1)	80,966 (62.2)
Yes	693,325 (33.7)	124,008 (28.8)	512,849 (34.3)	56,468 (43.3)	702,226 (34.1)	144,871 (33.6)	507,421 (33.9)	48,845 (37.5)
Chronic respiratory condition								
No	1,872,316 (91.0)	394,499 (91.5)	1,361,260 (90.9)	116,557 (89.5)	1,872,250 (91.0)	391,818 (90.9)	1,361,593 (91.0)	117,580 (90.3)
Yes	185,933 (9.0)	36,668 (8.5)	135,549 (9.1)	13,716 (10.5)	187,617 (9.1)	39,060 (9.1)	135,644 (9.1)	12,231 (9.4)
Social deprivation index (quintiles)								
1 (least deprived)	343,795 (16.7)	66,309 (15.4)	244,750 (16.4)	19,149 (14.7)	338,101 (16.4)	66,521 (15.4)	246,129 (16.4)	20,596 (15.8)
2	366,832 (17.8)	77,603 (18.0)	264,559 (17.7)	22,214 (17.1)	362,894 (17.6)	78,132 (18.1)	266,239 (17.8)	23,306 (17.9)
3	393,467 (19.1)	85,186 (19.8)	283,928 (19.0)	24,197 (18.6)	392,651 (19.1)	84,848 (19.7)	284,438 (19.0)	24,495 (18.8)
4	422,536 (20.5)	94,334 (21.9)	306,801 (20.5)	26,949 (20.7)	425,373 (20.7)	93,683 (21.7)	306,602 (20.5)	26,327 (20.2)
5 (most deprived)	449,430 (21.8)	92,908 (21.5)	336,361 (22.5)	30,443 (23.4)	457,832 (22.2)	92,534 (21.5)	333,883 (22.3)	28,688 (22.0)
Unknown	82,189 (4.0)	14,827 (3.4)	60,410 (4.0)	7,321 (5.6)	83,015 (4.0)	15,158 (3.5)	59,943 (4.0)	6,398 (4.9)
Smoking-related condition								
No	2,001,677 (97.3)	417,468 (96.8)	1,436,216 (96.0)	122,283 (93.9)	1,990,894 (96.7)	416,274 (96.5)	1,446,959 (96.7)	125,253 (96.1)
Yes	56,572 (2.7)	13,699 (3.2)	60,593 (4.0)	7,990 (6.1)	68,973 (3.4)	14,605 (3.4)	50,278 (3.4)	4,558 (3.5)
Alcohol-related condition								
No	2,025,242 (98.4)	426,071 (98.8)	1,474,072 (98.5)	127,232 (97.7)	2,028,053 (98.5)	424,201 (98.4)	1,474,250 (98.5)	127,614 (98.0)
Yes	33,007 (1.6)	5,096 (1.2)	22,737 (1.5)	3,041 (2.3)	31,814 (1.5)	6,677 (1.5)	22,987 (1.5)	2,197 (1.7)
Obesity-related condition								
No	2,015,058 (97.9)	424,354 (98.4)	1,464,716 (97.9)	126,523 (97.1)	2,016,463 (98.0)	421,848 (97.8)	1,465,808 (97.9)	126,805 (97.3)
Yes	43,191 (2.1)	6,813 (1.6)	32,093 (2.1)	3,750 (2.9)	43,404 (2.1)	9,030 (2.1)	31,429 (2.1)	3,006 (2.3)
Liver and pancreas disorder								
No	2,030,710 (98.7)	428,432 (99.4)	1,485,005 (99.2)	128,971 (99.0)	2,038,195 (99.0)	426,312 (98.9)	1,481,631 (99.0)	128,335 (98.5)
Yes	27,539 (1.3)	2,735 (0.6)	11,804 (0.8)	1,302 (1.0)	21,672 (1.1)	4,566 (1.1)	15,606 (1.0)	1,476 (1.1)
Non-steroidal anti-inflammatory								
No	1,732,982 (84.2)	364,847 (84.6)	1,245,484 (83.2)	109,615 (84.1)	1,725,349 (83.8)	361,483 (83.8)	1,255,350 (83.9)	107,885 (82.8)
Yes	325,267 (15.8)	66,320 (15.4)	251,325 (16.8)	20,658 (15.9)	334,517 (16.3)	69,396 (16.1)	241,887 (16.2)	21,927 (16.8)
Low-dose aspirin								
No	1,827,030 (88.8)	328,902 (76.3)	1,108,038 (74.0)	77,365 (59.4)	1,669,681 (81.1)	348,232 (80.8)	1,215,634 (81.2)	105,230 (80.8)
Yes	231,219 (11.2)	102,265 (23.7)	388,771 (26.0)	52,908 (40.6)	390,186 (19.0)	82,646 (19.2)	281,602 (18.8)	24,581 (18.9)
Antiplatelet agent								
No	2,042,260 (99.2)	423,613 (98.2)	1,459,937 (97.5)	122,258 (93.8)	2,021,734 (98.2)	423,714 (98.3)	1,472,331 (98.4)	127,585 (97.9)
Yes	15,989 (0.8)	7,554 (1.8)	36,872 (2.5)	8,015 (6.2)	38,133 (1.9)	7,164 (1.7)	24,906 (1.7)	2,226 (1.7)
Heparin								
No	2,044,349 (99.3)	428,538 (99.4)	1,487,559 (99.4)	129,411 (99.3)	2,046,403 (99.4)	428,086 (99.3)	1,487,529 (99.4)	128,922 (99.0)
Yes	13,900 (0.7)	2,629 (0.6)	9,250 (0.6)	862 (0.7)	13,463 (0.7)	2,792 (0.6)	9,708 (0.6)	889 (0.7)

Anticoagulant								
No	2,010,491 (97.7)	419,361 (97.3)	1,455,088 (97.2)	125,388 (96.3)	2,005,242 (97.4)	419,692 (97.3)	1,458,442 (97.4)	126,253 (96.9)
Yes	47,758 (2.3)	11,806 (2.7)	41,721 (2.8)	4,885 (3.7)	54,624 (2.7)	11,187 (2.6)	38,794 (2.6)	3,558 (2.7)
Oral corticosteroid								
No	1,944,371 (94.5)	409,134 (94.9)	1,416,044 (94.6)	123,291 (94.6)	1,947,198 (94.6)	407,439 (94.5)	1,415,769 (94.6)	122,676 (94.2)
Yes	113,878 (5.5)	22,033 (5.1)	80,765 (5.4)	6,982 (5.4)	112,668 (5.5)	23,439 (5.4)	81,468 (5.4)	7,135 (5.5)
Anxiolytic								
No	1,872,500 (91.0)	381,414 (88.5)	1,326,948 (88.7)	115,006 (88.3)	1,844,824 (89.6)	386,921 (89.7)	1,343,356 (89.7)	116,067 (89.1)
Yes	185,749 (9.0)	49,753 (11.5)	169,861 (11.3)	15,267 (11.7)	215,043 (10.4)	43,958 (10.2)	153,881 (10.3)	13,744 (10.6)
Hypnotic								
No	1,975,317 (96.0)	409,748 (95.0)	1,419,181 (94.8)	123,358 (94.7)	1,962,836 (95.4)	411,091 (95.3)	1,427,986 (95.4)	123,565 (94.9)
Yes	82,932 (4.0)	21,419 (5.0)	77,628 (5.2)	6,915 (5.3)	97,031 (4.7)	19,787 (4.6)	69,250 (4.6)	6,246 (4.8)
Antidepressant								
No	1,902,683 (92.4)	386,729 (89.7)	1,344,623 (89.8)	116,320 (89.3)	1,873,144 (91.0)	392,469 (91.0)	1,363,551 (91.1)	117,950 (90.5)
Yes	155,566 (7.6)	44,438 (10.3)	152,186 (10.2)	13,953 (10.7)	186,722 (9.1)	38,410 (8.9)	133,686 (8.9)	11,861 (9.1)
Antipsychotic								
No	2,044,795 (99.3)	427,542 (99.2)	1,484,359 (99.2)	129,004 (99.0)	2,044,152 (99.3)	427,614 (99.2)	1,486,009 (99.3)	128,817 (98.9)
Yes	13,454 (0.7)	3,625 (0.8)	12,450 (0.8)	1,269 (1.0)	15,715 (0.8)	3,265 (0.8)	11,227 (0.8)	995 (0.8)

Table S9. Association between covariates and hospitalization for COVID-19 examined in a fully adjusted model

	Fully adjusted model*			
	HR	**95%CI**		**P-value**
Statin exposure				
No exposure	1.00	.	.	.
Statin exposure	0.84	0.81	0.88	<.0001
Social deprivation index (quintiles)				
1 (least deprived)	1.00	.	.	.
2	1.18	1.07	1.31	0.0014
3	1.38	1.23	1.54	<.0001
4	1.42	1.27	1.59	<.0001
5 (most deprived)	1.58	1.42	1.75	<.0001
Unknown	1.34	0.98	1.82	0.0631
Smoking-related condition				
No	1.00	.	.	.
Yes	0.50	0.41	0.63	<.0001
Alcohol-related condition				
No	1.00	.	.	.
Yes	1.31	1.02	1.67	0.0322
Obesity-related condition				
No	1.00	.	.	.
Yes	1.49	1.25	1.79	<.0001
Liver failure				
No	1.00	.	.	.
Yes	1.69	1.34	2.12	<.0001
Non-steroidal anti-inflammatory				
No	1.00	.	.	.
Yes	1.11	1.03	1.21	0.0084
Low-dose aspirin				
No	1.00	.	.	.
Yes	1.13	1.06	1.22	0.0006
Antiplatelet agent				
No	1.00	.	.	.
Yes	1.58	1.29	1.93	<.0001
Heparin				
No	1.00	.	.	.
Yes	1.14	0.81	1.60	0.4629
Anticoagulant				
No	1.00	.	.	.
Yes	1.35	1.16	1.57	<.0001
Oral corticosteroid				
No	1.00	.	.	.
Yes	1.55	1.37	1.75	<.0001
Anxiolytic				
No	1.00	.	.	.
Yes	1.06	0.96	1.18	0.2398
Hypnotic				
No	1.00	.	.	.

	Fully adjusted model*			
	HR	**95%CI**		**P-value**
Yes	0.94	0.82	1.09	0.4046
Antidepressant				
No	1.00	.	.	.
Yes	1.10	0.98	1.22	0.0984
Antipsychotic				
No	1.00	.	.	.
Yes	1.91	1.40	2.60	<.0001

HR for hazard ratio; 95%CI for 95% confidence interval.

*Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).

Table S10. Association between statin exposure and in-hospital COVID-19 deaths

	Death N=1648	IPTW*		IPTW further adjusted model†	
		HR [95%CI]	P-value	HR [95%CI]	P-value
Statin exposure					
No exposure	914 (0.044)	1	.	1	.
Statin exposure	734 (0.036)	0.77 [0.69-0.85]	<.0001	0.76 [0.68-0.85]	<.0001
Type of statin					
No exposure	914 (0.044)	1	.	1	.
Atorvastatin	329 (0.040)	0.86 [0.73-1.01]	0.0584	0.83 [0.70-0.98]	0.0280
Fluvastatin	22 (0.040)	0.87 [0.48-1.57]	0.6457	0.88 [0.47-1.65]	0.6970
Pravastatin	118 (0.031)	0.66 [0.52-0.84]	0.0009	0.66 [0.51-0.85]	0.0014
Rosuvastatin	126 (0.033)	0.73 [0.58-0.93]	0.0093	0.72 [0.56-0.92]	0.0084
Simvastatin	139 (0.034)	0.73 [0.58-0.91]	0.0065	0.75 [0.59-0.96]	0.0212
Statin intensity					
No exposure	914 (0.044)	1	.	1	.
Low	142 (0.033)	0.72 [0.58-0.90]	0.0038	0.74 [0.59-0.94]	0.0116
Moderate	527 (0.035)	0.76 [0.68-0.86]	<.0001	0.75 [0.66-0.85]	<.0001
High	65 (0.050)	1.05 [0.71-1.55]	0.8103	1.00 [0.66-1.51]	0.9977
Statin intensity and its type					
No exposure	914 (0.044)	1	.	1	.
Low					
Fluvastatin 20/40	14 (0.040)	0.78 [0.39-1.56]	0.4890	0.82 [0.39-1.72]	0.6016
Pravastatin 10/20	91 (0.032)	0.65 [0.49-0.85]	0.0019	0.66 [0.50-0.88]	0.0041
Simvastatin 10	37 (0.034)	0.94 [0.59-1.50]	0.8084	1.01 [0.62-1.64]	0.9769
Moderate					
Atorvastatin 10/20	273 (0.038)	0.82 [0.69-0.98]	0.0278	0.80 [0.67-0.96]	0.0169
Fluvastatin 80	8 (0.038)	1.17 [0.37-3.73]	0.7888	1.08 [0.33-3.55]	0.9052
Pravastatin 40	27 (0.031)	0.72 [0.42-1.24]	0.2379	0.67 [0.38-1.17]	0.1628
Rosuvastatin 5/10	117 (0.032)	0.72 [0.57-0.92]	0.0093	0.71 [0.55-0.91]	0.0072
Simvastatin 20/40	102 (0.033)	0.67 [0.51-0.87]	0.0029	0.68 [0.52-0.91]	0.0079
High					
Atorvastatin 40/80	56 (0.051)	1.10 [0.71-1.71]	0.6626	1.02 [0.65-1.61]	0.9380
Rosuvastatin 20	9 (0.044)	0.85 [0.35-2.10]	0.7307	0.93 [0.37-2.34]	0.8697

HR for hazard ratio; 95%CI for 95% confidence interval; IPTW for inverse probability of treatment weighting.

*Conditional Cox proportional hazards model with IPTW.

†Conditional Cox proportional hazards model with IPTW further adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).

Table S11. Association between statin exposure and in-hospital deaths in COVID-19-related hospitalized individuals (N=9,396)

	Death* N = 1529	Unadjusted model†		Fully adjusted model‡		IPTW further adjusted model§	
		HR [95% CI]‖	P-value	HR [95% CI]‖	P-value	HR [95% CI]‖	P-value
Statin exposure							
No exposure	839 (16.70)	1	.	1	.	1	.
Statin exposure	690 (15.78)	0.94 [0.85-1.04]	0.2597	0.84 [0.76-0.93]	0.0012	0.87 [0.79-0.96]	0.0083
Type of statin							
No exposure	839 (16.70)	1	.	1	.	1	.
Atorvastatin	309 (15.90)	0.95 [0.83-1.08]	0.4297	0.85 [0.74-0.97]	0.0141	0.85 [0.74-0.97]	0.0191
Fluvastatin	21 (22.83)	1.44 [0.93-2.22]	0.0998	1.23 [0.80-1.90]	0.3445	1.33 [0.86-2.08]	0.2017
Pravastatin	113 (15.48)	0.93 [0.76-1.13]	0.4650	0.81 [0.67-0.99]	0.0402	0.84 [0.68-1.03]	0.0868
Rosuvastatin	121 (15.24)	0.91 [0.75-1.10]	0.3185	0.83 [0.68-1.00]	0.0515	0.88 [0.73-1.07]	0.1981
Simvastatin	126 (15.52)	0.93 [0.77-1.12]	0.4214	0.83 [0.69-1.00]	0.0553	0.89 [0.73-1.07]	0.2098
Statin intensity							
No exposure	839 (16.70)	1	.	1	.	1	.
Low	133 (17.10)	1.03 [0.86-1.24]	0.7353	0.91 [0.76-1.10]	0.3452	0.96 [0.80-1.16]	0.6716
Moderate	494 (15.29)	0.91 [0.82-1.02]	0.1034	0.82 [0.73-0.92]	0.0007	0.85 [0.76-0.95]	0.0050
High	63 (17.36)	1.04 [0.81-1.34]	0.7635	0.87 [0.67-1.13]	0.3038	0.85 [0.64-1.14]	0.2830
Statin intensity and its type							
No exposure	839 (16.70)	1	.	1	.	1	.
Fluvastatin 20/40	13 (22.41)	1.42 [0.82-2.45]	0.2102	1.27 [0.73-2.19]	0.3974	1.44 [0.84-2.45]	0.1813
Pravastatin 10/20	87 (16.20)	0.97 [0.78-1.21]	0.8087	0.86 [0.68-1.07]	0.1674	0.88 [0.70-1.10]	0.2616
Simvastatin 10	33 (18.03)	1.09 [0.77-1.54]	0.6311	0.99 [0.70-1.40]	0.9481	1.06 [0.75-1.51]	0.7270
Atorvastatin 10/20	255 (15.57)	0.93 [0.81-1.07]	0.2969	0.84 [0.73-0.97]	0.0151	0.85 [0.74-0.98]	0.0286
Fluvastatin 80	8 (23.53)	1.47 [0.73-2.95]	0.2775	1.18 [0.59-2.38]	0.6418	1.15 [0.53-2.53]	0.7223
Pravastatin 40	26 (13.47)	0.81 [0.55-1.19]	0.2842	0.70 [0.47-1.03]	0.0699	0.72 [0.47-1.09]	0.1162
Rosuvastatin 5/10	112 (15.20)	0.91 [0.74-1.10]	0.3240	0.83 [0.68-1.01]	0.0626	0.88 [0.72-1.07]	0.2051
Simvastatin 20/40	93 (14.79)	0.88 [0.71-1.09]	0.2396	0.79 [0.63-0.98]	0.0293	0.84 [0.67-1.04]	0.1054
Atorvastatin 40/80	54 (17.65)	1.06 [0.81-1.40]	0.6765	0.89 [0.67-1.17]	0.3935	0.84 [0.62-1.16]	0.2907
Rosuvastatin 20	9 (15.79)	0.93 [0.48-1.80]	0.8366	0.80 [0.41-1.55]	0.5091	0.91 [0.46-1.78]	0.7755

HR for hazard ratio; 95% CI for 95% confidence interval; IPTW for inverse probability of treatment weighting.

*There is a lower number of 119 individuals (44 in statin group and 75 in unexposed group) compared with the total number of deaths reported in Table 3 (n=1648). These individuals were not included in the present table as they died of COVID-19 but were hospitalized for other reasons than COVID-19.

†Cox proportional hazards model.

‡Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic), and influenza vaccination.

§Cox proportional hazards model with IPTW and further adjustment with the same variables as those in the full adjusted model.

‖The strength of the association between statins and in-hospital death for COVID-19 was less strong than that of Table 3. This may be due to the difference in the used designs: conventional Cox proportional hazards model in this table vs conditional Cox proportional hazards model on Table 3. The latter model could not be used here as the number of paired statin users and their matched controls was small (n=17) in this sub-sample of hospitalized individuals for COVID-19.

Table S12. Impact of history of influenza vaccination on the association between statin exposure and severe COVID-19 outcomes

a. Description of influenza vaccination according to statin exposure

	No exposure (n = 2,058,249)	Statin exposure (n = 2,058,249)	Standardized difference
Influenza vaccination since November 15, 2017*			
No	1,235,041 (60.0)	1,058,253 (51.4)	0.17357
Yes	823,208 (40.0)	999,996 (48.6)	

*Variable defined from ATC codes J07BB (at least one dispensing since November 15, 2017).

b. Association between statin exposure and hospitalization for COVID-19 in a fully adjusted conditional Cox proportional hazards model with further adjustment for history of influenza vaccination

		Hospitalization N = 9396	Unadjusted model*		Fully adjusted model†		IPTW further adjusted model‡	
			HR [95% CI]	P-value	HR [95% CI]	P-value	HR [95% CI]	P-value
Statin exposure	No	5,024 (0.24)	1	.	1	.	1	.
	Yes	4,372 (0.21)	0.87 [0.83-0.90]	<.0001	0.84 [0.80-0.87]	<.0001	0.83 [0.79-0.87]	<.0001

HR for hazard ratio; 95% CI for 95% confidence interval; IPTW for inverse probability of treatment weighting.

*Conditional Cox proportional hazards model.

†Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic), and influenza vaccination.

‡Conditional Cox proportional hazards model with IPTW and further adjustment with the same variables as those in the full adjusted model.

c. Association between statin exposure and in-hospital death for COVID-19 in a fully adjusted conditional Cox proportional hazards model with further adjustment for history of influenza vaccination

		Death N= 1648	Unadjusted model*		Fully adjusted model†		IPTW further adjusted model‡	
			HR [95% CI]	P-value	HR [95% CI]	P-value	HR [95% CI]	P-value
Statin exposure	No	914 (0.044)	1	.	1	.	1	.
	Yes	734 (0.036)	0.80 [0.73-0.88]	<.0001	0.77 [0.69-0.86]	<.0001	0.76 [0.68-0.85]	<.0001

HR for hazard ratio; 95% CI for 95% confidence interval; IPTW for inverse probability of treatment weighting.

*Conditional Cox proportional hazards model.

†Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic), and influenza vaccination.

‡Conditional Cox proportional hazards model with IPTW and further adjustment with the same variables as those in the full adjusted model.

Figure S1. Standardized differences before and after inverse probability of treatment weighting (IPTW)

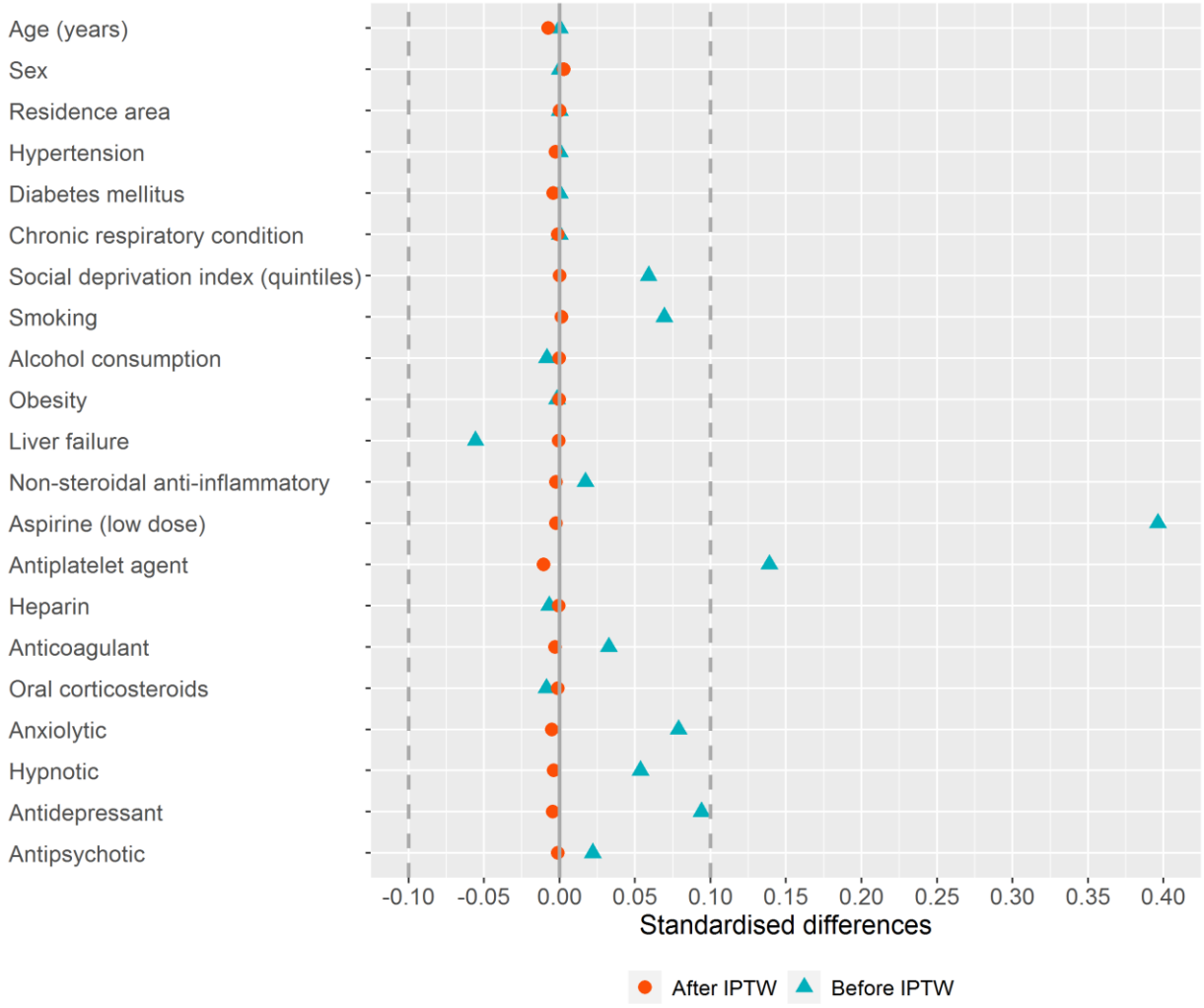
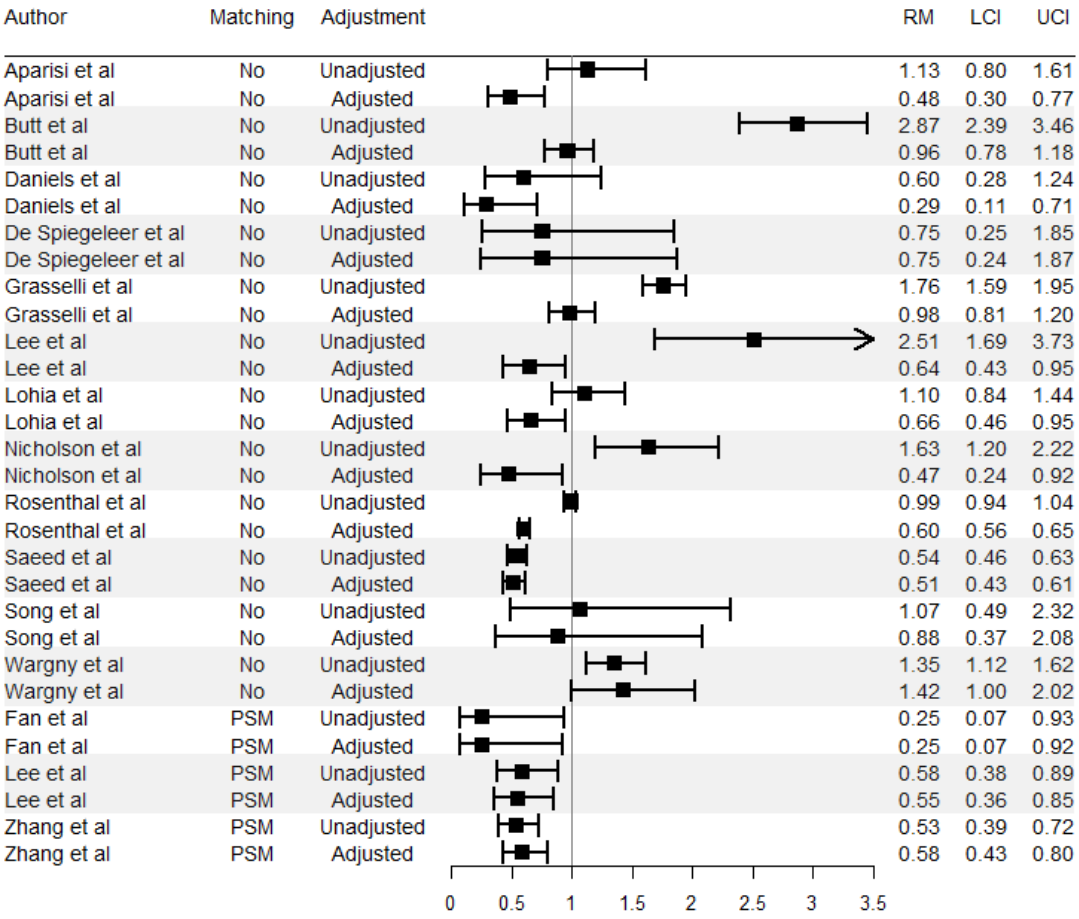


Figure S2. Association between statin exposure and in-hospital deaths from COVID-19: results from literature review



RM for ratio measures referring to effect measures such as odds ratio and hazard ratio; LCI for 95% lower limit of the confidence interval; UCI for 95% upper limit of the confidence interval; PSM for propensity score matching.