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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

Jérémie Botton and Laura Semenzato contributed equally to this work.

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.

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 antiplatelet agent, its early use by patients with COVID-19 was expected to reduce the risk of aggravation and the incidence of cardiovascular complications[1] and mortality,[2] although with inconsistencies.[3] 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."[4] 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.[5] Other studies have tended to observe a benefit in preventing the likelihood of SARS-CoV-2 infection, disease duration, or mortality.[6-9] Conversely, two meta-analyses suggested no association between the use of aspirin and mortality among patients with COVID-19, one for 1000 hospitalized patients[10] and the other for 6000 patients infected with COVID-19.[11]

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.

2 | METHODS

We selected patients from the French national health data system,[12] which covers the entire French population with any health care in the previous year (ie, 66 million people). We excluded twins and foreigners due to identification issues. We identified a history of comorbidities[13] 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 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.

Based on the mapping of diseases and expenditures in 2019,[13] we identified diabetes, cancers, chronic respiratory diseases, hepatic or pancreatic diseases, chronic renal failure, chronic inflammatory diseases, psychological or neurodegenerative diseases, rare diseases, and the most-prescribed drugs (ie, antihypertensive drugs, lipid-lowering drugs, antidepressants, hypnotics, neuroleptics, anxiolytics) as potential confounders or risk factors.

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.[12]

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 still hospitalized on 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.[14]

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

(Continues)

TABLE 1 (Continued)

	29 529 802		1 542 840		31 072 642	
	Without aspirin	%	With aspirin	%	All	%
Lifestyle habits						
Smoking disorders	1 302 878	4	73 773	5	1 376 651	4
Alcohol disorders	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

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, 5573 were hospitalized and 1804 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 Mehta[10] reported a risk ratio of 1.12 (95% CI, 0.84-1.50). Merzon et al[6] also analyzed whether the use of aspirin for primary prevention of cardiovascular

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

	Hospitalization for COVID-19		Intubation or death for COVID-19	
Population	**No aspirin**	**Aspirin, HR (95% CI)**	**No aspirin**	**Aspirin, HR (95% CI)**
Whole population				
No. of events/no. of individuals at risk	47 227/29 529,802	5573/1 542 840	10 629/29 529 802	1804/1 542 840
Adjustment for age and sex	1	1.33 (1.29-1.37)	1	1.40 (1.33-1.47)
Fully adjusted model[a]	1	1.03 (1.00-1.06)	1	1.04 (0.98-1.10)
People aged <70 y				
No. of events/no. of individuals at risk	26 406/22 078 928	1283/492 705	4516/22 078 928	1124/492 705
Adjustment for age and sex	1	1.76 (1.67-1.87)	1	2.01 (1.80-2.25)
Fully adjusted model[a]	1	1.05 (0.99-1.12)	1	0.95 (0.84-1.07)
Population without history of chronic respiratory disease				
No. of events/no. of individuals at risk	36 974/26 099 624	3944/1 201 609	7860/26 099 624	1257/1 201 609
Adjustment for age and sex	1	1.35 (1.31-1.40)	1	1.44 (1.35-1.53)
Fully adjusted model[a]	1	1.04 (1.00-1.08)	1	1.03 (0.96-1.10)
Patients identified with diabetes				
No. of events/no. of individuals at risk	6616/1 799 211	2235/518 809	1925/1 799 211	739/518 809
Adjustment for age and sex	1	1.07 (1.02-1.12)	1	1.10 (1.01-1.20)
Fully adjusted model[a]	1	1.06 (1.01-1.12)	1	1.07 (0.98-1.17)
Population with history of cancer				
No. of events/no. of individuals at risk	9560/2 396 191	3100/503 993	3139/2 396 191	1164/503 993
Adjustment for age and sex	1	1.17 (1.13-1.22)	1	1.22 (1.14-1.31)
Fully adjusted model[a]	1	1.02 (0.98-1.07)	1	1.07 (1.00-1.15)

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

[a]Adjustment 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.

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.[17] 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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