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

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

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

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

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

A better understanding of the determinants associated with COVID-19 helps to identify vulnerable individuals and to provide satisfactory health care management. Given the absence of a specific treatment for COVID-19, several existing drugs were thought to be beneficial, in particular those with anti-inflammatory or immunomodulatory activities such as statins.1 Besides their well-known lipid-lowering effect, statins have been reported to have pleiotropic beneficial actions by regulating numerous biological pathways implicated in anti-inflammatory, immune-modulatory, or anticoagulant actions. These drugs were found to be effective in previous outbreaks, namely those of hemagglutinin type 1 and neuraminidase type 1 (H1N1) influenza2,3 and the Ebola virus.3,4 It has also been shown that they have been useful for survival in SARS-CoV and Middle
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.

East respiratory syndrome coronavirus (MERS-CoV) infections. 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.

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. In 11 studies, ratio measures were close to 1. In 2 studies, an increased risk was observed. Most of these studies were conducted in hospitalized patients and/or patients tested for COVID-19. This could have led to a collider 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. 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]).
been extensively used in France to conduct real-life 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 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, 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.

**Data Source**

This cohort study used data from the SNDS, formerly known as SNIIRAM, established in 2006. 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. SNDS also contains sociodemographic data and, when applicable, the date of death.

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**Study Population**

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

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

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

**Noninclusion Criteria**

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

**Covariates**

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

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

Statistical Analysis

Categorical variables are reported as frequencies with percentages and continuous variables as means with SDs. To report the balance in each covariate between statin users and nonusers, the difference in proportions for categorical variables and means for continuous variables is standardized.76–78 The imbalance between the groups is defined as an absolute value >0.10.77

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

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

RESULTS

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

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

Statin users and nonusers were comparable regarding the most extensively studied covariates (ASD <0.10), except for low-dose aspirin (ASD, 0.40): statin users were more likely to use low-dose aspirin than nonusers (26.4% versus 11.2%, respectively). For
antiplatelet agents, the difference was marginal in terms of ASD (2.5% versus 0.8%; ASD, 0.14) (Table 1). ASDs were close to 0 for these variables after IPTW (Figure S1).

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

Table 2 shows the association between statin use—wife 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

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**Figure.** Flowchart of participants’ inclusion.
### Table 1. Baseline Characteristics According to Statin Exposure

| Matching variables | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|--------------------|--------------------------|-----------------------------|-------------------------|
| Age, y             | Mean (SD)                | 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)                |                         |
Table 1. Continued

| Alcohol-related condition | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|---------------------------|---------------------------|-----------------------------|-------------------------|
| 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 exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| 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 exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| No                        | 2 030 710 (98.7)          | 2 042 408 (99.2)            | −0.05568                |
| Yes                       | 27 539 (1.3)              | 15 841 (0.8)                |                         |

| NSAID                     | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| 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 exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| 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 exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| No                        | 2 042 260 (99.2)          | 2 005 808 (97.5)            | 0.13885                 |
| Yes                       | 15 989 (0.8)              | 52 441 (2.5)                |                         |

| Heparin                   | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| No                        | 2 044 349 (99.3)          | 2 045 508 (99.4)            | −0.00702                |
| Yes                       | 13 900 (0.7)              | 12 741 (0.6)                |                         |

| Anticoagulant             | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| 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 exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| No                        | 1 944 371 (94.5)          | 1 948 469 (94.7)            | −0.00878                |
| Yes                       | 113 878 (5.5)             | 109 780 (5.3)               |                         |

| Anxiolytic                | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| No                        | 1 872 500 (91.0)          | 1 823 388 (88.6)            | 0.07887                 |
| Yes                       | 185 749 (9.0)             | 234 881 (11.4)              |                         |

| Hypnotic                  | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| No                        | 1 975 317 (96.0)          | 1 952 287 (94.9)            | 0.05349                 |
| Yes                       | 82 932 (4.0)              | 105 962 (5.1)               |                         |

| Antidepressant            | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| No                        | 1 902 683 (92.4)          | 1 847 672 (89.8)            | 0.09399                 |
| Yes                       | 155 566 (7.6)             | 210 577 (10.2)              |                         |

| Antipsychotic             | No exposure (n=2 058 249) | Statin exposure (n=2 058 249) | Standardized difference |
|----------------------------|---------------------------|-----------------------------|-------------------------|
| 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)
be treated for cardiovascular conditions other than those listed in the noninclusion criteria, necessitating a higher use of low-dose aspirin and antiplatelet agents (Table S8). The absence of a lower risk of hospitalization among high-intensity statin users persisted after participants taking low-dose aspirin were excluded (Table S7).

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

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

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

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

**DISCUSSION**

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

**Possible Underlying Mechanisms**

COVID-19 is primarily a respiratory viral illness; however, it has widespread effects on the body including hypercoagulability, a hyperinflammatory state, and...
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; results that are consistent with the clinical presentation of symptomatic patients with COVID-19.83 The lower risk of hospitalization among statin users compared with nonusers that we found in this study, if causal, would likely be attributable to the pleiotropic beneficial effects of statins as anti-inflammatory, immune-modulatory, and anticoagulant agents.84 Indeed, several in vitro studies have supported the argument that statins may prevent individuals from being infected or having a serious COVID-19 outcome.85–88 SARS-CoV-2 infects type II pneumocytes present in the oral mucosa and lungs of the host by docking its spike protein onto ACE-285 on the plasma membrane.86 Lipid rafts—plasma membrane microdomains mainly composed of cholesterol, glycosphingolipids, and phospholipids—including ACE-2 are the sites of the initial binding, activation, internalization, and cell-to-cell transmission of SARS-CoV-2.87 They also are key

| Hospitalization N=9396 | Statin exposure | Unadjusted model* | Fully adjusted model† | IPTW further adjusted model‡ |
|------------------------|----------------|------------------|----------------------|-----------------------------|
|                        |                | HR (95% CI)      | P value              | HR (95% CI)                  | P value     | HR (95% CI)                  | P value     |
| 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 | 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 | 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 (0.88–1.18) | 0.9090 | 1.04 (0.88–1.23) | 0.6193 |

**Statin intensity and its type**

| No exposure | 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 (0.48–1.14) | 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.
regulators of immune and inflammatory responses following the infection. Depletion of cholesterol by statins is shown to disrupt lipid rafts, which, in turn, disturbs viral binding to ACE-2 cells and leads to a significant reduction in viral replication.88

Comparison With Other Studies

We found one study32 that examined the association between statin use and the risk of hospitalization for COVID-19. Oh et al concluded that the risk of developing COVID-19 was 35% lower in statin users compared with nonusers (odds ratio, 0.65; 95% CI, 0.60–0.71). However, the level of evidence was not sufficient given its design: first, the authors selected eligible participants based on a case-control design—COVID-19 patients matched with the general population for age, sex, and place of residence—and performed a second matching based on propensity score between statin users and nonusers. We also identified studies that focused on risk factors and drugs associated with SARS-CoV-2 infection, conducted on patients with varied conditions (history of diabetes,89 hypertension,90 undergoing transcatheter aortic valve implantation,91 or pancreas, biliary, or liver conditions92) or in the general population.93–97 Results of association with statin use in these studies were heterogeneous: a significantly lower risk,89,93,97 a lower risk but not statistically significant,90,91,95 and an increased risk of COVID-19 diagnosis.92,94,96 Our cohort study, specifically planned using a matched exposed/nonexposed design to examine the relationship between statin use and hospitalization

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

| Statin exposure | Unadjusted model* | Fully adjusted model† | IPTW further adjusted model‡ |
|----------------|------------------|------------------------|-----------------------------|
|                | HR (95% CI)      | P value                | HR (95% CI)                  | P value | HR (95% CI) | P value |
| No exposure    | 1.00 (1.00–1.00) | 1                      | 1.00 (1.00–1.00)             | 1       | 1.00 (1.00–1.00) | 1       |
| Statin exposure| 0.77 (0.69–0.86) | <0.0001                | 0.76 (0.68–0.85)             | <0.0001 |

Type of statin

| Type of statin | Unadjusted model* | Fully adjusted model† | IPTW further adjusted model‡ |
|----------------|------------------|------------------------|-----------------------------|
|                | HR (95% CI)      | P value                | HR (95% CI)                  | P value | HR (95% CI) | P value |
| Atorvastatin   | 0.80 (0.73–0.88) | <0.0001                | 0.77 (0.69–0.86)             | <0.0001 |
| Fluvastatin    | 0.88 (0.80–1.00) | 0.3375                 | 0.81 (0.74–1.02)             | 0.0849  |
| Pravastatin    | 0.70 (0.55–0.88) | 0.0027                 | 0.68 (0.53–0.87)             | 0.0023  |
| Rosuvastatin   | 0.71 (0.57–0.89) | 0.0035                 | 0.69 (0.54–0.88)             | 0.0023  |
| Simvastatin    | 0.73 (0.58–0.91) | 0.0048                 | 0.75 (0.59–0.94)             | 0.0142  |

Statin intensity

| Statin intensity | Unadjusted model* | Fully adjusted model† | IPTW further adjusted model‡ |
|-----------------|------------------|------------------------|-----------------------------|
|                 | HR (95% CI)      | P value                | HR (95% CI)                  | P value | HR (95% CI) | P value |
| Low             | 0.76 (0.61–0.94) | 0.0134                 | 0.76 (0.60–0.96)             | 0.0190  |
| Moderate        | 0.78 (0.70–0.88) | <0.0001                | 0.75 (0.66–0.86)             | <0.0001 |
| High            | 1.18 (0.83–1.69) | 0.3619                 | 1.06 (0.72–1.55)             | 0.7586  |

Statin intensity and its type

| Statin intensity and its type | Unadjusted model* | Fully adjusted model† | IPTW further adjusted model‡ |
|------------------------------|------------------|------------------------|-----------------------------|
|                              | HR (95% CI)      | P value                | HR (95% CI)                  | P value | HR (95% CI) | P value |
| Fluvastatin 20/40            | 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            | 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               | 1.00 (0.63–1.58) | 1.0000                 | 1.04 (0.65–1.68)             | 0.8569  | 1.01 (0.62–1.64) | 0.9769 |
| Atorvastatin 10/20           | 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               | 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               | 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            | 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            | 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           | 1.30 (0.88–1.94) | 0.1927                 | 1.13 (0.74–1.73)             | 0.5633  | 1.02 (0.65–1.61) | 0.9380 |
| Rosuvastin 20                | 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, antplatelet 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.
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                   |                              | HR (95% CI)           | P value                   |
| Age categories, y        |                                       |                                           |                       |                           |                               |                       |                           |
| 40–59                    | 862/395 018 (0.22)                     | 805/395 018 (0.20)                        | 0.90 (0.81–1.00)      | 0.0494                    | 62/395 018 (0.016)            | 42/395 018 (0.011)     | 0.64 (0.39–1.05)           | 0.0746                    |
| 60–69                    | 1437/683 378 (0.21)                    | 1237/683 378 (0.18)                       | 0.85 (0.78–0.92)      | 0.0001                    | 193/683 378 (0.028)           | 129/683 378 (0.019)    | 0.71 (0.55–0.92)           | 0.0107                    |
| 70–79                    | 1499/660 264 (0.23)                    | 1329/660 264 (0.20)                       | 0.84 (0.78–0.91)      | <0.0001                   | 268/660 264 (0.041)           | 242/660 264 (0.037)    | 0.87 (0.71–1.06)           | 0.1625                    |
| ≥80                      | 1206/319 589 (0.38)                    | 1001/319 589 (0.31)                       | 0.79 (0.72–0.86)      | <0.0001                   | 391/319 589 (0.122)           | 321/319,589 (0.100)    | 0.75 (0.63–0.89)           | 0.0011                    |
| Sex                      |                                       |                                           |                       |                           |                               |                       |                           |                           |
| Men                      | 2,841/958,989 (0.30)                   | 2,414/958,989 (0.25)                      | 0.82 (0.77–0.87)      | <0.0001                   | 567/958,989 (0.059)           | 454/958,989 (0.047)    | 0.77 (0.67–0.89)           | 0.0003                    |
| Women                    | 2,183/1,099,260 (0.20)                 | 1,958/1,099,260 (0.18)                    | 0.87 (0.81–0.93)      | <0.0001                   | 347/1,099,260 (0.032)         | 280/1,099,260 (0.025)  | 0.77 (0.64–0.92)           | 0.0034                    |
| Hypertension             |                                       |                                           |                       |                           |                               |                       |                           |                           |
| No                       | 3,249/1,198,186 (0.27)                 | 2,853/1,198,186 (0.24)                    | 0.84 (0.80–0.89)      | <0.0001                   | 614/1,198,186 (0.051)         | 471/1,198,186 (0.039)  | 0.74 (0.65–0.85)           | <0.0001                   |
| Yes                      | 1775/860 063 (0.21)                    | 1519/860 063 (0.18)                       | 0.84 (0.78–0.90)      | <0.0001                   | 300/860 063 (0.035)           | 263/860 063 (0.031)    | 0.85 (0.71–1.03)           | 0.0985                    |
| Diabetes                 |                                       |                                           |                       |                           |                               |                       |                           |                           |
| No                       | 2522/1,364,924 (0.18)                  | 2152/1,364,924 (0.16)                     | 0.83 (0.78–0.88)      | <0.0001                   | 416/1,364,924 (0.030)         | 343/1,364,924 (0.025)  | 0.79 (0.67–0.92)           | 0.0034                    |
| Yes                      | 2502/693,325 (0.36)                    | 2220/693,325 (0.32)                      | 0.85 (0.80–0.91)      | <0.0001                   | 498/693,325 (0.072)           | 391/693,325 (0.056)    | 0.77 (0.66–0.90)           | 0.0007                    |
| Chronic respiratory condition |                                   |                                           |                       |                           |                               |                       |                           |                           |
| No                       | 4279/1,872,316 (0.23)                  | 3746/1,872,316 (0.20)                     | 0.84 (0.80–0.88)      | <0.0001                   | 765/1,872,316 (0.041)         | 620/1,872,316 (0.033)  | 0.77 (0.69–0.87)           | <0.0001                   |
| Yes                      | 745/1,853,933 (0.40)                   | 626/1,853,933 (0.34)                      | 0.83 (0.74–0.94)      | 0.0024                    | 149/1,853,933 (0.080)         | 114/1,853,933 (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, 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 inhospital 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.

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 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, 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. 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. In other studies where this design was not applied, adjustment systematically decreased odds ratios or HRs. In certain cases, the direction of odds ratios or HRs changed drastically after adjustment: statin use was significantly associated with a higher risk in unadjusted analysis while it was associated with lower risk in adjusted analysis. In addition, not including adjusted ratio measures in

References 7,13,18,19,23,28,36,47,49.
meta-analyses, which is recommended by the Cochrane group.98 leads to spurious results, notably the absence of association between statin use and COVID-19 outcomes.100 Meta-analyses that did include adjusted ratio measures showed a lower risk of COVID-19 outcomes with the statin use.101,102

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

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SUPPLEMENTAL MATERIAL
Table S1. Non-inclusion criteria

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

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

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

Other codes were also detailed.

| Exclusion criteria                                      | Codes |
|--------------------------------------------------------|-------|
| **Lipid lowering drugs**                               |       |
| Fibrates                                               |       |
| ATC                                                    | C10AB |
| Bile acid sequestrants                                 |       |
| ATC                                                    | C10AC |
| Nicotinic acid and derivatives                          |       |
| ATC                                                    | C10AD |
| Other lipid lowering drugs (ezetimibe, PCSK9 inhibitors,* etc.) | C10AX |
| ATC                                                    |       |
| Combinations of lipid lowering drugs                   | C10B  |
|                                                        |       |
| **Cardiovascular and neurovascular diseases**          |       |
| Include following conditions:                          |       |
| Acute or chronic coronary artery disease               |       |
| Acute stroke or aftermath                              |       |
| Acute or chronic heart failure                         |       |
| Peripheral vascular disease                            |       |
| Arrhythmia or cardiac conduction disorders             |       |
| Valvular heart disease                                 |       |
| Acute pulmonary embolism                               |       |
| Other cardiovascular conditions                         |       |
| ICD-10                                                 |       |
| I 50 J 81 I 11 I 13 K 76 I 20 I 21 I 22 I 23 I 24 I 25 I 48 I 05 I 06 |       |
| I 07 I 08 I 34 I 35 I 36 I 37 I 38 I 39 I 44 I 45             |       |
| I 47 I 48 I 49 I 702 I 26                                 |       |
| I 739 I 74 0 I 74 3 I 74 4 I 74 5 G 46 I 60 I 61 I 62 I 63 I 64 |       |
| I 65 I 66 I 67 I 68 I 69 G 45 I 26 I 800 I 801 I 802       |       |
| I 803 I 808 I 809 I 81 I 82                               |       |
| I 70 I 73 I 74 only for those included in the list of long-term diseases |       |
|                                                        |       |
| **Other comorbidities**                                |       |
| Cancer                                                 |       |
| ICD-10                                                 |       |
| D 00 x D 09 x                                          |       |
| Z 08 Z 51 0 Z 51 1                                      |       |
| Kidney transplant, dialysis                            |       |
| ICD-10                                                 |       |
| N 18 (long-term diseases), Z 940                       |       |
| CCAM                                                   |       |
| J A E A 0 0 3, H N E A 0 0 2                             |       |
| J V J B 0 0 1, J V J F 0 0 4, J V J F 0 0 8, J V R P 0 0 4, J V R P 0 0 7, J V R P 0 0 8, YYYY 0 0 7 |       |
| Diagnosis related group                                |       |
| 2 7 C 0 6 2 4 M 3 9 Z 1 1 M 1 7                          |       |
| Billing code for dialysis session conducted at home, self-care dialysis, in a dialysis unit under medical supervision | 11K02, 28Z01-28Z04 |
|---------------------------------------------------------------|-------------------|
| Dementia                                                      | D11-D16, D20-24   |
| ICD-10                                                        | F00 F01 F02 F03 F051 G30 |
| ATC                                                           | N06DA04 N06DX01   |

*For PCSK9 inhibitors: any dispensing in the past year.
Table S2. Exposure of interest

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

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

**Types of statins**

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

**Classification of statins according to their intensity**

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

| Intensity (LDL-cholesterol lowering) | Dose 1 | Dose 2 |
|--------------------------------------|--------|--------|
| **Low (< 30%)**                      |        |        |
| Fluvastatin                          | 20     | 40     |
| Pravastatin                          | 10     | 20     |
| Simvastatin                          | 10     |        |
| **Moderate (30% - 49%)**             |        |        |
| Atorvastatin                         | 10     | 20     |
| Rosuvastatin                         | 5      | 10     |
| Simvastatin                          | 20     | 40     |
| Pravastatin                          | 40     |        |
| Fluvastatin                          | 80     |        |
| **High (≥50%)**                      |        |        |
| Atorvastatin                         | 40     | 80     |
| Rosuvastatin                         | 20     |        |
Table S3. Matching variables

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

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

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

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

| Covariates                  | Codes                                                                 |
|-----------------------------|----------------------------------------------------------------------|
| Hypertension ATC            | C02AB02, C02AC01, C02AC02, C02AC05, C02AC06, C02CA01, C02CA06, C02DC01, C02LA01, C03AA01, C03AA03, C03BA04, C03BA10, C03BA11, C03BX03, C03CA01, C03CA02, C03CA03, C03DA01, C03DB01, C03EA01, C03EA04, C07AA02, C07AA03, C07AA05, C07AA06, C07AA12, C07AA15, C07AA16, C07AA23, C07AB02, C07AB03, C07AB04, C07AB05, C07AB07, C07AB08, C07AB12, C07AG01, C07BA02, C07BB02, C07BB03, C07BB07, C07BB12, C07CA03, C07DA06, C07FB02, C07FB03, C08CA01, C08CA02, C08CA03, C08CA04, C08CA05, C08CA08, C08CA09, C08CA11, C08CA13, C08CX01, C08DA01, C08DB01, C08GA02, C09AA01, C09AA02, C09AA03, C09AA04, C09AA05, C09AA06, C09AA07, C09AA08, C09AA09, C09AA10, C09AA13, C09AA15, C09AA16, C09BA01, C09BA02, C09BA03, C09BA04, C09BA05, C09BA06, C09BA07, C09BA09, C09BA15, C09BB02, C09BB04, C09BB10, C09BX02, C09CA01, C09CA02, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08, C09DA01, C09DA02, C09DA03, C09DA04, C09DA06, C09DA07, C09DA08, C09DB01, C09DB02, C09DB04, C09XA02, C09XA52, C10BX03 |
| Diabetes mellitus ICD-10   | E10, E11, E12, E13, E14, G59.0, G63.2, G73.0, G99.0, H28.0, H36.0, I79.2, L97, M14.2, M14.6, N08.3 |
| ATC                         | A10 excluding benfluorex (A10BX06)                                   |
| Chronic respiratory condition ICD-10 | J40, J41, J42, J43, J44, J45, J46, J47, J96 (excluding J96.0, J96.9), J98 |
| ATC                         | R03 (drugs for obstructive airway diseases)                         |
Table S4. Covariates

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

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

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

Other codes were also detailed.

| Covariates                      | Codes                                                                 |
|---------------------------------|----------------------------------------------------------------------|
| Health behavior characteristics |                                                                      |
| Smoking-related condition       |                                                                      |
| ICD-10                          | Z716 F17 T652 Z720                                                    |
| ATC                             | N07BA                                                                |
| Primary care delivery           | Tobacco consultation service (9566, 9526, 9527) in the 5 years preceding index date (at least once) |
| Alcohol-related condition       |                                                                      |
| ICD-10                          | E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, R780, T51, X45, X65, Y15, Y90, Y91, Y573, Z502, Z714, or Z721 |
| ATC                             | N07BB01, N07BB03, N07BB04, N07BB05 at least 2 dispensing in the 5 years preceding index date M03BX01 (baclofen) without following neurological disease (ICD-10): C70, C71, C793, C794, D32, D33, D42, D43, G04, G05, G06, G09, G12, G13, G24, G25, G26, G31, G32, G35, G36, G37, G46, G80, G81, G82, G83, G91, G93, G95 |
| Laboratory test (NABM)          | 516, 517, 519 (gamma-GT)                                             |
| Obesity-related condition       |                                                                      |
| ICD-10                          | E66 excluding E66.03, E66.13, E66.83, E66.93 (since 2006)            |
| CCAM                            | HFCA001, HFCC003, HFFA001, HFFA011, HFFC004, HFFC018, HFGC900, HFKA001, HFKA002, HFKC001, HFLC900, HFLE002, HFMA009, HFMA010, HFMA011, HFMC006, HFMC007, HFMC008, HGCA009, HGCC027 (bariatric surgery) |
| Comorbidities or comediations   |                                                                      |
| Liver and pancreas disorder     |                                                                      |
| ICD-10                          | B18, I85, K70, K71, K72, K73, K74, K75, K76, K85, K86                |
| ATC/UCD/CIP                     | Treatment for chronic hepatitis B:                                    |
|                                 | J05AF08, J05AF10, J05AF11                                            |
|                                 | 9212525, 9212531 (UCD, Zeffix®)                                       |
|                                 | 3519671, 3519694 (CIP, Zeffix®)                                       |
|                                 | Treatment for chronic hepatitis B:                                    |
|                                 | L03AB05, L03AB09, L03AB10, L03AB11                                    |
|                                 | J05AB04                                                              |
|                                 | J05AP08, J05AP51, J05AP55, J05AP56, J05AX (3400930108765 (CIP), 3400894287391 (UCD)), J05AX14, J05AX15, J05AX16, J05AX65, J05AX67, J05AX68 |
| Laboratory test (NABM)          | 4125: hepatitis C genotype                                            |
|                                 | 4124: hepatitis C viral load                                         |
|                                 | 1000 to 1002 (Fibrotest®, Fibromètre®V, Hépascore®)                   |
| CCAM                            | HLQM002, HLHB001, HLHH001, HLHH005, HLHJ003 (liver biopsy, etc.)      |
| Medications (ATC)               |                                                                      |
| Non-steroidal anti-inflammatory drugs (ATC) | M01AE09, M01AE11, M01AE01, M01AE02, M01AB01, M01AE03, M01AB05, M01AB16, M01AH01, M01AH05, M01AC01, M01AC02, M01AC06, M01AX01, M01AX17, M01AB08, M01AE16, M01AX02, M01AX22, M01AX21 |
|-------------------------------------------|----------------------------------------------------------------------------------|
| Low-dose aspirin (CIP)                    | 18 CIP codes:                                                                    |
|                                           | 3400934744198                                                                    |
|                                           | 3400933247379                                                                    |
|                                           | 3400931893639                                                                    |
|                                           | 3400932703616                                                                    |
|                                           | 3400926939939                                                                    |
|                                           | 3400938206371                                                                    |
|                                           | 340093226558                                                                    |
|                                           | 3400934323492                                                                    |
|                                           | 3400934300141                                                                    |
|                                           | 3400930013953                                                                    |
|                                           | 3400930013984                                                                    |
|                                           | 3400930014035                                                                    |
|                                           | 3400930014066                                                                    |
|                                           | 3400935902269                                                                    |
|                                           | 3400935984814                                                                    |
|                                           | 3400926940188                                                                    |
|                                           | 3400930182543                                                                    |
|                                           | 3400930195697                                                                    |
| Antplatelet                               | 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.*
| Region                          | Population (January 1, 2021*) | No exposure | Statin exposure |
|--------------------------------|--------------------------------|-------------|-----------------|
| Auvergne-Rhône-Alpes           | 8,092,598 (12.4)               | 213,640 (10.4) | 213,640 (10.4) |
| Bourgogne-Franche-Comté        | 2,786,205 (4.3)                | 98,693 (4.8)  | 98,693 (4.8)    |
| Bretagne                       | 3,371,297 (5.2)                | 104,714 (5.1) | 104,714 (5.1)   |
| Centre-Val de Loire            | 2,562,431 (3.9)                | 95,625 (4.6)  | 95,625 (4.6)    |
| Corse                          | 349,273 (0.5)                  | 8,697 (0.4)   | 8,697 (0.4)     |
| Grand Est                       | 5,524,817 (8.5)                | 192,826 (9.4) | 192,826 (9.4)   |
| Hauts-de-France                | 5,977,46 (9.2)                 | 234,718 (11.4)| 234,718 (11.4)  |
| Île-de-France                  | 12,326,429 (18.9)              | 317,010 (15.4)| 317,010 (15.4)  |
| Normandie                      | 3,306,092 (5.1)                | 121,260 (5.9) | 121,260 (5.9)   |
| Nouvelle Aquitaine             | 6,039,767 (9.3)                | 199,285 (9.7) | 199,285 (9.7)   |
| Occitanie                      | 5,985,751 (9.2)                | 164,959 (8.0) | 164,959 (8.0)   |
| Pays de la Loire               | 3,838,060 (5.9)                | 125,184 (6.1) | 125,184 (6.1)   |
| Provence-Alpes-Côte d’Azur     | 5,089,661 (7.8)                | 133,389 (6.5) | 133,389 (6.5)   |
| Total                          | 65,249,843                     | 2,058,249    | 2,058,249       |

*Source: INSEE, Population census. Data available on the French Institute for Demographic Studies website (INED: https://www.ined.fr).
Table S6. Association between statin exposure and hospitalization for COVID-19

| Statin exposure          | Hospitalization N=9396 | IPTW\(^{*}\) | IPTW further adjusted model\(^{†}\) |
|--------------------------|------------------------|--------------|----------------------------------|
|                          | HR [95%CI]             | P-value      | HR [95%CI]                        | P-value |
| No exposure              | 5,024 (0.24)           | 1            | 1                                | .       |
| Statin exposure          | 4,372 (0.21)           | 0.85 [0.82-0.89] | <.0001                           | 0.84 [0.80-0.87] | <.0001 |

| Type of statin           |                       |              |                                  |
|--------------------------|------------------------|--------------|----------------------------------|
| No exposure              | 5,024 (0.24)           | 1            | 1                                | .       |
| Atorvastatin             | 1,944 (0.23)           | 0.91 [0.85-0.97] | 0.0035                           | 0.88 [0.83-0.94] | 0.0002 |
| Fluvastatin              | 92 (0.17)              | 0.69 [0.52-0.92] | 0.0114                           | 0.71 [0.53-0.95] | 0.0212 |
| Pravastatin              | 730 (0.19)             | 0.86 [0.77-0.95] | 0.0038                           | 0.84 [0.76-0.93] | 0.0012 |
| Rosuvastatin             | 794 (0.21)             | 0.82 [0.75-0.91] | <.0001                           | 0.80 [0.72-0.88] | <.0001 |
| Simvastatin              | 812 (0.20)             | 0.79 [0.72-0.87] | <.0001                           | 0.78 [0.71-0.87] | <.0001 |

| Statin intensity         |                       |              |                                  |
|--------------------------|------------------------|--------------|----------------------------------|
| No exposure              | 5,024 (0.24)           | 1            | 1                                | .       |
| Low                      | 778 (0.18)             | 0.79 [0.71-0.87] | <.0001                           | 0.78 [0.71-0.87] | <.0001 |
| Moderate                 | 3,231 (0.22)           | 0.85 [0.81-0.89] | <.0001                           | 0.83 [0.79-0.88] | <.0001 |
| High                     | 363 (0.28)             | 1.12 [0.95-1.31] | 0.1756                           | 1.04 [0.88-1.23] | 0.6193 |

| Statin intensity and its type |                       |              |                                  |
|-----------------------------|------------------------|--------------|----------------------------------|
| No exposure                 | 5,024 (0.24)           | 1            | 1                                | .       |
| Low                         |                        |              |                                  |
| 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 |
| Moderate                    |                        |              |                                  |
| 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 |
| High                        |                        |              |                                  |
| 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.

\(^\dagger\)Conditional Cox proportional hazards model with IPTW further adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).
Table S7. Association between statin exposure and hospital outcomes after excluding participants with low-dose aspirin

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

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

*Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).
| Matching variables | Before IPTW | After IPTW |
|--------------------|------------|------------|
| **Age (years)**    |            |            |
| Mean (SD)          | 68.65 (10.36) | 68.77 (10.45) |
| 40-59              | 395,018 (19.2) | 393,908 (19.1) |
| 60-69              | 683,378 (33.2) | 675,066 (32.8) |
| 70-79              | 660,264 (32.1) | 659,763 (32.1) |
| >=80               | 319,589 (15.5) | 331,128 (16.1) |
| **Sex**            |            |            |
| Men                | 958,989 (46.6) | 953,716 (46.3) |
| Women              | 1,099,260 (53.4) | 1,106,151 (53.7) |
| **Residence area** |            |            |
| Auvergne-Rhône-Alpes | 213,640 (10.4) | 211,820 (10.3) |
| Bourgogne-Franche-Comté | 98,693 (4.8) | 98,760 (4.8) |
| Bretagne           | 104,714 (5.1) | 103,224 (5.0) |
| Centre-Val de Loire | 95,625 (4.6) | 94,986 (4.6) |
| Corse              | 8,697 (0.4) | 9,048 (0.4) |
| Grand Est          | 192,826 (9.4) | 196,157 (9.5) |
| Hauts-de-France   | 234,718 (11.4) | 241,077 (11.7) |
| Ile-de-France      | 317,010 (15.4) | 313,047 (15.2) |
| Normandie          | 121,260 (5.9) | 122,824 (6.0) |
| Nouvelle-Aquitaine | 199,285 (9.7) | 198,574 (9.6) |
| Occitanie          | 164,959 (8.0) | 163,733 (8.0) |
| Overseas departments | 47,939 (2.3) | 48,232 (2.3) |
| Overseas territories | 310 (0.0) | 315 (0.0) |
| Pays de la Loire   | 125,184 (6.1) | 124,445 (6.0) |
| Provence-Alpes-Côte d’Azur | 133,389 (6.5) | 133,618 (6.5) |

| Covariates        | Before IPTW | After IPTW |
|--------------------|------------|------------|
| **Hypertension**   |            |            |
| No                 | 1,198,186 (58.2) | 1,194,456 (58.0) |
| Yes                | 860,063 (41.8) | 865,410 (42.0) |
| **Diabetes mellitus** |        |            |
| No                 |            |            |
| Yes                |            |            |
| Condition                                | No          | Yes          | p-value  |
|------------------------------------------|-------------|--------------|----------|
| Yes                                      | 1,364,924 (66.3) | 693,325 (33.7) | 0.00001  |
| Chronic respiratory condition            |             |              |          |
| No                                       | 1,872,316 (91.0) | 185,933 (9.0)   | 0.00001  |
| Social deprivation index (quintiles)     |             |              |          |
| 1 (least deprived)                       | 343,795 (16.7) | 56,468 (8.5)    | 0.00001  |
| 2                                        | 366,832 (17.8) | 60,410 (4.0)    | 0.00001  |
| 3                                        | 393,467 (19.1) | 93,531 (13.5)   | 0.00001  |
| 4                                        | 422,536 (20.5) | 73,531 (10.5)   | 0.00001  |
| 5 (most deprived)                        | 449,430 (21.8) | 135,549 (19.1)  | 0.00001  |
| Unknown                                  | 82,189 (4.0)   | 3,668 (0.5)     | 0.00001  |
| Smoking-related condition                |             |              |          |
| No                                       | 2,001,677 (97.3) | 56,572 (2.7)    | 0.00001  |
| Alcohol-related condition                |             |              |          |
| No                                       | 2,025,242 (98.4) | 56,572 (2.7)    | 0.00001  |
| Obesity-related condition                |             |              |          |
| No                                       | 2,015,058 (97.9) | 43,191 (2.1)    | 0.00001  |
| Liver and pancreas disorder              |             |              |          |
| No                                       | 2,030,710 (98.7) | 27,539 (1.3)    | 0.00001  |
| Non-steroidal anti-inflammatory          |             |              |          |
| No                                       | 1,732,982 (84.2) | 32,697 (1.7)    | 0.00001  |
| Low-dose aspirin                         |             |              |          |
| No                                       | 1,827,030 (88.8) | 231,219 (11.2)  | 0.00001  |
| Antiplatelet agent                       |             |              |          |
| No                                       | 2,042,260 (99.2) | 15,989 (0.8)   | 0.00001  |
| Heparin                                  |             |              |          |
| No                                       | 2,044,349 (99.3) | 13,900 (0.7)    | 0.00001  |
| Yes                                      | 1,364,924 (66.3) | 693,325 (33.7) | 0.00001  |
| Anti-inflammatory and platelet disorders |             |              |          |
| Yes                                      | 242,613 (98.2) | 7,554 (1.8)    | 0.00001  |
| Yes                                      | 1,459,937 (97.5) | 36,872 (2.5)   | 0.00001  |
| Yes                                      | 2,021,734 (98.2) | 8,015 (6.2)    | 0.00001  |
| Yes                                      | 2,046,403 (99.4) | 862 (0.7)      | 0.00001  |
| Yes                                      | 13,463 (0.7)    | 13,900 (0.7)   | 0.00001  |
| Yes                                      | 1,487,559 (99.4) | 2,629 (0.6)    | 0.00001  |
| Yes                                      | 1,29,411 (99.3) | 9,250 (0.6)    | 0.00001  |
| Yes                                      | 2,046,403 (99.4) | 862 (0.7)      | 0.00001  |
| Yes                                      | 13,463 (0.7)    | 13,900 (0.7)   | 0.00001  |
|               | No                      | Yes                     |
|---------------|-------------------------|-------------------------|
| **Anticoagulant** | 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) | 47,758 (2.3) 11,806 (2.7) 41,721 (2.8) 4,885 (3.7) 54,624 (2.7) 11,187 (2.6) 38,794 (2.6) 3,558 (2.7) |
| **Oral corticosteroid** | 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) | 113,878 (5.5) 22,033 (5.1) 80,765 (5.4) 112,668 (5.5) 23,439 (5.4) 81,468 (5.4) 7,135 (5.5) |
| **Anxiolytic** | 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) | 185,749 (9.0) 49,753 (11.5) 169,861 (11.3) 215,043 (10.4) 43,958 (10.2) 153,881 (10.3) 13,744 (10.6) |
| **Hypnotic** | 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) | 82,932 (4.0) 21,419 (5.0) 77,628 (5.2) 6,915 (5.3) 97,031 (4.7) 19,787 (4.6) 69,250 (4.6) 6,246 (4.8) |
| **Antidepressant** | 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) | 155,566 (7.6) 44,438 (10.3) 152,186 (10.2) 13,953 (10.7) 186,722 (9.1) 38,410 (8.9) 133,686 (8.9) 11,861 (9.1) |
| **Antipsychotic** | 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) | 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

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

*Fully adjusted model for association between covariates and hospitalization for COVID-19.
|                        | Fully adjusted model* |
|------------------------|-----------------------|
|                        | HR       | 95%CI    | P-value |
| **Yes**                | 0.94     | 0.82     | 1.09    | 0.4046  |
| **Antidepressant**     |          |          |         |
| No                     | 1.00     |          |         |
| Yes                    | 1.10     | 0.98     | 1.22    | 0.0984  |
| **Antipsychotic**      |          |          |         |
| No                     | 1.00     |          |         |
| Yes                    | 1.91     | 1.40     | 2.60    | <.0001  |

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

*Conditional Cox proportional hazards model adjusted for the following covariates: social deprivation index, smoking, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).
Table S10. Association between statin exposure and in-hospital COVID-19 deaths

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

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

*Conditional Cox proportional hazards model with IPTW.

†Conditional Cox proportional hazards model with IPTW further adjusted for the following covariates: social deprivation index, smoking-, alcohol-, and obesity-related conditions, liver failure, and concomitant medications (non-steroidal anti-inflammatory, low-dose aspirin, antiplatelet agent, heparin, anticoagulant, oral corticosteroid, anxiolytic, hypnotic, antidepressant, antipsychotic).
Table S11. Association between statin exposure and in-hospital deaths in COVID-19-related hospitalized individuals (N=9,396)

| Statin exposure       | Unadjusted model | Fully adjusted model | IPTW further adjusted model |
|-----------------------|------------------|----------------------|----------------------------|
| | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value |
| No exposure | 839 (16.70) | 1 | . | 1 | . | 1 | . |
| Statin exposure | 690 (15.78) | 0.94 [0.85-1.04] | 0.2597 | 0.84 [0.76-0.93] | 0.0012 | 0.87 [0.79-0.96] | 0.0083 |

| Type of statin        | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value |
|-----------------------|----------------|---------|----------------|---------|----------------|---------|
| No exposure | 839 (16.70) | 1 | . | 1 | . | 1 | . |
| Atorvastatin | 309 (15.90) | 0.95 [0.83-1.08] | 0.4297 | 0.85 [0.74-0.97] | 0.0141 | 0.85 [0.74-0.97] | 0.0191 |
| Fluvastatin | 21 (22.83)  | 1.44 [0.93-2.22] | 0.0998 | 1.23 [0.80-1.90] | 0.3445 | 1.33 [0.86-2.08] | 0.2017 |
| Pravastatin | 113 (15.48) | 0.93 [0.76-1.13] | 0.4650 | 0.81 [0.67-0.99] | 0.0402 | 0.84 [0.68-1.03] | 0.0868 |
| Rosuvastatin | 121 (15.24) | 0.91 [0.75-1.10] | 0.3185 | 0.83 [0.68-1.00] | 0.0515 | 0.88 [0.73-1.07] | 0.1981 |
| Simvastatin | 126 (15.52) | 0.93 [0.77-1.12] | 0.4214 | 0.83 [0.69-1.00] | 0.0553 | 0.89 [0.73-1.07] | 0.2098 |

| Statin intensity    | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value |
|---------------------|----------------|---------|----------------|---------|----------------|---------|
| No exposure | 839 (16.70) | 1 | . | 1 | . | 1 | . |
| Low     | 133 (17.10) | 1.03 [0.86-1.24] | 0.7353 | 0.91 [0.76-1.10] | 0.3452 | 0.96 [0.80-1.16] | 0.6716 |
| Moderate | 494 (15.29) | 0.91 [0.82-1.02] | 0.1034 | 0.82 [0.73-0.92] | 0.0007 | 0.85 [0.76-0.95] | 0.0050 |
| High    | 63 (17.36)  | 1.04 [0.81-1.34] | 0.7635 | 0.87 [0.67-1.13] | 0.3038 | 0.85 [0.64-1.14] | 0.2830 |

| Statin intensity and its type | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value | HR [95% CI]†  | P-value |
|------------------------------|----------------|---------|----------------|---------|----------------|---------|
| 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

| Influenza vaccination since November 15, 2017 | No exposure (n = 2,058,249) | Statin exposure (n = 2,058,249) | Standardized difference |
|---------------------------------------------|-----------------------------|---------------------------------|------------------------|
| 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$^\dagger$ | IPTW further adjusted model$^\ddagger$ |
|--------------------------|----------------------|-------------------------------|-------------------------------------|
| Statin exposure          |                      |                               |                                     |
| No                       | 5,024 (0.24)         | 1.00                          | 1.00                                |
| Yes                      | 4,372 (0.21)         | 0.87 [0.83-0.90]              | <.0001                              |

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

$^*$Conditional Cox proportional hazards model.

$^\dagger$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.

$^\ddagger$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$^\dagger$ | IPTW further adjusted model$^\ddagger$ |
|---------------|----------------------|-------------------------------|-------------------------------------|
| Statin exposure |                      |                               |                                     |
| No            | 914 (0.044)          | 1.00                          | 1.00                                |
| Yes           | 734 (0.036)          | 0.80 [0.73-0.88]              | <.0001                              |

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

$^*$Conditional Cox proportional hazards model.

$^\dagger$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.

$^\ddagger$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

| Author          | Matching | Adjustment | RM  | LCI   | UCI   |
|-----------------|----------|------------|-----|-------|-------|
| Aparisi et al   | No       | Unadjusted | 1.13| 0.80  | 1.61  |
| Aparisi et al   | No       | Adjusted   | 0.48| 0.30  | 0.77  |
| Butt et al      | No       | Unadjusted | 2.87| 2.39  | 3.46  |
| Butt et al      | No       | Adjusted   | 0.96| 0.78  | 1.18  |
| Daniels et al   | No       | Unadjusted | 0.60| 0.28  | 1.24  |
| Daniels et al   | No       | Adjusted   | 0.29| 0.11  | 0.71  |
| De Spiegeleer et al | No   | Unadjusted | 0.75| 0.25  | 1.85  |
| De Spiegeleer et al | No     | Adjusted   | 0.75| 0.24  | 1.87  |
| Grasselli et al | No       | Unadjusted | 1.76| 1.59  | 1.95  |
| Grasselli et al | No       | Adjusted   | 0.98| 0.81  | 1.20  |
| Lee et al       | No       | Unadjusted | 2.51| 1.69  | 3.73  |
| Lee et al       | No       | Adjusted   | 0.64| 0.43  | 0.95  |
| Lohia et al     | No       | Unadjusted | 1.10| 0.84  | 1.44  |
| Lohia et al     | No       | Adjusted   | 0.66| 0.46  | 0.95  |
| Nicholson et al | No       | Unadjusted | 1.63| 1.20  | 2.22  |
| Nicholson et al | No       | Adjusted   | 0.47| 0.24  | 0.92  |
| Rosenthal et al | No       | Unadjusted | 0.99| 0.94  | 1.04  |
| Rosenthal et al | No       | Adjusted   | 0.60| 0.56  | 0.65  |
| Saeed et al     | No       | Unadjusted | 0.54| 0.46  | 0.63  |
| Saeed et al     | No       | Adjusted   | 0.51| 0.43  | 0.61  |
| Song et al      | No       | Unadjusted | 1.07| 0.49  | 2.32  |
| Song et al      | No       | Adjusted   | 0.88| 0.37  | 2.08  |
| Wargny et al    | No       | Unadjusted | 1.35| 1.12  | 1.62  |
| Wargny et al    | No       | Adjusted   | 1.42| 1.00  | 2.02  |
| Fan et al       | PSM      | Unadjusted | 0.25| 0.07  | 0.93  |
| Fan et al       | PSM      | Adjusted   | 0.25| 0.07  | 0.92  |
| Lee et al       | PSM      | Unadjusted | 0.58| 0.38  | 0.89  |
| Lee et al       | PSM      | Adjusted   | 0.55| 0.36  | 0.85  |
| Zhang et al     | PSM      | Unadjusted | 0.53| 0.39  | 0.72  |
| Zhang et al     | PSM      | Adjusted   | 0.58| 0.43  | 0.80  |

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.