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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

Kim Bouillon , MD, PhD; Bérange Baricault , MSc; Laura Semenzato , MSc; Jérémie Botton , PharmD, PhD; Marion Bertrand , MSc; Jérôme Drouin , MSc; Rosemary Dray-Spira , MD, PhD; Alain Weill , MD; Mahmoud Zureik , MD, PhD

**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  $\geq 40$  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.<sup>1</sup> 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<sup>2,3</sup> and the Ebola virus.<sup>3,4</sup> 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 non-use, 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

<b>ASD</b>	absolute standardized difference
<b>CCAM</b>	French medical classification for clinical procedures ( <i>Classification Commune des Actes Médicaux</i> )
<b>CIP</b>	French coding scheme for identifying a single drug package ( <i>Code Identifiant de Présentation</i> )
<b>CNIL</b>	French Data Protection Office ( <i>Commission Nationale de l'Informatique et des Libertés</i> )
<b>IPTW</b>	inverse probability of treatment weighting
<b>MERS-CoV</b>	Middle East respiratory syndrome coronavirus
<b>PMSI</b>	National Hospital Discharge Database ( <i>Programme de Médicalisation des Systèmes d'Information</i> )

<b>SNDS</b>	French National Healthcare Data System ( <i>Système National des Données de Santé</i> )
<b>UCD</b>	French coding scheme used for identifying hospital drugs ( <i>Unité Commune de Dispensation</i> )

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

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.<sup>11–46</sup> In 11 studies, ratio measures were close to 1.<sup>47–57</sup> In 2 studies, an increased risk was observed.<sup>58,59</sup> 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.<sup>60</sup> 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 non-profit, 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.indiante.fr/>).

## Data Source

This cohort study used data from the SNDS, formerly known as SNIIRAM, established in 2006.<sup>61</sup>

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.<sup>62–73</sup> 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,<sup>68,74</sup> 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  $\geq 40$  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 non-proprietary 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.<sup>75</sup>

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, ezetimib, 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  $\geq 15$  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.<sup>76–78</sup> The imbalance between the groups is defined as an absolute value  $>0.10$ .<sup>77</sup>

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)<sup>79</sup>; 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.<sup>80</sup>

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.<sup>81</sup>

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

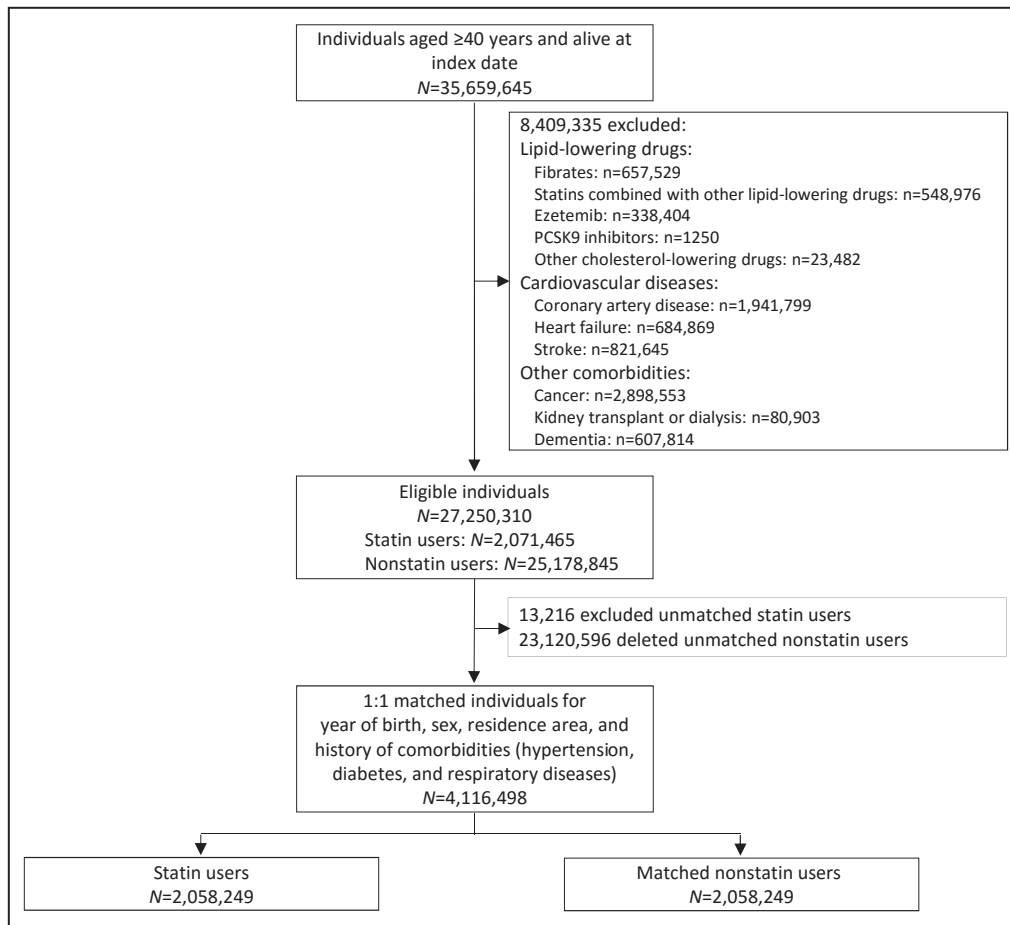
SNDS is a strictly anonymous database, comprising all reimbursement data derived from mandatory health insurance. The authors had access to the SNDS database, in the application of the provisions of articles R. 1461-12 et seq. of the French Public Health Code and the French data protection authority 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  $\geq 40$  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, atorvastatin 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  $\geq 40$  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<sup>82</sup>; results that are consistent with the clinical presentation of symptomatic patients with COVID-19.<sup>83</sup>

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.<sup>84</sup> Indeed, several in vitro studies have supported the argument that statins may prevent individuals from being infected or having a serious COVID-19 outcome.<sup>85–88</sup> 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<sup>85</sup> on the plasma membrane.<sup>86</sup> 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.<sup>87</sup> 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
Rosuvastatin	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.<sup>88</sup>

### Comparison With Other Studies

We found one study<sup>32</sup> 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,<sup>89</sup> hypertension,<sup>90</sup> undergoing transcatheter aortic valve implantation,<sup>91</sup> or pancreas, biliary, or liver conditions<sup>92</sup>) or in the general population.<sup>93–97</sup> Results of association with statin use in these studies were heterogeneous: a significantly lower risk,<sup>89,93,97</sup> a lower risk but not statistically significant,<sup>90,91,95</sup> and an increased risk of COVID-19 diagnosis.<sup>92,94,96</sup> 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	1775/660 063 (0.21)	1519/660 063 (0.18)	0.84 (0.78–0.90)	<0.0001	300/660 063 (0.035)	263/660 063 (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,<sup>75</sup> 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.<sup>11–46</sup>

## 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<sup>81</sup> 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,<sup>60</sup> 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.<sup>24,98</sup> 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.<sup>7,12,27</sup> In other studies where this design was not applied, adjustment systematically decreased odds ratios or HRs.<sup>†</sup> 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.<sup>7,18</sup> In addition, not including adjusted ratio measures in

<sup>†</sup>References 7,13,18,19,23,28,36,47,49.

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

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.<sup>103</sup> 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  $\geq 40$  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.

## ARTICLE INFORMATION

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### Disclosures

None.

### Supplemental Material

Tables S1–S12  
Figures S1–S2

## REFERENCES

- Rodrigues-Diez RR, Tejera-Muñoz A, Marquez-Exposito L, Rayego-Mateos S, Santos Sanchez L, Marchant V, Tejedor Santamaria L, Ramos AM, Ortiz A, Egido J, et al. Statins: could an old friend help in the fight against COVID-19? *Br J Pharmacol*. 2020;177:4873–4886. doi: [10.1111/bph.15166](https://doi.org/10.1111/bph.15166)
- Fedson DS. Treating influenza with statins and other immunomodulatory agents. *Antiviral Res*. 2013;99:417–435. doi: [10.1016/j.antiviral.2013.06.018](https://doi.org/10.1016/j.antiviral.2013.06.018)
- Fedson DS. Treating the host response to emerging virus diseases: lessons learned from sepsis, pneumonia, influenza and Ebola. *Ann Transl Med*. 2016;4:421. doi: [10.21037/atm.2016.11.03](https://doi.org/10.21037/atm.2016.11.03)
- Shrivastava-Ranjan P, Flint M, Bergeron É, McElroy AK, Chatterjee P, Albariño CG, Nichol ST, Spiropoulou CF. Statins suppress Ebola virus infectivity by interfering with glycoprotein processing. *MBio*. 2018;9. doi: [10.1128/mBio.00660-18](https://doi.org/10.1128/mBio.00660-18)
- Yuan S. Statins may decrease the fatality rate of Middle East respiratory syndrome infection. *MBio*. 2015;6. doi: [10.1128/mBio.01120-15](https://doi.org/10.1128/mBio.01120-15)
- Ho P, Zheng JQ, Wu CC, Hou YC, Liu WC, Lu CL, Zheng CM, Lu KC, Chao YC. Perspective adjunctive therapies for COVID-19: beyond antiviral therapy. *Int J Med Sci*. 2021;18:314–324. doi: [10.7150/ijms.51935](https://doi.org/10.7150/ijms.51935)
- Lee KC, Sewa DW, Phua GC. Potential role of statins in COVID-19. *Int J Infect Dis*. 2020;96:615–617. doi: [10.1016/j.ijid.2020.05.115](https://doi.org/10.1016/j.ijid.2020.05.115)
- Fedson DS, Opal SM, Rordam OM. Hiding in plain sight: an approach to treating patients with severe COVID-19 infection. *MBio*. 2020;11. doi: [10.1128/mBio.00398-20](https://doi.org/10.1128/mBio.00398-20)
- Tikoo K, Patel G, Kumar S, Karpe PA, Sanghavi M, Malek V, Srinivasan K. Tissue specific up regulation of ACE2 in rabbit model of atherosclerosis by atorvastatin: role of epigenetic histone modifications. *Biochem Pharmacol*. 2015;93:343–351. doi: [10.1016/j.bcp.2014.11.013](https://doi.org/10.1016/j.bcp.2014.11.013)
- Dong B, Zhang C, Feng JB, Zhao YX, Li SY, Yang YP, Dong QL, Deng BP, Zhu L, Yu QT, et al. Overexpression of ACE2 enhances plaque stability in a rabbit model of atherosclerosis. *Arterioscler Thromb Vasc Biol*. 2008;28:1270–1276. doi: [10.1161/ATVBAHA.108.164715](https://doi.org/10.1161/ATVBAHA.108.164715)
- Chacko SR, DeJoy R, Lo KB, Albano J, Peterson E, Bhargava R, Gu F, Salacup G, Pelayo J, Azmaiparashvili Z, et al. Association of pre-admission statin use with reduced in-hospital mortality in COVID-19. *Am J Med Sci*. 2021;361:725–730. doi: [10.1016/j.amjms.2021.03.001](https://doi.org/10.1016/j.amjms.2021.03.001)
- Fan Y, Guo T, Yan F, Gong M, Zhang XA, Li C, He T, Luo H, Zhang L, Chen M, et al. Association of statin use with the in-hospital outcomes of 2019-Coronavirus disease patients: a retrospective study. *Front Med*. 2020;7. doi: [10.3389/fmed.2020.584870](https://doi.org/10.3389/fmed.2020.584870)
- Daniels LB, Sitapati AM, Zhang J, Zou J, Bui QM, Ren J, Longhurst CA, Criqui MH, Messer K. Relation of statin use prior to admission to severity and recovery among COVID-19 inpatients. *Am J Cardiol*. 2020;136:149–155. doi: [10.1016/j.amjcard.2020.09.012](https://doi.org/10.1016/j.amjcard.2020.09.012)
- Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in Covid-19. *N Engl J Med*. 2020;382:2582. doi: [10.1056/NEJMc2021225](https://doi.org/10.1056/NEJMc2021225)
- Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW, Trelles-Garcia VP, Friedman HJ. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care Lond Engl*. 2020;24:429. doi: [10.1186/s13054-020-03154-4](https://doi.org/10.1186/s13054-020-03154-4)
- Greco S, D'Amuri A, Giorgini E, Luciani F, Lopreiato M, Fortunato V, Scopa A, Vestita G, Capatti E, Passaro A. Role of statins in coronavirus-related disease (COVID-19): a retrospective cohort study in Northern Italy. *High Blood Press Cardiovasc Prev*. 2021;28:355–364. doi: [10.1007/s40292-021-00452-y](https://doi.org/10.1007/s40292-021-00452-y)
- Gupta A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA, Redfors B, Eckhardt C, Bikdeli B, Platt J, Nalbandian A, et al. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. *Res Sq*. 2020. doi: [10.21203/rs.3.rs-56210/v1](https://doi.org/10.21203/rs.3.rs-56210/v1)
- Nicholson CJ, Wooster L, Sigurslid HH, Li RF, Jiang W, Tian W, Cardenas CL, Malhotra R. Estimating risk of mechanical ventilation and mortality among adult COVID-19 patients admitted to mass general Brigham: the VICE and DICE scores. *MedRxiv Prepr Serv Health Sci*. 2020. doi: [10.1101/2020.09.14.20194670](https://doi.org/10.1101/2020.09.14.20194670)
- Aparisi Á, Amat-Santos IJ, Otero DL, Marcos-Mangas M, González-Juanatey JR, San Román JA. Impact of statins in patients with COVID-19. *Rev Esp Cardiol*. 2021. doi: [10.1016/j.recesp.2021.01.009](https://doi.org/10.1016/j.recesp.2021.01.009)
- Saeed O, Castagna F, Agalliu I, Xue X, Patel SR, Rochlani Y, Kataria R, Vukelic S, Sims DB, Alvarez C, et al. Statin use and in-hospital mortality in patients with diabetes mellitus and COVID-19. *J Am Heart Assoc*. 2020;9:e018475. doi: [10.1161/JAHA.120.018475](https://doi.org/10.1161/JAHA.120.018475)
- Mallow PJ, Belk KW, Topmiller M, Hooker EA. Outcomes of hospitalized COVID-19 patients by risk factors: results from a United States hospital claims database. *J Health Econ Outcomes Res*. 2020;7:165–174. doi: [10.36469/jheor.2020.17331](https://doi.org/10.36469/jheor.2020.17331)
- Lee HY, Ahn J, Park J, Kyung Kang C, Won SH, Wook Kim D, Park JH, Chung KH, Joh JS, Bang JH et al. Beneficial effect of statins

- in COVID-19-related outcomes. *Arterioscler Thromb Vasc Biol*. 2021;41:e175–e182. doi: [10.1161/ATVBAHA.120.315551](https://doi.org/10.1161/ATVBAHA.120.315551)
23. Lohia P, Kapur S, Benjaram S, Mir T. Association between antecedent statin use and severe disease outcomes in COVID-19: a retrospective study with propensity score matching. *J Clin Lipidol*. 2021;15:451–459. doi: [10.1016/j.jacl.2021.03.002](https://doi.org/10.1016/j.jacl.2021.03.002)
  24. Lala A, Johnson KW, Januzzi JL, Russak AJ, Paranjpe I, Richter F, Zhao S, Somani S, Van Vleck T, Vaid A, et al. Prevalence and impact of myocardial injury in patients hospitalized with COVID-19 infection. *J Am Coll Cardiol*. 2020;76:533–546. doi: [10.1016/j.jacc.2020.06.007](https://doi.org/10.1016/j.jacc.2020.06.007)
  25. Memel ZN, Lee JJ, Foulkes AS, Chung RT, Thaweethai T, Bloom PP. Association of statins and 28-day mortality rates in patients hospitalized with severe acute respiratory syndrome coronavirus 2 infection. *J Infect Dis*. 2022;225:19–29. doi: [10.1093/infdis/jiab539](https://doi.org/10.1093/infdis/jiab539)
  26. Masana L, Correig E, Rodríguez-Borjabad C, Anoro E, Arroyo JA, Jericó C, Pedragosa A, Miret M, Náf S, Pardo A, et al. Effect of statin therapy on SARS-CoV-2 infection-related mortality in hospitalized patients. *Eur Heart J – Cardiovasc Pharmacother*. 2020. doi: [10.1093/ehjcvp/pvaa128](https://doi.org/10.1093/ehjcvp/pvaa128)
  27. Zhang XU, Qin JJ, Cheng XU, Shen L, Zhao YC, Yuan Y, Lei F, Chen MM, Yang H, Bai L, et al. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab*. 2020;32:176–187.e4. doi: [10.1016/j.cmet.2020.06.015](https://doi.org/10.1016/j.cmet.2020.06.015)
  28. Rosenthal N, Cao Z, Gundrum J, Sianis J, Safo S. Risk factors associated with in-hospital mortality in a US national sample of patients with COVID-19. *JAMA Netw Open*. 2020;3:e2029058. doi: [10.1001/jamanetworkopen.2020.29058](https://doi.org/10.1001/jamanetworkopen.2020.29058)
  29. Torres-Peña JD, Pérez-Belmonte LM, Fuentes-Jiménez F, López Carmona MD, Pérez-Martínez P, López-Miranda J, Carrasco Sánchez FJ, Vargas Núñez JA, del Corral Beamonte E, Magallanes Gamboa JO, et al. Prior treatment with statins is associated with improved outcomes of patients with COVID-19: data from the SEMI-COVID-19 registry. *Drugs*. 2021;81:685–695. doi: [10.1007/s40265-021-01498-x](https://doi.org/10.1007/s40265-021-01498-x)
  30. Ahlström B, Frithiof R, Hultström M, Larsson IM, Strandberg G, Lipcsey M. The Swedish covid-19 intensive care cohort: risk factors of ICU admission and ICU mortality. *Acta Anaesthesiol Scand*. 2021;65:525–533. doi: [10.1111/aas.13781](https://doi.org/10.1111/aas.13781)
  31. Oddy C, McCaul J, Keeling P, Allington J, Senn D, Soni N, Morrison H, Mawella R, Samuel T, Dixon J. Pharmacological predictors of morbidity and mortality in COVID-19. *J Clin Pharmacol*. 2021;61:1286–1300. doi: [10.1002/jcph.1878](https://doi.org/10.1002/jcph.1878)
  32. Oh TK, Song IA, Jeon YT. Statin therapy and the risk of COVID-19: a cohort study of the national health insurance service in South Korea. *J Pers Med*. 2021;11:116. doi: [10.3390/jpm11020116](https://doi.org/10.3390/jpm11020116)
  33. Bifulco M, Ciccarelli M, Bruzzese D, Dipasquale A, Lania AG, Mazziotti G, Gazzerò P. The benefit of statins in SARS-CoV-2 patients: further metabolic and prospective clinical studies are needed. *Endocrine*. 2020. doi: [10.1007/s12020-020-02550-8](https://doi.org/10.1007/s12020-020-02550-8)
  34. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tré G, Belmans L, Dobson R, Wynendael E, Van De Wiele C, Vandaele F, et al. The effects of ARBs, ACEis, and statins on clinical outcomes of COVID-19 infection among nursing home residents. *J Am Med Dir Assoc*. 2020;21:909–914.e2. doi: [10.1016/j.jamda.2020.06.018](https://doi.org/10.1016/j.jamda.2020.06.018)
  35. Ikari Y, Matsue Y, Torii S, Hasegawa M, Aihara K, Kuroda S, Sano T, Kitai T, Yonetsu T, Kohsaka S, et al. Association between statin use prior to admission and lower coronavirus disease 2019 (COVID-19) severity in patients with cardiovascular disease or risk factors. *Circ J*. 2021;85:939–943. doi: [10.1253/circj.CJ-21-0087](https://doi.org/10.1253/circj.CJ-21-0087)
  36. Song SL, Hays SB, Panton CE, Mylonas EK, Kalligeros M, Shehadeh F, Mylonakis E. Statin use is associated with decreased risk of invasive mechanical ventilation in COVID-19 patients: a preliminary study. *Pathog Basel Switz*. 2020;9:759. doi: [10.3390/pathogens9090759](https://doi.org/10.3390/pathogens9090759)
  37. Byttebier G, Belmans L, Alexander M, Saxberg BE, De Spiegeleer B, De Spiegeleer A, Devreker N, Van Praet JT, Vanhove K, Reybrouck R, et al. Hospital mortality in COVID-19 patients in Belgium treated with statins, ACE inhibitors and/or ARBs. *Hum Vaccines Immunother*. 2021;1–10. doi: [10.1080/21645515.2021.1920271](https://doi.org/10.1080/21645515.2021.1920271)
  38. Wander PL, Lowy E, Beste LA, Tulloch-Palomino L, Korpak A, Peterson AC, Young BA, Boyko EJ. Risk factors for adverse outcomes among 35 879 veterans with and without diabetes after diagnosis with COVID-19. *BMJ Open Diabetes Res Care*. 2021;9. doi: [10.1136/bmjdr-2021-002252](https://doi.org/10.1136/bmjdr-2021-002252)
  39. Bergqvist R, Ahlqvist VH, Lundberg M, Hergens MP, Sundström J, Bell M, Magnusson C. HMG-CoA reductase inhibitors and COVID-19 mortality in Stockholm, Sweden: a registry-based cohort study. *PLoS Medicine*. 2021;18:e1003820. doi: [10.1371/journal.pmed.1003820](https://doi.org/10.1371/journal.pmed.1003820)
  40. Choi D, Chen Q, Goonewardena SN, Pacheco H, Mejia P, Smith RL, Rosenson RS. Efficacy of statin therapy in patients with hospital admission for COVID-19. *Cardiovasc Drugs Ther*. 2021;1–9. doi: [10.1007/s10557-021-07263-2](https://doi.org/10.1007/s10557-021-07263-2)
  41. Daniels LB, Ren J, Kumar K, Bui QM, Zhang J, Zhang X, Sawan MA, Eisen H, Longhurst CA, Messer K. Relation of prior statin and anti-hypertensive use to severity of disease among patients hospitalized with COVID-19: findings from the American Heart Association's COVID-19 cardiovascular disease registry. *PLoS One*. 2021;16:e0254635. doi: [10.1371/journal.pone.0254635](https://doi.org/10.1371/journal.pone.0254635)
  42. Haji Aghajani M, Moradi O, Azhdari Tehrani H, Amini H, Pourheidari E, Hatami F, Rabiei MM, Sistanizad M. Promising effects of atorvastatin on mortality and need for mechanical ventilation in patients with severe COVID-19; a retrospective cohort study. *Int J Clin Pract*. 2021;75:e14434. doi: [10.1111/ijcp.14434](https://doi.org/10.1111/ijcp.14434)
  43. Lee SW, Kim SY, Moon SY, Yoo IK, Yoo EG, Eom GH, Kim JM, Shin JI, Jeong MH, Yang JM, et al. Statin use and COVID-19 infectivity and severity in South Korea: two population-based nationwide cohort studies. *JMIR Public Health Surveill*. 2021;7:e29379. doi: [10.2196/29379](https://doi.org/10.2196/29379)
  44. Lohia P, Kapur S, Benjaram S, Cantor Z, Mahabadi N, Mir T, Badr MS. Statins and clinical outcomes in hospitalized COVID-19 patients with and without Diabetes Mellitus: a retrospective cohort study with propensity score matching. *Cardiovasc Diabetol*. 2021;20:140. doi: [10.1186/s12933-021-01336-0](https://doi.org/10.1186/s12933-021-01336-0)
  45. Torres-Peña JD, Wang T, Wang X, Chu A, Goodman SG, van Diepen S, Jackiewicz CA, Kaul P, Udell J, Ko DT, et al. Statins and SARS-CoV-2 Infection: results of a population-based prospective cohort study of 469 749 adults from 2 Canadian provinces. *J Am Heart Assoc*. 2021;10:e022330. doi: [10.1161/JAHA.121.022330](https://doi.org/10.1161/JAHA.121.022330)
  46. Umakanthan S, Senthil S, John S, Madhavan MK, Das J, Patil S, Rameshwaram R, Cintham A, Subramaniam V, Yogi M, et al. The protective role of statins in COVID-19 patients: a retrospective observational study. *Transl Med Commun*. 2021;6:22. doi: [10.1186/s41231-021-00102-4](https://doi.org/10.1186/s41231-021-00102-4)
  47. Butt JH, Gerds TA, Schou M, Kragholm K, Phelps M, Havers-Borgersen E, Yafasova A, Gislason GH, Torp-Pedersen C, Køber L, et al. Association between statin use and outcomes in patients with coronavirus disease 2019 (COVID-19): a nationwide cohort study. *BMJ Open*. 2020;10:e044421. doi: [10.1136/bmjopen-2020-044421](https://doi.org/10.1136/bmjopen-2020-044421)
  48. Tan WYT, Young BE, Lye DC, Chew DEK, Dalan R. Statin use is associated with lower disease severity in COVID-19 infection. *Sci Rep*. 2020;10:17458. doi: [10.1038/s41598-020-74492-0](https://doi.org/10.1038/s41598-020-74492-0)
  49. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, et al. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med*. 2020;180:1345–1355. doi: [10.1001/jamainternmed.2020.3539](https://doi.org/10.1001/jamainternmed.2020.3539)
  50. Yetmar ZA, Challener DW, Tleyjeh IM, Sohail MR, Cerhan JR, Badley AD, O'Horo JC. Association between chronic statin use and 30-day mortality in hospitalized patients with COVID-19. *Mayo Clin Proc Innov Qual Outcomes*. 2021. doi: [10.1016/j.mayocpiqo.2021.02.002](https://doi.org/10.1016/j.mayocpiqo.2021.02.002)
  51. Ramos-Rincón JM, Pérez-Belmonte LM, Carrasco-Sánchez FJ, Jansen-Chaparro S, De-Sousa-Baena M, Bueno-Fonseca J, Pérez-Aguilar M, Arévalo-Cañas C, Bacete Cebrían M, Méndez-Bailón M, et al. Cardiometabolic therapy and mortality in very old patients with diabetes hospitalized due to COVID-19. *J Gerontol A Biol Sci Med Sci*. 2021;76:e102–e109. doi: [10.1093/gerona/glab124](https://doi.org/10.1093/gerona/glab124)
  52. Aye SK, Abbey EJ, Khalifa BAA, Nudotor RD, Osei AD, Chidambaram V, Osuji N, Khan S, Sallia EL, Oduwole MO, et al. Statins use and COVID-19 outcomes in hospitalized patients. *PLoS One*. 2021;16:e0256899. doi: [10.1371/journal.pone.0256899](https://doi.org/10.1371/journal.pone.0256899)
  53. El-Solh AA, Lawson Y, El-Solh DA. All-cause mortality in COVID-19 patients receiving statin therapy: analysis of veterans affairs database cohort study. *Intern Emerg Med*. 2021. doi: [10.1007/s11739-021-02848-z](https://doi.org/10.1007/s11739-021-02848-z)
  54. Kuno T, So M, Iwagami M, Takahashi M, Egorova NN. The association of statins use with survival of patients with COVID-19. *J Cardiol*. 2022;79:494–500. doi: [10.1016/j.jcc.2021.12.012](https://doi.org/10.1016/j.jcc.2021.12.012)
  55. Nateghi S, Gomari MM, Hosamirudisari H, Behnoush B, Razmjoofoard A, Azimi G, Ordoorkhani S, Jafarpour A, Faraji N. A historical cohort study to investigation of statins safety in COVID-19 hospitalized patients. *Therapie*. 2021. doi: [10.1016/j.therap.2021.10.006](https://doi.org/10.1016/j.therap.2021.10.006)

56. Russo V, Silverio A, Scudiero F, Attena E, D'Andrea A, Nunziata L, Parodi G, Celentani D, Varbella F, Albani S, et al. Preadmission statin therapy and clinical outcome in hospitalized patients with COVID-19: an Italian multicenter observational study. *J Cardiovasc Pharmacol*. 2021;78:e94–e100. doi: [10.1097/FJC.0000000000001041](https://doi.org/10.1097/FJC.0000000000001041)
57. Vila-Corcoles A, Sature-Gracia E, Vila-Rovira A, de Diego-Cabanes C, Forcadell-Peris MJ, Hospital-Guardiola I, Ochoa-Gondar O, Basora-Gallisa J. COVID-19-related and all-cause mortality among middle-aged and older adults across the first epidemic wave of SARS-CoV-2 infection in the region of Tarragona, Spain: results from the COVID19 TARRACO Cohort Study, March-June 2020. *medRxiv*. 2021;21:1795. doi: [10.1186/s12889-021-11879-2](https://doi.org/10.1186/s12889-021-11879-2)
58. Wargny M, Potier L, Gourdy P, Pichelin M, Amadou C, Benhamou P-Y, Bonnet JB, Bordier L, Bourron O, Chaumeil C, et al. Predictors of hospital discharge and mortality in patients with diabetes and COVID-19: updated results from the nationwide CORONADO study. *Diabetologia*. 2021;64:778–794. doi: [10.1007/s00125-020-05351-w](https://doi.org/10.1007/s00125-020-05351-w)
59. Cariou B, Goronflot T, Rimbart A, Boullu S, Le May C, Moulin P, Pichelin M, Potier L, Smati S, Sultan A, et al. Routine use of statins and increased COVID-19 related mortality in inpatients with type 2 diabetes: results from the CORONADO study. *Diabetes Metab*. 2020;47:101202. doi: [10.1016/j.diabet.2020.10.001](https://doi.org/10.1016/j.diabet.2020.10.001)
60. Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L, Sharp GC, Sterne J, Palmer TM, Davey Smith G, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. *Nat Commun*. 2020;11:5749. doi: [10.1038/s41467-020-19478-2](https://doi.org/10.1038/s41467-020-19478-2)
61. Tuppin P, Rudant J, Constantinou P, Gastaldi-Ménager C, Rachas A, de Roquefeuil L, Maura G, Caillol H, Tajahmady A, Coste J, et al. Value of a national administrative database to guide public decisions: from the système national d'information interrégimes de l'Assurance Maladie (SNIIRAM) to the système national des données de santé (SNDS) in France. *Rev Epidemiol Sante Publique*. 2017;65:S149–S167. doi: [10.1016/j.respe.2017.05.004](https://doi.org/10.1016/j.respe.2017.05.004)
62. Bouillon K, Bertrand M, Maura G, Blotière PO, Ricordeau P, Zureik M. Risk of bleeding and arterial thromboembolism in patients with non-valvular atrial fibrillation either maintained on a vitamin K antagonist or switched to a non-vitamin K-antagonist oral anticoagulant: a retrospective, matched-cohort study. *Lancet Haematol*. 2015;2:e150–e159. doi: [10.1016/S2352-3026\(15\)00027-7](https://doi.org/10.1016/S2352-3026(15)00027-7)
63. Bouillon K, Bertrand M, Boudali L, Ducimetière P, Dray-Spira R, Zureik M. Short-term risk of bleeding during heparin bridging at initiation of vitamin K antagonist therapy in more than 90 000 Patients with non-valvular atrial fibrillation managed in outpatient care. *J Am Heart Assoc Cardiovasc Cerebrovasc Dis*. 2016;5. doi: [10.1161/JAHA.116.004065](https://doi.org/10.1161/JAHA.116.004065)
64. Bouillon K, Bertrand M, Bader G, Lucot JP, Dray-Spira R, Zureik M. Association of hysteroscopic vs laparoscopic sterilization with procedural, gynecological, and medical outcomes. *JAMA*. 2018;319:375–387. doi: [10.1001/jama.2017.21269](https://doi.org/10.1001/jama.2017.21269)
65. Lemaitre M, Kirchgessner J, Rudnichi A, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Association between use of Thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. *JAMA*. 2017;318:1679–1686. doi: [10.1001/jama.2017.16071](https://doi.org/10.1001/jama.2017.16071)
66. Weill A, Nguyen P, Labidi M, Cadier B, Passeri T, Duranteau L, Bernat A-L, Yoldjian I, Fontanel S, Froelich S, et al. Use of high dose cyproterone acetate and risk of intracranial meningioma in women: cohort study. *BMJ*. 2021;372. doi: [10.1136/bmj.n37](https://doi.org/10.1136/bmj.n37)
67. Zureik M, Baricault B, Vabre C, Semenzato L, Drouin J, Cuenot F, Penso L, Herlemont P, Sbidian E, Weill A, et al. Nicotine-replacement therapy, as a surrogate of smoking, and the risk of hospitalization with Covid-19 and all-cause mortality: a nationwide, observational cohort study in France. *medRxiv*. 2020. doi: [10.1101/2020.07.28.20160630](https://doi.org/10.1101/2020.07.28.20160630)
68. Semenzato L, Botton J, Drouin J, Baricault B, Vabre C, Cuenot F, Penso L, Herlemont P, Sbidian E, Weill A, et al. Antihypertensive drugs and COVID-19 risk: a cohort study of 2 million hypertensive patients. *Hypertens Dallas Tex*. 2021;77:833–842. doi: [10.1161/HYPERTENSI/ONAHA.120.16314](https://doi.org/10.1161/HYPERTENSI/ONAHA.120.16314)
69. Roland N, Drouin J, Desplas D, Cuenot F, Dray-Spira R, Weill A, Zureik M. Effects of the Coronavirus Disease 2019 (COVID-19) lockdown on the use of contraceptives and ovulation inductors in France. *Obstet Gynecol*. 2021;137:415–417. doi: [10.1097/AOG.0000000000004281](https://doi.org/10.1097/AOG.0000000000004281)
70. Billioti de Gage S, Drouin J, Desplas D, Cuenot F, Dray-Spira R, Weill A, Zureik M. Intravitreal anti-vascular endothelial growth factor use in France during the Coronavirus disease 2019 pandemic. *JAMA Ophthalmol*. 2021;139:240–242. doi: [10.1001/jamaophth/2020.5594](https://doi.org/10.1001/jamaophth/2020.5594)
71. Meyer A, Drouin J, Zureik M, Weill A, Dray-Spira R. Colonoscopy in France during the COVID-19 pandemic. *Int J Colorectal Dis*. 2021;36:1073–1075. doi: [10.1007/s00384-020-03816-3](https://doi.org/10.1007/s00384-020-03816-3)
72. Meyer A, Semenzato L, Zureik M, Weill A, Carbonnel F, Dray-Spira R. Risk of severe COVID-19 in patients treated with inflammatory bowel disease medications: a French nationwide study. *Aliment Pharmacol Ther*. 2021. doi: [10.1111/apt.16410](https://doi.org/10.1111/apt.16410)
73. Semenzato L, Botton J, Drouin J, Cuenot F, Dray-Spira Y, Weill A, Zureik M. Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people. *Lancet Reg Health Eur*. 2021;8:100158. doi: [10.1016/j.lanepe.2021.100158](https://doi.org/10.1016/j.lanepe.2021.100158)
74. Rachas A, Gastaldi-Ménager C, Denis P, Lesuffleur T, Nicolas M, Pestel L, Mette C, Drouin J, Riviere S, Tajahmady A, et al. Prevalences and healthcare expenditures related to 58 health conditions from 2012 to 2017 in France: diseases and healthcare expenditure mapping, a national population-based study. *medRxiv*. 2020. doi: [10.1101/2020.09.21.20198853](https://doi.org/10.1101/2020.09.21.20198853)
75. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. *Circulation*. 2019;139:e1082–e1143. doi: [10.1161/CIR.0000000000000625](https://doi.org/10.1161/CIR.0000000000000625)
76. Cohen J. The statistical power of abnormal-social psychological research: a review. *J Abnorm Soc Psychol*. 1962;65:145–153. doi: [10.1037/h0045186](https://doi.org/10.1037/h0045186)
77. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Commun Stat - Simul Comput*. 2009;38:1228–1234. doi: [10.1080/03610910902859574](https://doi.org/10.1080/03610910902859574)
78. Yang D, Dalton J. A unified approach to measuring the effect size between two groups using SAS 2012.
79. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015;34:3661–3679. doi: [10.1002/sim.6607](https://doi.org/10.1002/sim.6607)
80. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol*. 2008;168:656–664. doi: [10.1093/aje/kwn164](https://doi.org/10.1093/aje/kwn164)
81. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-Value. *Ann Intern Med*. 2017;167:268–274. doi: [10.7326/M16-2607](https://doi.org/10.7326/M16-2607)
82. Bryce C, Grimes Z, Pujadas E, Ahuja S, Beasley MB, Albrecht R, Hernandez T, Stock A, Zhao Z, AlRasheed MR, et al. Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience. *Mod Pathol*. 2021;1–12. doi: [10.1038/s41379-021-00793-y](https://doi.org/10.1038/s41379-021-00793-y)
83. Coronavirus disease 2019 (COVID-19) - Symptoms, diagnosis and treatment. *BMJ Best Pract* 2021. <https://bestpractice.bmj.com/topic/en-gb/3000201> (Accessed June 28, 2021).
84. Castiglione V, Chiriaco M, Emdin M, Taddei S, Vergaro G. Statin therapy in COVID-19 infection. *Eur Heart J Cardiovasc Pharmacother*. 2020;6:258–259. doi: [10.1093/ehjcvp/pvaa042](https://doi.org/10.1093/ehjcvp/pvaa042)
85. Xudong X, Junzhu C, Xingxiang W, Furong Z, Yanrong L. Age- and gender-related difference of ACE2 expression in rat lung. *Life Sci*. 2006;78:2166–2171. doi: [10.1016/j.lfs.2005.09.038](https://doi.org/10.1016/j.lfs.2005.09.038)
86. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, Somasundaran M, Sullivan JL, Luzuriaga K, Greenough TC, et al. Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*. 2003;426:450–454. doi: [10.1038/nature02145](https://doi.org/10.1038/nature02145)
87. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Yi, Yang P, Zhang Y, Deng W, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med*. 2005;11:875–879. doi: [10.1038/nm1267](https://doi.org/10.1038/nm1267)
88. Gordon D. Statins may be a key therapeutic for Covid-19. *Med Hypotheses*. 2020;144. doi: [10.1016/j.mehy.2020.110001](https://doi.org/10.1016/j.mehy.2020.110001)
89. Maddaloni E, D'Onofrio L, Alessandri F, Mignogna C, Leto G, Coraggio L, Sterpetti S, Pascarella G, Mezzaroma I, Lichtner M, et al. Clinical features of patients with type 2 diabetes with and without Covid-19: a case control study (CoViDiab I). *Diabetes Res Clin Pract*. 2020;169. doi: [10.1016/j.diabres.2020.108454](https://doi.org/10.1016/j.diabres.2020.108454)



90. Vila-Corcoles A, Satue-Gracia E, Ochoa-Gondar O, Torrente-Fraga C, Gomez-Bertomeu F, Vila-Rovira A, Hospital-Guardiola I, Diego-Cabanes C, Bejarano-Romero F, Rovira-Veciana D, et al. Use of distinct anti-hypertensive drugs and risk for COVID-19 among hypertensive people: a population-based cohort study in Southern Catalonia, Spain. *J Clin Hypertens*. 2020;22:1379–1388. doi: [10.1111/jch.13948](https://doi.org/10.1111/jch.13948)
91. Kibler M, Dietrich L, Kanso M, Carmona A, Marchandot B, Matsushita K, Trimaille A, How-Choong C, Odier A, Gennesseaux G, et al. Risk and severity of COVID-19 and ABO blood group in transcatheter aortic valve patients. *J Clin Med*. 2020;9:3769. doi: [10.3390/jcm9113769](https://doi.org/10.3390/jcm9113769)
92. Dayem Ullah AZM, Sivapalan L, Kocher HM, Chelala C. COVID-19 in patients with hepatobiliary and pancreatic diseases: a single-centre cross-sectional study in East London. *BMJ Open*. 2021;11. doi: [10.1136/bmjopen-2020-045077](https://doi.org/10.1136/bmjopen-2020-045077)
93. Hippisley-Cox J, Young D, Coupland C, Channon KM, Tan PS, Harrison DA, Rowan K, Aveyard P, Pavord ID, Watkinson PJ. Risk of severe COVID-19 disease with ACE inhibitors and angiotensin receptor blockers: cohort study including 8.3 million people. *Heart*. 2020;106:1503–1511. doi: [10.1136/heartjnl-2020-317393](https://doi.org/10.1136/heartjnl-2020-317393)
94. Ho FK, Celis-Morales CA, Gray SR, Katikireddi SV, Niedzwiedz CL, Hastie C, Ferguson LD, Berry C, Mackay DF, Gill JMR, et al. Modifiable and non-modifiable risk factors for COVID-19, and comparison to risk factors for influenza and pneumonia: results from a UK Biobank prospective cohort study. *BMJ Open*. 2020;10:e040402. doi: [10.1136/bmjopen-2020-040402](https://doi.org/10.1136/bmjopen-2020-040402)
95. Huh K, Ji W, Kang M, Hong J, Bae GH, Lee R, Na Y, Choi H, Gong SY, Jung J. Association of previous medications with the risk of COVID-19: a nationwide claims-based study from South Korea. *MedRxiv*. 2020. doi: [10.1101/2020.05.04.20089904](https://doi.org/10.1101/2020.05.04.20089904)
96. Yan H, Valdes AM, Vijay A, Wang S, Liang L, Yang S, Wang H, Tan X, Du J, Jin S, et al. Role of drugs used for chronic disease management on susceptibility and severity of COVID-19: a large case-control study. *Clin Pharmacol Ther*. 2020;108:1185–1194. doi: [10.1002/cpt.2047](https://doi.org/10.1002/cpt.2047)
97. Satué-Gracia EM, Vila-Córcoles A, de Diego-Cabanes C, Vila-Rovira A, Torrente-Fraga C, Gómez-Bertomeu F, Hospital-Guardiola I, Ochoa-Gondar O, Martín-Luján F. Susceptibility and risk of SARS-COV-2 infection among middle-aged and older adults in Tarragona area, Spain. *Med Clin (Barc)*. 2021. doi: [10.1016/j.medcli.2021.03.027](https://doi.org/10.1016/j.medcli.2021.03.027)
98. Ganjali S, Bianconi V, Penson PE, Pirro M, Banach M, Watts GF, Sahebkar A. Commentary: Statins, COVID-19, and coronary artery disease: killing two birds with one stone. *Metabolism*. 2020;113:154375. doi: [10.1016/j.metabol.2020.154375](https://doi.org/10.1016/j.metabol.2020.154375)
99. Higgins J, Li T, Deeks J. Chapter 6: choosing effect measures and computing estimates of effect. *Cochrane Handb Syst Rev Interv*. Version 62, Cochrane; 2021.
100. Hariyanto TI, Kurniawan A. Statin and outcomes of coronavirus disease 2019 (COVID-19): a systematic review, meta-analysis, and meta-regression. *Nutr Metab Cardiovasc Dis*. 2021. doi: [10.1016/j.numecd.2021.02.020](https://doi.org/10.1016/j.numecd.2021.02.020)
101. Kollias A, Kyriakoulis KG, Kyriakoulis IG, Nitsotolis T, Poulakou G, Stergiou GS, Syrigos K. Statin use and mortality in COVID-19 patients: updated systematic review and meta-analysis. *Atherosclerosis*. 2021;330:114–121. doi: [10.1016/j.atherosclerosis.2021.06.911](https://doi.org/10.1016/j.atherosclerosis.2021.06.911)
102. Diaz-Arocutipa C, Melgar-Talavera B, Alvarado-Yarasca Á, Saravia-Bartra MM, Cazorla P, Belzusarri I, Hernandez AV. Statins reduce mortality in patients with COVID-19: an updated meta-analysis of 147 824 patients. *Int J Infect Dis*. 2021;110:374–381. doi: [10.1016/j.ijid.2021.08.004](https://doi.org/10.1016/j.ijid.2021.08.004)
103. Taylor F, Huffman MD, Macedo AF, Moore TH, Burke M, Davey Smith G, Ward K, Ebrahim S, Gay HC. Statins for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2021;2021. doi: [10.1002/14651858.CD004816.pub5](https://doi.org/10.1002/14651858.CD004816.pub5)

# 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
<b>Lipid lowering drugs</b>	
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
<b>Cardiovascular and neurovascular diseases</b>	
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
<b>Other comorbidities</b>	
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
<b>Low (&lt; 30%)</b>		
Fluvastatin	20	40
Pravastatin	10	20
Simvastatin	10	
<b>Moderate (30% - 49%)</b>		
Atorvastatin	10	20
Rosuvastatin	5	10
Simvastatin	20	40
Pravastatin	40	
Fluvastatin	80	
<b>High (≥50%)</b>		
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
<b>Health behavior characteristics</b>	
<b>Smoking-related condition</b>	
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)
<b>Alcohol-related condition</b>	
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)
<b>Obesity-related condition</b>	
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)
<b>Comorbidities or comedications</b>	
<b>Liver and pancreas disorder</b>	
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.)
<b>Medications (ATC)</b>	

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
<b>Auvergne-Rhône-Alpes</b>	8,092,598	(12,4)	213,640 (10.4)	213,640 (10.4)
<b>Bourgogne-Franche-Comté</b>	2,786,205	(4,3)	98,693 (4.8)	98,693 (4.8)
<b>Bretagne</b>	3,371,297	(5,2)	104,714 (5.1)	104,714 (5.1)
<b>Centre-Val de Loire</b>	2,562,431	(3,9)	95,625 (4.6)	95,625 (4.6)
<b>Corse</b>	349,273	(0,5)	8,697 (0.4)	8,697 (0.4)
<b>Grand Est</b>	5,524,817	(8,5)	192,826 (9.4)	192,826 (9.4)
<b>Hauts-de-France</b>	5,977,46	(9,2)	234,718 (11.4)	234,718 (11.4)
<b>Île-de-France</b>	12,326,429	(18,9)	317,010 (15.4)	317,010 (15.4)
<b>Normandie</b>	3,306,092	(5,1)	121,260 (5.9)	121,260 (5.9)
<b>Nouvelle Aquitaine</b>	6,039,767	(9,3)	199,285 (9.7)	199,285 (9.7)
<b>Occitanie</b>	5,985,751	(9,2)	164,959 (8.0)	164,959 (8.0)
<b>Pays de la Loire</b>	3,838,060	(5,9)	125,184 (6.1)	125,184 (6.1)
<b>Provence-Alpes-Côte d'Azur</b>	5,089,661	(7,8)	133,389 (6.5)	133,389 (6.5)
<b>Total</b>	<b>65,249,843</b>		<b>2,058,249</b>	<b>2,058,249</b>

\*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
<b>Statin exposure</b>					
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
<b>Type of statin</b>					
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
<b>Statin intensity</b>					
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
<b>Statin intensity and its type</b>					
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 <sup>*</sup>	
	HR [95%CI]	P-value
<b>Hospitalization for COVID-19</b>		
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
<b>In-hospital deaths for COVID-19</b>		
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.

<sup>\*</sup>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)
<b>Matching variables</b>								
<b>Age (years)</b>								
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)
<b>Age categories</b>								
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)
<b>Sex</b>								
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)
<b>Residence area</b>								
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)
<b>Covariates</b>								
<b>Hypertension</b>								
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)
<b>Diabetes mellitus</b>								

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)
<b>Chronic respiratory condition</b>								
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)
<b>Social deprivation index (quintiles)</b>								
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)
<b>Smoking-related condition</b>								
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)
<b>Alcohol-related condition</b>								
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)
<b>Obesity-related condition</b>								
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)
<b>Liver and pancreas disorder</b>								
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)
<b>Non-steroidal anti-inflammatory</b>								
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)
<b>Low-dose aspirin</b>								
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)
<b>Antiplatelet agent</b>								
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)
<b>Heparin</b>								
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)

<b>Anticoagulant</b>								
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)
<b>Oral corticosteroid</b>								
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)
<b>Anxiolytic</b>								
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)
<b>Hypnotic</b>								
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)
<b>Antidepressant</b>								
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)
<b>Antipsychotic</b>								
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*			P-value
	HR	95%CI		
<b>Statin exposure</b>				
No exposure	1.00	.	.	.
Statin exposure	0.84	0.81	0.88	<.0001
<b>Social deprivation index (quintiles)</b>				
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
<b>Smoking-related condition</b>				
No	1.00	.	.	.
Yes	0.50	0.41	0.63	<.0001
<b>Alcohol-related condition</b>				
No	1.00	.	.	.
Yes	1.31	1.02	1.67	0.0322
<b>Obesity-related condition</b>				
No	1.00	.	.	.
Yes	1.49	1.25	1.79	<.0001
<b>Liver failure</b>				
No	1.00	.	.	.
Yes	1.69	1.34	2.12	<.0001
<b>Non-steroidal anti-inflammatory</b>				
No	1.00	.	.	.
Yes	1.11	1.03	1.21	0.0084
<b>Low-dose aspirin</b>				
No	1.00	.	.	.
Yes	1.13	1.06	1.22	0.0006
<b>Antiplatelet agent</b>				
No	1.00	.	.	.
Yes	1.58	1.29	1.93	<.0001
<b>Heparin</b>				
No	1.00	.	.	.
Yes	1.14	0.81	1.60	0.4629
<b>Anticoagulant</b>				
No	1.00	.	.	.
Yes	1.35	1.16	1.57	<.0001
<b>Oral corticosteroid</b>				
No	1.00	.	.	.
Yes	1.55	1.37	1.75	<.0001
<b>Anxiolytic</b>				
No	1.00	.	.	.
Yes	1.06	0.96	1.18	0.2398
<b>Hypnotic</b>				
No	1.00	.	.	.

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

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

<sup>\*</sup>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
<b>Statin exposure</b>					
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
<b>Type of statin</b>					
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
<b>Statin intensity</b>					
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
<b>Statin intensity and its type</b>					
No exposure	914 (0.044)	1	.	1	.
<u>Low</u>					
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
<u>Moderate</u>					
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
<u>High</u>					
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
<b>Statin exposure</b>							
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
<b>Type of statin</b>							
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
<b>Statin intensity</b>							
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
<b>Statin intensity and its type</b>							
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

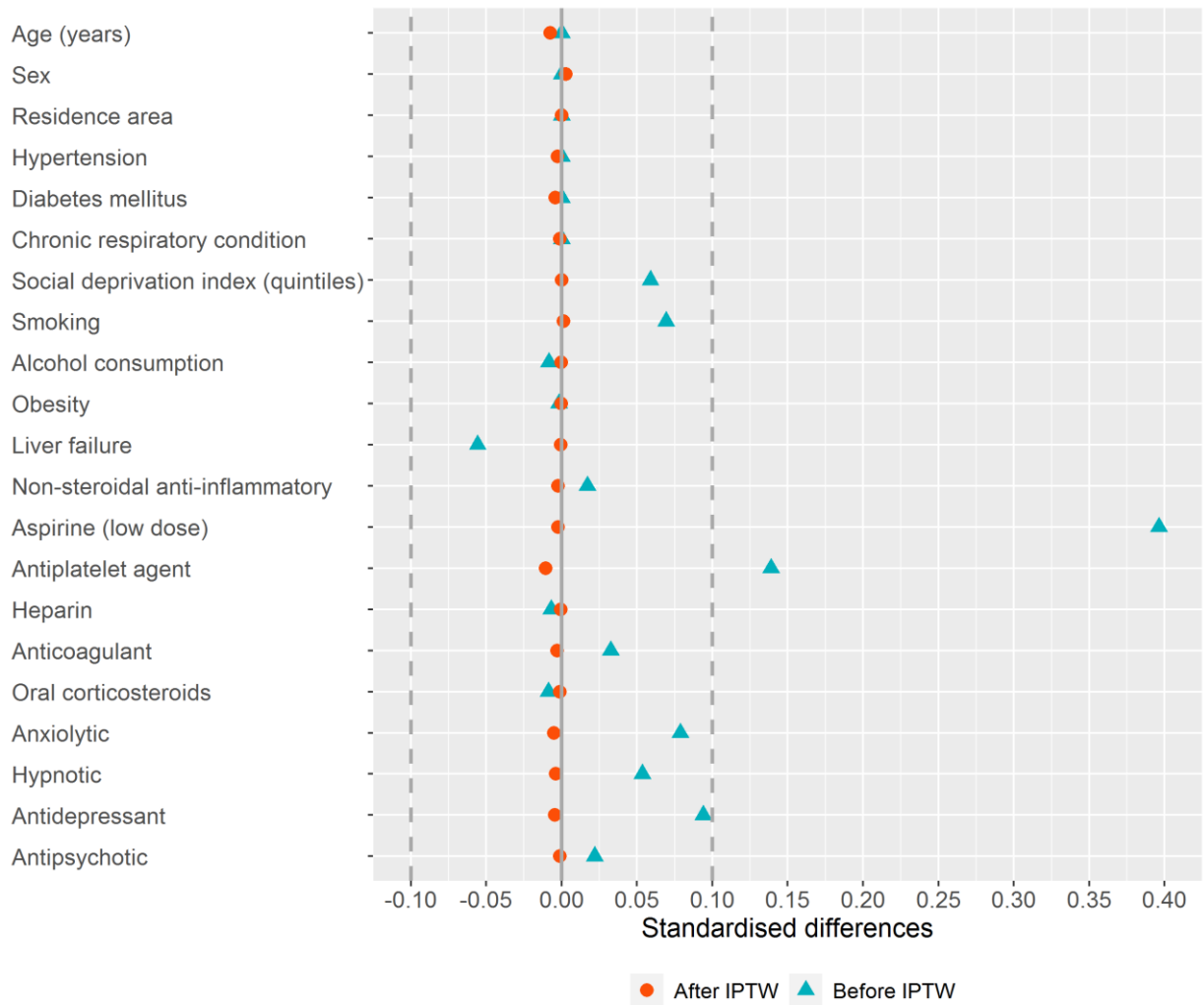
HR for hazard ratio; 95% CI for 95% confidence interval; IPTW for inverse probability of treatment weighting.

\*Conditional Cox proportional hazards model.

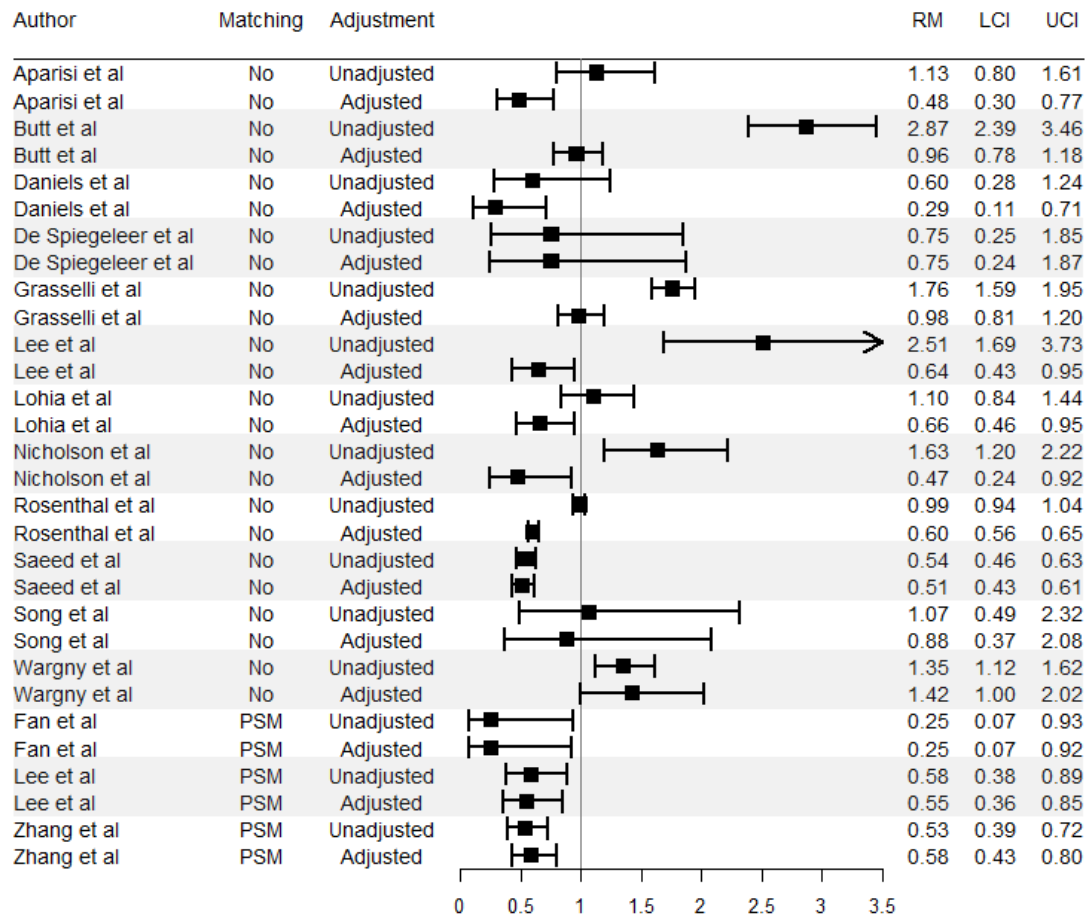
†Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral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