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Research paper

Chronic diseases, health conditions and risk of COVID-19-related hospitalization and in-hospital mortality during the first wave of the epidemic in France: a cohort study of 66 million people

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ABSTRACT

Background: From the beginning of the COVID-19 pandemic, age (most importantly), male gender and various comorbidities were found to be associated with severe forms of COVID-19. However, there was little information provided for an entire country such as France, which was severely affected throughout the epidemic.
Methods: In France, the SNDS, comprising all health insurance reimbursements and benefits, and the PMSI, comprising hospital data, can be used to estimate the risk associated with about fifty diseases or health conditions for hospitalization primarily related to COVID-19 and COVID-19-related deaths. A cohort was constituted comprising all people alive on February 15, 2020. Data were censored at 15 June 2020 for COVID-19-related hospitalization and at 15 July 2020 for death for patients still hospitalized for COVID-19 on 15 June 2020. Cox proportional hazards models were used to estimate hazard ratios (HR) for the associations between each comorbidity (n=47) and the risk of COVID-19-related hospitalization or death. These associations were determined with adjustment for age and gender, and then in models including all variables (adjusted hazard ratios [aHR]).
Findings: In a population of 66,050,090 people, 87,809 people (134 per 100,000) were hospitalized for COVID-19 between February 15, 2020 and June 15, 2020 and a subgroup of 15,661 people (24 per 100,000) died in hospital.
A much higher risk was observed with increasing age, reaching a risk of hospitalization for COVID-19 more than five fold higher and a risk of COVID-19-related in-hospital mortality more than 100-fold higher in people aged 85 years and older (absolute risks of 750 and 268 per 100,000, respectively) compared to people aged 40 to 44 years.
Men were at higher risk of COVID-19-related hospitalization aHR 1·38 [1·36-1·40]) and COVID-19-related in-hospital mortality (aHR 2·08 [2·01-2·16]) compared to women. Positive associations between social deprivation index and risk of COVID-19 were also observed. Almost all chronic health conditions were positively associated with an increased risk of COVID-19-related hospitalization and in-hospital mortality, with the exception of dyslipidaemia, which was negatively associated. The strongest associations for both COVID-19-related hospitalization and in-hospital mortality were observed in people with Down syndrome (7·0 [6·1-8·1] and 22·9 [17·1-30·7], respectively), mental retardation (3·8 [3·5-4·2] and 7·3 [6·1-8·8], respectively), kidney transplantation (4·6 [4·2-5·0] and 7·1 [6·0-8·4], respectively), lung transplantation (3·5 [2·4-5·3] and 6·2 [2·8-14·0], respectively) end-stage renal disease on dialysis (4·2 [3·9-4·4] and 4·7 [4·2-5·2], respectively) and active lung cancer (2·6 [2·4-2·8] and 4·0 [3·5-4·6], respectively).
Interpretation: This national cohort study confirms the associations with most diseases and health conditions in France and provides data on less frequent health conditions, which could be useful particularly to target priority populations during present and future vaccination campaigns.
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Research in context

Evidence before this study

- Age is the main risk factor of developing a severe form of COVID-19.
- Male sex and a number of comorbidities (cardiovascular, obesity, hypertension, active cancer…) were associated to a higher risk of hospitalization and in-hospital-death for COVID-19.

Added value of this study

- A quite-comprehensive analysis in French population, with 66 million individuals, during the first epidemic wave.
- 47 comorbidities studied and associated to the risk of hospitalization and in-hospital-death for COVID-19.
- Except for dyslipidaemia (negatively associated), all comorbidities were positively associated to the development of severe forms of COVID-19.
- Seven comorbidities were associated in general population with adjusted relative risks of hospitalization for COVID-19 greater than 2 and death greater than 4: Down's syndrome, mental deficiency, kidney transplantation, lung transplantation, cystic fibrosis, end-stage chronic renal failure on dialysis, active lung cancer.

Implications of all the available evidence

Risk estimation is useful for targeting priority populations for prevention and during vaccination campaigns.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection first appeared in China at the end of 2019 and rapidly developed into a global pandemic, as the virus rapidly spread throughout the world, infecting 147 million people and killing more than 3,1 million people as of April 25, 2021.

Right from the beginning of the pandemic, age was recognized as the primary risk factor for COVID-19-related hospitalization and/or death, and patients with certain comorbidities were also identified as presenting an excess risk[1-3]. In a study based on 17 million patients (29% of the English population and 72% of all patients registered in the NHS database) including 10,900 COVID-19-related deaths, patients with cardiovascular disease, diabetes, chronic respiratory diseases including severe asthma, obesity, recent history of haematological malignancy or other cancers, and patients with kidney, liver, neurological or autoimmune diseases had an excess risk of COVID-19-related death [4]. Another study conducted in Danish patients tested by polymerase chain reaction (PCR) reported similar results: with nearly 425,000 patients tested, 11,122 were positive cases, 20% of whom were hospitalized. Among the most common comorbidities, patients with hypertension, obesity or diabetes were at higher risk of hospitalization and death. The authors also showed that kidney diseases diagnosed in hospital and organ transplantation were major risk factors, and patients with substance abuse, alcohol-related disorders or mental illness appeared to be more susceptible to COVID-19 [5]

France has a mandatory national social protection system that therefore covers the entire population. In 2018, 35% of the French population had a diagnosis of a chronic disease [6]. As a result of this large population, our study was able to identify the sociodemographic characteristics and comorbidities associated with an excess risk of COVID-19-related hospitalization or death in France.

2. Methods

2.1. Data sources

We conducted a cohort study on the National Health Data System (SNDS) that covers the entire French population, i.e. 67 million inhabitants, and which has been extensively used in France to conduct pharmaco-epidemiology studies [7–21] including studies on the COVID-19 pandemic.

Since 2006, a unique, anonymous individual identifier links data derived from two main 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). Each patient is identified by a unique identifier (encrypted twice in the SNDS) for data collection. The INSEE number (INSEE: Institut National de la Statistique et des Études Économiques - French National Institute for Statistics and Economic Studies) is a combination of 13 figures attributed to each French person at birth or at the time of legal immigration of any person residing in France. INSEE is responsible for assigning this registration number at the time of civil status registration. All adults legally residing in France have a national health insurance card ("Carte Vitale"), equipped with an electronic chip. When dispensing a drug, the pharmacist scans the bar code on the drug package (brand name, dose strength, number of tablets) and records the patient's identifier by means of the Carte Vitale. Patients must also present their Carte Vitale whenever they are admitted to hospital, as funding of the patient's hospital stay and treatment outside of hospital is dependent on the patient's identifier.

The DCIR includes individual data concerning reimbursements of outpatient medical care, laboratory tests and drugs, coded according to the Anatomical Therapeutic Chemical (ATC) classification. Health expenditure for people with long-term diseases (LTDs), such as cancer or diabetes, is 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).

Patients receiving at least one health care reimbursement after 15 February 2019 were identified from the SNDS and were included in this study. Infants born in 2020, twins under the age of 18 years and foreign residents were excluded due to identification difficulties, and we also excluded people with missing data for age and sex or who died before 15 February 2020, which was considered to be the COVID-19 epidemic start date in France for this study.

2.2. Sociodemographic characteristics and chronic diseases

We considered the patient's age, gender and region of residence as demographic variables. Age was defined from patient's year of birth as a categorical variable by five-year age-groups. 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 labour force and the unemployment rate for the person's town of residence [22].

Cartographie des Pathologies et des Dépenses (mapping of diseases and expenditure) is a tool developed from the DCIR and PMSI databases, allowing identification of diseases by means of medical algorithms [23] (47 diseases were studied in the present study) based on the reasons for hospitalization, LTD diagnoses and/or reimbursement of specific treatments for certain diseases, for a given year and over a period of the previous 4 years. The detailed definition of these disease

identification algorithms is publicly available in French (https://www.ameli.fr/fileadmin/user_upload/documents/Methodologie_medicale_cartographie.pdf). Mapping algorithms allowed the identification of patients presenting a number of different diseases in 2019 and were completed by the identification of obese patients, smokers, people with alcohol or opioid use disorders, people with Down syndrome, and heart, lung or liver transplant recipients. The main characteristics of these algorithms are presented in supplementary material table S1. The following chronic diseases were considered: cardiometabolic diseases, such as obesity, diabetes, hypertension, dyslipidaemia and/or lipid-lowering drug treatment or cardiovascular diseases (stroke and stroke 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 cancer 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, certain chromosomal anomalies (Down syndrome), haemophilia, HIV infection, liver disease, severe chronic kidney disease, heart, lung and liver transplantation.

2.3. Endpoints

Hospital stays are usually entered into the SNDS database in July of the following year. However, in April 2020, the French government encouraged hospitals to implement an exceptional, fast-track data entry of all COVID-19-related hospital stays (weekly or fortnightly) called "fast-track" PMSI. Index date was defined for both outcomes (hospitalization and death) at February, 15 considered as the start date of the epidemic in France. Our study was based on hospital discharge data available as of 30 September 2020. We choose to restrict analyses to September 2020 in order to have completeness of data over our study period, which covers the first epidemic wave in France. There were much fewer hospitalizations between June, 15 and the end of September in France. At this time, 95% of patients hospitalized for COVID-19 were able to be linked to reimbursement data by means of the anonymized identifier, with 87,809 patients admitted before 15 June 2020 with a principal diagnosis or related diagnosis of COVID-19 (and not hospitalized for another cause with an associated diagnosis of COVID-19), corresponding to the first wave of the epidemic. Among these 87,809 patients, 15,661 hospitalized patients had died from COVID-19 by 15 July 2020. Deaths were identified from civil registry records and hospital notifications. 94·4% of all deaths were identified in both data records, while 5·6% of deaths were only notified by the hospitals at the time of the analysis. However, a long and permanent discontinuation of healthcare utilisation was observed for these 5·6% of deaths, which tends to support accurate identification of the death.

The primary endpoint was COVID-19-related hospitalization since 15 February 2020. The secondary endpoint was COVID-19-related death during hospitalization since 15 February 2020. Data were censored at 15 June 2020 for COVID-19-related hospitalization and at 15 July 2020 for death for patients still hospitalized for COVID-19 on 15 June 2020.

2.4. Statistical analysis

We described the crude associations between outcomes and sociodemographic characteristics as well as the various comorbidities identified.

Cox proportional hazards models were used to estimate the associations between each comorbidity and the risk of COVID-19-related hospitalization or death. Reference group corresponded to patients without the comorbidity considered. These associations were determined after initial adjustment for age and gender, and then with multivariable adjustment including all of the variables indicated above.

Analyses stratified by age were performed by distinguishing patients under the age of 80 years from those aged 80 years and older.

We used also the number of comorbidities as a categorical variable from 0 to 4; then 5 or higher, corresponding to the sum of all the 47 comorbidities identified. Analyses including categories of number of comorbidities were adjusted on age and sex or adjusted on age, sex, socio-demographic variables and lifestyle habits. In supplementary analyses we divided our 4-month follow-up period into two 2-month sub-analysis periods, from February, 15 to April, 15 and from April, 16 to June, 15.

As an alternative to our main multivariable Cox regression models to study the risk of COVID-19-related hospitalization and in-hospital mortality we performed multivariable logistic regression models. Estimates obtained were almost identical between multivariable Cox regression and multivariable logistic regression models (Table S4); results presented below are based on Cox model.

All statistical analyses were performed with SAS software, version 9·4 (SAS Institute Inc.).

2.5. Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not for-profit sectors.

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 processing of health care claims (electronic or paper claims) and data from health care facilities (PMSI).

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

3. Results

A total of 66,050,090 individuals with at least one health care reimbursement after 15 February 2019 were identified (Figure 1). The cohort description is presented in Table 1. The median age was 43 years (interquartile range (IQR) 22 -62 years), with a median age of 70 years (IQR 54-83) for hospitalized patients and 83 years (IQR 73 to 89) for deceased patients. Of these 66 million people, 3·8 million (5·8%) were identified with diabetes, 11·9 million (18%) with hypertension, 6·7 million (10%) with dyslipidaemia or lipid-lowering drug use, 5 million (7·6%) with cardiovascular disease, 3·5 million (5·3%) with chronic respiratory disease and 4·3 million (6·5%) with neurotic or mood disorders or antidepressant use.

Between 15 February and 15 June 2020, 87,809 patients (133 per 100,000) were hospitalized for COVID-19, 15,661 (24 per 100,000) of whom died in hospital. The median length of stay in the general population of subjects hospitalized for COVID-19 was 8 days

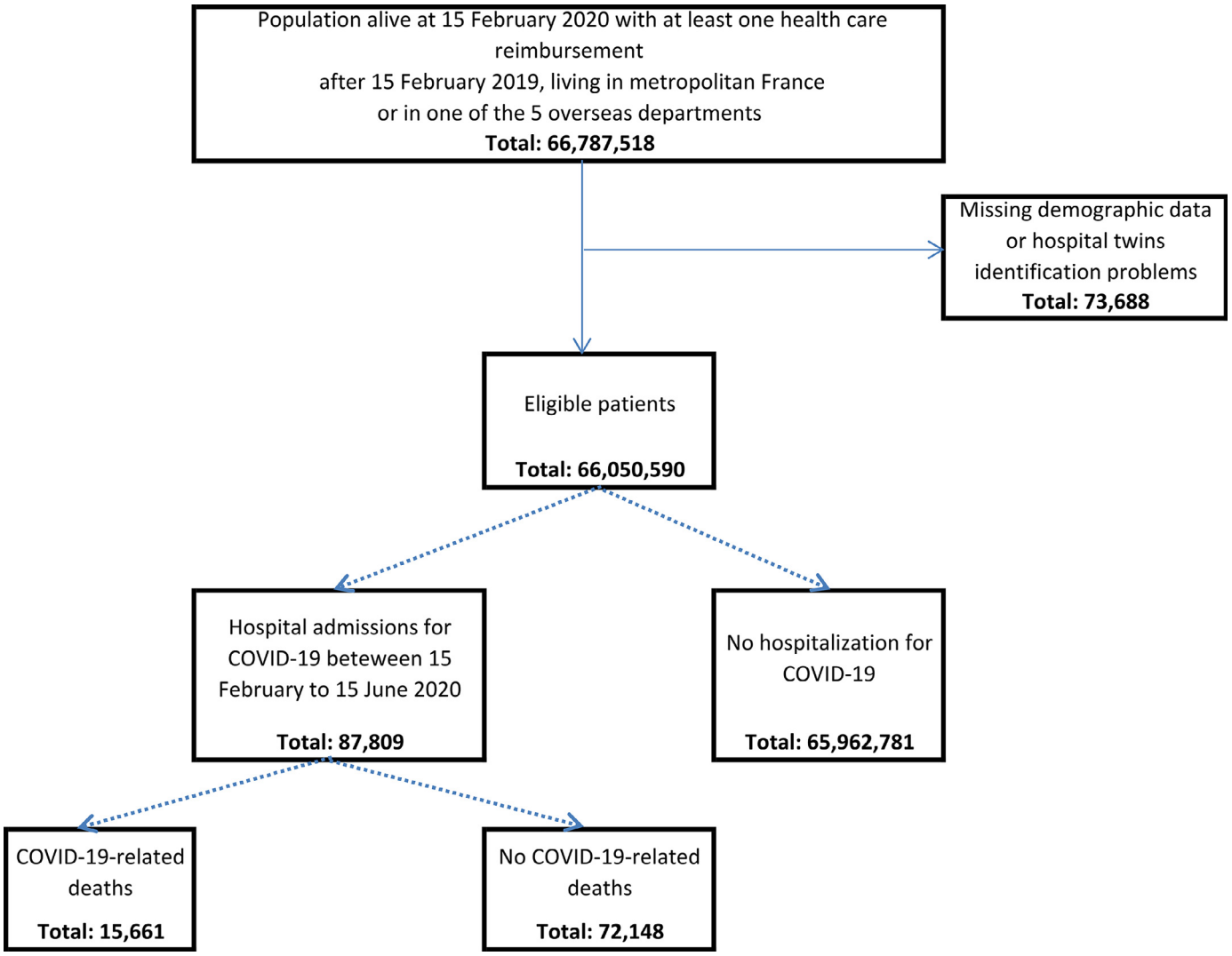

Figure 1. Flow-chart

(interquartile range: 2 to 14 days).The absolute risk of in-hospital mortality exceeded 300 per 100,000 for six conditions: end-stage renal disease on dialysis (745 per 100,000), dementia (including Alzheimer's disease) (462 per 100,000), lung transplantation (446 per 100,000), heart failure (376 per 100,000), active lung cancer (334 per 100,000) and kidney transplantation (322 per 100,000).

Associations between sociodemographic factors or chronic diseases and risk of COVID-19-related hospitalization or in-hospital mortality are presented in Table 2 and Figures 2a and 2b. Age was by far the leading risk factor for COVID-19-related hospitalization and death (Figures 2a and 2b). After adjusting for gender, the risk of COVID-19-related hospitalization or death increased exponentially with age. Compared to the risk observed in the 40- to 44-year age-group, the risk of hospitalization doubled in the 60- to 64-year age-group (HR 2·29; 95%CI 2·20 - 2·39), tripled in the 70- to 74-year age-group (HR 2·99; 95%CI 2·88 - 3·12), and was 6-fold higher in the 80- to 84-year age-group (HR 6·01; 95%CI 5·77 - 6·25) and 12-fold higher in patients aged 90 years and older (HR 12·21; 95%CI 11·73 - 12·71) [Absolute risk for hospitalization: 870 per 100,000]. An even stronger association was observed for the risk of death with, compared to the 40- to 44-year age-group, a 12-fold increased risk in the 60- to 64-year age-group (HR 12·60; 95%CI 9·62 - 16·51), a 30-fold increased risk in the 70- to 74-year age-group (HR 32·77; 95%CI 25·16 - 42·67), a 100-fold increased risk in the 80- to 84-year age-group (HR 106·43; 95%CI 81·87 - 138·36) and an almost 300-fold increased risk in people aged 90 years and older (HR 280·42; 95%CI 215·83 - 364·34) [Absolute risk of death: 322 per 100,000]. These hazard ratios were attenuated after taking all comorbidities into account. Men were at higher risk for COVID-19-related hospitalization (adjusted HR [aHR] 1·38; 95%CI 1·36-1·40) and in-hospital mortality (aHR 2·08; 95%CI 2·01-2·16) than women. As expected, Ile-de-France and Grand Est were the two regions most severely affected by the first wave of the epidemic, with a risk of COVID-19-related hospitalization or death more than tenfold higher than the risk of death observed in Bretagne or Nouvelle Aquitaine. A constantly increasing risk of COVID-19-related hospitalization and death was also observed according to the deprivation index: individuals in the most deprived quintile had an aHR of 1·45 (95%CI 1·42-1·48) and 1·38 (95%CI 1·31-1·45), respectively, compared to individuals in the least deprived quintile.

Smoking was negatively associated with the risk of COVID-19-related hospitalization (aHR 0·86; 95%CI 0·84-0·89) and positively

Table 1
Description of the cohort: sample size, number of patients hospitalized for COVID-19 and number of COVID-19-related deaths in hospital.

	Number		Number of hospitalizations with COVID-19		Number of in-hospital death with COVID-19	
	66,050,590	colomn %	**87,809**	% (within stratum)	**15,661**	% (within stratum)
Characteristics sociodemographic						
Age (years) - mean (SD)	43 (24)		67 (19)		80 (12)	
Age - no (%)						
< **5**	2,928,823	4·4%	161	0·01%	1	0·00%
5 - 9	3,912,876	5·9%	115	0·00%	1	0·00%
10 - 14	4,005,913	6·1%	133	0·00%		0·00%
15 - 19	3,881,938	5·9%	393	0·01%	2	0·00%
20 - 24	3,619,129	5·5%	1,123	0·03%	3	0·00%
25 - 29	3,727,718	5·6%	1,772	0·05%	7	0·00%
30 - 34	4,100,006	6·2%	2,285	0·06%	19	0·00%
35 - 39	4,209,706	6·4%	2,780	0·07%	45	0·00%
40 - 44	4,113,768	6·2%	3,252	0·08%	57	0·00%
45 - 49	4,416,462	6·7%	4,554	0·10%	100	0·00%
50 - 54	4,417,700	6·7%	5,746	0·13%	273	0·01%
55 - 59	4,366,478	6·6%	6,705	0·15%	417	0·01%
60 - 64	4,084,019	6·2%	7,381	0·18%	711	0·02%
65 - 69	3,846,402	5·8%	7,478	0·19%	1,119	0·03%
70 - 74	3,690,137	5·6%	8,662	0·23%	1,655	0·04%
75 - 79	2,301,857	3·5%	7,548	0·33%	1,795	0·08%
80 - 84	1,893,802	2·9%	8,727	0·46%	2,657	0·14%
85 - 89	1,449,669	2·2%	9,562	0·66%	3,303	0·23%
90 - 110	1,084,187	1·6%	9,432	0·87%	3,496	0·32%
Sex						
Women	34,328,810	52·0%	41,043	0·12%	6,302	0·018%
Men	31,721,780	48·0%	46,766	0·15%	9,359	0·030%
Regions - no (%)						
Ile de France	11,979,153	291·2%	30,009	0·25%	5,612	0·05%
Grand Est	5,399,178	131·2%	12,939	0·24%	2,894	0·05%
Hauts-de-France	5,889,172	143·2%	8,852	0·15%	1,729	0·03%
Auvergne-Rhône-Alpes	7,930,539	192·8%	8,535	0·11%	1,499	0·02%
Bourgogne-Franche-Comté	2,715,812	66·0%	4,303	0·16%	872	0·03%
Centre-Val-de-Loire	2,533,193	61·6%	2,264	0·09%	408	0·02%
Provence-Alpes-Côte d'Azur	5,211,475	126·7%	7,971	0·15%	772	0·01%
Occitanie	5,908,406	143·6%	3,161	0·05%	444	0·01%
Nouvelle-Aquitaine	5,951,085	144·7%	2,724	0·05%	388	0·01%
Normandie	3,243,885	78·9%	2,455	0·08%	379	0·01%
Pays de la Loire	3,767,317	91·6%	2,319	0·06%	359	0·01%
Bretagne	3,302,556	80·3%	1,289	0·04%	212	0·01%
Corse	248,255	6·0%	193	0·08%	27	0·01%
Guadeloupe	375,670	9·1%	122	0·03%	23	0·01%
Martinique	350,992	8·5%	148	0·04%	16	0·00%
Guyane	190,720	4,6%	168	0·09%	8	0·00%
La Réunion	876,870	21·3%	157	0·02%	3	0·00%
Mayotte	101,513	2·5%	161	0·16%	13	0·01%
Unknown	74,799	1·8%	39	0·05%	3	0·00%
Social deprivation index (quintiles) - no (%)						
1 (the least deprivation)	12,950,270	19·6%	20,893	0·16%	3,847	0·03%
2	12,768,656	19·3%	14,699	0·12%	2,536	0·02%
3	12,690,988	19·2%	14,375	0·11%	2,451	0·02%
4	12,498,209	18·9%	15,117	0·12%	2,814	0·02%
5 (the most deprivation)	12,277,322	18·6%	20,860	0·17%	3,734	0·03%
Unknown	2,865,145	4·3%	1,865	0·07%	279	0·01%
Lifestyle habits						
Smoking - no (%)	2,343,597	3·5%	3,995	0·17%	799	0·03%
Alcoholism - no (%)	871,686	1·3%	1,768	0·20%	319	0·04%
Opioide addiction - no (%)	208,109	0·3%	308	0·15%	18	0·01%
Comorbidities* - no (%)						
Cardiometabolic						
Obesity	875,385	1·3%	2,461	0·28%	296	0·03%
Diabetes	3,806,155	5·8%	19,231	0·51%	4,798	0·13%
Dyslipidemia and lipid-lowering treatments	6,711,385	10·2%	23,617	0·35%	5,679	0·08%
Hereditary metabolic diseases or amyloidosis	113,702	0·2%	317	0·28%	82	0·07%
Hypertension	11,942,507	18·1%	43,544	0·36%	10,716	0·09%
Coronary diseases	1,954,933	3·0%	10,678	0·55%	3,124	0·16%
Obliterating arterial disease of the lower limb	643,753	1·0%	4,231	0·66%	1,395	0·22%
Cardiac rhythm or conduction disturbances	2,273,991	3·4%	16,254	0·71%	5,210	0·23%
Heart failure	694,978	1·1%	7,578	1·09%	2,613	0·38%

(*continued*)

Table 1 (*Continued*)

	Number		Number of hospitalizations with COVID-19		Number of in-hospital death with COVID-19	
	66,050,590	colomn %	**87,809**	% (within stratum)	**15,661**	% (within stratum)
Valvular diseases	645,480	1·0%	4,802	0·74%	1,593	0·25%
Stroke	855,651	1·3%	5,626	0·66%	1,748	0·20%
Respiratory						
Chronic respiratory diseases (excluding cystic fibrosis)	3,522,735	5·3%	12,789	0·36%	3,064	0·09%
Cystic fibrosis	8,584	0·0%	32	0·37%	6	0·07%
Pulmonary embolism	149,031	0·2%	1,065	0·71%	309	0·21%
Cancer						
Female breast cancer (active)	211,500	0·3%	630	0·30%	142	0·07%
Female breast cancer (under surveillance)	477,360	0·7%	1,250	0·26%	284	0·06%
Colorectal cancer (active)	127,752	0·2%	615	0·48%	167	0·13%
Colorectal cancer (under surveillance)	207,976	0·3%	898	0·43%	250	0·12%
Lung cancer (active)	66,785	0·1%	621	0·93%	223	0·33%
Lung cancer (under surveillance)	49,399	0·1%	301	0·61%	100	0·20%
Prostate cancer (active)	202,266	0·3%	1,029	0·51%	337	0·17%
Prostate cancer (under surveillance)	297,872	0·5%	1,424	0·48%	445	0·15%
Other cancers (active)	713,122	1·1%	3,944	0·55%	1,240	0·17%
Other cancers (under surveillance)	885,598	1·3%	3,451	0·39%	963	0·11%
Inflammatoy and skin diseases						
Chronic inflammatory bowel diseases	268,185	0·4%	600	0·22%	78	0·03%
Rheumatoid arthritis and related diseases	287,753	0·4%	1,172	0·41%	268	0·09%
Ankylosing spondylitis and related diseases	222,067	0·3%	569	0·26%	90	0·04%
Psoriasis	297,025	0·4%	787	0·26%	142	0·05%
Psychological and neurodegenerative diseases						
Neurotic and Mood Disorders, use of antidepressant treatments	4,264,936	6·5%	14,574	0·34%	3,402	0·08%
Psychotics disorders, use of neuroleptics treatments	762,620	1·2%	3,384	0·44%	940	0·12%
Psychiatric disorders starting in childhood	165,622	0·3%	146	0·09%	25	0·02%
Down syndrom	33,541	0·1%	208	0·62%	48	0·14%
Epilepsy	321,047	0·5%	1,302	0·41%	292	0·09%
Multiple sclerosis	113,064	0·2%	324	0·29%	58	0·05%
Paraplegia	91,416	0·1%	463	0·51%	103	0·11%
Myopathy or myasthenia gravis	46,191	0·1%	153	0·33%	41	0·09%
Parkinson disease	244,730	0·4%	1,934	0·79%	645	0·26%
Dementias (including Alzheimer's disease)	610,320	0·9%	7,850	1·29%	2,819	0·46%
Mental impairment	126,180	0·2%	583	0·46%	120	0·10%
Other pathologies						
Hemophilia or severe hemostasis disorders	49,786	0·1%	167	0·34%	39	0·08%
HIV infection	146,204	0·2%	575	0·39%	64	0·04%
Liver diseases	397,282	0·6%	2,170	0·55%	487	0·12%
Chronic dialysis	45,924	0·1%	1,099	2·39%	342	0·74%
Renal transplant	42,525	0·1%	547	1·29%	137	0·32%
Cardiac translant	1,669	0·0%	22	1·32%	4	0·24%
Liver transplant	5,021	0·0%	27	0·54%	4	0·08%
Lung transplant	1,345	0·0%	25	1·86%	6	0·45%

associated with the risk of COVID-19-related in-hospital mortality (aHR 1·10; 95%CI 1·01-1·18) in multivariable analysis.

Most chronic diseases were positively associated with the risk of COVID-19-related hospitalization and in-hospital mortality, with the exception of dyslipidaemia, which was negatively associated (aHR 0·89; 95%CI 0·87-0·90 and aHR 0·84; 95%CI 0·81-0·88, respectively) in multivariable analysis.

The strongest positive associations with the risk of COVID-19-related hospitalization were observed in patients with Down syndrome (aHR 7·03; 95%CI 6·13-8·07), mental retardation (aHR 3·83; 95%CI 3·52-4·16), lung transplantation (aHR 3·53; 95%CI 2·35-5·29), kidney transplantation (aHR 4·55; 95%CI 4·18-4·95), end-stage renal disease on dialysis (aHR 4·16; 95%CI 3·92-4·42) and active lung cancer (aHR 2·60; 95%CI 2·40-2·81). Diabetes (aHR 1·64; 95%CI 1·61-1·67), obesity (aHR 1·63; 95%CI 1·57-1·70), hypertension (aHR 1·17; 95%CI 1·15-1·19), cardiovascular diseases (highest aHR for heart failure with aHR 1·44; 95%CI 1·40-1·48), chronic respiratory diseases (aHR 1·56; 95%CI 1·53-1·59), active cancers and neurodegenerative diseases were associated with an excess risk of COVID-19-related hospitalization.

In multivariable analysis, these same comorbidities were also associated with a higher risk of COVID-19-related in-hospital mortality: Down syndrome (aHR 22·9; 95%CI 17·1-30·7) (absolute risk: 143 per 100,000), mental retardation (aHR 7·31; 95%CI 6·05-8·82), lung transplantation (aHR 6·2; 95%CI 2·75-14,0), kidney transplantation (aHR 7·08; 95%CI 5·97-8·40), end-stage renal disease on dialysis (aHR 4·65; 95%CI 4·17-5·19) and active lung cancer (aHR 4·00; 95%CI 3·50-4·57). Patients with diabetes (aHR 1·75; 95%CI 1·68-1·81), obesity

Table 2
Hazard ratio (HR) and 95% confidence interval (95%CI) for the criteria for COVID-19-related hospitalization and in-hospital death (Note: some associations were not estimated due to insufficient sample sizes).

	Hospitalization with COVID-19			In-hospital death with COVID-19		
	Number of events	Age-sex adj	Fully adj	Number of events	Age-sex adj	Fully adj
Characteristics						
sociodemographic						
Age - no (%)						
< **5**	161	0·07 (0·06 - 0·08)	0·07 (0·06 - 0·08)	1	0·02 (0 - 0·17)	0·03 (0 - 0·19)
5 - 9	115	0·04 (0·03 - 0·04)	0·04 (0·03 - 0·05)	1	0·02 (0 - 0·13)	0·02 (0 - 0·14)
10 - 14	133	0·04 (0·03 - 0·05)	0·05 (0·04 - 0·05)			
15 - 19	393	0·13 (0·11 - 0·14)	0·14 (0·13 - 0·16)	2	0·04 (0·01 - 0·15)	0·04 (0·01 - 0·17)
20 - 24	1,123	0·39 (0·37 - 0·42)	0·43 (0·4 - 0·46)	3	0·06 (0·02 - 0·19)	0·07 (0·02 - 0·21)
25 - 29	1,772	0·6 (0·57 - 0·64)	0·62 (0·59 - 0·66)	7	0·14 (0·06 - 0·3)	0·14 (0·06 - 0·31)
30 - 34	2,285	0·71 (0·67 - 0·75)	0·72 (0·68 - 0·76)	19	0·34 (0·2 - 0·57)	0·34 (0·21 - 0·58)
35 - 39	2,780	0·84 (0·8 - 0·88)	0·85 (0·81 - 0·9)	45	0·78 (0·52 - 1·15)	0·79 (0·53 - 1·17)
40 - 44	3,252	1	1	57	1	1
45 - 49	4,554	1·3 (1·24 - 1·36)	1·28 (1·22 - 1·34)	100	1·63 (1·18 - 2·25)	1·58 (1·14 - 2·19)
50 - 54	5,746	1·64 (1·57 - 1·72)	1·56 (1·49 - 1·62)	273	4·44 (3·34 - 5·91)	4·14 (3·11 - 5·51)
55 - 59	6,705	1·94 (1·86 - 2·03)	1·74 (1·67 - 1·82)	417	6·88 (5·22 - 9·08)	6·03 (4·57 - 7·95)
60 - 64	7,381	2·29 (2·2 - 2·39)	1·97 (1·89 - 2·05)	711	12·6 (9·62 - 16·51)	10·54 (8·04 - 13·81)
65 - 69	7,478	2·47 (2·38 - 2·58)	2·03 (1·95 - 2·12)	1,119	21·15 (16·21 - 27·6)	17·03 (13·04 - 22·24)
70 - 74	8,662	2·99 (2·88 - 3·12)	2·32 (2·22 - 2·42)	1,655	32·77 (25·16 - 42·67)	24·95 (19·13 - 32·53)
75 - 79	7,548	4·21 (4·04 - 4·39)	2·94 (2·82 - 3·07)	1,795	57·64 (44·28 - 75·03)	39·69 (30·44 - 51·76)
80 - 84	8,727	6·01 (5·77 - 6·25)	3·78 (3·63 - 3·95)	2,657	106·43 (81·87 - 138·36)	65·34 (50·16 - 85·11)
85 - 89	9,562	8·82 (8·48 - 9·18)	5·01 (4·8 - 5·23)	3,303	181·69 (139·84 - 236·08)	100·28 (77 - 130·61)
90 - 110	9,432	12·21 (11·73 - 12·71)	6·44 (6·16 - 6·72)	3,496	280·42 (215·83 - 364·34)	144·06 (110·59 - 187·65)
Male sex - no (%)	46,766	1·46 (1·44 - 1·48)	1·38 (1·36 - 1·4)	9,359	2·26 (2·19 - 2·34)	2·08 (2·01 - 2·16)
Regions - no (%)						
Ile de France	30,009	1	1	5,612	1	1
Grand Est	12,939	0·81 (0·79 - 0·83)	0·7 (0·68 - 0·71)	2,894	0·88 (0·84 - 0·92)	0·74 (0·7 - 0·78)
Hauts-de-France	8,852	0·55 (0·54 - 0·57)	0·45 (0·44 - 0·46)	1,729	0·55 (0·52 - 0·58)	0·45 (0·43 - 0·48)
Auvergne-Rhône-Alpes	8,535	0·37 (0·36 - 0·38)	0·35 (0·34 - 0·35)	1,499	0·31 (0·29 - 0·33)	0·28 (0·27 - 0·3)
Bourgogne-Franche-Comté	4,303	0·49 (0·48 - 0·51)	0·43 (0·42 - 0·45)	872	0·45 (0·42 - 0·48)	0·39 (0·36 - 0·42)
Centre-Val-de-Loire	2,264	0·28 (0·27 - 0·29)	0·26 (0·24 - 0·27)	408	0·23 (0·21 - 0·25)	0·21 (0·19 - 0·23)
Provence-Alpes-Côte d'Azur	7,971	0·48 (0·47 - 0·49)	0·46 (0·45 - 0·47)	772	0·22 (0·2 - 0·23)	0·2 (0·18 - 0·21)
Occitanie	3,161	0·17 (0·16 - 0·17)	0·15 (0·15 - 0·16)	444	0·11 (0·1 - 0·12)	0·1 (0·09 - 0·11)
Nouvelle-Aquitaine	2,724	0·14 (0·13 - 0·14)	0·13 (0·12 - 0·13)	388	0·09 (0·08 - 0·1)	0·08 (0·07 - 0·09)
Normandie	2,455	0·25 (0·24 - 0·26)	0·21 (0·2 - 0·22)	379	0·18 (0·16 - 0·2)	0·15 (0·14 - 0·17)
Pays de la Loire	2,319	0·21 (0·2 - 0·21)	0·19 (0·19 - 0·2)	359	0·15 (0·13 - 0·17)	0·14 (0·13 - 0·16)
Bretagne	1,289	0·12 (0·12 - 0·13)	0·12 (0·11 - 0·13)	212	0·1 (0·08 - 0·11)	0·09 (0·08 - 0·1)
Corse	193	0·24 (0·21 - 0·27)	0·22 (0·19 - 0·25)	27	0·15 (0·1 - 0·22)	0·13 (0·09 - 0·2)
Guadeloupe	122	0·11 (0·09 - 0·13)	0·11 (0·09 - 0·13)	23	0·11 (0·07 - 0·16)	0·11 (0·07 - 0·17)
Martinique	148	0·14 (0·12 - 0·16)	0·14 (0·12 - 0·17)	16	0·07 (0·04 - 0·12)	0·08 (0·05 - 0·13)
Guyane	168	0·55 (0·47 - 0·64)	0·56 (0·48 - 0·66)	8	0·2 (0·1 - 0·4)	0·22 (0·11 - 0·44)
La Réunion	157	0·08 (0·07 - 0·1)	0·08 (0·07 - 0·09)	3	0·01 (0 - 0·03)	0·01 (0 - 0·03)
Mayotte	161	1·14 (0·98 - 1·33)	1·24 (1·05 - 1·47)	13	0·82 (0·48 - 1·42)	1·06 (0·61 - 1·86)
Unknown	39	0·2 (0·14 - 0·27)	0·21 (0·15 - 0·29)	3	0·07 (0·02 - 0·23)	0·08 (0·03 - 0·25)
Social deprivation index (quintiles) - no (%)						
1 (the least deprivation)	20,893	1	1	3,847	1	1
2	14,699	0·71 (0·69 - 0·72)	1·09 (1·06 - 1·11)	2,536	0·66 (0·63 - 0·69)	1·12 (1·06 - 1·18)
3	14,375	0·65 (0·64 - 0·67)	1·15 (1·12 - 1·17)	2,451	0·57 (0·54 - 0·6)	1·2 (1·13 - 1·27)
4	15,117	0·68 (0·66 - 0·69)	1·22 (1·19 - 1·25)	2,814	0·63 (0·6 - 0·66)	1·25 (1·19 - 1·32)
5 (the most deprivation)	20,860	0·97 (0·95 - 0·99)	1·45 (1·42 - 1·48)	3,734	0·86 (0·82 - 0·9)	1·38 (1·31 - 1·45)
Unknown	1,865	0·42 (0·4 - 0·44)	1·07 (1·01 - 1·14)	279	0·33 (0·29 - 0·37)	1·08 (0·94 - 1·24)
Lifestyle habits						
Smoking	3,995	1·2 (1·16 - 1·24)	0·86 (0·84 - 0·89)	799	1·88 (1·75 - 2·02)	1·1 (1·01 - 1·18)
Alcoholism	1,768	1·61 (1·54 - 1·69)	1·18 (1·12 - 1·24)	319	2·21 (1·98 - 2·48)	1·36 (1·21 - 1·52)
Opioid addiction	308	1·42 (1·27 - 1·59)	1·11 (0·99 - 1·25)	18	1·74 (1·09 - 2·77)	1·05 (0·66 - 1·67)
Comorbidities						
Cardiometabolic						
Obesity	2,461	2·37 (2·28 - 2·47)	1·63 (1·57 - 1·7)	296	2·55 (2·27 - 2·86)	1·56 (1·39 - 1·76)
Diabetes	19,231	2·03 (2 - 2·07)	1·64 (1·61 - 1·67)	4,798	2·14 (2·07 - 2·21)	1·75 (1·68 - 1·81)
Dyslipidemia and lipid-lowering treatments	23,617	1·22 (1·2 - 1·24)	0·89 (0·87 - 0·9)	5,679	1·15 (1·11 - 1·19)	0·84 (0·81 - 0·88)
Hereditary metabolic diseases or amyloidosis	317	1·38 (1·23 - 1·54)	1·11 (0·99 - 1·24)	82	1·64 (1·32 - 2·03)	1·24 (1 - 1·54)
Hypertension	43,544	1·46 (1·44 - 1·48)	1·17 (1·15 - 1·19)	10,716	1·44 (1·39 - 1·49)	1·15 (1·1 - 1·19)
Coronary diseases	10,678	1·57 (1·54 - 1·6)	1·14 (1·12 - 1·17)	3,124	1·61 (1·55 - 1·68)	1·16 (1·11 - 1·21)
Obliterating arterial disease of the lower limb	4,231	1·77 (1·72 - 1·83)	1·26 (1·22 - 1·3)	1,395	2·02 (1·91 - 2·13)	1·41 (1·33 - 1·5)
Cardiac rhythm or conduction disturbances	16,254	1·97 (1·94 - 2·01)	1·37 (1·34 - 1·4)	5,210	2·16 (2·08 - 2·24)	1·41 (1·35 - 1·46)
Heart failure	7,578	2·54 (2·48 - 2·6)	1·44 (1·4 - 1·48)	2,613	2·8 (2·68 - 2·92)	1·54 (1·47 - 1·62)
Valvular diseases	4,802	1·8 (1·74 - 1·85)	1·15 (1·11 - 1·19)	1,593	1·95 (1·85 - 2·06)	1·2 (1·14 - 1·27)
Stroke	5,626	1·83 (1·78 - 1·88)	1·33 (1·29 - 1·37)	1,748	1·98 (1·88 - 2·08)	1·39 (1·32 - 1·47)
Respiratory						
Chronic respiratory diseases (excluding cystic fibrosis)	12,789	1·92 (1·88 - 1·96)	1·56 (1·53 - 1·59)	3,064	1·98 (1·9 - 2·06)	1·48 (1·42 - 1·55)
Cystic fibrosis	32	6·19 (4·37 - 8·75)	3·74 (2·62 - 5·34)	6		
Pulmonary embolism	1,065	2·13 (2 - 2·26)	1·44 (1·35 - 1·53)	309	2·29 (2·05 - 2·56)	1·45 (1·3 - 1·63)
Cancer						
Female breast cancer (active)	630	1·49 (1·38 - 1·62)	1·41 (1·3 - 1·52)	142	1·99 (1·69 - 2·36)	1·8 (1·52 - 2·12)
Female breast cancer (under surveillance)	1,250	1·04 (0·98 - 1·1)	0·97 (0·92 - 1·02)	284	1·22 (1·08 - 1·37)	1·1 (0·97 - 1·23)
Colorectal cancer (active)	615	1·55 (1·43 - 1·67)	1·36 (1·25 - 1·47)	167	1·63 (1·4 - 1·9)	1·4 (1·2 - 1·63)

(*continued*)

Table 2 (*Continued*)

	Hospitalization with COVID-19			In-hospital death with COVID-19		
	Number of events	Age-sex adj	Fully adj	Number of events	Age-sex adj	Fully adj
Colorectal cancer (under surveillance)	898	1·13 (1·06 - 1·21)	1·04 (0·97 - 1·11)	250	1·09 (0·96 - 1·24)	0,98 (0,86 - 1,11)
Lung cancer (active)	621	3·6 (3·33 - 3·9)	2·6 (2·4 - 2·81)	223	5·7 (4·99 - 6·5)	4 (3,5 - 4,57)
Lung cancer (under surveillance)	301	1·97 (1·76 - 2·21)	1·37 (1·22 - 1·53)	100	2·56 (2·1 - 3·12)	1,7 (1,4 - 2,07)
Prostate cancer (active)	1,029	1·21 (1·13 - 1·28)	1·19 (1·12 - 1·27)	337	1·21 (1·08 - 1·35)	1,2 (1,08 - 1,34)
Prostate cancer (under surveillance)	1,424	1·05 (1 - 1·11)	1·01 (0·96 - 1·07)	445	0·96 (0·87 - 1·05)	0,92 (0,83 - 1,01)
Other cancers (active)	3,944	1·82 (1·76 - 1·88)	1·65 (1·59 - 1·7)	1,240	2·14 (2·01 - 2·26)	1,95 (1,84 - 2,07)
Other cancers (under surveillance)	3,451	1·23 (1·19 - 1·27)	1·14 (1·1 - 1·18)	963	1·25 (1·17 - 1·33)	1,18 (1,1 - 1,26)
Inflammatory and skin diseases						
Chronic inflammatory bowel diseases	600	1·48 (1·37 - 1·61)	1·28 (1·18 - 1·38)	78	1·23 (0·99 - 1·54)	0,98 (0,78 - 1,22)
Rheumatoid arthritis and related diseases	1,172	1·6 (1·51 - 1·7)	1·48 (1·39 - 1·56)	268	1·64 (1·45 - 1·85)	1,53 (1,35 - 1,72)
Ankylosing spondylitis and related diseases	569	1·48 (1·36 - 1·6)	1·25 (1·15 - 1·35)	90	1·41 (1·15 - 1·74)	1,13 (0,91 - 1,39)
Psoriasis	787	1·3 (1·21 - 1·39)	1·12 (1·04 - 1·2)	142	1·17 (0·99 - 1·38)	1 (0,85 - 1,18)
Psychological and neurodegenerative diseases						
Neurotic and Mood Disorders, use of antidepressant treatments	14,574	1·6 (1·57 - 1·63)	1·31 (1·28 - 1·33)	3,402	1·8 (1·73 - 1·87)	1,36 (1,3 - 1,41)
Psychotics disorders, use of neuroleptics treatments	3,384	2·18 (2·11 - 2·26)	1·61 (1·56 - 1·67)	940	3·03 (2·83 - 3·23)	2,13 (1,99 - 2,28)
Psychiatric disorders starting in childhood	146	3·31 (2·82 - 3·9)	2·05 (1·74 - 2·41)	25	7·68 (5·19 - 11·38)	3,31 (2,23 - 4,93)
Down syndrom	208	8·93 (7·79 - 10·23)	7·03 (6·13 - 8·07)	48	40·39 (30·37 - 53·71)	22,87 (17,04 - 30,69)
Epilepsy	1,302	2·29 (2·16 - 2·41)	1·52 (1·44 - 1·61)	292	2·37 (2·11 - 2·66)	1,44 (1,28 - 1,62)
Multiple sclerosis	324	2·11 (1·89 - 2·35)	1·74 (1·55 - 1·94)	58	3·39 (2·62 - 4·39)	2,63 (2,02 - 3,42)
Paraplegia	463	2·77 (2·52 - 3·03)	1·95 (1·78 - 2·15)	103	3·34 (2·75 - 4·05)	2,23 (1,83 - 2,73)
Myopathy or myasthenia gravis	153	1·83 (1·56 - 2·15)	1·37 (1·17 - 1·61)	41	2·47 (1·82 - 3·36)	1,88 (1,38 - 2,55)
Parkinson disease	1,934	1·88 (1·79 - 1·97)	1·52 (1·45 - 1·59)	645	2·04 (1·88 - 2·2)	1,63 (1,5 - 1,76)
Dementias (including Alzheimer's disease)	7,850	2·66 (2·6 - 2·73)	2·04 (1·99 - 2·1)	2,819	3·06 (2·93 - 3·2)	2,16 (2,06 - 2,26)
Mental impairment	583	4·25 (3·92 - 4·61)	3·83 (3·52 - 4·16)	120	7·98 (6·67 - 9·56)	7,31 (6,05 - 8,82)
Other pathologies						
Hemophilia or severe hemostasis disorders	167	1·74 (1·49 - 2·03)	1·47 (1·26 - 1·71)	39	1·96 (1·43 - 2·69)	1,66 (1,22 - 2,28)
HIV infection	575	2·74 (2·53 - 2·98)	1·88 (1·73 - 2·04)	64	2·7 (2·11 - 3·46)	1,93 (1,51 - 2,47)
Liver diseases	2,170	2·65 (2·54 - 2·77)	1·5 (1·43 - 1·57)	487	3·16 (2·89 - 3·46)	1,57 (1,42 - 1,72)
Chronic dialysis	1,099	7·3 (6·88 - 7·75)	4·16 (3·92 - 4·42)	342	7·92 (7·11 - 8·82)	4,65 (4,17 - 5,19)
Renal transplant	547	7·18 (6·61 - 7·81)	4·55 (4·18 - 4·95)	137	11·29 (9·53 - 13·36)	7,09 (5,98 - 8,42)
Cardiac transplant	22	9·28 (6·12 - 14·08)	2·15 (1·41 - 3·27)	4	17·1 (6·41 - 45·58)	2,63 (0,98 - 7,04)
Liver transplant	27	3·25 (2·23 - 4·74)	0·84 (0·58 - 1·23)	4	3·92 (1·47 - 10·46)	0,72 (0,27 - 1,94)
Lung transplant	25	14·3 (9·7 - 21·08)	3·53 (2·35 - 5·29)	6	19·14 (8·53 - 42·97)	7,04 (3,15 - 15,73)

(aHR 1·56; 95%CI 1·39-1·76), hypertension (aHR 1·15; 95%CI 1·10-1·19), cardiovascular disease (highest risk for heart failure with aHR 1·54; 95%CI 1·47-1·62), chronic respiratory disease (aHR 1·48; 95%CI 1·42-1·55), active cancers and neurodegenerative diseases had an excess risk of in-hospital mortality. Stratified multivariable analyses showed stronger associations between the endpoints associated with severe forms of COVID-19 and certain chronic diseases, such as diabetes or cancer (Table 3 and Figures 3a and 3b) in patients under the age of 80 years. The hazard ratios for in-hospital mortality associated with active female breast cancer or active lung cancer were higher in patients under the age of 80 years (aHR 3·30; 95%CI 2·68-4·07 and aHR 5·03; 95%CI 4·30-5·89, respectively) than among patients 80 years and older (aHR 1·01; 95%CI 0·77-1·34 and aHR 2·21; 95%CI 1·68-2·9, respectively). A strong association between deprivation index and risk of developing a severe form of COVID-19 was observed in patients under the age of 80 years with a twofold higher risk of death after adjustment between the most deprived patients *versus* the least deprived patients (aHR 1·99; 95%CI 1·84-2·16), while the risk ratio was close to 1 in patients aged 80 years and older. In our cohort, 67% patients had no comorbidity. Analysis of the number of comorbidities showed an increase in risk of developing a severe form of COVID-19 with each additional comorbidity (Table 4). Patients with 5 or more comorbidities had a higher risk of hospitalization for COVID-19 (aHR 5·61 95%CI 5·47 - 5·76) and a higher risk of in-hospital-death for COVID-19 (aHR 10.00 95%CI 9·26 - 10·79) compared to those without any comorbidity. Associations between hospitalization and in-hospital death with COVID-19 and number of comorbidities were also stronger in patients younger than 80 compared to those aged 80 and older (Table S3).

70,805 patients were hospitalized in the first sub-period (from February, 15 to April, 15, 2020) with 13,247 in-hospital death (18·7% of hospitalized patients); 17,004 patients were hospitalized in the second sub-period (from April, 16 to June, 15, 2020) with 2,414 in-hospital death (14·2% of hospitalized patients). Smoking, alcoholism and opioid addiction were positively associated with hospitalization and in-hospital death for COVID during the 2nd sub-period. For chronic conditions, we observe similar trends in the results (Table S2).

4. Discussion

In this vast, almost comprehensive national cohort study on 66,050,090 patients, most of the chronic diseases studied were associated with an excess risk of COVID-19-related hospitalization and in-hospital mortality.

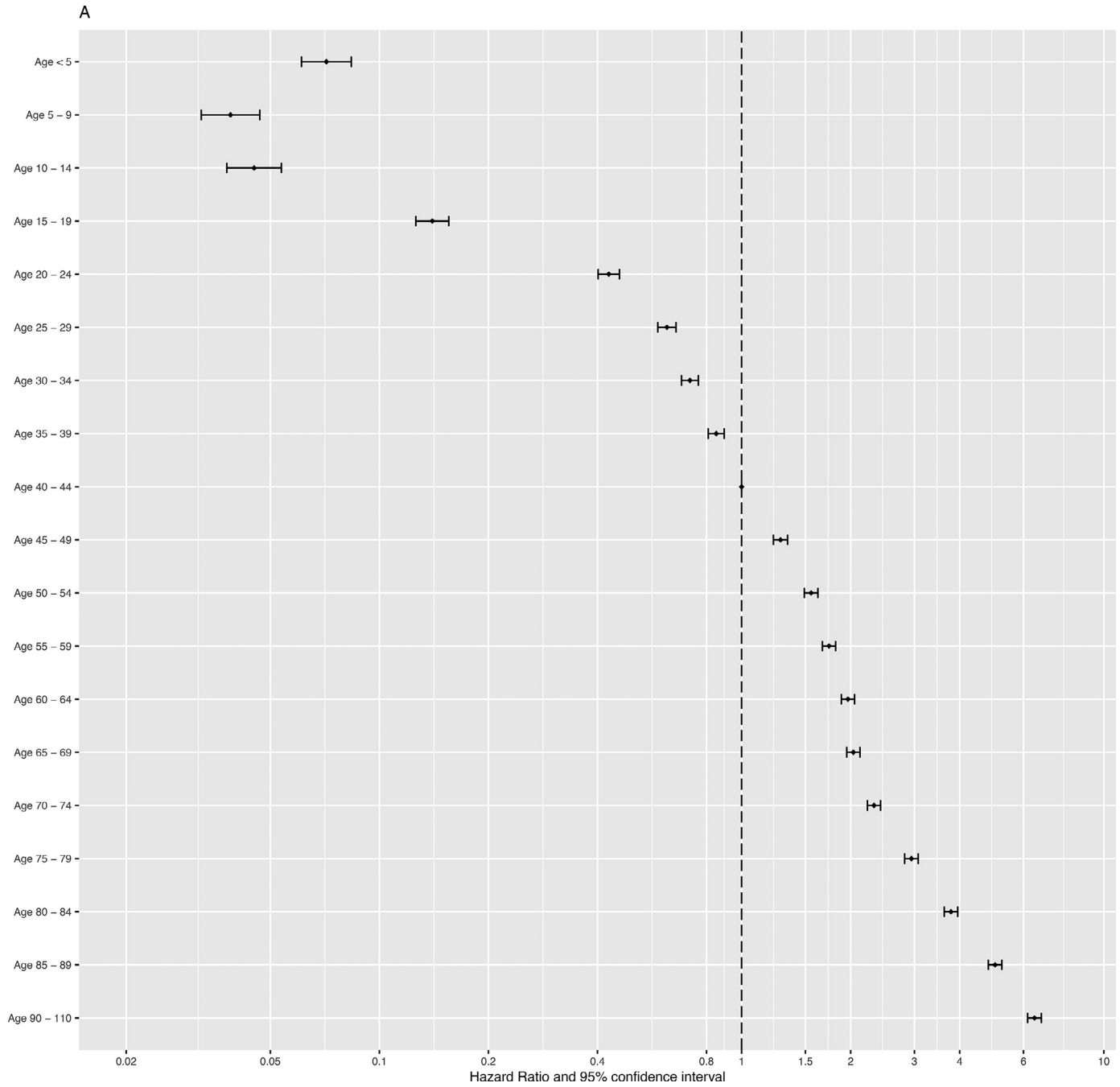

Figure 2a. Hazard ratios of COVID-19-related hospitalization estimated from a Cox model with multivariable adjustment (for reasons of scale, age (A) and sociodemographic variables (B) (with the exception of the region which is not represented) are presented on a separate graph from comorbidities (C)). Logarithmic scale.

Age was by far the main risk factor, with a 100-fold higher risk of death among people aged 85 to 89 years compared to people aged 40 to 44 years, while the risk of death was 20-fold higher among people aged 80 years compared to people aged 50 to 60 years in the study by Williamson et al[4] and 30-fold higher among people aged 80 to 90 years compared to people aged 50 to 60 years in the study by Reilev et al [5]. We know that older people are at greater risk of severe disease or death, likely due to their declining immune defences, with less well controlled viral replication and an accentuated inflammatory response. Cytokines also appear to directly contribute to hypercoagulability and consequently predispose to the risk of ischaemia and thrombosis [3]. The association between age and risk of COVID-19 has been known since the beginning of the epidemic and has been extensively described. The weaker associations observed before and after taking all comorbidities into account show that the effect of age can be partly explained by the increased risk of these diseases with advancing age. Male gender is also systematically associated with severe forms of COVID-19. As reported by Zheng *et al* [27], the X chromosome and sex hormones could have a protective role against COVID-19 in women by participating in innate and adaptive immunity. It is also possible that at least part of the risk difference between men and women is related to a higher prevalence of risk-taking behaviour among men, making them more likely to develop certain comorbidities or to be contaminated by the virus.

We identified an excess risk in the most socioeconomically deprived patients after multivariable adjustment, suggesting, as in

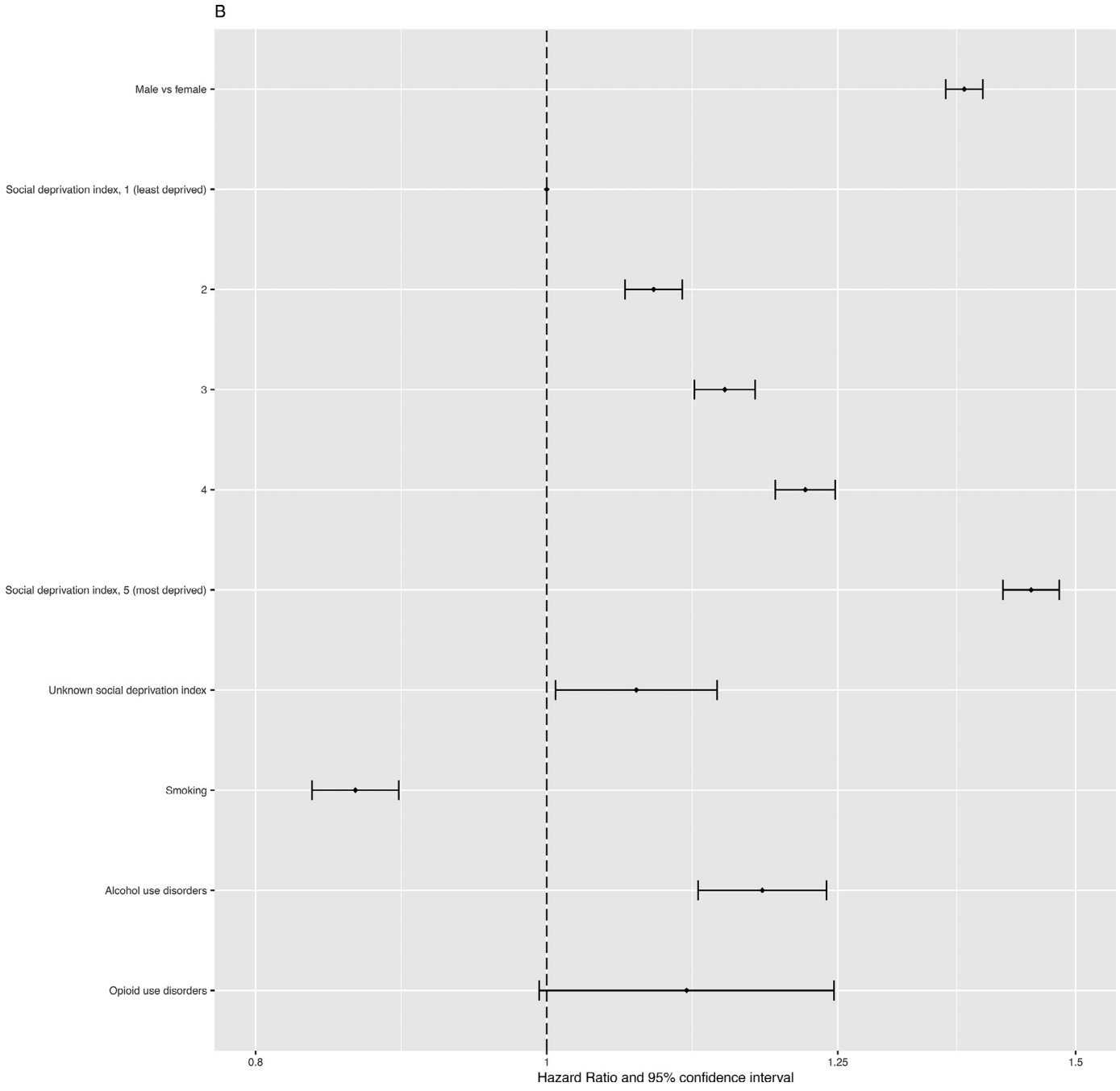

Figure 2a. Continued.

the study by Williamson *et al* [4], that social factors (housing, number of family members in the household, transportation, occupation, etc.) in addition to medical factors may also play a role in the development of severe forms of COVID-19. As mentioned by Bambra et al, [28] inequalities in COVID-19 are related to existing inequalities in chronic diseases and the social determinants of health. Social interactions linked to professional activity are very variable among the working population, depending on the profession, the possibility of teleworking, the use or otherwise of public transport, etc. During the lockdown period, lower-paid workers might have been more likely to be designated as key workers and required to work, thus being more exposed to the virus. Some of these disparities were likely reduced or even disappeared among retirees, which could explain our results stratified by age. Moreover, some of the elderly live in community within skilled nursing facilities or receive caregiver care. These contacts may have more impact on the risk of contracting the virus than the social level of the individual itself.

Another major risk factor for the development of severe forms of COVID-19 is obesity, probably linked to a pro-inflammatory response [29]. However, obesity was underestimated in our study, as we only considered the most severe forms of obesity requiring hospitalization or bariatric surgery, as body mass index (BMI) is not available in the SNDS database. Although the specific effect of obesity therefore cannot be directly interpreted, part of the variability of obesity as an adjustment factor can probably be taken into account in other chronic diseases, such as diabetes, or, to a lesser extent, hypertension

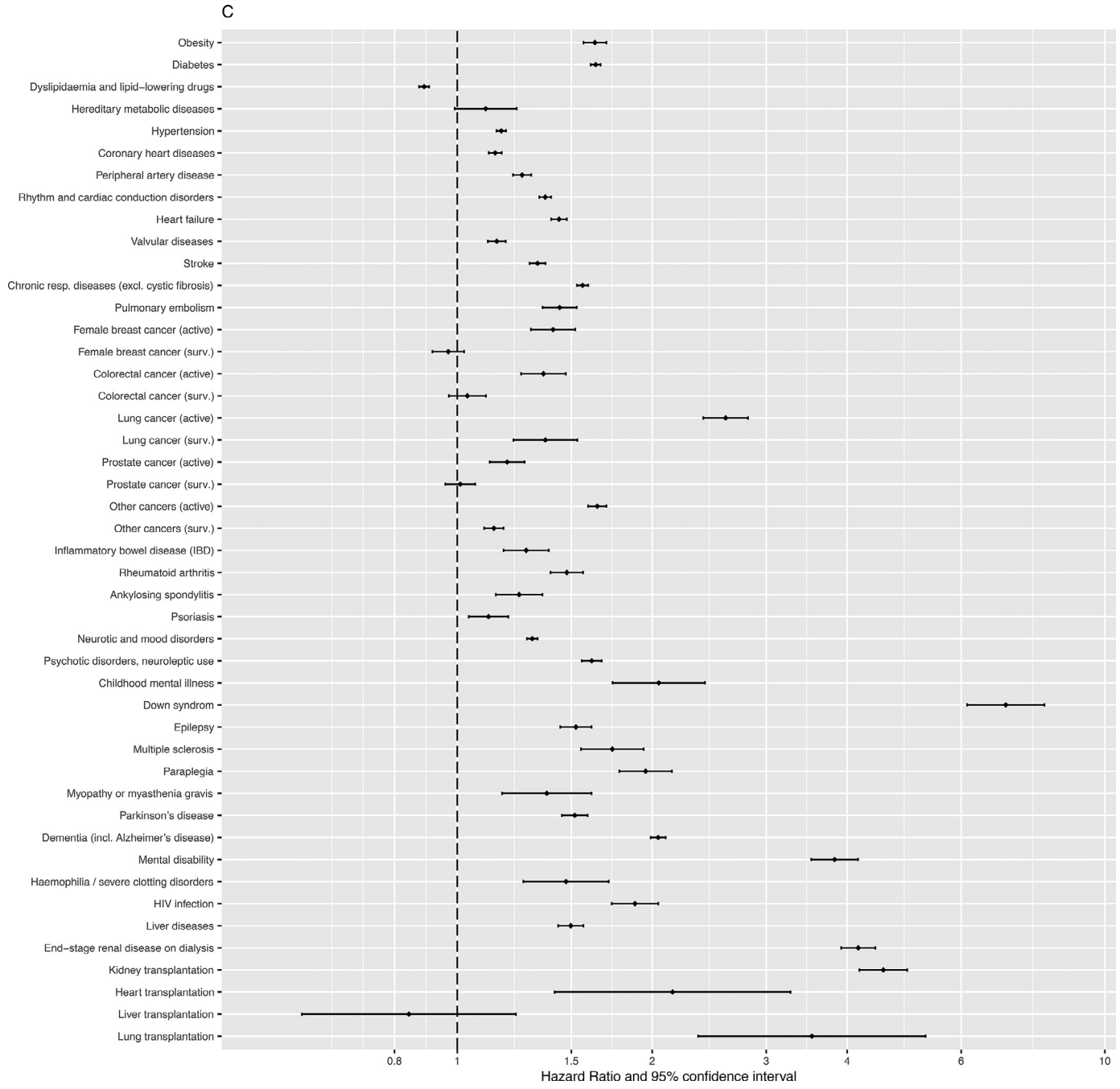

Figure 2a. Continued.

and cardiovascular diseases, thereby reducing the potential residual confounding bias.

While the risk of mortality has often been reported to be about twofold higher in patients with kidney disease [4,29–32], the risk of mortality in end-stage renal disease on dialysis patients in our study was estimated to be about fourfold higher, similar to the excess risk reported by Williamson *et al* [4].

Two studies have reported the risk of death to be about threefold higher among organ transplant recipients (without distinction) [4,5]. We more specifically studied the risk of kidney, heart, lung and liver transplantation and observed a risk heterogeneity ranging from aHR 0·72 (0·27 - 1·94) for liver transplantation to 7·08 (5·97 - 8·4) for kidney transplantation.

The excess risk associated with diabetes varies significantly between studies [4,5,29–35]. This heterogeneity could be explained by the level of HbA1c [4,31] or the type [33] of diabetes, and could also be related to the use of different definitions of diabetes or different ways of taking adjustment factors into account in these studies. The excess risk of 1·8 estimated in our study is similar to those reported by Williamson *et al*[4] and Reilev *et al* [5]. The risk associated with treatment of hypertension appears to be lower than reported in the literature [1–3] and several possible explanations can be proposed for this difference. A large number of cardiovascular diseases were considered in multivariable analysis. Adjustment for intermediate factors could reduce the association between hypertension and severity of

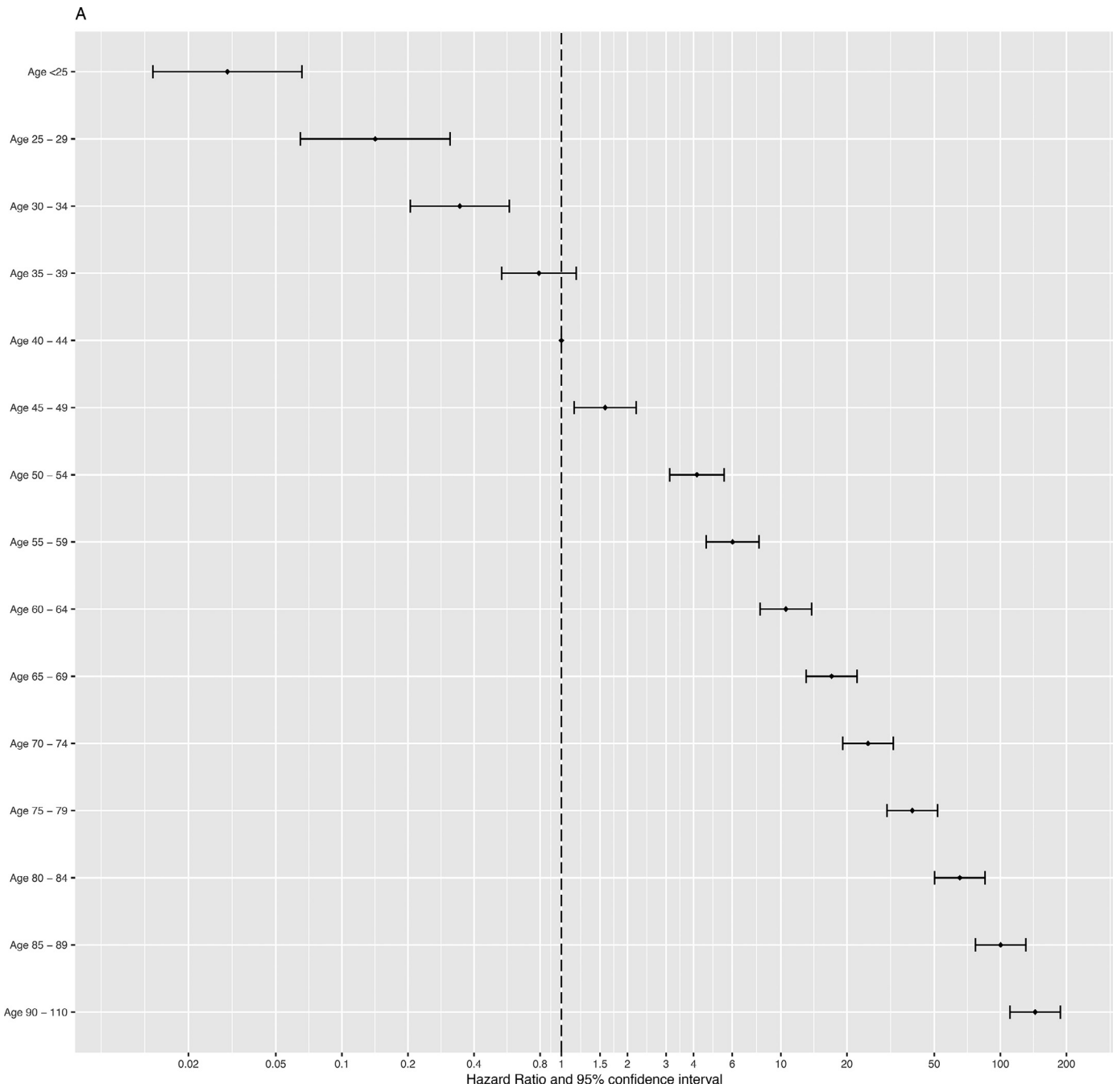

Figure 2b. Hazard ratios of COVID-19-related in-hospital mortality estimated from a Cox model with multivariable adjustment (for reasons of scale, age (A) and sociodemographic variables (B) (with the exception of the region which is not represented) are presented on a separate graph from comorbidities (C)). Logarithmic scale

COVID-19. Another possible explanation could be the use of different antihypertensive drugs in the population: we showed that the risk of developing a severe form of COVID-19 was lower in patients treated with angiotensin-converting enzyme (ACE) inhibitors or sartans compared to patients treated with calcium channel blockers (CCB) [21]. We also found higher risks of COVID-19-related hospitalization and in-hospital mortality among patients with cardiovascular disease [4,5,29,30,34,36], particularly heart failure (aHR 1·44; 95%CI 1·4-1·48 and aHR 1·54; 95%CI 1·47-1·62, respectively).

The excess risk observed for chronic respiratory diseases appeared to be consistent with the literature [4,5,29,30,32,36].

Patients with active cancer were also at higher risk of death than patients with cancer in remission [4·25], with a maximum fourfold higher risk among patients with active lung cancer.

Mental illness and neurodegenerative diseases were associated with a higher risk of COVID-19-related hospitalization and in-hospital mortality with a nearly 7-fold higher risk of death in people with mental retardation. People with psychotic disorders and dementia were twice as likely to die in hospital, a risk in the lower range of

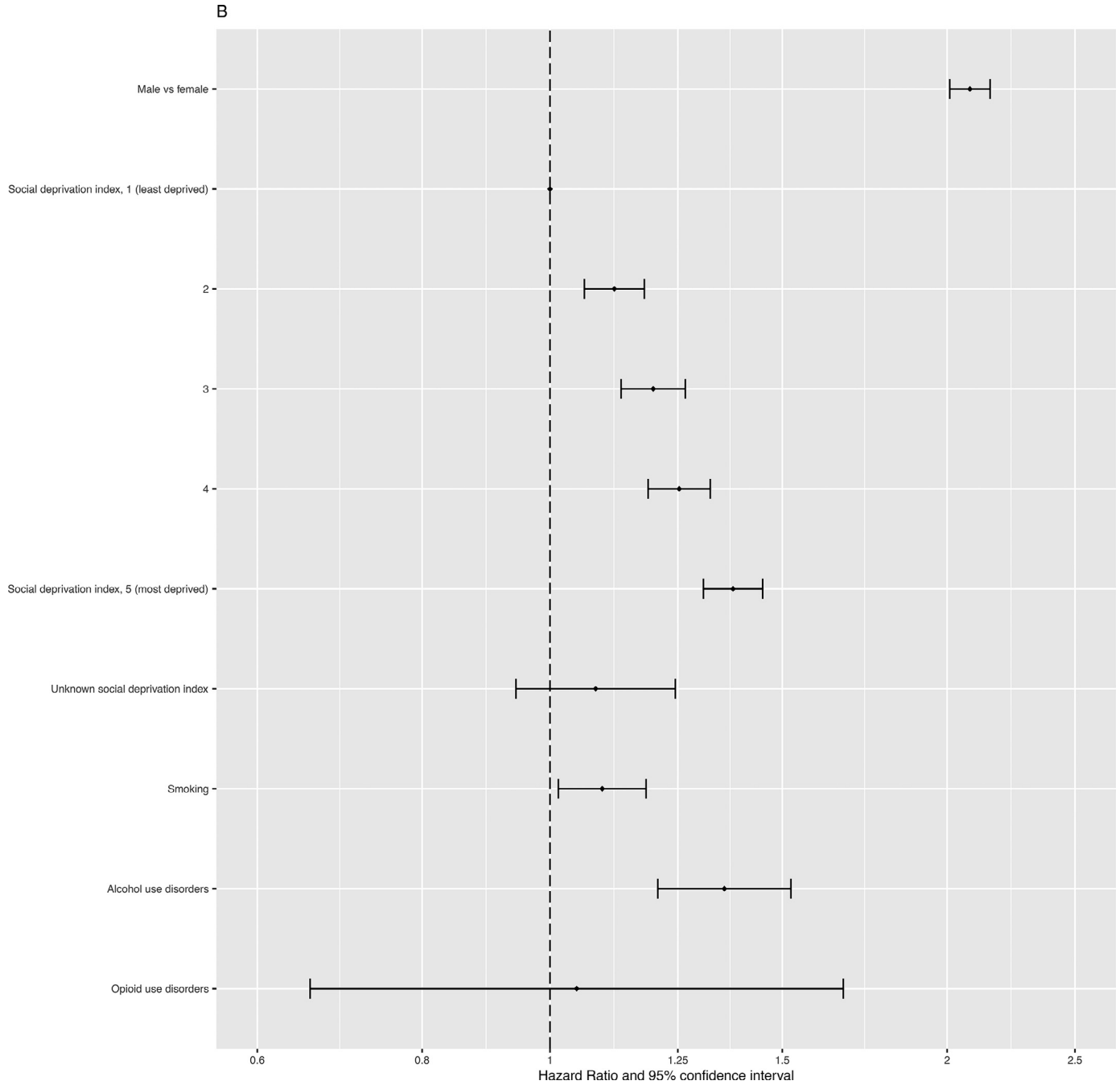

Figure 2b. Continued.

current estimates [4,30,32,34]. However, it is difficult to explain this observed excess risk. Although, on the one hand, we could hypothesize that some patients with mental illness might have less contact with the outside world and would therefore be less likely to be infected with the SARS-CoV-2 virus, it is also possible that some patients may have more difficulty complying with certain public health recommendations [30].

Dyslipidaemia, identified by the use of lipid-lowering drugs including statins or coded during hospitalization, is one of the only comorbidities associated with a lower risk of COVID-19-related hospitalization or in-hospital mortality. The nature of this association is not known. The anti-inflammatory property of statins [29,32,36] and its potential implication on this association should be investigated.

The objective of our study was not to assess a causal effect of the comorbidities identified, but rather to identify the main predictive factors independently associated with the risk of COVID-19-related hospitalization or in-hospital mortality. It is therefore possible that we may have adjusted for intermediate factors. For example, because hypertension, diabetes and obesity are comorbidities that increase the risk of developing other forms of cardiovascular disease, their risk in relation to COVID-19 may have been underestimated in adjusted models.

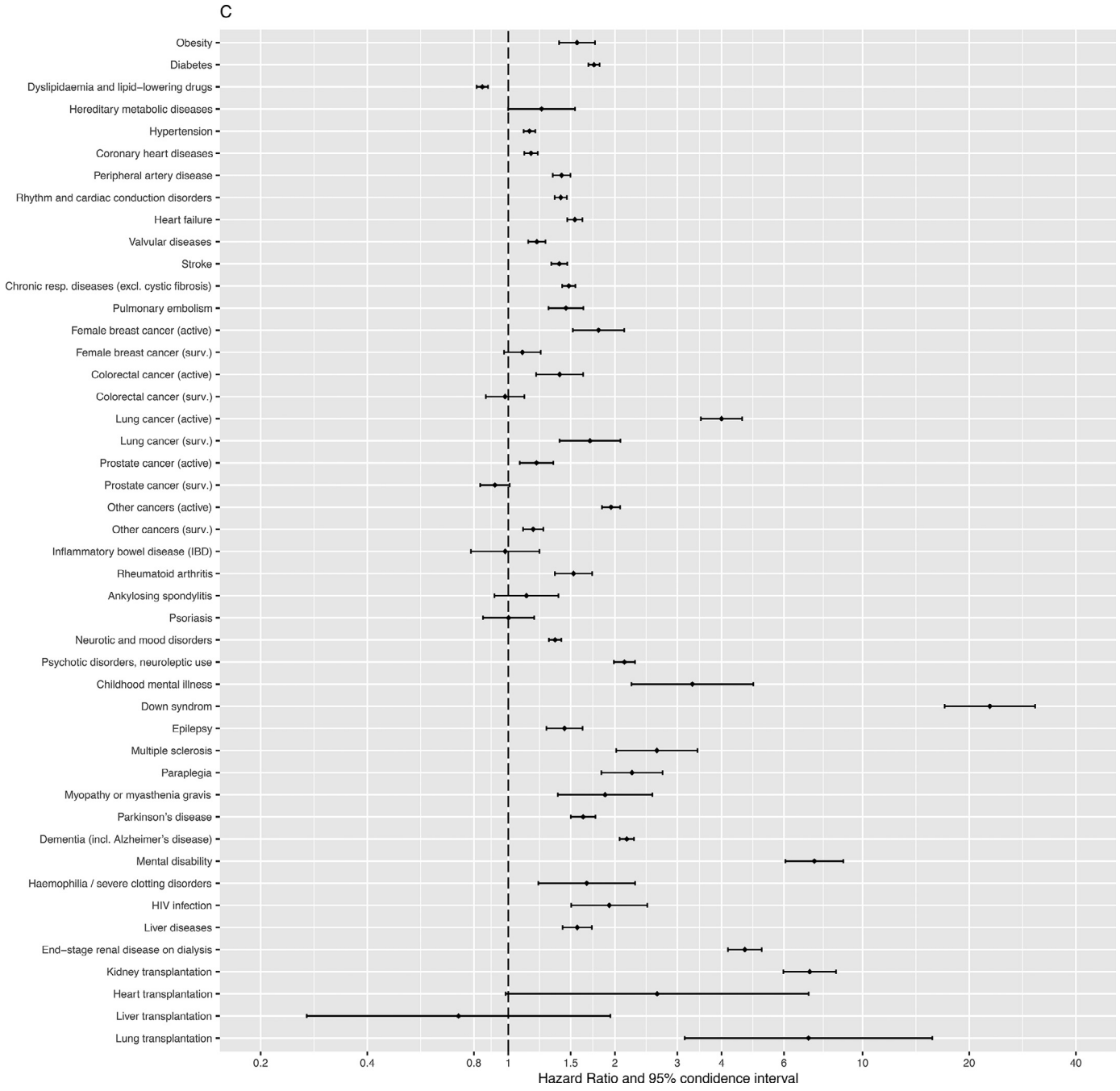

Figure 2b. Continued.

Santé Publique France (the French center comparable to US Centers for Disease Control and Prevention) has estimated 103,451 hospitalizations for COVID-19 in France between 1st March and 16 June 2020, including 19,090 deaths in hospital; 10,457 deaths occured in nursing home. According to the "fast-track" PMSI, 105,434 patients were hospitalized in relation to COVID-19 between 15 February and 15 June 2020, including 93,406 patients admitted with a principal diagnosis or related diagnosis of COVID-19. We decided not to consider in our analyses patients hospitalized for other causes with an associated diagnosis of COVID-19 during their hospital stay. Linking of COVID-19 patients with our study population resulted in analysis of almost all hospitalized patients, with 87,809 COVID-19-related hospitalizations, i.e. 94% (figure established after linking with reimbursement data and application of the same inclusion criteria as in our study population).

The SNDS is a claims database that has enabled us to conduct one of the most comprehensive studies to date, with the analysis of a large number of comorbidities allowing identification of people at higher risk of COVID-19-related hospitalization and death. Our general population study based on comprehensive claims data should limit the risk of selection bias. In addition, the fact that our analysis of mortality was not confined to patients hospitalized during the study

Table 3
Hazard ratio (HR) and 95% Confidence Interval (95%CI) for the criteria for COVID-19-related hospitalization and in-hospital mortality: stratification for people 80 years and older *vs*. other people on adjusted analysis (Note: some associations were not estimated due to insufficient sample sizes; models were adjusted for age as a categorical variable).

	Hospitalization with COVID-19						In-hospital death with COVID-19			
	< 80 years			80 years nd older			< 80 years		80 years and older	
	Sample size	Number of events	HR	Sample size	Number of events	HR	Number of events	HR	Number of events	HR
Characteristics sociodemographic										
Male sex - no (%)	30,065,855	34,299	1·36 (1·34 - 1·38)	1,655,925	12,467	1·41 (1·37 - 1·45)	4,345	2·25 (2·12 - 2·39)	5,014	2·01 (1·92 - 2·1)
Regions - no (%)										
Ile de France	11,391,095	21,613	1	588,058	8,396	1	2,626	1	2,986	1
Grand Est	5,034,098	8,369	0·65 (0·63 - 0·67)	365,080	4,570	0·85 (0·82 - 0·89)	1,159	0·58 (0·54 - 0·62)	1,735	0·92 (0·86 - 0·99)
Hauts-de-France	5,547,664	5,888	0·41 (0·4 - 0·42)	341,508	2,964	0·59 (0·56 - 0·62)	661	0·31 (0·28 - 0·34)	1,068	0·61 (0·56 - 0·66)
Auvergne-Rhône-Alpes	7,400,076	5,072	0·31 (0·3 - 0·32)	530,463	3,463	0·44 (0·42 - 0·46)	473	0·19 (0·18 - 0·21)	1,026	0·37 (0·34 - 0·4)
Bourgogne-Franche-Comté	2,500,374	2,613	0·4 (0·38 - 0·42)	215,438	1,690	0·53 (0·51 - 0·56)	266	0·25 (0·22 - 0·29)	606	0·54 (0·5 - 0·6)
Centre-Val-de-Loire	2,336,449	1,375	0·24 (0·22 - 0·25)	196,744	889	0·32 (0·29 - 0·34)	120	0·13 (0·11 - 0·16)	288	0·29 (0·26 - 0·33)
Provence-Alpes-Côte d'Azur	4,813,164	6,355	0·56 (0·54 - 0·58)	398,311	1,616	0·28 (0·26 - 0·29)	263	0·15 (0·13 - 0·17)	509	0·25 (0·23 - 0·27)
Occitanie	5,458,331	2,192	0·17 (0·16 - 0·17)	450,075	969	0·14 (0·13 - 0·15)	152	0·07 (0·06 - 0·09)	292	0·12 (0·11 - 0·14)
Nouvelle-Aquitaine	5,462,379	1,803	0·13 (0·13 - 0·14)	488,706	921	0·13 (0·12 - 0·14)	122	0·06 (0·05 - 0·07)	266	0·1 (0·09 - 0·12)
Normandie	3,009,313	1,718	0·22 (0·21 - 0·23)	234,572	737	0·21 (0·2 - 0·23)	155	0·13 (0·11 - 0·15)	224	0·18 (0·16 - 0·21)
Pays de la Loire	3,500,482	1,448	0·18 (0·17 - 0·19)	266,835	871	0·23 (0·21 - 0·25)	103	0·09 (0·07 - 0·11)	256	0·19 (0·17 - 0·22)
Bretagne	3,050,605	807	0·12 (0·11 - 0·12)	251,951	482	0·13 (0·12 - 0·15)	62	0·06 (0·05 - 0·08)	150	0·12 (0·1 - 0·14)
Corse	229,184	139	0·23 (0·2 - 0·28)	19,071	54	0·2 (0·15 - 0·26)	10	0·11 (0·06 - 0·2)	17	0·17 (0·11 - 0·28)
Guadeloupe	353,603	96	0·12 (0·1 - 0·15)	22,067	26	0·09 (0·06 - 0·13)	13	0·12 (0·07 - 0·22)	10	0·1 (0·05 - 0·19)
Martinique	326,972	119	0·16 (0·13 - 0·2)	24,020	29	0·1 (0·07 - 0·14)	6	0·06 (0·03 - 0·14)	10	0·1 (0·05 - 0·18)
Guyane	187,765	154	0·58 (0·49 - 0·69)	2,955	14	0·41 (0·24 - 0·7)	3	0·11 (0·03 - 0·34)	5	0·43 (0·18 - 1·06)
La Réunion	850,247	149	0·09 (0·08 - 0·11)	26,623	8	0·02 (0·01 - 0·04)	2	0·01 (0 - 0·04)	1	0·01 (0 - 0·06)
Mayotte	100,381	146	1·21 (1·01 - 1·44)	1,132	15	1·43 (0·85 - 2·39)	9	0·9 (0·45 - 1·82)	4	1·15 (0·42 - 3·1)
Unknown	70,750	32	0·25 (0·17 - 0·35)	4,049	7	0·13 (0·06 - 0·27)	0		3	0·16 (0·05 - 0·49)
Social deprivation index (quintiles) - no (%)										
1 (the least deprivation)	12,188,387	13,762	1	761,883	7,131	1	1,359	1	2,488	1
2	12,005,297	10,291	1·14 (1·11 - 1·17)	763,359	4,408	0·97 (0·93 - 1·01)	1,027	1·35 (1·24 - 1·46)	1,509	0·97 (0·9 - 1·03)
3	11,805,221	9,837	1·2 (1·17 - 1·24)	885,767	4,538	1·01 (0·97 - 1·05)	966	1·55 (1·41 - 1·69)	1,485	0·98 (0·91 - 1·05)
4	11,565,049	10,006	1·29 (1·26 - 1·33)	933,160	5,111	1·03 (0·99 - 1·08)	1,094	1·61 (1·48 - 1·76)	1,720	1·02 (0·95 - 1·09)
5 (the most deprivation)	11,355,163	14,862	1·64 (1·6 - 1·69)	922,159	5,998	1·04 (1 - 1·08)	1,664	1·99 (1·84 - 2·16)	2,070	1·02 (0·95 - 1·09)
Unknown	2,703,815	1,330	1·11 (1·03 - 1·21)	161,330	535	0·97 (0·88 - 1·07)	95	1·29 (1 - 1·66)	184	0·94 (0·8 - 1·11)
Lifestyle habits										
Smoking	2,278,613	3,078	0·78 (0·75 - 0·81)	70,956	917	1·26 (1·17 - 1·35)	472	0·96 (0·87 - 1·07)	327	1·18 (1·05 - 1·33)
Alcoholism	679,184	1,544	1·14 (1·08 - 1·2)	20,266	224	1·26 (1·1 - 1·44)	241	1·23 (1·07 - 1·42)	78	1·2 (0·95 - 1·5)
Opioide addiction	207,516	298	1·09 (0·97 - 1·22)	593	10	1·86 (1 - 3·45)	14	0·82 (0·48 - 1·39)	4	2·23 (0·84 - 5·94)
Comorbidities										
Cardiometabolic										
Obesity	853,075	2,202	1·58 (1·52 - 1·65)	22,310	259	1·52 (1·35 - 1·72)	214	1·46 (1·27 - 1·68)	82	1·48 (1·19 - 1·84)
Diabetes	3,020,096	12,419	1·81 (1·77 - 1·85)	786,059	6,812	1·39 (1·35 - 1·43)	2,312	2·11 (1·99 - 2·24)	2,486	1·49 (1·42 - 1·56)
Dyslipidemia and lipid-lowering treatments	5,169,559	14,127	0·88 (0·86 - 0·9)	1,541,826	9,490	0·88 (0·85 - 0·9)	2,485	0·86 (0·81 - 0·91)	3,194	0·81 (0·77 - 0·85)
Hereditary metabolic diseases or amyloidosis	99,810	200	1·09 (0·94 - 1·25)	13,892	117	1·12 (0·93 - 1·34)	35	1·17 (0·84 - 1·64)	47	1·26 (0·95 - 1·68)
Hypertension	8,848,157	23,479	1·25 (1·23 - 1·28)	3,094,350	20,065	0·99 (0·96 - 1·02)	3,809	1·28 (1·21 - 1·36)	6,907	1·01 (0·97 - 1·07)
Coronary diseases	1,337,250	5,204	1·17 (1·13 - 1·21)	617,683	5,474	1·13 (1·1 - 1·17)	1,080	1·14 (1·06 - 1·23)	2,044	1·16 (1·1 - 1·23)
Obliterating arterial disease of the lower limb	427,503	1,970	1·2 (1·15 - 1·26)	216,250	2,261	1·31 (1·25 - 1·37)	523	1·41 (1·28 - 1·55)	872	1·38 (1·29 - 1·49)
Cardiac rhythm or conduction disturbances	1,200,780	5,451	1·36 (1·32 - 1·41)	1,073,211	10,803	1·37 (1·34 - 1·41)	1,256	1·43 (1·33 - 1·55)	3,954	1·4 (1·34 - 1·47)
Heart failure	303,886	2,336	1·45 (1·38 - 1·52)	391,092	5,242	1·48 (1·43 - 1·53)	661	1·89 (1·71 - 2·08)	1,952	1·5 (1·42 - 1·59)
Valvular diseases	338,688	1,536	1·1 (1·04 - 1·17)	306,792	3,266	1·17 (1·13 - 1·22)	371	1·14 (1·02 - 1·28)	1,222	1·22 (1·15 - 1·31)
Stroke	537,146	2,356	1·4 (1·35 - 1·47)	318,505	3,270	1·27 (1·22 - 1·32)	539	1·54 (1·4 - 1·69)	1,209	1·32 (1·24 - 1·4)
Respiratory										
Chronic respiratory diseases (excluding cystic fibrosis)	6,011,758	15,522	1·68 (1·64 - 1·72)	1,033,712	10,056	1·35 (1·3 - 1·39)	2,500	1·64 (1·54 - 1·76)	3,628	1·38 (1·3 - 1·46)

(*continued on next page*)

Table 3 (*Continued*)

	Hospitalization with COVID-19						In-hospital death with COVID-19			
	< 80 years			80 years nd older			< 80 years		80 years and older	
	Sample size	Number of events	HR	Sample size	Number of events	HR	Number of events	HR	Number of events	HR
Cystic fibrosis	8,441	28	3·73 (2·54 - 5·46)	143	4	3·27 (1·23 - 8·7)	4		2	
Pulmonary embolism	98,968	479	1·57 (1·44 - 1·72)	50,063	586	1·33 (1·22 - 1·44)	101	1·7 (1·39 - 2·07)	208	1·35 (1·17 - 1·55)
Cancer										
Female breast cancer (active)	181,015	446	1·57 (1·43 - 1·72)	30,485	184	1·12 (0·97 - 1·3)	93	3·3 (2·68 - 4·07)	49	1·01 (0·76 - 1·34)
Female breast cancer (under surveillance)	364,727	560	0·9 (0·82 - 0·97)	112,633	690	1·04 (0·96 - 1·12)	75	1·11 (0·88 - 1·4)	209	1·09 (0·95 - 1·26)
Colorectal cancer (active)	96,847	386	1·55 (1·4 - 1·71)	30,905	229	1·11 (0·97 - 1·26)	96	2·01 (1·64 - 2·46)	71	0·97 (0·77 - 1·22)
Colorectal cancer (under surveillance)	133,880	352	1·04 (0·93 - 1·15)	74,096	546	1·03 (0·95 - 1·12)	63	0·98 (0·76 - 1·25)	187	0·99 (0·85 - 1·14)
Lung cancer (active)	57,656	488	2·78 (2·54 - 3·04)	9,129	133	1·96 (1·65 - 2·32)	170	5·03 (4·3 - 5·89)	53	2·21 (1·68 - 2·9)
Lung cancer (under surveillance)	39,321	191	1·44 (1·25 - 1·66)	10,078	110	1·23 (1·02 - 1·49)	45	1·69 (1·26 - 2·27)	55	1·69 (1·3 - 2·21)
Prostate cancer (active)	141,643	491	1·22 (1·12 - 1·34)	60,623	538	1·16 (1·07 - 1·27)	111	1·25 (1·03 - 1·51)	226	1·2 (1·05 - 1·37)
Prostate cancer (under surveillance)	190,629	567	0·99 (0·91 - 1·07)	107,243	857	1·03 (0·96 - 1·1)	125	0·92 (0·77 - 1·1)	320	0·95 (0·84 - 1·06)
Other cancers (active)	529,287	2,335	1·96 (1·88 - 2·04)	183,835	1,609	1·33 (1·26 - 1·4)	619	2·99 (2·74 - 3·26)	621	1·44 (1·32 - 1·56)
Other cancers (under surveillance)	641,791	1,593	1·17 (1·11 - 1·23)	243,807	1,858	1·1 (1·05 - 1·16)	290	1·25 (1·11 - 1·41)	673	1·13 (1·04 - 1·22)
Inflammatoy and skin diseases										
Chronic inflammatory bowel diseases	253,396	453	1·27 (1·15 - 1·39)	14,789	147	1·32 (1·12 - 1·55)	38	0·91 (0·66 - 1·26)	40	1·03 (0·76 - 1·41)
Rheumatoid arthritis and related diseases	227,136	661	1·55 (1·43 - 1·67)	60,617	511	1·39 (1·27 - 1·51)	105	1·83 (1·51 - 2·23)	163	1·36 (1·17 - 1·59)
Ankylosing spondylitis and related diseases	207,427	431	1·22 (1·11 - 1·34)	14,640	138	1·28 (1·08 - 1·51)	48	1·13 (0·85 - 1·51)	42	1·09 (0·81 - 1·48)
Psoriasis	269,082	590	1·13 (1·04 - 1·23)	27,943	197	1·06 (0·92 - 1·22)	73	1·02 (0·81 - 1·28)	69	1·02 (0·81 - 1·3)
Psychological and neurodegenerative diseases										
Neurotic and Mood Disorders, use of antidepressant treatments	3,488,916	7,510	1·25 (1·22 - 1·28)	776,020	7,064	1·37 (1·33 - 1·41)	1,026	1·33 (1·24 - 1·42)	2,376	1·36 (1·29 - 1·43)
Psychotics disorders, use of neuroleptics treatments	650,189	2,100	1·76 (1·69 - 1·85)	112,431	1,284	1·39 (1·31 - 1·47)	425	3·01 (2·71 - 3·34)	515	1·63 (1·49 - 1·79)
Psychiatric disorders starting in childhood	164,897	133	2·03 (1·7 - 2·41)	725	13	1·74 (1·01 - 3)	22	3·76 (2·45 - 5·77)	3	1·12 (0·36 - 3·46)
Down syndrom	33,508	208	6·93 (6·04 - 7·96)	33	0		48	23·67 (17·61 - 31·8)	0	
Epilepsy	282,167	878	1·66 (1·55 - 1·78)	38,880	424	1·22 (1·11 - 1·34)	151	1·8 (1·52 - 2·12)	141	1·12 (0·95 - 1·32)
Multiple sclerosis	109,704	276	1·65 (1·47 - 1·87)	3,360	48	2·29 (1·73 - 3·05)	41	2·63 (1·91 - 3·63)	17	2·59 (1·61 - 4·19)
Paraplegia	83,637	378	2·08 (1·87 - 2·31)	7,779	85	1·43 (1·15 - 1·77)	71	2·61 (2·04 - 3·33)	32	1·54 (1·09 - 2·19)
Myopathy or myasthenia gravis	41,388	105	1·33 (1·09 - 1·61)	4,803	48	1·39 (1·04 - 1·84)	22	2·13 (1·4 - 3·25)	19	1·57 (1 - 2·47)
Parkinson disease	129,111	683	1·65 (1·53 - 1·78)	115,619	1,251	1·42 (1·34 - 1·51)	178	1·98 (1·7 - 2·31)	467	1·48 (1·35 - 1·63)
Dementias (including Alzheimer's disease)	125,611	1,418	2·8 (2·65 - 2·97)	484,709	6,432	1·86 (1·8 - 1·92)	432	3·31 (2·97 - 3·69)	2,387	2·02 (1·91 - 2·12)
Mental impairment	123,835	541	3·66 (3·35 - 3·99)	2,345	42	4·21 (3·11 - 5·71)	101	7·04 (5·71 - 8·67)	19	6·1 (3·88 - 9·57)
Other pathologies										
Hemophilia or severe hemostasis disorders	43,908	109	1·48 (1·23 - 1·79)	5,878	58	1·42 (1·1 - 1·84)	16	1·66 (1·01 - 2·71)	23	1·65 (1·1 - 2·48)
HIV infection	144,393	562	1·87 (1·72 - 2·04)	1,811	13	0·93 (0·54 - 1·6)	59	1·92 (1·48 - 2·48)	5	0·93 (0·39 - 2·24)
Liver diseases	358,039	1,696	1·51 (1·43 - 1·59)	39,243	474	1·3 (1·18 - 1·42)	317	1·62 (1·44 - 1·83)	170	1·29 (1·11 - 1·51)
Chronic dialysis	32,235	718	4·71 (4·36 - 5·08)	13,689	381	3·24 (2·92 - 3·59)	180	5·16 (4·42 - 6·03)	162	3·7 (3·16 - 4·34)
Renal transplant	40,779	513	4·41 (4·04 - 4·82)	1,746	34	3·05 (2·18 - 4·27)	123	6·66 (5·54 - 8)	14	3·65 (2·16 - 6·18)
Cardiac translant	1,669	22	1·97 (1·29 - 3)				4	1·51 (0·56 - 4·07)	0	
Liver transplant	5,021	27	0·77 (0·52 - 1·12)				4	0·56 (0·21 - 1·51)	0	
Lung transplant	1,345	25	3·28 (2·18 - 4·92)				6	5·05 (2·25 - 11·35)	0	

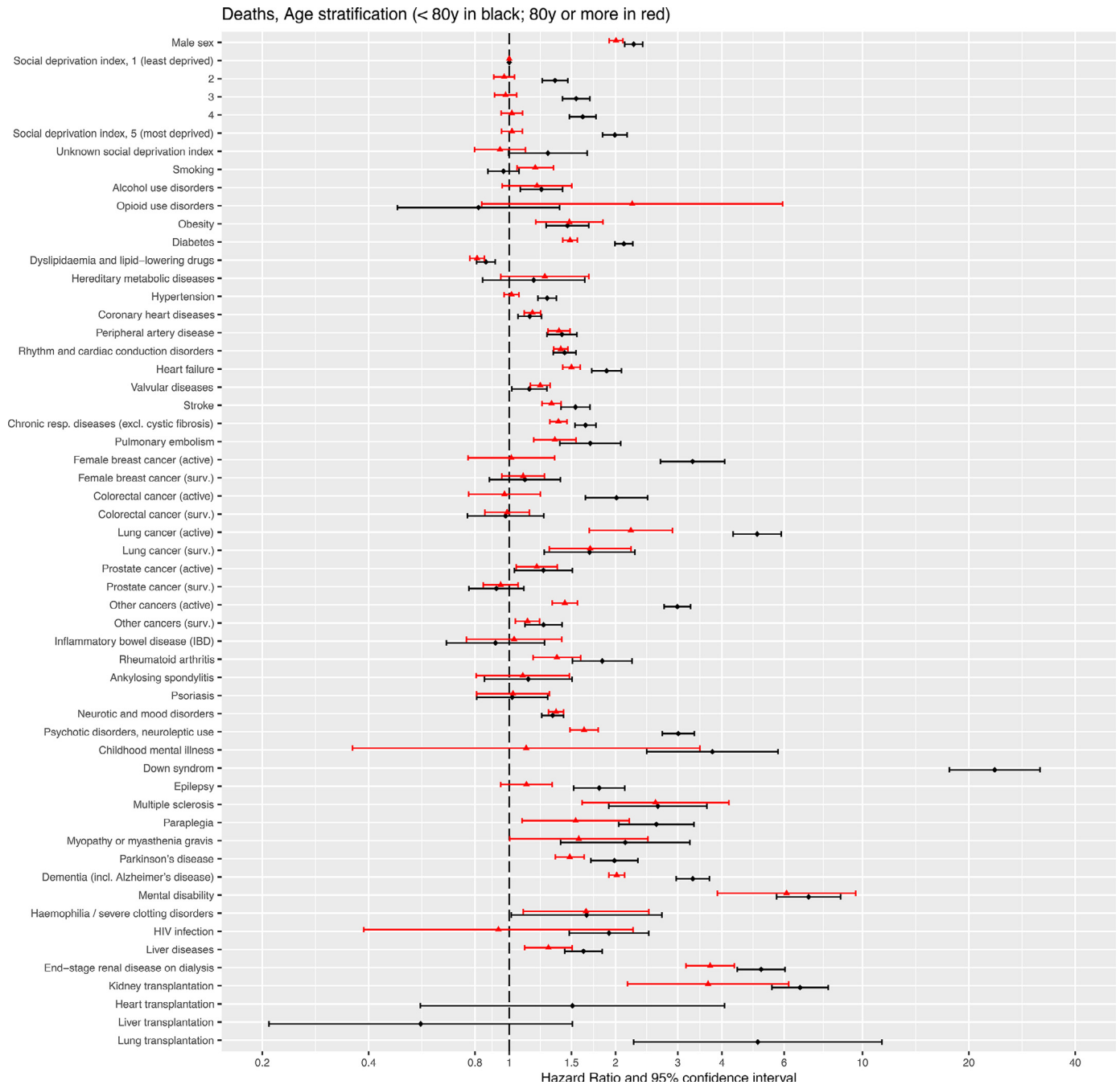

Figure 3a. Hazard ratios of COVID-19-related hospitalization estimated from a Cox model with multivariable adjustment stratified for age: < 80 years and 80 years and over. Logarithmic scale (Note: some associations were not estimated due to an insufficient sample sizes).

and that our analysis of the risk of hospitalization was not confined to patients tested positive for COVID-19 should avoid any collision bias.

Our study presented some limitations. First, although the SNDS data are globally comprehensive, behavioural characteristics, such as obesity or smoking are underestimated in this database.

Second, in the analysis of the number of comorbidities, we observed that the greater the number of comorbidities, the higher the risk, reaching a 5-fold increase in the risk of hospitalization and a 10-fold increase in the risk of in-hospital death in patients with 5 or more comorbidities compared to those without any. However, this analysis, carried out according to the number of comorbidities, does not take into account the specific nature of each pathology, so all comorbidities thus have an equivalent weight in our definition.

Third, many patients living in Etablissements d'Hébergement de Personnes Agées Dépendantes (EHPAD) [skilled nursing facilities] died from COVID-19 without being admitted to hospital, but the number of people concerned cannot be precisely determined [37].

As of June 8, 2021 according to Santé Publique France, there were 110,166 COVID-19-related deaths, 83,737 of which occurred in hospital (76%), and although we focused our analysis on patients requiring admission specifically for SARS-CoV-2 infection, diagnostic errors may nevertheless have occurred, especially at the beginning of the

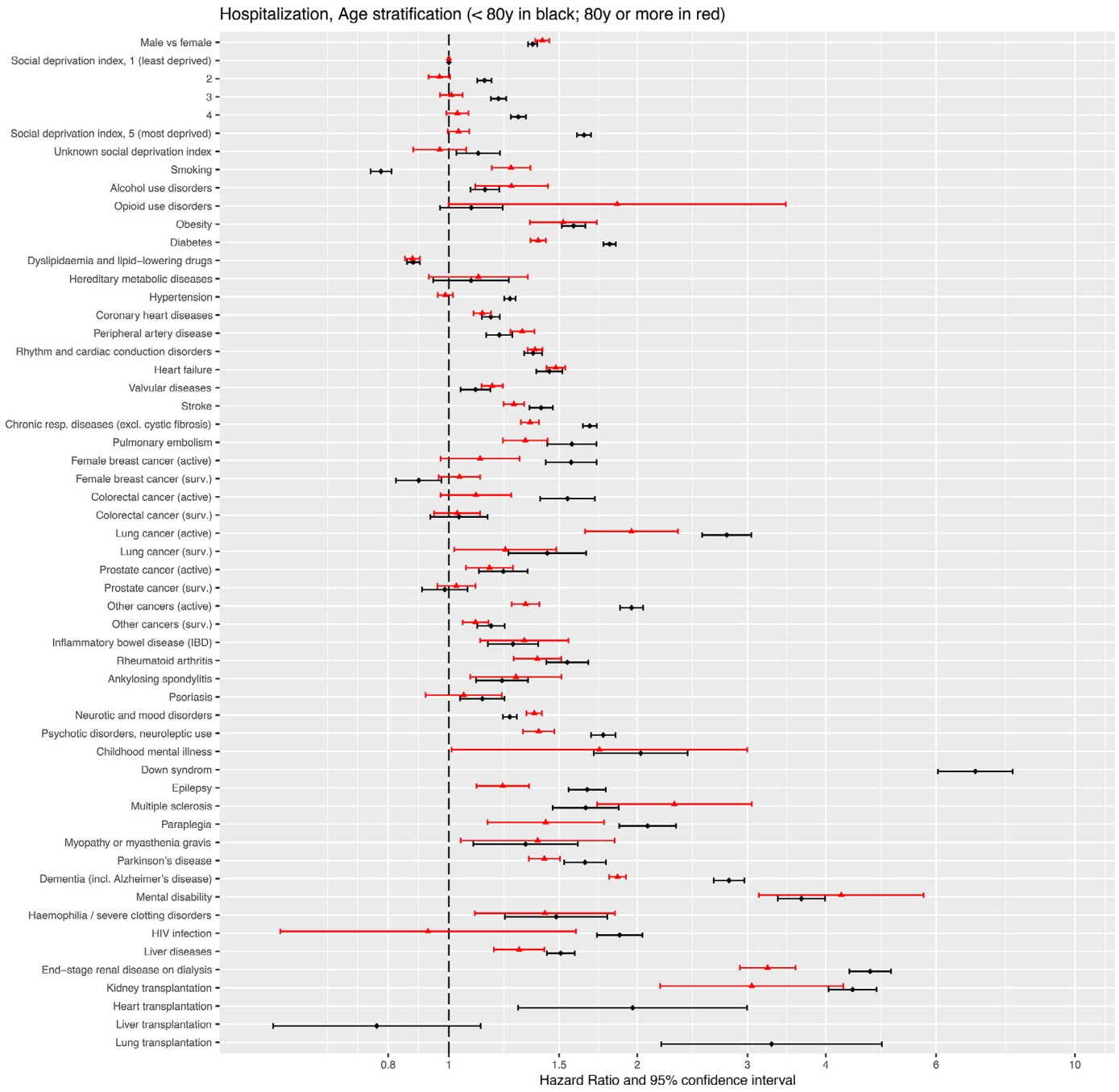

Figure 3b. Hazard ratios of COVID-19-related in-hospital mortality estimated from a Cox model with multivariable adjustment stratified for age: < 80 years and 80 years and over. Logarithmic scale (Note: some associations were not estimated due to an insufficient sample sizes).

epidemic when PCR analyses were not readily available throughout France.

Finally, the health measures implemented changed significantly during the study period, with lockdown between 17 March and 11 May 2020, followed by the introduction of less restrictive measures, such as social distancing and barrier measures or the mandatory use of masks on public transport. Hospital management of COVID-19 also evolved during the epidemic. These measures may have had a partial impact on the size of the estimated associations

In conclusion, during the first wave of the pandemic in France, age has been the main risk factor for COVID-19-related hospitalization or in-hospital mortality. In addition, most of the comorbidities considered, i.e. Down syndrome, kidney or lung transplantation, end-stage renal disease on dialysis, diabetes, obesity, hypertension, history of cardiovascular disease, chronic respiratory disease, active cancer and neurodegenerative disease, have constituted strong risk factors of developing a severe form of COVID-19. Socioeconomic deprivation has also played a role in majoring COVID-19-related morbidity and mortality. The results of this study should provide patients and health care professionals with a better understanding of the chronic diseases associated with a higher risk of developing more severe forms of COVID-19 in order to optimize the management of these patients. It may also help to guide health authorities when determining those populations constituting priority targets of present and future vaccination campaigns.

Table 4
Hazard ratio (HR) and 95% Confidence Interval (95%CI) for the criteria for COVID-19-related hospitalization and in-hospital mortality depending of number of comorbidities.

		Hospitalization with COVID-19			In-hospital death with COVID-19		
	Sample size	Number of events	Age-sex adj	Fully adj*	Number of events	Age-sex adj	Fully adj*
Number of comorbidities							
0	43,963,101	22,565	1	1	977	1	1
1	10,497,070	15,118	1.59 (1.56 - 1.63)	1.58 (1.54 - 1.61)	1,843	2.19 (2.02 - 2.37)	2.15 (1.99 - 2.33)
2	5,083,578	13,519	2.19 (2.14 - 2.25)	2.13 (2.08 - 2.19)	2,622	3.45 (3.19 - 3.73)	3.3 (3.06 - 3.57)
3	3,249,867	12,636	2.83 (2.76 - 2.9)	2.72 (2.65 - 2.79)	2,960	4.65 (4.31 - 5.03)	4.38 (4.05 - 4.73)
4	1,762,726	9,604	3.65 (3.55 - 3.75)	3.49 (3.4 - 3.59)	2,584	6.27 (5.79 - 6.78)	5.82 (5.38 - 6.3)
5 or more	1,494,248	14,367	5.9 (5.75 - 6.05)	5.61 (5.47 - 5.76)	4,675	10.99 (10.19 - 11.86)	10 (9.26 - 10.79)

* Adjusted on age, sex, sociodemographic variables, lifestyle habits; not adjusted on comorbidities.

Data sharing Statement

According to data protection and the French regulation, 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, is able to access SNDS data upon authorization from the French Data Protection Office (CNIL), in order to carry out a study, a research or an evaluation of public interest (https://www.snds.gouv.fr/SNDS/Processus-d-acces-aux-donnees and https://www.indsante.fr/).

Contributor statement

All authors conceived and designed the experiments. LS, JB and JD analyzed the data. All authors interpreted the results. LS, JB, AW and MZ 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. LS and JD 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. MZ is the guarantor.

Conflicts of Interest

All authors declare no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanepe.2021.100158.

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