Characteristics associated with the residual risk of severe COVID-19 after a complete vaccination schedule: A cohort study of 28 million people in France

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Summary

Background Prior to the availability of vaccines, the risk factors for developing severe forms of COVID-19 were mostly older age and various comorbidities such as diabetes, cardiovascular diseases, mental disorders, transplantations, and kidney disease. Although vaccines have been shown to be highly effective in preventing severe forms of COVID-19, a residual risk may persist, despite vaccination, for certain population groups.

Methods The study was based on data from the national COVID-19 vaccination database (VAC-SI) coupled with the National Health Data System (SNDS), which contains comprehensive reimbursement and hospitalisation data for all of France. All people fully vaccinated by July 31, 2021, with a double-injection vaccine, i.e., the mRNA BNT162b2, mRNA-1273, or ChAdOx1 nCoV-19 vaccines, or a single dose for people with a previous confirmed SARS-CoV-2 infection were included and followed until August 31, 2021. Cox proportional hazard models were performed to estimate adjusted hazard ratios (aHR) for COVID-19-related hospitalisation or in-hospital death associated with age, gender, deprivation index, comorbidities, and immunosuppressive or oral corticosteroid therapy from day 14 after full-vaccination.

Findings In a population of 28,031,641 fully vaccinated individuals with an average follow-up of 80 days, 5,345 (87 hospitalisations per 100,000 person-years) were hospitalised for COVID-19 and 996 (16 in-hospital death per 100,000 person-years) died in hospital. In multivariable analysis, a higher risk was observed with increasing age, male gender, and social deprivation. Most of the 47 chronic conditions considered were positively associated with an increased risk of COVID-19-related hospitalisation and a slight excess risk of death. The risk of hospitalisation and in-hospital death for COVID-19 also increased with the use of immunosuppressants (aHR 3.3 [2.8-3.8] and 2.4 [1.7-3.5], respectively) and oral corticosteroids (aHR 2.8 [2.5-3.1] and 4.1 [3.3-5.1]).

Less than 10% (519/5,345) of hospitalised cases and 2% (24/996) of those who died in hospital had no identified comorbidities. There was a strong association between an increasing number of comorbidities and the risk of hospitalisation and in-hospital death (e.g., 5+ versus none, aHR 10.1 95%CI 9.0-11.5 and 17.8 95%CI 11.5-27.4, respectively).

Interpretation Although vaccination has dramatically reduced the occurrence of severe forms of COVID-19, a residual risk remains for the elderly, immunocompromised, and polypathological populations and warrants complementary preventive measures.

Funding None.

Keywords: Vaccination; COVID-19; Hospitalisation; Death; Medical factors; Organ transplant; Immunosuppressive treatments; Oral corticosteroids; Sociodemographic factors; SNDS; PMSI

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Research in context

Evidence before this study

We searched Pubmed for articles written in English using the keywords (COVID-19 vaccine AND risk factors of severe COVID-19 AND immunocompromised), limited to "human" studies and that had been brought up to date on February 25, 2022. We selected articles that included risk factors against severe COVID-19 outcomes after completing the full vaccination schedule. We identified eight articles responding to our criteria: four reported general risk factors of COVID-19 among fully vaccinated individuals and the four others focused on immunocompromised patients. These studies were generally underpowered and focused on a limited number of comorbidities.

Added value of this study

The present cohort study, based on nationwide population-based data in France, included more than 28 million fully vaccinated individuals aged 12 years or older. This is the largest worldwide study, to date, to analyze associations between the residual risk of Covid-19 hospitalization or in-hospital death despite vaccination and 47 chronic conditions among the comprehensive French population vaccinated by July 2021.

In a population of 28,031,641 fully vaccinated individuals with an average follow-up of 80 days, 5,345 (87 hospitalisations per 100,000 person-years) were hospitalized for COVID-19 and, among them, 996 (16 in-hospital death per 100,000 person-years) died in hospital. Most of the chronic conditions were positively associated with an increased risk of COVID-19-related hospitalization and death. The risk of hospitalization and in-hospital death for COVID-19 also increased with use of immunosuppressants and oral corticosteroids and were strongly associated with an increasing number of comorbidities.

Implications of all the available evidence

Although vaccination has dramatically reduced the occurrence of severe COVID-19, our findings highlight the remaining residual risk concentrated among the elderly, immunocompromised, and polypathological populations that require complementary preventive measures.

Introduction

Prior to mass vaccination, the risk factors for severe COVID-19 were age, male gender, social deprivation, and chronic conditions, such as cardiovascular disease, diabetes, chronic respiratory diseases, obesity, a recent history of haematological malignancy or other cancers, liver, neurological or autoimmune diseases, and, most importantly, kidney diseases, mental retardation, and organ transplantation.[1–4]

The COVID-19 vaccination campaign began in France on December 27, 2020, first with two messenger RNA (mRNA) vaccines, mRNA BNT162b2 vaccine (by Pfizer-BioNTech©) and mRNA-1273 vaccine (by Moderna©), then with adenovirus ChAdOx1 nCoV-19 vaccine (by Oxford-AstraZeneca©) in February 2021 and lastly with Ad26.COV2.S vaccine (Janssen©) in April 2021. There were differences in the target populations between vaccines and prioritisation over time: vaccines went first to healthcare workers, individuals living in nursing homes, those aged 75 years or older, and those with severe or multiple chronic conditions and were then extended in mid-April to all people aged 55 and over, in mid-May to all adults, and in mid-June to adolescents aged 12 and over.[5] In France, strong viral circulation persisted during the first three months of 2021 after a second epidemic wave at the end of 2020. Two other epidemic peaks occurred: between March and April 2021, a period characterized by high circulation of the Alpha variant of SARS-CoV-2, and between mid-July and mid-October 2021, a period characterized by high circulation of the Delta variant of SARS-CoV-2.

Vaccination has greatly reduced the risk of developing severe forms of COVID-19, resulting in a reduction in the risk of hospitalisation by 90% and the risk of death by more than 85%.[6–12] This has led to a majority of unvaccinated individuals among hospitalised and deceased patients: at the end of July 2021, admissions for critical care in France were 12 times lower within the fully vaccinated population than among unvaccinated individuals.[11–13]

However, a residual risk of severe COVID-19 remains, despite vaccination. A small number of studies have analysed the risk factors for severe COVID-19 among vaccinated patients.[14,15] However, due to the effectiveness of the vaccination, they were generally underpowered and focused on a limited number of comorbidities.

This study aimed to identify sociodemographic and medical characteristics associated with an excess risk of COVID-19-related hospitalisations or deaths in the entire French population with a complete vaccination schedule (without booster) by August 31, 2021.

Methods

Data sources

We conducted a cohort study using the National Health Data System (SNDS), which covers the entire French population, i.e., 67 million inhabitants, and which has been extensively used in France to conduct pharmacoepidemiology studies.[16–19]

Since 2006, an anonymous individual identifier has linked data derived from the two main SNDS databases: the DCIR (*Datamart de Consommation Inter-Regimes*, the national health insurance reimbursement database) and

the PMSI (*Programme de Médicalisation des Systèmes d'Information*, the national hospital database).

The DCIR includes individual data concerning reimbursements for outpatient medical care, laboratory tests, and prescribed drugs, coded according to the Anatomical Therapeutic Chemical (ATC) classification. Health expenditures for people with long-term diseases (LTDs), such as cancer, diabetes, or organ transplant, are fully covered financially and their diagnoses are registered according to the International Classification of Diseases, 10th Revision (ICD-10).

The PMSI indicates the dates of admission and discharge for all public or private hospital stays in France. Medical diagnoses are coded according to the ICD-10 classification and the main medical or surgical procedures are coded according to the *Classification Commune des Actes Médicaux* (CCAM - medical professional procedures).

The COVID-19 vaccination status (vaccine products, dates of first and second injections) was determined from the French national information system on COVID-19 vaccination (VAC-SI) database. Information on SARS-CoV-2 infection (based on a positive reverse transcription polymerase chain reaction [rtPCR] or antigen test) was derived from the French national information system on SARS-CoV-2 testing (SI-DEP) database.

People aged 12 years or over with at least one healthcare reimbursement in 2020 and a completed vaccination schedule for at least 14 days (index date) as of July 31, 2021, were identified from the SNDS and included. In accordance with the French official recommendations during the study period, the vaccination schedule was considered to be complete after two injections or after a single injection for people with a confirmed previous diagnosis of SARS-CoV-2 infection.[20,21] The Ad26.COV2.S authorized vaccine, representing one million individuals over the study period and administered in one injection, was not considered. Twins and foreign residents were excluded due to identification and follow-up difficulties. The study flow chart is presented in Figure 1.

Sociodemographic characteristics and chronic diseases

Sociodemographic variables included age, gender, and the region of residence. To calculate estimates on a sufficient number of subjects in each age subgroup, age was categorized as follows: 12-34/35-44/45-54 years/five-year age-groups for those aged 55 years or over. We considered the social deprivation index as an estimation of socioeconomic status. This indicator, at the level of the city of residence, has been extensively used[4,11,12,19] and is based on the median household income, percentage of high school graduates in the population over the age of 15, percentage of manual workers in the labour force, and unemployment rate.[22]

We defined comorbidities using the *Cartographie des Pathologies et des Dépenses* (mapping of diseases and expenditures), a tool developed from the DCIR and PMSI databases that allows the identification of diseases in a given year by means of medical algorithms[23] based on the reasons for hospitalisation, LTD diagnoses, and/or reimbursement of specific treatments for certain diseases in the previous four years. The detailed definition of these disease identification algorithms is publicly available in French (https://assurance-maladie.ameli.fr/sites/default/files/2020_methode-reperage-pathologies_cartographie.pdf). The mapping of diseases and expenditures allowed the identification of patients presenting with 41 of these comorbidities in 2020 and was completed by the identification of obese patients, people with Down syndrome, people with psoriasis, heart, lung, or liver transplant recipients, smokers, people with alcohol or opioid-use disorders, and patients treated with immunosuppressants or oral corticosteroids. The main characteristics of these algorithms are presented in Supplementary Material Table S1. Thus, the 47 chronic diseases considered were cardiometabolic diseases, such as obesity, diabetes, hypertension, dyslipidaemia and/or lipid-lowering drug treatment, cardiovascular diseases (stroke and its sequelae, heart failure, coronary heart disease, cardiac arrhythmias or conduction disorders, valvular heart disease, peripheral artery disease), chronic respiratory diseases (excluding cystic fibrosis), pulmonary embolism, female breast, lung, prostate, colorectal, and other cancers, distinguishing active cancers from cancers under surveillance or in remission, inflammatory diseases or skin diseases (chronic inflammatory bowel disease [IBD], rheumatoid arthritis, ankylosing spondylitis and related diseases, psoriasis), mental and behavioural disorders, neurodegenerative diseases, Down syndrome, haemophilia, HIV infection, liver disease, severe chronic kidney disease, and heart, lung, and liver transplantation.

Immunosuppressive treatment was identified by at least two dispensations of an immunosuppressive drug in the past three months prior to vaccination and oral corticosteroid use by at least four dispensations of these drugs in the six months prior to vaccination (Table S1).

Endpoints

Based on information from hospital discharge data as of 31 August 2021, two endpoints were considered. The primary endpoint was COVID-19-related hospitalisation, with a date of hospital admission between the 14th day after complete vaccination and August 31, 2021. The secondary endpoint was death during COVID-19-related hospitalisation. Individuals were censored at the occurrence of the outcome of interest, administration of a booster dose, death (excluding in-hospital COVID-19-related death) or until the end of the study on August 31, 2021. We focused our analysis on patients requiring admission specifically for SARS-CoV-2 infection; we did not consider patients hospitalised for another cause

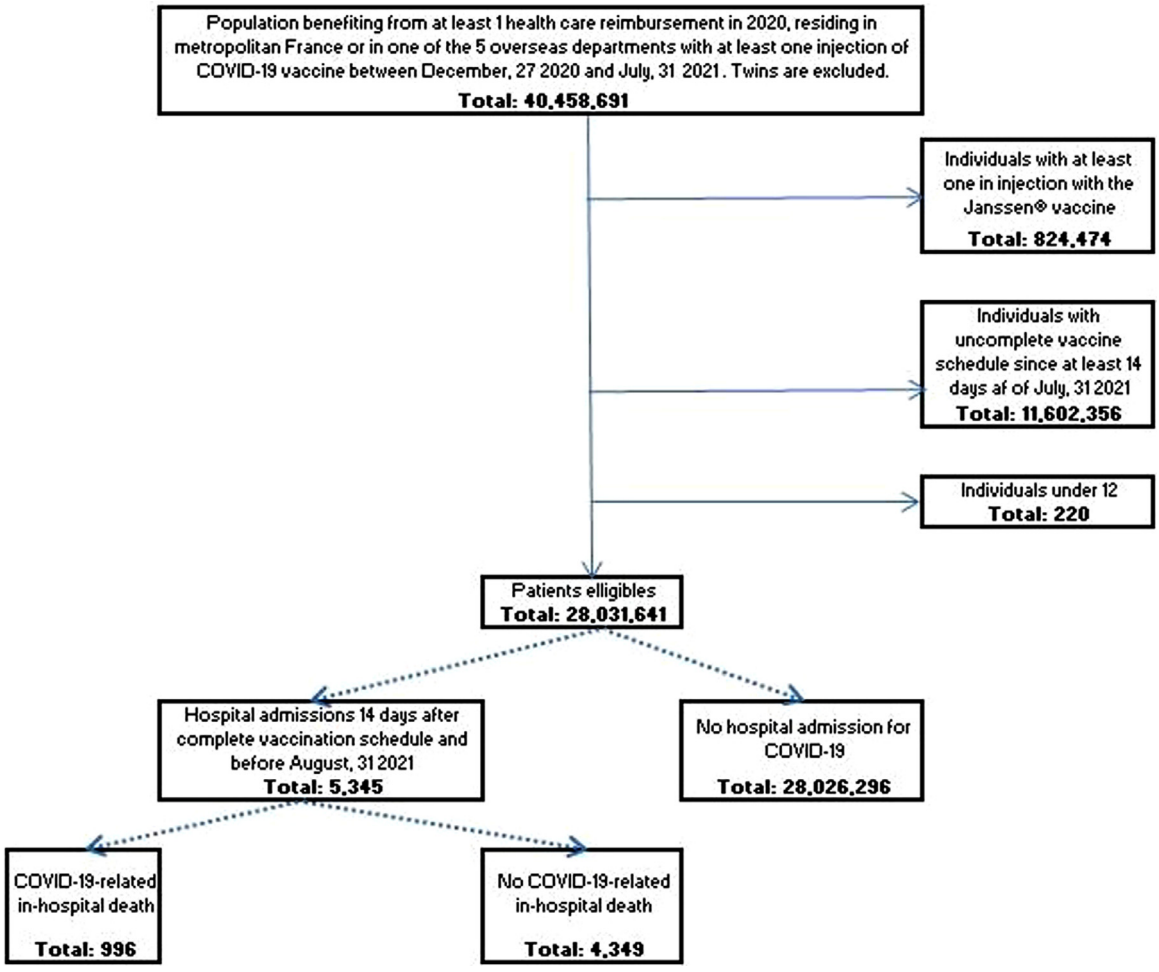


Figure 1. Flow-chart.

even if SARS-COV-2 infection was recorded during hospital stay. Deaths were identified from civil registry records and hospital notifications. Overall, 93.2% of all deaths were identified in both data records, whereas 6.8% of deaths were only notified by the hospitals at the time of the analysis.

Statistical analysis

Cox proportional hazards models were used to estimate the association between each comorbidity and the risk of COVID-19-related hospitalisation or death. These associations were determined after an initial adjustment for age and gender and then with multivariable adjustment including all variables indicated above (except immunosuppressive or oral corticosteroid treatment) and the vaccine product administered. Adjustment for immunosuppressive or oral corticosteroid treatment was performed in an additional step. We also investigated the association between outcomes and the number of comorbidities among the 47 considered, defined as a categorical variable, ranging from 0 to 5 or more. Complementary analyses stratified by age (12-54/55-74/75 years and older) were also performed (Table S2). We ran the model dividing the period into two sub-periods, to assess the consistency of the associations over time: first, individuals fully vaccinated until June, 2021 and followed until this date; second, individuals not censored before July 1, 2021 and followed until August 31, 2021 (Table S3). Supplementary analyses were also performed among patients without any comorbidity (Table S4). All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc.).

Regulatory approval and ethical aspects

The National Health Data System (SNDS) is a set of strictly anonymous databases comprising all mandatory national health insurance reimbursement data, particularly data derived from the processing of healthcare claims (electronic or paper claims) and data from healthcare facilities (PMSI).

EPI-PHARE has direct access to the SNDS from the permanent regulatory access of its constitutive bodies, the French National Agency for the Safety of Medicines and Health Products and the French National Health Insurance. This permanent access is given according French Decree No. 2016-1871 of December 26, 2016 relating to the processing of personal data called the "National Health Data System"[24] and French law articles Art. R. 1461-13[25] and 14.[26] This study was declared prior to its initiation on the EPI-PHARE registry of studies requiring the use of the SNDS.

Role of the funding source

None.

Results

In total, 28,031,641 individuals had a complete vaccination schedule for at least 14 days as of July 31, 2021, i.e., nearly half of the French population aged at least 12 years eligible for vaccination at this date. The average follow-up time was 80 days (median of 67 days, interquartile range (IQR) 48-105 days). The cohort is described in Table 1. Among vaccinated individuals, 5345 (87 hospitalisations per 100,000 person-years) experienced a COVID-19-related hospitalisation, of whom 996 (16 in-hospital death per 100,000 person-years) died in hospital. The median age was 59 years (IQR 42 -72) for the entire cohort, 79 years (IQR 67-87) for hospitalised patients, and 86 years (IQR 78 à 91) for deceased patients.

Associations between sociodemographic factors or chronic diseases and the risk of COVID-19-related hospitalisation or in-hospital mortality are presented in Table 2 and Figure 2a and b. After adjustment, the risk of COVID-19-related hospitalisation gradually increased with age, reaching a four-fold higher risk in the 85- to 89-year age-group (aHR 4.0 95% CI 3.5-4.7) relative to the 45 to 54-year age-group. The risk of in-hospital death was also strongly associated with age. The risk of in-hospital death was two-fold higher in the 55- to 64-year age-group (aHR 2.3 95% CI 1.1-4.8) than the 45- to 54-year age-group and reached a 38-fold increased risk in the 85- to 89-year age-group (aHR 38.0 95% CI 19.2-75.2).

Men were at a higher risk of COVID-19-related hospitalisation (aHR 1.6; 95%CI 1.5-1.7) and in-hospital mortality (aHR 2.0; 95%CI 1.7-2.3) than women.

Overall, 17% of vaccinated individuals lived in one of the most deprived areas (fifth quintile), whereas 22% lived in one of the least deprived areas (first quintile). These figures were of 21% and 23% for hospitalised patients, respectively. Vaccinated individuals who lived in one of the most deprived areas had an approximately 30% higher risk of hospitalisation than those who lived in one of the least deprived areas (aHR of 1.3 [95% CI 1.2 -1.4]) while aHR were not significant for the other deprivation quintiles. The risk of in-hospital death consistently increased with the deprivation index, reaching a risk of 1.5 (CI 95% 1.2-1.9) for people living in one of the most deprived areas.

In multivariable analysis, most of the 47 chronic conditions were positively associated with a risk of COVID-19-related hospitalisation and in-hospital mortality, with the exception of dyslipidaemia, which was negatively associated (aHR 0.9 [95% CI 0.8-0.9] and aHR 0.8 [95% CI 0.7-0.9] respectively). Dyslipidaemia was positively associated with the risk of COVID-19-related hospitalisation when adjusting for age and sex only (HR 1.2 [95% CI 1.1-1.3]) and negatively associated in fully adjusted model (aHR 0.9 [95% CI 0.8-0.9]). The association was reversed by adjusting for cardiovascular comorbidities (table S5). Obesity (aHR 1.6; 95% CI 1.4-1.9), hypertension (aHR 1.2; 95% CI 1.1-1.3), cardiovascular diseases, including heart failure (aHR 1.7; 95% CI 1.5-1.8), non-cystic fibrosis chronic respiratory diseases (aHR 2.0; 95% CI 1.9-2.1), cystic fibrosis (aHR 6.3; 95% CI 3.4-11.7), active lung cancer (aHR 3.5; 95% CI 2.7-4.4), neurodegenerative diseases, mental disability (aHR 3.6; CI 95% 2.5-5.0), Down Syndrome (aHR 4.0; 95% CI 2.1-7.3), end stage renal disease treated with dialysis (aHR 7.0; 95% CI 5.9-8.2), kidney transplantation (aHR 32.1; 95% CI 28.0-36.9), and lung transplantation (aHR 13.7; 95% CI 8.1-23.2) were associated with an increased risk of COVID-19-related hospitalisation. Heart failure (aHR 2.0; 95% CI 1.7-2.4), end-stage chronic renal failure treated with dialysis (aHR 8.6; 95% CI 6.3-11.7), active lung cancer (aHR 6.5; 95% CI 4.2-10.0), and other active cancers (aHR 4.1; 95% CI 3.5-4.9) were associated with an increased risk of in-hospital death. Diabetic patients were at a higher risk of COVID-19-related hospitalisation and in-hospital death (aHR 2.1 [95% CI 1.9-2.3] and 2.2 [95% CI 1.8-2.8] for insulin-treated patients, respectively, and 1.5 [95% CI 1.4-1.6] and 1.3 [95% CI 1.1-1.5] for non-insulin-treated patients, respectively).

Patients treated with immunosuppressants or oral corticosteroids had an increased risk of hospitalisation (aHR 3.3 [95% CI 2.8-3.8] and aHR 2.8 [95% CI 2.5-3.1], respectively) and in-hospital death (aHR 2.4 [95% CI 1.7-3.5] and aHR 4.1 [95% CI 3.3-5.1], respectively). Taking these treatments into account led to a significant decrease in the magnitude of the associations between the risk of developing a severe form of COVID-19 and certain comorbidities, especially organ transplants and inflammatory diseases (Table 3).

Kidney transplant patients had a 32-fold higher risk of COVID-19-related hospitalisation in multivariable analysis before adjustment for immunosuppressive and oral corticosteroid treatment (aHR 32.1 95% CI 28.0-36.9) and a six-fold higher risk in multivariable analysis after adjustment for these treatments (aHR 5.9 95% CI 4.8-7.1). They had a 34-fold excess risk of in-hospital death in multivariable analysis before adjustment for

	Number of individuals		Number of COVID-19-related hospitalisations		Number of COVID-19-related in-hospital death	
	28,031,641	% per category	5,345	% hospitalisation	996	% death
Sociodemographic characteristics						
Age (year) - mean (std)	57 (19)		75 (16)		84 (10)	
Age						
12−34	4,054,333	14.5%	137	2.6%	1	0.1%
35−44	3,296,014	11.8%	193	3.6%	1	0.1%
45−54	4,493,286	16.0%	282	5.3%	9	0.9%
55−64	5,245,162	18.7%	560	10.5%	32	3.2%
65−69	2,742,007	9.8%	398	7.4%	40	4.0%
70−74	2,843,089	10.1%	545	10.2%	75	7.5%
75−79	2,037,745	7.3%	677	12.7%	125	12.6%
80−84	1,460,767	5.2%	738	13.8%	171	17.2%
85−89	1,097,507	3.9%	879	16.4%	241	24.2%
90−110	761,731	2.7%	936	17.5%	301	30.2%
Sex						
Male	12,824,911	45.8%	3,023	56.6%	590	59.2%
Female	15,206,730	54.2%	2,322	43.4%	406	40.8%
Regions						
Ile de France	5,035,147	18.0%	1,113	20.8%	215	21.6%
Grand Est	2,381,850	8.5%	342	6.4%	70	7.0%
Hauts-de-France	2,556,555	9.1%	459	8.6%	86	8.6%
Auvergne-Rhône-Alpes	3,402,553	12.1%	547	10.2%	89	8.9%
Bourgogne-Franche-Comté	1,169,044	4.2%	181	3.4%	42	4.2%
Centre-Val-de-Loire	1,129,706	4.0%	142	2.7%	26	2.6%
Provence-Alpes-Côte d'Azur	2,067,769	7.4%	972	18.2%	130	13.1%
Occitanie	2,507,955	8.9%	518	9.7%	103	10.3%
Nouvelle-Aquitaine	2,698,926	9.6%	341	6.4%	78	7.8%
Normandie	1,467,749	5.2%	252	4.7%	59	5.9%
Pays de la Loire	1,647,232	5.9%	204	3.8%	41	4.1%
Bretagne	1,484,755	5.3%	131	2.5%	28	2.8%
Corse	134,735	0.5%	41	0.8%	8	0.8%
Guadeloupe	49,243	0.2%	33	0.6%	7	0.7%
Martinique	44,384	0.2%	29	0.5%	5	0.5%
Guyana	29,250	0.1%	5	0.1%	2	0.2%
Reunion Island	204,618	0.7%	33	0.6%	7	0.7%
Mayotte	17,741	0.1%	2	0.0%		0.0%
Unknown	2,429	0.0%		0.0%		0.0%
Social deprivation index (quintiles)						
1 (the least deprived)	6,220,349	22.2%	1,223	22.9%	192	19.3%
2	5,565,683	19.9%	922	17.2%	176	17.7%
3	5,454,882	19.5%	998	18.7%	188	18.9%
4	5,258,723	18.8%	891	16.7%	188	18.9%
5 (the most deprived)	4,778,866	17.0%	1,129	21.1%	210	21.1%
Unknown	753,138	2.7%	182	3.4%	42	4.2%
Lifestyle habits						
Smoking	1,381,762	4.9%	330	6.2%	51	5.1%
Alcoholism	313,564	1.1%	97	1.8%	20	2.0%
Opioid addiction	44,544	0.2%	5	0.1%	1	0.1%
Complete vaccination schedule at inclusion						
Double injections of mRNA BNT162b2 vaccine	19,970,320	71.2%	4,262	79.7%	885	88.9%

Table 1 *(Continued)*

	Number of individuals		Number of COVID-19-related hospitalisations		Number of COVID-19-related in-hospital death	
	28,031,641	% per category	5,345	% hospitalisation	996	% death
Double injections of ChAdOx1 nCoV-19 vaccine	3,087,012	11.0%	416	7.8%	35	3.5%
Double injections of mRNA-1273 vaccine	2,391,921	8.5%	234	4.4%	38	3.8%
One injection of mRNA BNT162b2 vaccine	1,598,411	5.7%	300	5.6%	33	3.3%
Double injections of ChAdOx1 nCoV-19 and mRNA BNT162b2 vaccines	510,134	1.8%	24	0.4%	1	0.1%
One injection of mRNA-1273 vaccine	204,370	0.7%	33	0.6%	2	0.2%
Double injections of ChAdOx1 nCoV-19 vaccine and mRNA-1273 vaccines	126,259	0.5%	9	0.2%		0.0%
One injection of ChAdOx1 nCoV-19 vaccine	114,799	0.4%	65	1.2%	2	0.2%
Double injections of mRNA-1273 and mRNA BNT162b2 vaccines	21,757	0.1%	1	0.0%		0.0%
Double injections of mRNA BNT162b2 and mRNA-1273 vaccines	6,658	0.0%	1	0.0%		0.0%
Comorbidities						
Immunosuppressive treatments						
Immunosuppressant	320,536	1.1%	507	9.5%	80	8.0%
Oral corticosteroids	285,628	1.0%	592	11.1%	146	14.7%
Cardiometabolics						
Obesity	489,064	1.7%	165	3.1%	21	2.1%
Diabetes	2,655,580	9.5%	1,465	27.4%	284	28.5%
Non-insulin-treated	2,089,135	7.5%	925	17.3%	160	16.1%
Insulin-treated	566,445	2.0%	540	10.1%	124	12.4%
Dyslipidaemia and lipid-lowering treatments	5,145,663	18.4%	1,869	35.0%	361	36.2%
Hereditary metabolic diseases or amyloidosis	66,061	0.2%	33	0.6%	5	0.5%
Hypertension	8,691,380	31.0%	3,451	64.6%	746	74.9%
Coronary diseases	1,449,141	5.2%	999	18.7%	245	24.6%
Obliterating arterial disease of the lower limb	438,192	1.6%	355	6.6%	86	8.6%
Cardiac rhythm or conduction disturbances	1,613,709	5.8%	1,519	28.4%	428	43.0%
Heart failure	451,596	1.6%	767	14.3%	237	23.8%
Valvular diseases	454,099	1.6%	441	8.3%	147	14.8%
Stroke	575,427	2.1%	433	8.1%	108	10.8%
Pulmonary embolism	101,328	0.4%	91	1.7%	21	2.1%
Respiratory diseases						
Chronic respiratory diseases (excluding cystic fibrosis)	1,889,996	6.7%	1,180	22.1%	238	23.9%
Cystic fibrosis	4,296	0.0%	13	0.2%	1	0.1%
Cancer						
Female breast cancer (active)	152,528	0.5%	55	1.0%	14	1.4%
Female breast cancer (under surveillance)	352,983	1.3%	103	1.9%	15	1.5%

Table 1 *(Continued)*

	Number of individuals		Number of COVID-19-related hospitalisations		Number of COVID-19-related in-hospital death	
	28,031,641	% per category	5,345	% hospitalisation	996	% death
Colorectal cancer (active)	85,592	0.3%	59	1.1%	11	1.1%
Colorectal cancer (under surveillance)	158,605	0.6%	109	2.0%	17	1.7%
Lung cancer (active)	48,208	0.2%	70	1.3%	22	2.2%
Lung cancer (under surveillance)	38,524	0.1%	39	0.7%	13	1.3%
Prostate cancer (active)	149,648	0.5%	76	1.4%	15	1.5%
Prostate cancer (under surveillance)	242,499	0.9%	140	2.6%	39	3.9%
Other cancers (active)	501,251	1.8%	603	11.3%	174	17.5%
Other cancers (under surveillance)	638,718	2.3%	350	6.5%	83	8.3%
Inflammatory and skin diseases						
Chronic inflammatory bowel diseases	163,400	0.6%	41	0.8%	5	0.5%
Rheumatoid arthritis and related diseases	199,018	0.7%	138	2.6%	33	3.3%
Ankylosing spondylitis and related diseases	143,192	0.5%	58	1.1%	11	1.1%
Psoriasis	181,746	0.6%	56	1.0%	5	0.5%
Psychological and neurodegenerative diseases						
Neurotic and Mood Disorders, use of antidepressant treatments	2,711,777	9.7%	1,120	21.0%	256	25.7%
Psychotics disorders, use of neuroleptics treatments	381,370	1.4%	238	4.5%	41	4.1%
Psychiatric disorders starting in childhood	24,329	0.1%	8	0.1%		0.0%
Down syndrome	17,737	0.1%	10	0.2%	4	0.4%
Epilepsy	147,886	0.5%	96	1.8%	16	1.6%
Multiple sclerosis	67,310	0.2%	25	0.5%	2	0.2%
Paraplegia	51,372	0.2%	37	0.7%	6	0.6%
Myopathy or myasthenia gravis	27,544	0.1%	25	0.5%	8	0.8%
Parkinson disease	184,877	0.7%	155	2.9%	43	4.3%
Dementias (including Alzheimer's disease)	398,832	1.4%	574	10.7%	157	15.8%
Mental impairment	64,531	0.2%	35	0.7%	3	0.3%
Other pathologies						
Haemophilia or severe haemostasis disorders	29,407	0.1%	17	0.3%	4	0.4%
HIV infection	78,810	0.3%	23	0.4%	7	0.7%
Liver diseases	221,300	0.8%	184	3.4%	39	3.9%
Chronic dialysis	36,561	0.1%	155	2.9%	46	4.6%
Renal transplant	32,279	0.1%	259	4.8%	43	4.3%
Cardiac transplant	1,131	0.0%	7	0.1%	1	0.1%
Liver transplant	3,572	0.0%	10	0.2%	4	0.4%
Lung transplant	1,036	0.0%	18	0.3%	1	0.1%

***Table 1*: Description of the cohort: sample size, number of patients with a COVID-19 -related hospitalisation, and number of COVID-19-related in-hospital deaths among fully vaccinated individuals as of July 31, 2021.**

	Hospitalisations			In-hospital death		
	Number of events	HR adjusted for age and sex only	Fully adjusted model (without adjustment for immunosuppressive treatment)	Number of events	HR adjusted for age and sex only	Fully adjusted model (without adjustment for immunosuppressive treatment)
Sociodemographic characteristics						
Age						
12–34	137	0.67 (0.54 - 0.82)	0.79 (0.64 - 0.97)	1	0.15 (0.02 - 1.16)	0.17 (0.02 - 1.37)
35–44	193	1.05 (0.87 - 1.26)	1.14 (0.95 - 1.37)	1	0.17 (0.02 - 1.32)	0.18 (0.02 - 1.40)
45–54	282	1	1	9	1	1
55–64	560	1.47 (1.27 - 1.69)	1.16 (1.01 - 1.35)	32	2.69 (1.28 - 5.63)	2.28 (1.08 - 4.80)
65–69	398	1.93 (1.65 - 2.24)	1.38 (1.18 - 1.61)	40	6.26 (3.04 - 12.89)	4.78 (2.30 - 9.92)
70–74	545	2.23 (1.93 - 2.57)	1.57 (1.35 - 1.82)	75	10.24 (5.13 - 20.46)	7.56 (3.75 - 15.26)
75–79	677	2.76 (2.40 - 3.18)	1.94 (1.67 - 2.24)	125	18.27 (9.28 - 35.97)	12.55 (6.30 - 25.03)
80–84	738	4.06 (3.53 - 4.66)	2.67 (2.30 - 3.09)	171	34.22 (17.48 - 66.99)	21.49 (10.82 - 42.68)
85–89	879	6.68 (5.83 - 7.65)	4.02 (3.47 - 4.65)	241	67.39 (34.59 - 131.27)	37.96 (19.15 - 75.23)
90–110	936	10.48 (9.15 - 12.00)	5.86 (5.05 - 6.79)	301	127.64 (65.64 - 248.20)	65.28 (32.93 - 129.39)
Male sex	3023	1.89 (1.79 - 1.99)	1.61 (1.52 - 1.71)	590	2.39 (2.11 - 2.72)	1.97 (1.71 - 2.27)
Social deprivation index (quintiles)						
1 (the least deprived)	1223	1	1	192	1	1
2	922	0.81 (0.75 - 0.88)	0.95 (0.86 - 1.03)	176	0.96 (0.78 - 1.18)	1.25 (1.01 - 1.56)
3	998	0.83 (0.76 - 0.90)	0.95 (0.87 - 1.04)	188	0.93 (0.76 - 1.13)	1.28 (1.03 - 1.61)
4	891	0.74 (0.68 - 0.80)	0.98 (0.89 - 1.08)	188	0.90 (0.74 - 1.10)	1.33 (1.06 - 1.66)
5 (the most deprived)	1129	1.02 (0.94 - 1.11)	1.29 (1.17 - 1.41)	210	1.10 (0.90 - 1.33)	1.50 (1.20 - 1.87)
Unknown	182	1.77 (1.44 - 2.16)	0.94 (0.75 - 1.18)	42	2.93 (1.87 - 4.60)	1.54 (0.97 - 2.43)
Lifestyle habits						
Smoking	330	1.85 (1.66 - 2.07)	1.03 (0.91 - 1.16)	51	2.22 (1.67 - 2.95)	1.01 (0.75 - 1.37)
Alcoholism	97	1.97 (1.61 - 2.41)	1.16 (0.94 - 1.43)	20	2.95 (1.89 - 4.60)	1.60 (0.99 - 2.56)
Opioid addiction	5	1.23 (0.51 - 2.97)	0.73 (0.30 - 1.76)	1	3.61 (0.51 - 25.78)	1.68 (0.23 - 12.08)
Comorbidities						
Immunosuppressive treatments						
Immunosuppressant	507	10.94 (9.97 - 12.00)		80	11.87 (9.42 - 14.96)	
Oral corticosteroids	592	7.12 (6.53 - 7.76)		146	8.24 (6.91 - 9.83)	
Cardiometabolics						
Obesity	165	3.04 (2.60 - 3.55)	1.61 (1.37 - 1.88)	21	3.38 (2.19 - 5.23)	1.57 (1.01 - 2.45)
Diabetes	1465			284		
Non-insulin-treated	925	1.73 (1.61 - 1.86)	1.49 (1.38 - 1.61)	160	1.38 (1.16 - 1.65)	1.26 (1.06 - 1.50)
Insulin-treated	540	3.75 (3.42 - 4.10)	2.10 (1.90 - 2.32)	124	3.96 (3.27 - 4.80)	2.24 (1.82 - 2.75)

Table 2 *(Continued)*

	Hospitalisations			In-hospital death		
	Number of events	HR adjusted for age and sex only	Fully adjusted model (without adjustment for immunosuppressive treatment)	Number of events	HR adjusted for age and sex only	Fully adjusted model (without adjustment for immunosuppressive treatment)
Dyslipidaemia and lipid-lowering treatments	1869	1.18 (1.11 - 1.25)	0.86 (0.80 - 0.92)	361	1.00 (0.87 - 1.14)	0.75 (0.65 - 0.87)
Hereditary metabolic diseases or amyloidosis	33	1.93 (1.37 - 2.71)	1.29 (0.91 - 1.82)	5	1.47 (0.61 - 3.55)	0.87 (0.36 - 2.10)
Hypertension	3451	1.63 (1.53 - 1.74)	1.20 (1.13 - 1.29)	746	1.57 (1.35 - 1.82)	1.21 (1.03 - 1.41)
Coronary diseases	999	1.77 (1.65 - 1.90)	1.21 (1.12 - 1.31)	245	1.88 (1.62 - 2.18)	1.27 (1.08 - 1.50)
Obliterating arterial disease of the lower limb	355	1.92 (1.73 - 2.15)	1.14 (1.02 - 1.28)	86	1.92 (1.54 - 2.40)	1.13 (0.90 - 1.42)
Cardiac rhythm or conduction disturbances	1519	2.27 (2.13 - 2.42)	1.43 (1.33 - 1.53)	428	2.79 (2.45 - 3.19)	1.61 (1.39 - 1.86)
Heart failure	767	3.50 (3.23 - 3.79)	1.68 (1.53 - 1.83)	237	4.33 (3.72 - 5.04)	1.99 (1.68 - 2.36)
Valvular diseases	441	1.96 (1.78 - 2.17)	1.11 (1.00 - 1.24)	147	2.68 (2.24 - 3.19)	1.40 (1.16 - 1.69)
Stroke	433	1.72 (1.55 - 1.90)	1.25 (1.13 - 1.39)	108	1.74 (1.42 - 2.13)	1.27 (1.03 - 1.56)
Pulmonary embolism	91	2.23 (1.81 - 2.74)	1.46 (1.18 - 1.80)	21	2.17 (1.41 - 3.35)	1.40 (0.91 - 2.16)
Respiratory diseases						
Chronic respiratory diseases (excluding cystic fibrosis)	1180	2.63 (2.47 - 2.81)	1.99 (1.86 - 2.14)	238	2.50 (2.16 - 2.89)	1.77 (1.51 - 2.07)
Cystic fibrosis	13	27.41 (15.86 - 47.37)	6.31 (3.41 - 11.69)	1	28.96 (4.07 - 206.03)	9.61 (1.26 - 73.43)
Cancer						
Female breast cancer (active)	55	1.99 (1.52 - 2.60)	1.89 (1.44 - 2.47)	14	3.20 (1.88 - 5.46)	2.83 (1.66 - 4.84)
Female breast cancer (under surveillance)	103	1.20 (0.99 - 1.47)	1.16 (0.96 - 1.42)	15	0.90 (0.54 - 1.50)	0.85 (0.51 - 1.42)
Colorectal cancer (active)	59	2.03 (1.57 - 2.63)	1.66 (1.29 - 2.15)	11	1.77 (0.98 - 3.20)	1.36 (0.75 - 2.47)
Colorectal cancer (under surveillance)	109	1.59 (1.31 - 1.92)	1.43 (1.18 - 1.72)	17	1.00 (0.62 - 1.62)	0.89 (0.55 - 1.43)
Lung cancer (active)	70	5.13 (4.05 - 6.50)	3.45 (2.72 - 4.38)	22	9.41 (6.15 - 14.38)	6.48 (4.21 - 9.96)
Lung cancer (under surveillance)	39	2.90 (2.12 - 3.97)	1.85 (1.34 - 2.54)	13	4.66 (2.69 - 8.05)	3.21 (1.85 - 5.58)
Prostate cancer (active)	76	1.01 (0.80 - 1.27)	1.01 (0.80 - 1.27)	15	0.81 (0.48 - 1.35)	0.80 (0.48 - 1.34)
Prostate cancer (under surveillance)	140	1.00 (0.84 - 1.18)	0.96 (0.81 - 1.14)	39	1.09 (0.79 - 1.51)	1.02 (0.74 - 1.42)
Other cancers (active)	603	3.55 (3.26 - 3.87)	3.03 (2.77 - 3.30)	174	4.79 (4.06 - 5.65)	4.12 (3.48 - 4.88)
Other cancers (under surveillance)	350	1.44 (1.29 - 1.60)	1.37 (1.22 - 1.52)	83	1.44 (1.15 - 1.80)	1.48 (1.17 - 1.86)
Inflammatory and skin diseases						
Chronic inflammatory bowel diseases	41	1.60 (1.18 - 2.18)	1.29 (0.95 - 1.75)	5	1.27 (0.53 - 3.06)	0.96 (0.40 - 2.31)
Rheumatoid arthritis and related diseases	138	2.64 (2.23 - 3.12)	2.34 (1.98 - 2.78)	33	3.08 (2.18 - 4.36)	2.73 (1.92 - 3.87)
Ankylosing spondylitis and related diseases	58	2.28 (1.76 - 2.95)	1.64 (1.27 - 2.13)	11	2.71 (1.49 - 4.91)	1.65 (0.90 - 3.01)
Psoriasis	56	1.37 (1.05 - 1.78)	1.18 (0.90 - 1.53)	5	0.65 (0.27 - 1.57)	0.57 (0.24 - 1.38)
Psychological and neurodegenerative diseases						
Neurotic and Mood Disorders, use of antidepressant treatments	1120	1.72 (1.61 - 1.84)	1.35 (1.26 - 1.44)	256	1.90 (1.64 - 2.20)	1.51 (1.30 - 1.75)
Psychotics disorders, use of neuroleptics treatments	238	2.21 (1.94 - 2.52)	1.67 (1.46 - 1.91)	41	1.74 (1.27 - 2.39)	1.32 (0.95 - 1.82)

Table 2 *(Continued)*

	Hospitalisations			In-hospital death		
	Number of events	HR adjusted for age and sex only	Fully adjusted model (without adjustment for immunosuppressive treatment)	Number of events	HR adjusted for age and sex only	Fully adjusted model (without adjustment for immunosuppressive treatment)
Psychiatric disorders starting in childhood	8	3.31 (1.65 - 6.62)	2.32 (1.15 - 4.68)			0
Down syndrome	10	4.72 (2.53 - 8.80)	3.89 (2.08 - 7.28)	4	56.96 (20.91 - 155.20)	45.13 (16.03 - 127.09)
Epilepsy	96	2.51 (2.05 - 3.07)	1.68 (1.37 - 2.06)	16	2.00 (1.22 - 3.29)	1.34 (0.81 - 2.20)
Multiple sclerosis	25	3.14 (2.12 - 4.66)	3.01 (2.02 - 4.50)	2	2.29 (0.57 - 9.19)	2.16 (0.53 - 8.76)
Paraplegia	37	3.45 (2.50 - 4.76)	1.88 (1.35 - 2.62)	6	3.45 (1.54 - 7.70)	1.89 (0.84 - 4.29)
Myopathy or myasthenia gravis	25	4.17 (2.82 - 6.18)	2.72 (1.83 - 4.04)	8	7.50 (3.74 - 15.04)	4.74 (2.34 - 9.60)
Parkinson disease	155	1.70 (1.45 - 2.00)	1.45 (1.24 - 1.71)	43	1.91 (1.40 - 2.59)	1.64 (1.21 - 2.24)
Dementias (including Alzheimer's disease)	574	2.05 (1.86 - 2.25)	1.70 (1.54 - 1.88)	157	2.03 (1.70 - 2.44)	1.67 (1.38 - 2.02)
Mental impairment	35	3.54 (2.54 - 4.95)	3.56 (2.54 - 5.00)	3	3.09 (0.99 - 9.62)	3.12 (0.97 - 10.04)
Other pathologies						
Haemophilia or severe haemostasis disorders	17	2.38 (1.48 - 3.83)	2.05 (1.27 - 3.30)	4	2.88 (1.08 - 7.70)	2.41 (0.90 - 6.44)
HIV infection	23	2.06 (1.36 - 3.10)	1.15 (0.76 - 1.74)	7	6.39 (3.02 - 13.51)	2.73 (1.27 - 5.86)
Liver diseases	184	3.90 (3.36 - 4.52)	1.54 (1.31 - 1.80)	39	4.73 (3.43 - 6.51)	1.52 (1.06 - 2.17)
Chronic dialysis	155	13.51 (11.51 - 15.86)	6.97 (5.90 - 8.24)	46	18.20 (13.51 - 24.50)	8.55 (6.26 - 11.68)
Renal transplant	259	56.76 (49.99 - 64.45)	32.12 (28.00 - 36.85)	43	78.46 (57.40 - 107.24)	33.87 (24.18 - 47.43)
Cardiac transplant	7	49.57 (23.59 - 104.17)	4.63 (2.18 - 9.82)	1	114.68 (16.02 - 820.72)	6.92 (0.94 - 50.66)
Liver transplant	10	20.06 (10.80 - 37.25)	1.90 (1.00 - 3.62)	4	97.15 (35.97 - 262.39)	6.22 (2.15 - 18.01)
Lung transplant	18	135.96 (85.43 - 216.38)	13.70 (8.09 - 23.22)	1	119.23 (16.76 - 848.28)	11.39 (1.47 - 88.52)

***Table 2*: Hazard ratios (HR) and 95% confidence intervals (95%CI) for COVID-19-related hospitalisation and in-hospital mortality criteria).**
Multivariable models were adjusted for all the variables cited above but also for the region of residence and the type of vaccine administered. Some associations were not estimated due to insufficient sample size. For example, compared to individuals aged 45-54, individuals aged 85-89 had a 4-times increased risk of hospitalisation (aHR 4.02 95CI 3.47 - 4.65) and a 38-times increased risk of in-hospital death (aHR 37.96 95%CI 19.15 - 75.23) in multivariable analysis.

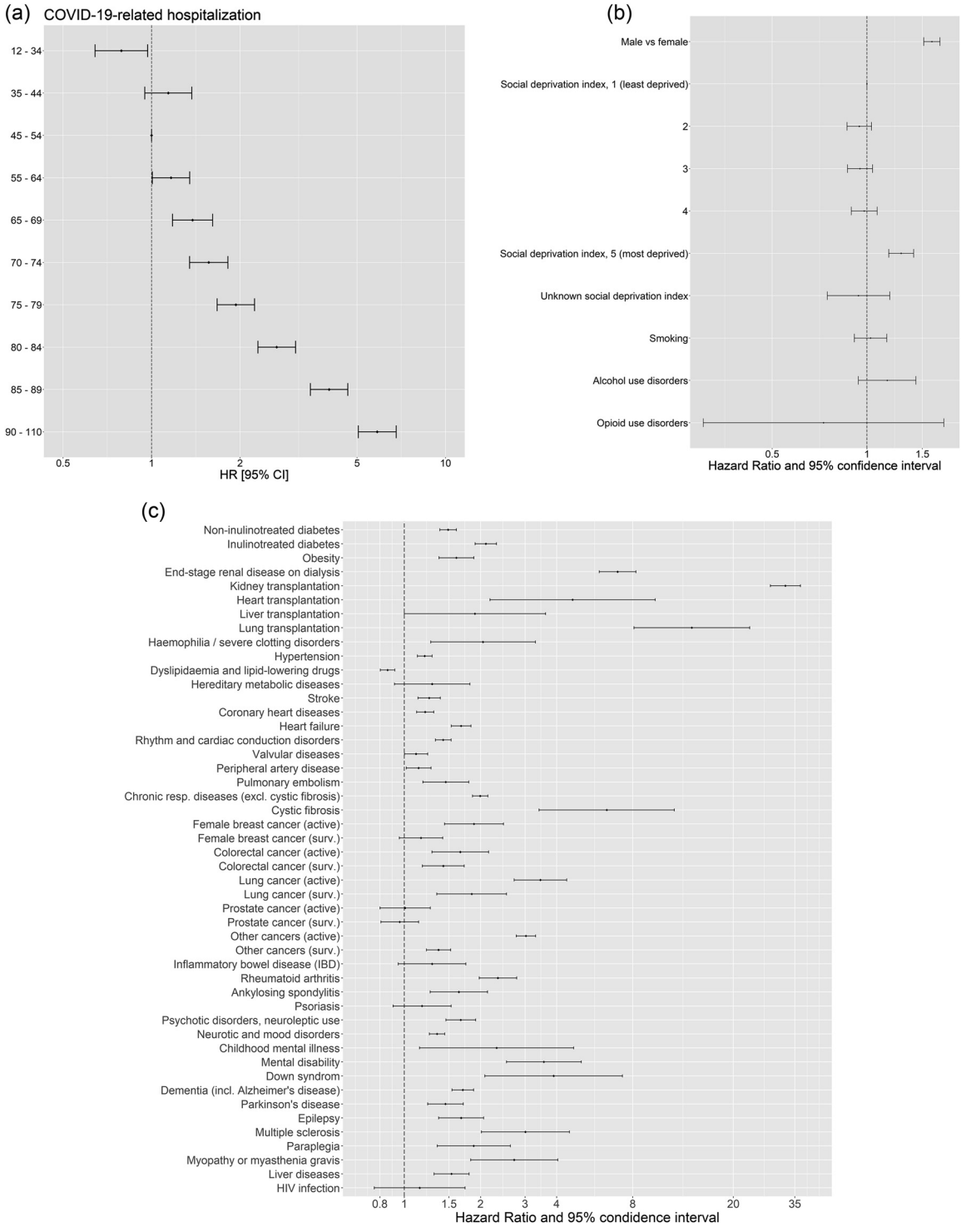
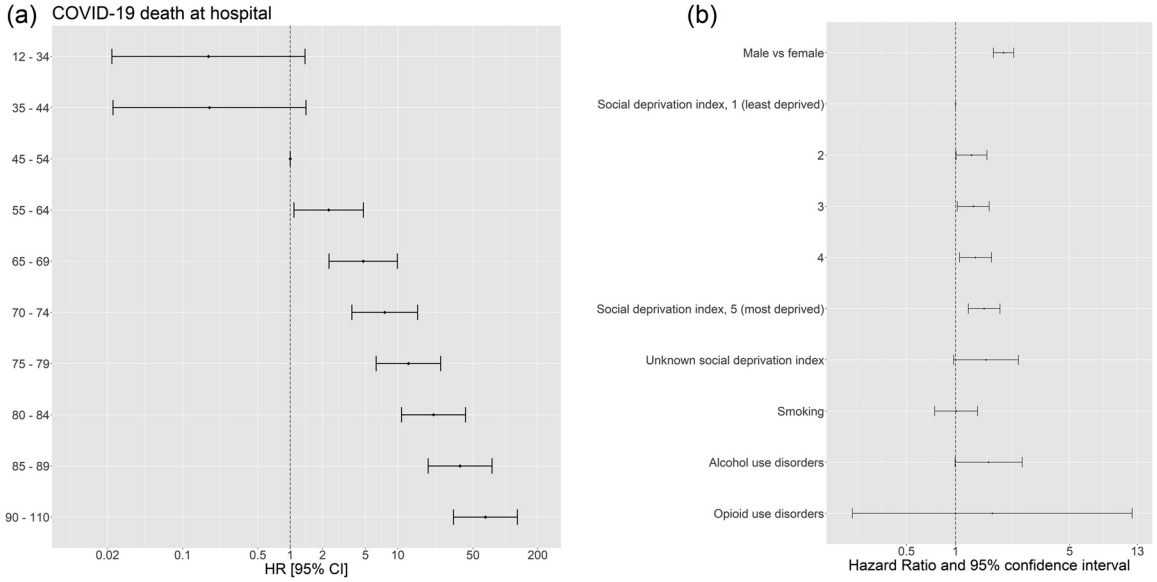


Figure 2. a. Hazard ratios of COVID-19-related hospitalisation estimated from a Cox model with multivariable adjustment.



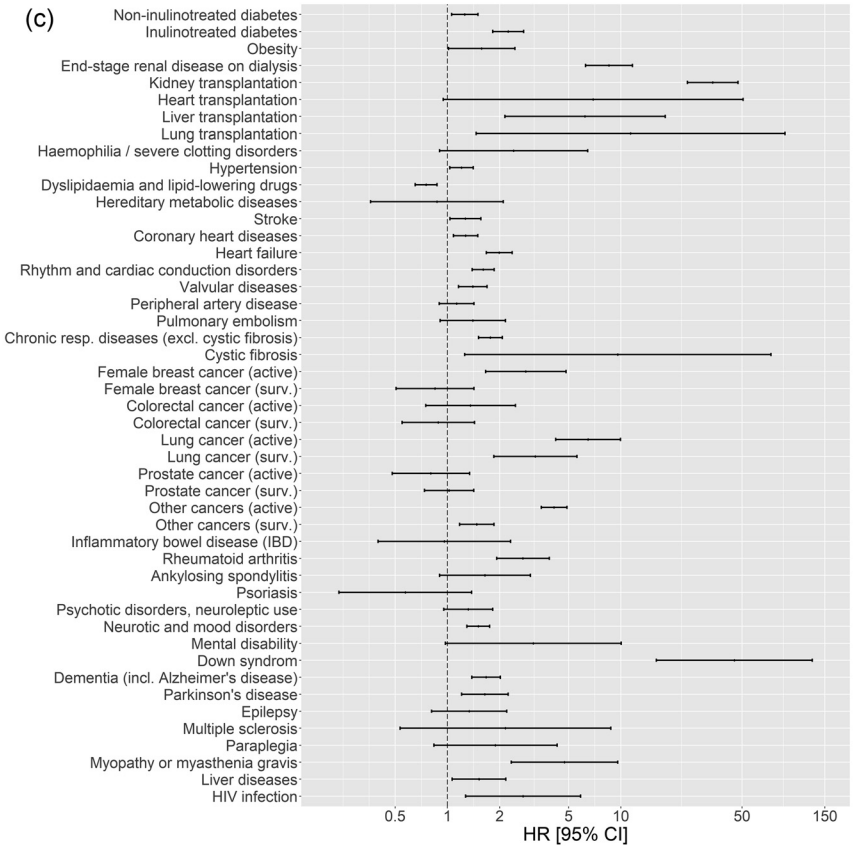


Figure 2. b. Hazard ratios of COVID-19-related death estimated from a Cox model with multivariable adjustment.

	Hospitalisations		In-hospital death	
	Number of events	Fully adjusted model (with adjustment for immunosuppressive treatment)	Number of events	Fully adjusted model (with adjustment for immunosuppressive treatment)
Sociodemographic characteristics				
Age				
12–34	137	0.81 (0.66 - 1.00)	1	0.18 (0.02 - 1.43)
35–44	193	1.15 (0.95 - 1.38)	1	0.18 (0.02 - 1.44)
45–54	282	1	9	1
55–64	560	1.17 (1.01 - 1.35)	32	2.30 (1.09 - 4.83)
65–69	398	1.38 (1.18 - 1.61)	40	4.67 (2.25 - 9.71)
70–74	545	1.57 (1.36 - 1.83)	75	7.51 (3.72 - 15.17)
75–79	677	1.97 (1.70 - 2.28)	125	12.68 (6.36 - 25.31)
80–84	738	2.72 (2.35 - 3.15)	171	21.64 (10.88 - 43.02)
85–89	879	4.15 (3.58 - 4.80)	241	38.65 (19.48 - 76.68)
90–110	936	6.13 (5.29 - 7.11)	301	67.96 (34.25 - 134.85)
Male sex	3,023	1.61 (1.52 - 1.71)	590	1.97 (1.71 - 2.28)
Social deprivation index (quintiles)				
1 (the least deprived)	1,223	1	192	1
2	922	0.94 (0.86 - 1.03)	176	1.26 (1.01 - 1.56)
3	998	0.95 (0.87 - 1.04)	188	1.28 (1.03 - 1.61)
4	891	0.98 (0.90 - 1.08)	188	1.34 (1.07 - 1.68)
5 (the most deprived)	1,129	1.29 (1.18 - 1.41)	210	1.51 (1.21 - 1.89)
Unknown	182	0.93 (0.74 - 1.17)	42	1.54 (0.97 - 2.43)
Lifestyle habits				
Smoking	330	1.02 (0.90 - 1.14)	51	0.98 (0.73 - 1.33)
Alcoholism	97	1.19 (0.97 - 1.47)	20	1.66 (1.03 - 2.67)
Opioid addiction	5	0.74 (0.31 - 1.78)	1	1.73 (0.24 - 12.43)
Comorbidities				
Immunosuppressive treatments				
Immunosuppressant	507	3.25 (2.79 - 3.78)	80	2.39 (1.66 - 3.45)
Oral corticosteroids	592	2.78 (2.49 - 3.11)	146	4.14 (3.34 - 5.14)
Cardiometabolics				
Obesity	165	1.62 (1.39 - 1.90)	21	1.62 (1.04 - 2.51)
Diabetes	1,465		284	
Non-insulin-treated	925	1.50 (1.39 - 1.62)	160	1.27 (1.07 - 1.52)
Insulin-treated	540	2.06 (1.87 - 2.27)	124	2.20 (1.79 - 2.70)
Dyslipidaemia and lipid-lowering treatments	1,869	0.86 (0.81 - 0.92)	361	0.76 (0.66 - 0.88)
Hereditary metabolic diseases or amyloidosis	33	1.24 (0.88 - 1.75)	5	0.85 (0.35 - 2.04)
Hypertension	3,451	1.19 (1.11 - 1.27)	746	1.20 (1.02 - 1.40)
Coronary diseases	999	1.21 (1.11 - 1.30)	245	1.26 (1.07 - 1.48)
Obliterating arterial disease of the lower limb	355	1.15 (1.03 - 1.29)	86	1.14 (0.90 - 1.43)
Cardiac rhythm or conduction disturbances	1,519	1.42 (1.32 - 1.53)	428	1.61 (1.39 - 1.86)
Heart failure	767	1.68 (1.54 - 1.84)	237	1.98 (1.67 - 2.35)
Valvular diseases	441	1.11 (1.00 - 1.23)	147	1.39 (1.15 - 1.68)
Stroke	433	1.27 (1.14 - 1.40)	108	1.28 (1.05 - 1.58)
Pulmonary embolism	91	1.41 (1.15 - 1.74)	21	1.33 (0.86 - 2.06)
Respiratory diseases				
Chronic respiratory diseases (excluding cystic fibrosis)	1,180	1.94 (1.81 - 2.08)	238	1.70 (1.45 - 1.99)
Cystic fibrosis	13	4.22 (2.33 - 7.66)	1	5.51 (0.75 - 40.68)
Cancer				
Female breast cancer (active)	55	1.91 (1.46 - 2.49)	14	2.86 (1.67 - 4.88)
Female breast cancer (under surveillance)	103	1.18 (0.97 - 1.44)	15	0.86 (0.52 - 1.45)
Colorectal cancer (active)	59	1.67 (1.29 - 2.16)	11	1.34 (0.74 - 2.42)

Table 3 *(Continued)*

	Hospitalisations		In-hospital death	
	Number of events	Fully adjusted model (with adjustment for immunosuppressive treatment)	Number of events	Fully adjusted model (with adjustment for immunosuppressive treatment)
Colorectal cancer (under surveillance)	109	1.42 (1.17 - 1.72)	17	0.88 (0.55 - 1.43)
Lung cancer (active)	70	3.19 (2.51 - 4.05)	22	5.73 (3.72 - 8.82)
Lung cancer (under surveillance)	39	1.86 (1.36 - 2.56)	13	3.21 (1.85 - 5.57)
Prostate cancer (active)	76	0.95 (0.76 - 1.20)	15	0.73 (0.44 - 1.22)
Prostate cancer (under surveillance)	140	0.96 (0.81 - 1.14)	39	1.02 (0.73 - 1.41)
Other cancers (active)	603	2.86 (2.62 - 3.12)	174	3.90 (3.29 - 4.63)
Other cancers (under surveillance)	350	1.35 (1.21 - 1.51)	83	1.46 (1.16 - 1.84)
Inflammatory and skin diseases				
Chronic inflammatory bowel diseases	41	0.98 (0.72 - 1.34)	5	0.82 (0.34 - 1.97)
Rheumatoid arthritis and related diseases	138	1.01 (0.83 - 1.22)	33	1.12 (0.76 - 1.65)
Ankylosing spondylitis and related diseases	58	1.17 (0.90 - 1.53)	11	1.38 (0.76 - 2.53)
Psoriasis	56	1.09 (0.84 - 1.43)	5	0.54 (0.23 - 1.31)
Psychological and neurodegenerative diseases				
Neurotic and Mood Disorders, use of antidepressant treatments	1,120	1.33 (1.24 - 1.43)	256	1.48 (1.27 - 1.72)
Psychotics disorders, use of neuroleptics treatments	238	1.68 (1.47 - 1.93)	41	1.34 (0.97 - 1.85)
Psychiatric disorders starting in childhood	8	2.33 (1.16 - 4.71)		
Down syndrome	10	4.13 (2.21 - 7.73)	4	49.62 (17.68 - 139.32)
Epilepsy	96	1.65 (1.35 - 2.03)	16	1.32 (0.80 - 2.17)
Multiple sclerosis	25	2.19 (1.46 - 3.27)	2	2.01 (0.50 - 8.15)
Paraplegia	37	1.94 (1.39 - 2.70)	6	1.82 (0.80 - 4.11)
Myopathy or myasthenia gravis	25	1.93 (1.29 - 2.86)	8	3.14 (1.54 - 6.39)
Parkinson disease	155	1.47 (1.25 - 1.73)	43	1.67 (1.22 - 2.27)
Dementias (including Alzheimer's disease)	574	1.73 (1.57 - 1.91)	157	1.72 (1.42 - 2.07)
Mental impairment	35	3.64 (2.59 - 5.11)	3	3.14 (0.97 - 10.09)
Other pathologies				
Haemophilia or severe haemostasis disorders	17	1.91 (1.19 - 3.07)	4	2.15 (0.80 - 5.76)
HIV infection	23	1.12 (0.74 - 1.69)	7	2.52 (1.17 - 5.43)
Liver diseases	184	1.49 (1.27 - 1.75)	39	1.52 (1.07 - 2.18)
Chronic dialysis	155	6.77 (5.73 - 8.01)	46	8.39 (6.14 - 11.47)
Renal transplant	259	5.85 (4.82 - 7.11)	43	6.28 (3.95 - 9.98)
Cardiac transplant	7	1.54 (0.72 - 3.28)	1	1.99 (0.27 - 14.65)
Liver transplant	10	1.12 (0.59 - 2.14)	4	3.82 (1.30 - 11.25)
Lung transplant	18	4.92 (2.93 - 8.24)	1	4.13 (0.55 - 31.08)

***Table 3*: Hazard ratios (HR) and 95% confidence intervals (95%CI) for COVID-19-related hospitalisation and in-hospital mortality criteria in a multivariable model adjusted for immunosuppressant treatment.**
Multivariable models were adjusted for all the variables cited above but also for the region of residence and the type of vaccine administered. Some associations were not estimated due to insufficient sample size. For example, compared to individuals aged 45-54, individuals aged 85-89 had a 4-times increased risk of hospitalisation (aHR 4.15 95%CI 3.58 - 4.80) and a 39-times increased risk of in-hospital death (aHR 38.65 95%CI 19.48 - 76.68) in multivariable analysis adjusted for immunosuppressive treatment and oral corticosteroids use.

immunosuppressive and oral corticosteroid treatment (aHR 33.9 95% CI 24.2-47.4) and a six-fold excess risk in multivariable analysis after adjustment for these treatments (aHR 6.3 95% CI 4.0-10.0). Patients with inflammatory bowel disease (IBD) had a 30% higher risk of being hospitalised than other vaccinated patients (aHR 1.3 95% CI 1.0-1.8) in multivariable analysis before adjustment for immunosuppressive and oral corticosteroid treatment, whereas the association was no longer significant after additional adjustment for these treatments (aHR 1.0 95% CI 0.7-1.3). We obtained similar results for patients with rheumatoid arthritis and ankylosing spondylitis.

The proportion of patients without any comorbidity was 50% among fully vaccinated people, less than 10% (519/5,345) among hospitalised patients, and 2% (24/996) among deceased patients (Table 4). Conversely, 4% of fully vaccinated, 27% of hospitalised, and 39% of deceased patients had five or more identified comorbidities. There was a sharp increase in the risk of developing a severe form of COVID-19 with an increasing number of comorbidities. Vaccinated individuals with a

	Number of individuals	% per number of comorbidities in vaccinated population	COVID-19-related hospitalisation				In-hospital death		
			Number of events	% among hospitalised vaccinated individuals	HR adjusted for age and sex only	Multivariable model	Number of events	HR adjusted for age and sex only	Multivariable model
Number of comorbidities	28,031,641		5,345				996		
0	13,882,319	50%	519	10%	1	1	24	1	1
1	5,795,477	21%	658	12%	2.20 (1.95 - 2.49)	2.22 (1.97 - 2.51)	68	2.34 (1.45 - 3.76)	2.35 (1.46 - 3.78)
2	3,530,910	13%	878	16%	3.80 (3.36 - 4.29)	3.82 (3.38 - 4.32)	140	4.73 (3.02 - 7.40)	4.73 (3.02 - 7.41)
3	2,406,816	9%	974	18%	5.38 (4.76 - 6.08)	5.38 (4.75 - 6.09)	185	7.19 (4.62 - 11.19)	7.15 (4.59 - 11.15)
4	1,324,756	5%	873	16%	7.84 (6.91 - 8.89)	7.80 (6.87 - 8.86)	190	11.21 (7.20 - 17.47)	11.11 (7.12 - 17.32)
5 or more	1,091,363	4%	1,443	27%	13.96 (12.37 - 15.75)	13.80 (12.21 - 15.60)	389	23.07 (14.96 - 35.58)	22.58 (14.61 - 34.88)

***Table 4*: Hazard ratios (HR) and 95% confidence intervals (95%CI) for COVID-19-related hospitalisation and in-hospital mortality according to the number of comorbidities.**
Multivariable models were adjusted for age, gender, deprivation index, region of residence, type of vaccine administered and lifestyle habits variables. For example, compared to individuals without any comorbidity, individuals with at least 5 comorbidities had a 14-times increased risk of hospitalisation (aHR 13.80 95%CI 12.21 - 15.60) and a 23-times increased risk of in-hospital death (aHR 22.58 95%CI 14.61 - 34.88) in multivariable analysis.

single comorbidity had a two-fold higher risk of being hospitalised for COVID-19 than those without any (aHR 2.2 95% CI 2.0-2.5), reaching a 13-fold higher risk for patients with at least five comorbidities (aHR 13.8 95% CI 12.2-15.6). Similarly, people with a single comorbidity had a two-fold higher risk of in-hospital death than those without any (aHR 2.4 95% CI 1.5-3.8), reaching a 22-fold increased risk for patients with at least five comorbidities (aHR 22.6 95% CI 14.6-34.9) (Table 4).

Stratified multivariable analyses did not show any noticeable difference in associations between endpoints and comorbidities according to age group (Tables S2a and S2b) and among patients without any comorbidity, immunosuppressive treatment and oral corticosteroid use (Table S4).

Discussion

Among 28 million fully vaccinated individuals, most of the 47 chronic conditions considered in this study were positively associated with a risk of COVID-19-related hospitalisation and in-hospital mortality, with the exception of dyslipidaemia, which was negatively associated in multivariable analysis. The strongest associations were observed for people with kidney transplantation, lung transplantation, end-stage renal disease on dialysis, cystic fibrosis, Down syndrome, mental disability, and active lung cancer. Older age and immunosuppressant and oral corticosteroid therapy, as well as an increasing number of comorbidities, were particularly highly associated with the risk of COVID-19-related hospitalisation and in-hospital death among fully vaccinated people.

Several studies have been conducted to identify the risk factors for developing a severe form of COVID-19 among vaccinated populations.[14,15,27–29] From a US database of 465 facilities,[14] among 1.2 million people vaccinated between December 2020 and October 2021, 2,246 developed COVID-19, of whom 327 were hospitalised and 31 died. The authors found an increased risk of a severe form of COVID-19 among immunocompromised vaccinated individuals, those aged 65 and over, and those presenting certain comorbidities, such as lung and liver diseases, chronic renal failure, diabetes, cardiovascular diseases, or neurological diseases. The percentage of subjects with at least four of these comorbidities increased with COVID-19 severity: 19% among the 2,057 people with a mild form, 57% among the 153 admitted to an emergency room, and 78% among the 36 who died. Although methodological differences limit comparability, these percentages can be put into perspective with the 9% (entire population with no severe form of COVID-19), 43% (COVID-19-related hospitalised patients), and 58% (COVID-19-related deaths) from our study.

We estimate a 30% higher risk of COVID-19-related hospitalisation for individuals living in one of the most

deprived areas relative to those living in one of the least deprived areas and a 50% higher risk of in-hospital death. Higher risks of COVID-19-related hospitalisation and in-hospital death were already observed among unvaccinated individuals the most deprived compared to the less deprived.[4] Although the deprivation index is an ecological indicator that must be interpreted with caution, it is worth to mention the consistency with other studies using more accurate socioeconomic indicators.[27,28]

The association between dyslipidaemia and COVID-19-related hospitalisation changed from positive to negative after adjusting for cardiovascular diseases, which are confounding factors if we hypothesize that they could influence both treatment of dyslipidaemia and severe COVID-19. This negative association after adjustment for comorbidities has been largely observed in other studies.[30–33] The unbiased association would be the adjusted association if we hypothesize that cardiovascular disease could influence both dyslipidaemia treatment and severe COVID-19. Alternatively, if we assume that dyslipidaemia would lead to cardiovascular disease, then the adjustment would obscure the total positive effect of dyslipidaemia on the risk of severe COVID-19.

The objective of our study was not to assess the vaccine effectiveness against COVID-19-related hospitalisation or in-hospital death (extensively demonstrated, including in French studies[11,12]). Hence, the unvaccinated population was not considered. We chose a Public Health perspective by modelling the risk of developing severe COVID-19 at the overall vaccinated population-level, combining the risk that an individual in the vaccinated population be infected, and the risk that an individual infected in the vaccinated population experienced severe COVID-19 disease. The objective of our study was also not to assess a causal effect of the comorbidities identified but rather to identify the main characteristics associated with the population-level risk of COVID-19-related hospitalisation or in-hospital mortality, independently of other risk factors, among fully-vaccinated people. Given that the various risk factors of severe COVID-19 may be interrelated, we could have adjusted for intermediate factors; therefore, estimated associations should be interpreted with caution. For example, because hypertension, diabetes, and obesity increase the risk of developing other forms of cardiovascular disease, their risk in relation to COVID-19 may have been underestimated in adjusted models. In addition, by reducing vaccine effectiveness against COVID-19-associated hospitalisation,[34] immunosuppressive and oral corticosteroid treatments are other intermediate factors in the relationship between certain comorbidities and the risk of a severe form of COVID-19.

We present estimations before and after adjustment for immunosuppressive treatment and oral corticosteroid use (which also have immunosuppressive properties). The estimation before adjustment represents the overall effect of the comorbidity, whereas adjustment makes it possible to estimate the effect of the pathology itself, without considering the reduction in vaccine effectiveness by immunosuppressants potentially taken as part of the treatment of the same pathology. Indeed, literature reviews of real-world studies[34,35] have reported lower vaccine effectiveness against SARS-COV-2 infection, symptomatic COVID-19 illness and COVID-19-related hospitalisation in the immunocompromised population than in the general population: vaccine effectiveness of widely available COVID-19 vaccines in the immunocompromised population ranged from 63% to 100% against COVID-19-related hospitalisation, whereas it ranged from 81% to 92% in the general population. In a US real-world study of nearly 1.2 million people fully vaccinated with the BNT162b2 mRNA vaccine,[36] a small number of COVID-19 vaccine breakthrough infections (N = 978, 0.08%) were found. Nearly 40% of such cases occurred among the 212,000 (18%) individuals identified as being members of the immunocompromised population. These results can be put into perspective with the 320,536 individuals receiving immunosuppressive treatments in our study, who represent 1% of the population who had a complete vaccination schedule but 9.5% of COVID-19-related hospitalised patients. In addition, the lower vaccine effectiveness against COVID-19-related hospitalisation among immunocompromised individuals appears to vary according to the pathology, with lower protection among organ or stem-cell transplant recipients than those with a haematological malignancy or those who have intrinsic immune conditions or primary immunodeficiencies, among whom the protection is lower than for those with solid malignancy, on dialysis, or with rheumatic or inflammatory disorders.[35,37] Part of the effect of certain pathologies may be due to the associated immunosuppressive treatment, such as for renal and pulmonary transplant recipients or, to a lesser extent, patients with myopathy or myasthenia, multiple sclerosis, or IBD. As suggested by Galmiche et al.,[37] specific targeted strategies might therefore be implemented in these populations, such as additional doses (currently recommended in France), heterologous vaccination, increased doses (as in hepatitis B vaccine) to enhance immunogenicity, prophylactic administration of monoclonal antibodies, or 'cocooning' vaccination of relatives and healthcare workers. Oral corticosteroids given as chronic treatment may have a potential immunosuppressive effect and thus increase the risk of COVID-19 infection and thereby the risk of developing severe forms. Whether this association is causal would need further investigation.

The SNDS is a claims database that allowed us to analyse the risk of COVID-19-related hospitalisation and in-hospital death for individuals with a large number of comorbidities from the exhaustive population benefiting from a complete vaccination schedule as of

July 31, 2021, thus limiting selection bias. Because the probability to be tested and so to be identified as an individual tested positive may depend on the risk factors studied, not restricting the analysis of the risk of hospitalisation to individuals tested positive for COVID-19, should avoid any collision bias.[38] The same is true for not restricting the study of mortality on hospitalised individuals because the probability of hospitalisation may as well depend on the risk factors studied.

We chose not to include patients vaccinated with the Ad26.COV2.S vaccine due to its low effectiveness against SARS-COV-2 infection and COVID-19-related hospitalisation,[39,40] including in our population,[19] and the evolution of its vaccination schedule, initially with a single injection and then with the need for a booster vaccination. The proportion of people vaccinated with the Ad26.COV2.S vaccine remained limited, with less than one million vaccinated individuals at the time of the analysis, i.e. 2% of the eligible population.

This study had several limitations. Information was incomplete for certain variables, in particular, for behavioural characteristics, such as obesity, tobacco dependence, or alcohol consumption, which are significantly underestimated in this database. However, this should not substantially modify the associations between the various comorbidities and the risk of developing a severe form of COVID-19, except probably for obesity. The SNDS also does not include information on the individual level of exposure to the virus. Part of the screening test history was not available, in particular, for those carried out before November 2020. The history of COVID-19 was therefore not exhaustive and some people with a positive SARS-COV-2 test in 2020 and a single injection may not have been included in our study. Although we focused on patients requiring admission specifically for SARS-CoV-2 infection, diagnostic errors may have occurred, but are likely rare due to the invoicing nature of the codifications recorded by public and private healthcare establishments. The information related to vaccination is qualitative, as it was entered by a healthcare professional and used to obtain a COVID-19 vaccine passport. Withdrawal of the patient's consent concerning integration of his/her pseudonymized data in the VAC-SI database is, however, legally possible, even if probably marginal, and thus without any impact on the estimates. Finally, the beta and delta variants were predominant in France over the time period analysed and therefore our estimates may not apply to a period of high circulation of other variants, such as the Omicron variant.

In conclusion, although vaccination has dramatically reduced the occurrence of severe forms of COVID-19, the residual risk is concentrated within elderly, immunocompromised, and polypathological populations and warrants complementary preventive measures.

Contributors

L.S., J.B., J.D., B.B., M.B., M.J., F.C., S.L., R.D., A.W. and M.Z. (all authors) conceived and designed the experiments. L.S., J.B. and J.D. analyzed the data. All authors interpreted the results. L.S., J.B., S.L., F.C., R.D., A.W. and M.Z. wrote the first and the revised drafts of the manuscript. All the authors contributed to the writing of the manuscript. All the authors agreed with the results and conclusions of the manuscript. All authors have read, and confirm that they meet, ICMJE criteria for authorship. L.S., J.D. and B. B. had full access to raw data. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. M.Z. is the guarantor.

Data sharing statement

According to the principles of data protection and French regulations, the authors cannot publicly release the data from the French National Health Data System (SNDS). However, any person or structure, public or private, for-profit or non-profit, can access SNDS data upon authorisation from the French Data Protection Office (CNIL Commission Nationale de l'Informatique et des Libertés) to carry out a study, research, or an evaluation of public interest (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://www.indsante.fr/).

Declaration of interests

None.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.lanepe.2022.100441.

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