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BRIEF REPORT

No association of low-dose aspirin with severe COVID-19 in France: A cohort of 31.1 million people without cardiovascular disease

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Abstract

Background: Aspirin at low doses has been reported to be a potential drug candidate to treat or prevent severe coronavirus disease 2019 (COVID-19).

Objectives: We aimed to explore whether low-dose aspirin used for primary cardiovascular prevention was associated with a lower risk of severe COVID-19.

Method: A large cohort of patients without known cardiovascular comorbidities was constructed from the entire French population registered in national health care databases. In total, 31.1 million patients aged ≥40 years, including 1.5 million reimbursed for low-dose aspirin at least at three time points during the 6 months before the epidemic, were followed until hospitalization with a COVID-19 diagnosis or intubation/death for hospitalized patients.

Results: Cox models adjusted for age and sex showed a positive association between low-dose aspirin and the risk of hospitalization (hazard ratio [HR], 1.33; 95% confidence interval [CI], 1.29-1.37) or death/intubation (HR, 1.40 [95% CI, 1.33-1.47]). In fully adjusted models, associations were close to null (HR, 1.03 [95% CI, 1.00-1.06] and 1.04 [95% CI, 0.98-1.10], respectively).

Conclusion: There was no evidence for an effect of low-dose aspirin for primary cardiovascular prevention in reducing severe COVID-19.

KEYWORDS

aspirin, COVID-19, pharmacoepidemiology, primary cardiovascular prevention, public health
1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has been a pandemic since 2020. The virus spread rapidly, infecting >500 million people, and killing >6 million as of May 27, 2022. In addition to vaccination, there is hope of finding a drug to treat or prevent severe coronavirus disease 2019 (COVID-19).

One top-listed drug has been aspirin at low doses (ie, <320 mg). Platelets appear to be hyperreactive in COVID-19, and because aspirin is an antplatelet agent, its early use by patients with COVID-19 was expected to reduce the risk of aggravation and the incidence of cardiovascular complications and mortality, although with inconsistencies. Authors have argued that “improvement in clinical outcomes, including decreased mortality with aspirin in hospitalized patients with coronavirus disease 2019 infection justifies a sufficiently powered randomized controlled primary prevention trial.” Aspirin was thus added to the RECOVERY trial, the largest clinical trial of treatments for patients hospitalized with COVID-19 in the United Kingdom, which recently concluded that there was no effect of aspirin on reducing 28-day mortality. Other studies have tended to observe a benefit in preventing the likelihood of SARS-CoV-2 infection, disease duration, or mortality. Conversely, two meta-analyses suggested no association between the use of aspirin and mortality among patients with COVID-19, one for 1000 hospitalized patients and the other for 6000 patients infected with COVID-19.

To our knowledge, no study has analyzed this issue in a more general population than that of hospitalized patients or patients with SARS-CoV-2 infection. We sought to determine whether low-dose aspirin used for primary cardiovascular prevention was associated with a lower risk of severe COVID-19 in a large general population.

We considered the age, sex, and region of residence of the patients as demographic variables. Age was defined as a categorical variable by 5-year age group. We used the social deprivation index as a measure of socioeconomic status. This indicator is based on the median household income, the percentage of high school graduates in the population over the age of 15, the percentage of manual workers in the labor force, and the unemployment rate for the person’s town of residence.

Essentials
- Aspirin at low doses has been reported to be a potential drug candidate to treat or prevent severe COVID-19.
- We built a large cohort of 31.1 million people aged ≥40 years from the overall French population.
- Aspirin used for primary cardiovascular prevention was not associated with a lower risk of COVID-19 hospitalization.
- The results did not show any evidence for an effect of low-dose aspirin to reduce severe COVID-19.

2 | METHODS

We selected patients from the French national health data system, which covers the entire French population with any healthcare in the previous year (ie, 66 million people). We excluded twins and foreigners due to identification issues. We identified a history of comorbidities from 2015 to 2019. We selected patients aged ≥40 years because the risk of severe COVID-19 in younger patients was lower and because treatment with aspirin for primary cardiovascular prevention could involve specific populations. Because our aim was to study aspirin use for primary cardiovascular prevention, patients with known cardiovascular comorbidities were excluded.

We identified patients who were reimbursed for low-dose aspirin (drugs with a dosage <320 mg) at least at three time points during the 6 months before February 15, 2020, defined as the start of the epidemic in France. COVID-19 identification was available from hospital stay discharge according to an exceptional, fast-track modality during the epidemic. Details can be found in other publications.

Cox models were used to estimate the association between the use of aspirin at low doses and the risk of COVID-19 hospitalization or death or intubation for COVID-19 from February 15, 2020. Patients who died from another cause were censored at the date of death. Patients with no hospitalization were censored on June 15, 2020. For the death or intubation outcome, we followed patients until June 15 up to July 15. Models were adjusted for age, sex, region of residence, social deprivation index, known pathologies in 2019, and most-prescribed drugs, as defined above.

We also reported the results for the subpopulation without known chronic respiratory diseases and for patients identified with diabetes or a history of cancer to observe whether our results were robust in these more homogeneous populations. We also restricted the analysis to people aged <70 years to conform to the 2019 American College of Cardiology/American Heart Association guidelines.

3 | RESULTS AND DISCUSSION

Among 31.1 million patients aged ≥40 without known cardiovascular comorbidities, 1.5 million were reimbursed for low-dose aspirin at least at three time points during the 6 months before February 15, 2020 (Table 1). Treated patients were older (median, 73 years; interquartile range, 66-82 vs 56 years; interquartile range, 48–67)
TABLE 1  Descriptive characteristics of the population according to low-dose aspirin use

|                          | 29 529 802 Without aspirin | 1 542 840 With aspirin | 31 072 642 All |
|--------------------------|-----------------------------|------------------------|----------------|
| Age, y                   |                             |                        |                |
| 40-44                    | 4 046 539                   | 10 659                 | 4 057 198      |
|                          | 14%                         | 1%                     | 13%            |
| 45-49                    | 4 286 500                   | 22 160                 | 4 308 660      |
|                          | 15%                         | 1%                     | 14%            |
| 50-54                    | 4 185 066                   | 47 366                 | 4 232 432      |
|                          | 14%                         | 3%                     | 14%            |
| 55-59                    | 3 986 618                   | 89 705                 | 4 076 323      |
|                          | 14%                         | 6%                     | 13%            |
| 60-64                    | 3 524 607                   | 148 282                | 3 672 889      |
|                          | 12%                         | 10%                    | 12%            |
| 65-69                    | 3 079 360                   | 220 825                | 3 300 185      |
|                          | 10%                         | 14%                    | 11%            |
| 70-74                    | 2 702 088                   | 286 990                | 2 989 078      |
|                          | 9%                          | 9%                     | 10%            |
| 75-79                    | 1 490 241                   | 225 566                | 1 715 807      |
|                          | 5%                          | 15%                    | 6%             |
| 80-84                    | 1 067 642                   | 210 289                | 1 277 931      |
|                          | 4%                          | 14%                    | 4%             |
| 85-89                    | 700 127                     | 164 316                | 864 443        |
|                          | 2%                          | 11%                    | 3%             |
| 90-110                   | 461 014                     | 116 682                | 577 696        |
|                          | 2%                          | 8%                     | 2%             |
| Sex                      |                             |                        |                |
| Male                     | 13 209 347                  | 738 174                | 13 947 521     |
|                          | 45%                         | 48%                    | 45%            |
| Female                   | 16 320 455                  | 804666                 | 17 125 121     |
|                          | 55%                         | 52%                    | 55%            |
| Social deprivation index |                             |                        |                |
| 1 (less deprived)        | 5 857 379                   | 252 710                | 6 110 089      |
|                          | 20%                         | 16%                    | 20%            |
| 2                        | 5 689 922                   | 270 157                | 5 960 079      |
|                          | 19%                         | 18%                    | 19%            |
| 3                        | 5 742 704                   | 298 991                | 6 041 695      |
|                          | 19%                         | 19%                    | 19%            |
| 4                        | 5 687 095                   | 321 989                | 6 009 084      |
|                          | 19%                         | 21%                    | 19%            |
| 5 (more deprived)        | 5 350 544                   | 339 682                | 5 690 226      |
|                          | 18%                         | 22%                    | 18%            |
| Unknown                  | 1 202 158                   | 59 311                 | 1 261 469      |
|                          | 4%                          | 4%                     | 4%             |
| Region                   | 5 024 017                   | 220 396                | 5 244 413      |
|                          | 17%                         | 14%                    | 17%            |
|                          | 2 393 925                   | 150 197                | 2 544 122      |
|                          | 8%                          | 10%                    | 8%             |
|                          | 2 453 813                   | 172 154                | 2 625 967      |
|                          | 8%                          | 11%                    | 8%             |
|                          | 3 531 535                   | 166 886                | 3 698 421      |
|                          | 12%                         | 11%                    | 12%            |
|                          | 1 266 782                   | 70 052                 | 1 336 834      |
|                          | 4%                          | 5%                     | 4%             |
|                          | 1 168 066                   | 64 352                 | 1 232 418      |
|                          | 4%                          | 4%                     | 4%             |
|                          | 2 420 497                   | 121 946                | 2 542 443      |
|                          | 8%                          | 8%                     | 8%             |
|                          | 2 759 923                   | 135 684                | 2 895 607      |
|                          | 9%                          | 9%                     | 9%             |
|                          | 2 845 838                   | 150 977                | 2 996 815      |
|                          | 10%                         | 10%                    | 10%            |
|                          | 1 453 996                   | 86 128                 | 1 540 124      |
|                          | 5%                          | 6%                     | 5%             |
|                          | 1 699 068                   | 86 375                 | 1 785 443      |
|                          | 6%                          | 6%                     | 6%             |
|                          | 1 547 673                   | 72 602                 | 1 620 275      |
|                          | 5%                          | 5%                     | 5%             |
|                          | 120 091                     | 7118                   | 127 209        |
|                          | 0%                          | 0%                     | 0%             |
|                          | 186 608                     | 11 412                 | 198 020        |
|                          | 1%                          | 1%                     | 1%             |
|                          | 185 789                     | 7161                   | 192 950        |
|                          | 1%                          | 0%                     | 1%             |
|                          | 62 645                      | 1734                   | 64 379         |
|                          | 0%                          | 0%                     | 0%             |
|                          | 348 991                     | 15 278                 | 364 269        |
|                          | 1%                          | 1%                     | 1%             |
|                          | 32 191                      | 964                    | 33 155         |
|                          | 0%                          | 0%                     | 0%             |
|                          | 28 354                      | 1424                   | 29 778         |
|                          | 0%                          | 0%                     | 0%             |
and less often women (52% vs 55%). In total, 47,227 patients were hospitalized and 10,629 died or were intubated in the nontreated group. In the treated group, 5,573 were hospitalized and 1,804 died or were intubated.

Cox models adjusted for age and sex showed positive associations between low-dose aspirin and the risk of hospitalization (hazard ratio [HR], 1.33 [95% confidence interval (CI), 1.29-1.37]; see Table 2) or death/intubation (HR, 1.40 [95% CI, 1.33-1.47]). In fully adjusted models, the associations were close to null (HR, 1.03 [95% CI, 1.00-1.06]; and HR, 1.04 [95% CI, 0.98-1.10], respectively). We observed the same trends for people aged <70 years and for those with a history of cancer. Despite a stronger crude association between low-dose aspirin and the risk of COVID-19 among people aged <70 years, multivariable associations showed no association for hospitalization or death/intubation (HR, 1.05 [95% CI, 0.99-1.12] and HR, 0.95 [95% CI, 0.84-1.07], respectively). The results were very similar using models restricted to patients without a known chronic respiratory disease history. In models restricted to patients with diabetes, models adjusted for age and sex were already closer to a null association, with no substantial change in fully adjusted associations. These results do not support using aspirin for primary cardiovascular prevention in patients with diabetes to prevent severe COVID-19.15

Administrative health care databases help in the analysis of whether patients treated with a given drug had a lower probability to be infected or severely affected.12,16 The database does not guarantee that the subjects actually took the drug dispensed, but patients considered in the aspirin group had received at least three dispensations at different times, which reduces this drawback. Furthermore, little information is available on lifestyle, no information is available on ethnicity, and we know that other variables, such as obesity or smoking, are underestimated, which may result in residual confounding. However, we do not believe this strongly biased our results, especially after adjusting for the other variables, including a large number of chronic diseases and health conditions. Finally, it is difficult to disentangle the effect of low-dose aspirin from that of the disease for which it is used, but excluding people with a history of cardiovascular diseases likely limited the association between the risk of atherosclerotic cardiovascular disease and COVID-19. However, as a result, these results are not generalizable to the population with cardiovascular comorbidities.

To our knowledge, this study is the largest to date on the relationship between the use of aspirin for cardiovascular prevention and the risk of severe COVID-19 and the only one on a general comprehensive population. Our results are in accordance with those of the recent RECOVERY trial,5 which showed no effect of aspirin on 28-day mortality (rate ratio, 0.96 [95% CI, 0.89-1.04]). A meta-analysis of three studies reported by Salah and Mehta10 reported a risk ratio of 1.12 (95% CI, 0.84-1.50). Merzon et al16 also analyzed whether the use of aspirin for primary prevention of cardiovascular

| TABLE 1 (Continued) |
|----------------------|
| 29 529 802           |
| Without aspirin %    |
| 1 302 878            |
| 4                    |
| 73 773               |
| 5                    |
| 1 376 651            |
| 4                    |
| 553 845              |
| 2                    |
| 31 268               |
| 2                    |
| 585 113              |
| 2                    |
| 1 542 840            |
| With aspirin %       |
| 1 302 878            |
| 4                    |
| 73 773               |
| 5                    |
| 1 376 651            |
| 4                    |
| 553 845              |
| 2                    |
| 31 268               |
| 2                    |
| 585 113              |
| 2                    |
| 31 072 642           |
| All %                |
| 1 302 878            |
| 4                    |
| 73 773               |
| 5                    |
| 1 376 651            |
| 4                    |
| 553 845              |
| 2                    |
| 31 268               |
| 2                    |
| 585 113              |
| 2                    |
| **Lifestyle habits** |
| **Smoking disorders**|
| 1 302 878            |
| 4                    |
| 73 773               |
| 5                    |
| 1 376 651            |
| 4                    |
| 553 845              |
| 2                    |
| 31 268               |
| 2                    |
| 585 113              |
| 2                    |
| **Comedications and medical history** |
| **Obesity**          |
| 278 831              |
| 1                    |
| 14 895               |
| 1                    |
| 293 726              |
| 1                    |
| **Diabetes**         |
| 2 004 441            |
| 7                    |
| 587 924              |
| 38                   |
| 2 592 365            |
| 8                    |
| **Cancer (active)**  |
| 810 002              |
| 3                    |
| 82 353               |
| 5                    |
| 892 355              |
| 3                    |
| **Cancer (in remission)** |
| 1 193 233            |
| 4                    |
| 126 196              |
| 8                    |
| 1 319 429            |
| 4                    |
| **Lipid-lowering treatment** |
| 3 185 161            |
| 11                   |
| 870 493              |
| 56                   |
| 4 055 654            |
| 13                   |
| **Antihypertensive treatment** |
| 7 059 445            |
| 24                   |
| 1 155 141            |
| 75                   |
| 8 214 586            |
| 26                   |
| **Chronic respiratory diseases** |
| 1 647 193            |
| 6                    |
| 165 019              |
| 11                   |
| 1 812 212            |
| 6                    |
| **Chronic inflammatory disease** |
| 580 416              |
| 2                    |
| 43 670               |
| 3                    |
| 624 086              |
| 2                    |
| **Degenerative diseases** |
| 406 366              |
| 1                    |
| 83 636               |
| 5                    |
| 490 002              |
| 2                    |
| **Neurological diseases** |
| 342 106              |
| 1                    |
| 26 420               |
| 2                    |
| 368 526              |
| 1                    |
| **Psychological diseases** |
| 1 310 239            |
| 4                    |
| 88 309               |
| 6                    |
| 1 398 548            |
| 5                    |
| **Hypnotic, neuroleptic, anxiolytic treatments** |
| 3 503 424            |
| 12                   |
| 362 392              |
| 23                   |
| 3 865 816            |
| 12                   |
| **HIV**              |
| 100 725              |
| 0                    |
| 4650                 |
| 0                    |
| 105 375              |
| 0                    |
| **Hepatic or pancreatic diseases** |
| 322 138              |
| 1                    |
| 29 555               |
| 2                    |
| 351 693              |
| 1                    |
| **Chronic renal failure** |
| 32 143               |
| 0                    |
| 9000                 |
| 1                    |
| 41 143               |
| 0                    |
| **Rare diseases**     |
| 88 081               |
| 0                    |
| 7302                 |
| 0                    |
| 95 383               |
| 0                    |
disease was associated with COVID-19 and showed an association with a lower likelihood of COVID-19 relative to nonusers, with an adjusted odds ratio of 0.71 (95% CI, 0.52–0.99), in a population restricted to tested patients only. Restriction to the tested population only may have been a source of bias if aspirin users did not have the same probability of being tested.

Several medications have shown disappointing results once studied in the overall population, despite initial conclusive studies carried out on hospitalized patients. Negative associations between drug use and COVID-19 mortality in hospitalized populations have been shown to possibly occur through a collider bias effect, leading to spurious associations. This can occur when the probability to be hospitalized with COVID-19 is different between treated and untreated populations when the risk of death is the outcome. A similar mechanism can occur when studying the risk of hospitalization in patients testing positive for COVID-19, especially when the test could itself be dependent on the severity of the COVID-19, again, if the probability of being tested positive is different by treatment group.

In conclusion, we did not identify low-dose aspirin as a possible candidate to prevent severe COVID-19 in a general population of more than 30 million people. To determine whether aspirin in secondary cardiovascular prevention could have a preventive effect would require a specific study.

**AUTHOR CONTRIBUTIONS**

JB and LS contributed equally to this work, performing the analyses and preparing the first draft. JD and OSL suggested this study and provided the hypotheses. RDS, AW, and MZ supervised the work, especially the design of the study and the statistical analyses. All the authors read the manuscript, made comments, suggested modifications, and approved the final version.

**RELATIONSHIP DISCLOSURE**

The authors declare no conflicts of interest.

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**TABLE 2** Associations between low-dose aspirin in the previous 6 months and the risk of hospitalization or intubation/death for COVID-19 for patients aged ≥40 without known cardiovascular comorbidities and in specific populations

| Population | Hospitalization for COVID-19 | Intubation or death for COVID-19 |
|------------|-----------------------------|----------------------------------|
|            | No aspirin | Aspirin, HR (95% CI) | No aspirin | Aspirin, HR (95% CI) |
| Whole population | 47 227 /29 529,802 | 5573 /1 542 840 | 10 629 /29 529 802 | 1804 /1 542 840 |
| No. of events/no. of individuals at risk | 1 | 1.33 (1.29–1.37) | 1 | 1.40 (1.33–1.47) |
| Adjustment for age and sex | 1 | 1.03 (1.00–1.06) | 1 | 1.04 (0.98–1.10) |
| Fully adjusted model a | | | | |
| People aged <70 y | 36 974 /26 099 624 | 3944 /1 201 609 | 7860 /26 099 624 | 1257 /1 201 609 |
| No. of events/no. of individuals at risk | 1 | 1.35 (1.31–1.40) | 1 | 1.44 (1.35–1.53) |
| Adjustment for age and sex | 1 | 1.04 (1.00–1.08) | 1 | 1.03 (0.96–1.10) |
| Fully adjusted model a | | | | |
| Population without history of chronic respiratory disease | 36 974 /26 099 624 | 3944 /1 201 609 | 7860 /26 099 624 | 1257 /1 201 609 |
| No. of events/no. of individuals at risk | 1 | 1.07 (1.02–1.12) | 1 | 1.10 (1.01–1.20) |
| Adjustment for age and sex | 1 | 1.06 (1.01–1.12) | 1 | 1.07 (0.98–1.17) |
| Fully adjusted model a | | | | |
| Patients identified with diabetes | 6616 /1 799 211 | 2235 /518 809 | 1925 /1 799 211 | 739 /518 809 |
| No. of events/no. of individuals at risk | 1 | 1.17 (1.13–1.22) | 1 | 1.22 (1.14–1.31) |
| Adjustment for age and sex | 1 | 1.02 (0.98–1.07) | 1 | 1.07 (1.00–1.15) |
| Fully adjusted model a | | | | |
| Population with history of cancer | 9560 /2 396 191 | 3100 /503 993 | 3139 /2 396 191 | 1164 /503 993 |
| No. of events/no. of individuals at risk | 1 | 1.17 (1.13–1.22) | 1 | 1.22 (1.14–1.31) |
| Adjustment for age and sex | 1 | 1.02 (0.98–1.07) | 1 | 1.07 (1.00–1.15) |
| Fully adjusted model a | | | | |

Note: Hazard ratio (HR) and 95% confidence intervals (CI) of Cox models adjusted either for age and sex only or fully adjusted.

aAdjustment for age, sex, region of residence, deprivation index, known pathologies in 2019 (ie, diabetes, chronic respiratory disease, hepatic or pancreatic diseases, chronic renal failure, chronic inflammatory diseases, psychological or neurodegenerative diseases, rare diseases, cancers) and most-prescribed drugs (ie, antihypertensive drugs, lipid-lowering drugs, antidepressants, hypnotics, neuroleptics, anxiolytics), when applicable.
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