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# The risk of hospitalization for psychotic disorders following hospitalization for COVID-19: a French nationwide longitudinal study

Baptiste Pignon (✉ [baptistepignon@yahoo.fr](mailto:baptistepignon@yahoo.fr))

APHP <https://orcid.org/0000-0003-0526-3136>

Valentina Decio

Philippe Pirard

Olivier Bouaziz

Emmanuelle Corruble

Assistance Publique-Hôpitaux de Paris, Hôpitaux Universitaires Paris Sud

Pierre Geoffroy

Viviane Kovess-Masfety

Marion Leboyer

<https://orcid.org/0000-0001-5473-3697>

Cédric Lemogne

Université Paris Cité, AP-HP, INSERM <https://orcid.org/0000-0002-3487-4721>

Jonathan Messika

Vittorio Perduca

Franck Schurhof

Nolwenn Regnault

Sarah Tebeka

Hopital Louis Mourier, APHP

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## Article

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## Abstract

COVID-19, like other infectious diseases, may be a risk factor for a first episode of psychosis or psychotic relapse. We aimed to compare the proportions of hospitalizations for psychotic disorders in the 12 months following discharge from hospital for either COVID-19 or for another reason in the adult general population in France during the first wave of the pandemic.

We conducted a retrospective longitudinal nationwide study using the national French administrative healthcare database. Psychotic disorders were first studied as a whole, and then chronic and acute disorders separately. The role of several adjustment factors, including sociodemographics, a history of psychotic disorder, the duration of the initial hospitalization, and the level of care received during that hospitalization, were also analyzed.

Between 1 January 2020 and 30 June 2020, a total of 14,622 patients were hospitalized for psychotic disorders in the 12 months following discharge from hospital for either COVID-19 or another reason. Initial hospitalization for COVID-19 (vs. another reason) was associated with a lower rate of subsequent hospitalization for psychotic disorders (0.31 % vs. 0.51 %, OR = 0.60, 95% CI [0.53-0.67]). This was true for both chronic and acute disorders, even after adjusting for the various study variables. Importantly, a history of psychotic disorder was a major determinant of hospitalization for psychotic disorders (aOR = 126.56, 95% CI [121.85-131.46]).

Our results suggest that individuals initially hospitalized for COVID-19 (vs. another reason) present a lower risk of hospitalization for first episodes of psychotic symptoms/disorders or for psychotic relapse in the 12 months following discharge. This finding contradicts and invalidates the hypothesis that there is a higher risk of psychotic disorders after a severe COVID-19.

## Introduction

From the beginning of the COVID-19 pandemic and related restrictions, concerns have been raised about its impact on mental health in the general population, specifically subjects without a history of psychiatric disorders – who may experience a first episode of psychiatric disorders – and also those with such a history, especially psychotic disorders [1, 2]. Severe infectious diseases, both bacterial and viral, are known to be a risk factor for psychotic disorders, and several longitudinal studies have found consistent significant associations [3–5]. Many studies hypothesize that the development of psychotic disorders (or relapse in those with a history of psychotic disorders) is not related to the diseases themselves but to abnormal immune response and neuroinflammation [6–8]. It is possible that such an abnormal response can occur after SARS-COV-2 infection, increasing the risk of first-episode psychosis (FEP) [9]. Moreover, SARS-COV-2 infection – especially severe forms – represents a stressor and a negative life event, and could cause or trigger a psychotic disorder [10–12].

Subjects with a history of schizophrenia or other psychotic disorder have been shown to be at risk of developing COVID-19, especially severe forms [13–15]. Severe infection is associated with anxiety symptoms, sleep disorders, and delusional ideations; it therefore could be a risk factor for FEP or psychotic relapse [16]. Moreover, isolation measures imposed on patients with COVID-19 may have increased the risk of psychotic relapse through reduced access to mental health care and/or interrupted medication, especially during lockdown periods [17–19].

International data from the first studies on COVID-19 on the psychiatric consequences of the disease highlighted posttraumatic stress, anxiety, and depressive symptoms [20–23]. Several cases of novel psychotic symptoms and FEP subsequent to COVID-19 infection have been reported [16, 24–27], and large databases are necessary to comprehensively study the risk of psychotic disorders after severe COVID-19. Of the 2,358,318 subjects hospitalized in New York between March 2020 and August 2021, COVID-19 was associated with a higher risk of psychotic disorder, particularly concerning hospitalized subjects who were COVID-19 positive (in comparison to COVID-19 negative:  $\beta = 5.52$  95% CI [3.41–7.64] for non-hospitalized COVID-19,  $\beta = 6.01$  95% CI [3.90–8.13] for hospitalized COVID-19) [28]. Taquet *et al.* studied retrospective cohort data from the electronic health records of almost 90 million patients in several countries (the USA, the UK, Australia, Spain, Bulgaria, India, Malaysia, and Taiwan) with different follow-up times (90 days, 6 months, 2 years) [29–31]. They found a significantly higher risk of psychotic disorders following SARS-COV-2 infection, in comparison to other infections, with hazard-ratios (HR) ranging from 1.17 to 2.03 (depending on the follow-up duration considered). Interestingly, the rates of psychotic disorders following COVID-19 disease were higher in patients requiring hospitalization (HR = 2.22, 95% CI [1.92–2.57], in comparison to COVID-19 without hospitalization) or intensive care unit (ICU) (HR = 1.48, 95% CI [1.14–1.92], in comparison to COVID-19 without ICU) [29]. However, they did not separately specify the risks of acute and chronic psychotic disorders. Furthermore, their findings contrast with other studies which did not find such a high risk of psychotic disorders following COVID-19 infection, when comparing samples to carefully matched controls [32].

Following these studies, we analyzed the whole French Metropolitan general population [33] and found a slightly – but significantly – higher rate of hospitalization for psychiatric disorders in the 12 months following hospitalization for COVID-19 in comparison to hospitalization for another reason (unadjusted odds-ratio (OR) = 1.20, 95% confidence interval (95% CI) [1.18–1.23]). The rate was also higher when looking specifically at psychotic disorders (OR = 1.11, 95% CI [1.05–1.19]). Importantly, the significance of the associations varied according to the

adjustment factors. In the fully adjusted model, (*i.e.*, taking into account socio-demographic characteristics, history of psychiatric disorders and the levels of care intensity), the association was not significant.

In the present study, we focused on psychotic disorders. More specifically, we described the different kinds of psychotic disorders, and separately analyzed acute *vs.* chronic psychotic disorders. Indeed, showing different patterns of association for different psychotic disorders – especially acute psychotic disorders which may reflect FEP – could add significant knowledge about the relationships between COVID-19 and psychotic disorders. Moreover, we could analyze if the psychotic disorder was the main reason of the hospitalization (“*main*” diagnosis) or if it was considered a comorbid condition of the main reason of the hospitalization (“*associated*” diagnosis). In this last case, we could investigate how COVID-19 could increase global health vulnerability among subjects with psychotic disorders (by analyzing different types of hospitalization, in psychiatric and non-psychiatric wards).

To act on these research possibilities, using the same dataset employed for our study on psychiatric disorders in the whole French Metropolitan general population [33], the present longitudinal study aimed to determine the risk of hospitalization for different non-affective psychotic disorders in the 12 months following discharge from hospital for COVID-19 during the first wave of pandemic, in comparison to discharge from hospital for another reason. Different types of psychotic disorders were described, as well as acute and chronic disorders. The role of adjustment variables – including the level of social deprivation, a history of psychotic disorders, and the characteristics of hospitalization for COVID-19 (duration, level of care received) – were also separately analyzed.

## Methods

### Data sources

The present study used data from France’s national administrative healthcare database *Système National des Données de Santé* (SNDS), which covers almost the country’s entire population of 67 million inhabitants (*i.e.*, 66.3 million in 2020). It includes admission and discharge data for all public and private hospital stays. The different data sources which comprise the SNDS are described elsewhere [33]. For all hospitalizations, medical diagnoses are coded according to the International Classification of Diseases 10<sup>th</sup> edition (ICD-10), while the main medical and surgical procedures performed are coded according to France’s *Classification Commune des Actes Médicaux* (CCAM, or Common Classification of Medical Procedures). Medical diagnoses are coded as *principal* (*i.e.*, the main reason for hospitalization), or *associated* (*i.e.*, a comorbidity that is not the main reason for hospitalization).

For the present study, we also used the *Cartographie des Pathologies et des Dépenses* (CPD, or Diseases and Expense Mapping) database in the SNDS to identify the presence of a history of psychotic disorder over the five years preceding the study period for each individual included. The CPD database’s medical algorithms are based on SNDS data on hospitalizations, filled prescriptions, and free complete healthcare coverage for long-term diseases; the algorithms are publicly available in French [34, 35].

### Study design and participants

This retrospective longitudinal study aimed to compare the risk of hospitalization for a psychotic disorder during the 12 months following hospital discharge from a medical, surgical, or obstetrics ward in adult patients (*i.e.*, 18 years or over) who had either been hospitalized for COVID-19 or for another reason between 1 January 2020 and 30 June 2020 (*i.e.*, first wave of the pandemic) in Metropolitan France. Subjects brought to an emergency department (ED) visit but not subsequently admitted to hospital were not considered. For each individual, a reference hospital stay (*i.e.*, either COVID-19 or another reason) was selected. For patients hospitalized more than once during the study period, if at least one of these was COVID-19 related (N = 85,514), then it was considered the reference hospital stay. For patients hospitalized more than once for COVID-19 (N = 7,521), the hospitalization where the most intensive level of medical care was provided was considered the reference stay. This care intensity criterion was also adopted to define the reference stay for patients with more than one hospitalization for pathologies other than COVID-19 during the study period. More information concerning this data is available elsewhere [33].

### Outcomes

The main outcome was hospitalization where a psychotic disorder of any type was diagnosed in the 12 months following discharge from the reference hospital stay (*i.e.*, COVID-19 or another reason). We searched for inpatient admissions to medical, surgical, obstetrics, and psychiatric wards for the following non-affective psychotic disorders (ICD-10 codes):

- F20: Schizophrenia;

- F21: Schizotypal disorder;
- F22: Delusional disorder;
- F23: Acute and transient psychotic disorders
- F24: Shared psychotic disorder;
- F25: Schizoaffective disorders;
- F28: Other nonorganic psychotic disorders;
- F29: Unspecified nonorganic psychotic disorders.

More specifically, the two types outcomes considered were: i) hospitalizations *with* a diagnosis (*i.e.*, principal or associated) of a psychotic disorder, and ii) hospitalizations *for* a psychotic disorder (*i.e.*, principal diagnosis only). Psychotic disorders were studied first as a whole (*i.e.*, F20-F29), and then separately for acute (F23) and chronic (F20, F21, F22 and F25) disorders.

## Adjustment variables

### Sociodemographic characteristics

Age, sex, and region of residence (among the 13 regions in metropolitan France) were considered. Age, calculated from the individual's year of birth, was categorized into four age groups (18-39 years, 40-59 years, 60-74 years, 75+ years). Socioeconomic status of the city of residence was also considered. This was measured using the French Deprivation Index (Fdep), an indicator based on median household income, the percentage of higher education graduates in the population over 15 years old, the percentage of manual workers in the labor force, and the unemployment rate of the individual's city of residence [36].

### History of psychotic disorders

The CBD database (8<sup>th</sup> version) was used to assess whether a patient had a history of psychotic disorders in the five years preceding the study period (summarized using a dichotomous variable). An individual was considered to have had a psychotic history for a specific year if one of the following elements was found in the SNDS for that year: i) declaration by a healthcare professional that the patient had a psychotic disorder officially recognized as a long-term disease; (ii) hospitalization(s) with a diagnosed psychotic disorder in a psychiatric or non-psychiatric hospital ward or in a healthcare center during at least one of the previous two years; (iii) hospitalization(s) with a diagnosed psychotic disorder in a psychiatric ward or non-psychiatric health establishment during the previous 5 years (*i.e.*,  $n$  to  $n-4$ ) and receiving prescribed antipsychotics drugs on at least three different occasions during year  $n$  [35].

### Characteristics of the reference hospital stay

Median duration (in days) and level of clinical care received were used to characterize the reference hospital stay. We defined three levels of care intensity for these stays (*i.e.*, whether for COVID-19 or for another reason). These three levels were defined according to the care provided in general for different degrees of COVID-19 disease severity (for the complete list of procedures used to define the levels of clinical care provided in this context, see Decio *et al.* [33]). The first level corresponded to patients with the mildest level of respiratory difficulty and admitted to a general hospital ward; these patients required no or low-flow oxygen (up to 15 L/minute). The second level corresponded to patients admitted to an ICU, irrespective of the level (*i.e.*, type and flowrate) of oxygen supply therapy, and patients who received high-flow nasal oxygen or non-invasive ventilation. The third and most intense level of care corresponded to patients who were hospitalized in an ICU and required at least invasive ventilatory support.

## Statistical analysis

We used logistic regression models to estimate and compare the risks of hospitalization where there was a diagnosis of i) a psychotic disorder (all kinds), (ii) an acute psychotic disorder, and (iii) a chronic psychotic disorder according to the reference hospital stay type (*i.e.*, COVID-19 *vs.* for another reason). For each of these three types of diagnosis, we first considered both hospitalization *with* (*i.e.*, principal or associated diagnosis) a psychotic disorder. We then considered only principal diagnoses of a psychotic disorder (*i.e.*, hospitalization *for* a psychotic disorder). For these six outcomes, when the association between the risk of hospitalization for or with one of the three types of diagnosis (any, acute, chronic) and a COVID-19-related reference hospital stay was significant – according to the chi-square test (without adjustment) – then four models were successively performed as follows:

- *Model 1* described the crude associations between outcomes, and the reason for the reference hospital stay (i.e., COVID-19 vs. another reason);
- *Model 2*: model 1 plus socio-demographic variables;
- *Model 3*: model 2 plus the history of psychotic disorders variable;
- *Model 4*: model 3 plus the two characteristics of the reference hospital stay variables (i.e., median duration and level of clinical care).

Statistical analyses were performed using SAS software, version 7.1 (SAS Institute Inc., Cary, NC, USA).

## Role of funding source, regulatory approval and ethical aspects

This research was conducted as part of the surveillance activities of the French agency for public health (*Santé publique France*, SpF). It did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The SNDS comprises a set of strictly pseudonymized databases. By law, SpF has permanent regulatory access to SNDS data for the performance of its missions (articles *L. 1461-3* and *R1461-13* and following of the French public health code [37]). Access to personal data in these systems for research purposes is subject to obtaining an authorization from the *Commission nationale de l'informatique et des libertés* (CNIL, National Commission on Information Technology and Civil Liberties), after approval by the *Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé* (CESREES, Ethics and Scientific Committee for Research, Studies and Evaluation in the field of health).

## Results

### Study cohort and description of patients hospitalized for psychotic disorders

Between 1 January 2020 and 30 June 2020, there were a total of 96,313 hospitalizations (i.e., reference hospital stays) for COVID-19 and 2,979,775 hospitalizations for another reason in metropolitan France. The characteristics of the whole hospitalized population are available in supplementary materials (*Supplementary Table 1*). Among these patients, in the 12 months following discharge from their reference hospital stay, 14,622 were hospitalized for a psychotic disorder (all kinds) (i.e., principal diagnosis only, see above). The characteristics of these patients are presented in Table 1. Those initially hospitalized for COVID-19 were older than those initially hospitalized for another reason (mean age: 68.5 years for COVID-19 vs. 59.9 for another reason). They were also more likely to live in the least socially deprived areas (FDep: 30.00% vs. 17.71%), and to have a history of psychotic disorders (89.83% vs. 78.35%). Furthermore, concerning the reference hospital stay (i.e., COVID-19 or another reason), they were more likely to have received a higher level (i.e., more intense) of clinical care during their reference hospital stay (ICU: 12.88% vs. 6.19%; ICU with invasive procedure: 8.14 vs. 2.44%), and to have had a longer stay (median [interquartile interval] = 8 [3–14] vs. 1 [0–3] days). The characteristics of both principal and associated diagnoses of the psychotic disorders studied were similar (see *Supplementary Table 2*). Note that among patients hospitalized with acute psychotic disorders, those *without* a history of psychotic disorders (44.14% for principal diagnosis only; 54.73% for principal or associated diagnosis) were more frequent than among patients with chronic psychotic disorders (25.21%, 20.15%).

Table 1

Comparison of patients previously hospitalized for COVID-19 and those previously hospitalized for another reason among patients hospitalized for a psychotic disorder (principal diagnoses only) in the 12 months following discharge from the previous hospitalization.

	Total (N = 14,622)	Hospitalizations for COVID-19 (N = 295)	Hospitalizations for another reason (N = 14,327)	<i>p</i> - values <sup>1</sup>
<i>Sex: N (%)</i>				
Male	6,369 (43.56)	145 (49.15)	6,224 (43.44)	0.050
Female	8,253 (56.44)	150 (50.85)	8,103 (56.56)	
<i>Age groups (years): N (%)</i>				
18–39	5,644 (38.60)	41 (13.90)	5,603 (39.11)	< 0.001
40–59	5,492 (37.56)	115 (38.98)	5,377 (37.53)	
60–74	2,464 (16.85)	101 (34.24)	2,363 (16.49)	
75+	1,022 (6.99)	38 (12.88)	984 (6.87)	
<i>Region: N (%)</i>				
Île-de-France	2,635 (18.02)	120 (40.68)	2,515 (17.55)	< 0.001
Centre-Val de Loire	423 (2.89)	8 (2.71)	415 (2.90)	
Bourgogne-Franche-Comté	738 (5.05)	10 (3.39)	728 (5.08)	
Normandy	569 (3.89)	11 (3.73)	558 (3.89)	
Hauts-de-France	1,196 (8.18)	28 (9.49)	1,168 (8.15)	
Grand Est	1,009 (6.90)	33 (11.19)	976 (6.81)	
Pays de la Loire	936 (6.40)	10 (3.39)	926 (6.46)	
Brittany	1052 (7.19)	7 (2.37)	1,045 (7.29)	
Nouvelle-Aquitaine	984 (6.73)	7 (2.37)	977 (6.82)	
Occitanie	1,560 (10.67)	15 (5.08)	1,545 (10.78)	
Auvergne-Rhône-Alpes	1,969 (13.47)	23 (7.80)	1,946 (13.58)	
Provence-Alpes-Côte d'Azur	1,499 (10.25)	23 (7.80)	1,476 (10.30)	
Corsica	52 (0.36)	0 (0)	52 (0.36)	
<i>French deprivation index (FDep, quintiles): N (%)</i>				
1 (least deprived)	2,591 (17.96)	87 (30.00)	2,504 (17.71)	< 0.001
2	2,615 (18.12)	30 (10.34)	2,585 (18.28)	
3	3,299 (22.86)	46 (15.86)	3,253 (23.01)	
4	3,009 (20.85)	52 (17.93)	2,957 (20.91)	

	Total (N = 14,622)	Hospitalizations for COVID-19 (N = 295)	Hospitalizations for another reason (N = 14,327)	p- values <sup>1</sup>
5 (most deprived)	2,916 (20.21)	75 (25.86)	2,841 (20.09)	
<i>History of psychotic disorder: N (%)</i>				
No	11,721 (80.16)	265 (89.83)	11,456 (78.35)	< 0.001
Yes	2,901 (19.84)	30 (10.17)	2,871 (20.04)	
<i>Duration of reference hospital stay (median [Interquartile interval], in days)</i>	1 [0–3]	8 [3–14]	1 [0–3]	< 0.0001
<i>Level of clinical care received in reference hospital stay: N (%)</i>				
General hospital ward (medical, surgery, obstetrics)	13,323 (92.12)	233 (78.98)	13,090 (91.37)	< 0.001
Intensive care unit	925 (6.33)	38 (12.88)	887 (6.19)	
Intensive care unit with invasive procedure	374 (2.56)	24 (8.14)	350 (2.44)	
Legends: <sup>1</sup> chi-square tests or T-tests				

## Hospitalization rates for psychotic disorders

### Principal and associated diagnoses

Between 1 January 2020 and 30 June 2020, among patients hospitalized in metropolitan France in the 12 months following discharge from their reference hospital stay, 27,614 were hospitalized *with* a diagnosis of a psychotic disorder (*i.e.*, principal or associated diagnosis). Of these, only 1,019 had a COVID-19-related reference hospital stay (1,019 / 96,313 initially hospitalized for COVID-19 = 1.06%); this proportion was significantly higher than the number of reference hospital stays for another reason (26,595 / 2,797,775 = 0.95%, p-value of chi-square test < 0.001). This significant difference was found for all the different psychotic disorders studied, except schizophrenia (non-significant variation: 0.45% after initial COVID-19 hospitalization *vs.* 0.43% after hospitalization for another reason, p-value = 0.215). The rate of hospitalization for subjects with a chronic psychotic disorder was not significantly different (0.76% *vs.* 0.73%, p-value = 0.345). Because of this, subjects hospitalized *with* a chronic psychotic disorder were not studied in the multivariable models). Unlike chronic disorders, acute psychotic disorders were significantly more frequent after a COVID-19-related reference stay (0.05% *vs.* 0.11%, p-value < 0.001).

Importantly, these variations, as well as the associations, were consistently significant when considering only admissions to a hospital psychiatric department (see *Supplementary Table 3*).

### Principal diagnoses

When only principal (*i.e.*, hospitalized *for* a psychotic disorder) diagnoses of psychotic disorders were considered, the opposite result was found: 0.31% hospitalization for a psychotic disorder (all kinds) after a COVID-19-related reference hospital stay, and 0.51% after a stay for another reason (p-value < 0.001). Schizophrenia rates were consistent with this overall pattern (0.17% *vs.* 0.25%, p-value < 0.001), and with the rates for most of the different psychotic disorders studied. The same was true for acute (0.02% *vs.* 0.08%, p-value < 0.001) and chronic (0.27% *vs.* 0.41%, p-value < 0.001) psychotic disorders.

Details on hospitalization rates *for* the different psychotic disorders (principal diagnosis) are shown in Fig. 1. Details on hospitalization *with* a psychotic disorder can be found in the supplementary materials (*Supplementary Table 4*).

## Risk of hospitalization for a psychotic disorder according to the type of reference hospital stay

### Principal or associated diagnosis of a psychotic disorder



The unadjusted model (Model 1) shows that the risk of hospitalization with a diagnosis (*i.e.*, principal or associated) of a psychotic disorder (all kinds) was higher after COVID-19 hospitalization (OR = 1.11, 95% CI [1.05–1.19], *p*-value < 0.001). Model 2, which was adjusted for socio-demographic characteristics, was consistent with Model 1. Interestingly, younger age group, male sex, and to a lesser extent the level of deprivation of the city of residence (negative association), were associated with a higher risk of hospitalization with a diagnosis of psychotic disorder irrespective of the initial hospital type. After adjustment for a history of psychotic disorders (Model 3), these three associations were no longer significant (*p*-value = 0.058), whereas the association with a history of psychotic disorders was strong (adjusted OR (aOR) = 116.28). Finally, in Model 4, which took into account the duration and the level of care of the initial hospital stay, the association between hospitalization for COVID-19 and the risk of subsequent hospitalization for a psychotic disorder was reversed: aOR = 0.90, 95% CI [0.84–0.97] (*p*-value = 0.006). Moreover, the duration of the reference hospital stay (positive association: aOR = 1.01), ICU care (negative association: aOR = 0.89) and care in an ICU with an invasive procedure (positive association: aOR = 1.09), were all associated with the risk of hospitalization *with* a diagnosis of psychotic disorder. The details of the different models for hospitalization *with* a diagnosis (*i.e.*, principal or associated) of a psychotic disorder (all kinds) are available in the supplementary materials (*Supplementary Table 5*).

Unlike what was found for psychotic disorders in general (*i.e.*, all kinds), Model 1 revealed a negative association with hospitalization *with* an acute psychotic disorder (aOR = 0.49, 95% CI [0.38–0.66], *p*-value < 0.001). The three other models were consistent with Model 1. The details of all the different models concerning hospitalization *with* an acute psychotic disorder are available in the supplementary materials (*Supplementary Table 6*).

## Principal diagnosis of psychotic disorders

Model 1 shows that the risk of hospitalization *for* (*i.e.*, principal diagnosis only) a psychotic disorder (all kinds) was lower after COVID-19 hospitalization than after hospitalization for another reason (OR = 0.60, 95% CI [0.53–0.67], *p*-value < 0.001). With regard to the three other models, unlike the findings for diagnosis *with* a psychotic order (see above), this association was consistent with Model 1 (Model 2: aOR = 0.69, Model 3: aOR = 0.57, Model 4: aOR = 0.67, all *p*-values < 0.001). The association between the various adjustment variables of these models and the main study outcome was consistent with the corresponding models in the analysis of hospitalizations *with* a psychotic disorder (see above), except for the duration of the reference hospital stay (which was negatively associated (aOR = 0.76)), the level of social deprivation (slight difference), and care in an ICU with an invasive procedure (non-significant association). The details of the different models for principal diagnoses are available in Table 2.

Table 2  
 Association of previous COVID-19 hospitalization with subsequent (12-month) hospitalization for a psychotic disorder (i.e., principal diagnosis only)

	Model 1*			Model 2*			Model 3*			Model 4*		
	OR	[95% CI]	p-values	aOR	[95% CI]	p-values	aOR	[95% CI]	p-values	aOR	[95% CI]	p-values
<i>Hospitalization for COVID-19</i>												
No (reference)	1			1			1			1		
Yes	<b>0.60</b>	<b>[0.53–0.67]</b>	<b>&lt; 0.001</b>	<b>0.69</b>	<b>[0.62–0.78]</b>	<b>&lt; 0.001</b>	<b>0.57</b>	<b>[0.50–0.65]</b>	<b>&lt; 0.001</b>	<b>0.67</b>	<b>[0.59–0.76]</b>	<b>&lt; 0.001</b>
<i>Sex</i>												
Male (reference)				1			1			1		
Female				<b>0.49</b>	<b>[0.48–0.51]</b>	<b>&lt; 0.001</b>	<b>0.71</b>	<b>[0.69–0.73]</b>	<b>&lt; 0.001</b>	<b>0.71</b>	<b>[0.68–0.74]</b>	<b>&lt; 0.001</b>
<i>Age (years)</i>												
18–39 (reference)				1			1			1		
40–59				<b>0.88</b>	<b>[0.85–0.92]</b>	<b>&lt; 0.001</b>	<b>0.62</b>	<b>[0.60–0.65]</b>	<b>&lt; 0.001</b>	<b>0.65</b>	<b>[0.62–0.68]</b>	<b>&lt; 0.001</b>
60–74				<b>0.31</b>	<b>[0.29–0.32]</b>	<b>&lt; 0.001</b>	<b>0.30</b>	<b>[0.28–0.31]</b>	<b>&lt; 0.001</b>	<b>0.33</b>	<b>[0.31–0.35]</b>	<b>&lt; 0.001</b>
75+				<b>0.12</b>	<b>[0.11–0.12]</b>	<b>&lt; 0.001</b>	<b>0.15</b>	<b>[0.14–0.16]</b>	<b>&lt; 0.001</b>	<b>0.17</b>	<b>[0.16–0.19]</b>	<b>&lt; 0.001</b>
<i>French deprivation index (FDep, quintiles)</i>												
1 (least deprived) (reference)				1			1			1		
2				<b>0.89</b>	<b>[0.84–0.94]</b>	<b>&lt; 0.001</b>	<b>0.92</b>	<b>[0.86–0.94]</b>	<b>0.0053</b>	<b>0.91</b>	<b>[0.86–0.97]</b>	<b>0.004</b>
3				1.05	[1.00–1.11]	0.062	<b>0.93</b>	<b>[0.88–0.99]</b>	<b>0.021</b>	<b>0.93</b>	<b>[0.88–0.99]</b>	<b>0.026</b>
4				0.98	[0.93–1.04]	0.547	<b>0.89</b>	<b>[0.84–0.94]</b>	<b>&lt; 0.001</b>	<b>0.89</b>	<b>[0.84–0.95]</b>	<b>0.002</b>
5 (most deprived)				1.00	[0.94–1.06]	0.960	<b>0.89</b>	<b>[0.84–0.95]</b>	<b>&lt; 0.001</b>	<b>0.90</b>	<b>[0.84–0.96]</b>	<b>&lt; 0.001</b>
<i>History of psychotic disorders</i>												
No (reference)							1			1		
Yes							<b>126.56</b>	<b>[121.85–131.46]</b>	<b>&lt; 0.001</b>	<b>127.71</b>	<b>[122.95–132.66]</b>	<b>&lt; 0.001</b>
<i>Reference hospital stay duration (days) - median (IQ)</i>										<b>0.96</b>	<b>[0.96–0.97]</b>	<b>&lt; 0.001</b>
<i>Level of clinical care received in reference hospital stay</i>												
General hospital ward (reference)										1		
Intensive care unit										<b>0.76</b>	<b>[0.71–0.82]</b>	<b>&lt; 0.001</b>
Intensive care unit with invasive procedure										1.04	[0.93–1.17]	0.508

Model 1*	Model 2*	Model 3*	Model 4*
<p>Legend:</p> <p>Abbreviations: 95% CI: 95% confidence interval, aOR: adjusted odds-ratio, OR: odds-ratio.</p> <p>Model 1: unadjusted, Model 2: adjusted for sociodemographic variables, Model 3: Model 2 + history of psychotic disorders, Model 4: Model 3 + characteristics of the reference hospital stay</p> <p>Significant associations are in bold.</p>			

With regard to acute psychotic disorders, the association with the main study outcome was consistent and significantly stronger than for psychotic disorders (all kinds): OR = 0.26, 95% CI [0.16–0.40], p-value < 0.001 (Model 1). This significant association was attenuated after the various model adjustments: Model 2: aOR = 0.38, Model 3: aOR = 0.36, Model 4: aOR = 0.50 (all p-values < 0.001). The details of the different models concerning hospitalization *for* an acute psychotic disorder are available in Table 3.

Table 3

Association of previous COVID-19 hospitalization with subsequent (12-month) hospitalization for an acute psychotic disorder (i.e., principal diagnosis only)

	Model 1*			Model 2*			Model 3*			Model 4*		
	OR	[95% CI]	p-values	aOR	[95% CI]	p-values	aOR	[95% CI]	p-values	aOR	[95% CI]	p-values
<i>Hospitalization for COVID-19</i>												
No (reference)	1			1			1			1		
Yes	0.26	[0.16–0.40]	< 0.001	0.38	[0.24–0.59]	< 0.001	0.36	[0.23–0.57]	< 0.001	0.50	[0.32–0.79]	< 0.001
<i>Sex</i>												
Male (reference)				1			1			1		
Female				0.47	[0.43–0.52]	< 0.001	0.69	[0.63–0.76]	< 0.001	0.73	[0.66–0.79]	0.003
<i>Age (years)</i>												
18–39 (reference)				1			1			1		
40–59				0.48	[0.43–0.53]	< 0.001	0.41	[0.38–0.46]	< 0.001	0.45	[0.40–0.50]	< 0.001
60–74				0.13	[0.11–0.15]	< 0.001	0.14	[0.12–0.17]	< 0.001	0.18	[0.16–0.21]	< 0.001
75+				0.06	[0.05–0.08]	< 0.001	0.09	[0.07–0.10]	< 0.001	0.12	[0.10–0.15]	< 0.001
<i>French deprivation index (FDep, quintiles)</i>												
1 (least deprived) (reference)				1			1			1		
2				1.03	[0.82–1.13]	0.334	1.10	[0.95–1.27]	0.218	1.10	[0.95–1.27]	0.212
3				0.54	[0.26–1.04]	0.954	0.94	[0.81–1.09]	0.405	0.95	[0.81–1.10]	0.170
4				1.07	[0.93–1.24]	0.936	0.95	[0.81–1.10]	0.464	0.95	[0.82–1.11]	0.533
5 (tmost deprived)				1.00	[0.87–1.17]	0.845	0.95	[0.81–1.11]	0.497	0.96	[0.83–1.12]	0.638
<i>History of psychotic disorders</i>												
No (reference)												
Yes							35.80	[32.75–39.14]	< 0.001	34.65	[31.68–37.89]	< 0.001
Reference hospital stay duration (days) - median (IQ)										0.87	[0.85–0.88]	< 0.001
<i>Level of clinical care received in reference hospital stay</i>												
General hospital ward (reference)										1		
Intensive care unit										0.64	[0.51–0.81]	< 0.001
Intensive care unit with invasive procedure										0.65	[0.41–1.04]	0.071

Model 1*	Model 2*	Model 3*	Model 4*
Legend:			
Abbreviations: 95% CI: 95% confidence interval, aOR: adjusted odds-ratio, OR: odds-ratio.			
Model 1: unadjusted, Model 2: adjusted for sociodemographic variables, Model 3: Model 2 + history of psychotic disorders, Model 4: Model 3 + characteristics of the reference hospital stay.			
Significant associations are in bold.			

With regard to chronic psychotic disorders, the different associations were also consistent with psychotic disorders (all kinds) analyses (Model 1: OR = 0.63, Model 2: OR = 0.72, Model 3: OR = 0.87, Model 4: OR = 0,69, all p-values < 0.001). The details of the different models concerning hospitalization *for* a chronic psychotic disorder are available in Table 4.

Table 4

Association of COVID-19 hospitalization with further hospitalization for a chronic psychotic disorders (i.e., principal diagnosis only)

	Model 1*			Model 2*			Model 3*			Model 4*		
	OR	[95% CI]	p-values	aOR	[95% CI]	p-values	aOR	[95% CI]	p-values	aOR	[95% CI]	p-values
<i>Hospitalizations for COVID-19</i>												
No (reference)	1			1			1			1		
Yes	<b>0.63</b>	<b>[0.56–0.71]</b>	<b>&lt; 0.001</b>	<b>0.72</b>	<b>[0.63–0.81]</b>	<b>&lt; 0.001</b>	<b>0.87</b>	<b>[0.80–0.95]</b>	<b>&lt; 0.001</b>	<b>0.69</b>	<b>[0.60–0.78]</b>	<b>&lt; 0.0001</b>
<i>Sex</i>												
Male (reference)				1			1			1		
Female				<b>0.46</b>	<b>[0.450.48]</b>	<b>&lt; 0.001</b>	<b>0.7</b>	<b>[0.68–0.72]</b>	<b>&lt; 0.001</b>	<b>0.69</b>	<b>[0.66–0.71]</b>	<b>&lt; 0.0001</b>
<i>Age</i>												
18–39 (reference)				1			1			1		
40–59				<b>0.94</b>	<b>[0.90–0.98]</b>	<b>0.002</b>	<b>0.79</b>	<b>[0.76–0.83]</b>	<b>0.002</b>	<b>0.69</b>	<b>[0.66–0.72]</b>	<b>&lt; 0.001</b>
60–74				<b>0.31</b>	<b>[0.30–0.33]</b>	<b>&lt; 0.001</b>	<b>0.53</b>	<b>[0.50–0.55]</b>	<b>&lt; 0.001</b>	<b>0.34</b>	<b>[0.32–0.36]</b>	<b>&lt; 0.001</b>
75+				<b>0.12</b>	<b>[0.11–0.13]</b>	<b>&lt; 0.001</b>	<b>0.51</b>	<b>[0.48–0.53]</b>	<b>&lt; 0.001</b>	<b>0.18</b>	<b>[0.17–0.20]</b>	<b>&lt; 0.001</b>
<i>French deprivation index (quintiles)</i>												
1 (the least deprivation) (reference)				1			1			1		
2				<b>0.88</b>	<b>[0.82–0.93]</b>	<b>&lt; 0.001</b>	<b>0.92</b>	<b>[0.88–0.97]</b>	<b>0.003</b>	<b>0.9</b>	<b>[0.84–0.97]</b>	<b>0.003</b>
3				1.06	[1.00–1.12]	0.066	<b>0.92</b>	<b>[0.88–0.97]</b>	<b>0.002</b>	<b>0.93</b>	<b>[0.87–0.99]</b>	<b>0.033</b>
4				0.99	[0.94–1.06]	0.851	<b>0.88</b>	<b>[0.84–0.93]</b>	<b>&lt; 0.001</b>	<b>0.9</b>	<b>[0.84–0.96]</b>	<b>0.002</b>
5 (the most deprivation)				0.99	[0.93–1.06]	0.821	<b>0.89</b>	<b>[0.85–0.94]</b>	<b>&lt; 0.001</b>	<b>0.88</b>	<b>[0.82–0.95]</b>	<b>&lt; 0.001</b>
<i>History of psychotic disorders</i>												
No (reference)							1			1		
Yes							<b>123.26</b>	<b>[119.51–127.13]</b>	<b>&lt; 0.001</b>	<b>155.45</b>	<b>[148.84–162.36]</b>	<b>&lt; 0.001</b>
<i>Reference hospitalization stay (days) - median (IQ)</i>										<b>0.97</b>	<b>[0.96–0.97]</b>	<b>&lt; 0.001</b>
<i>Level of clinical care received in reference hospital stay</i>												
General hospital wards (reference)										1		
Intensive care unit										<b>0.78</b>	<b>[0.72–0.84]</b>	<b>&lt; 0.001</b>

Model 1*	Model 2*	Model 3*	Model 4*
			1.08 [0.96–1.22] 0.210
Intensive care unit with invasive procedures			
Legends:			
Abbreviations: 95% CI: 95% confidence interval, aOR: adjusted odds-ratio, OR: odds-ratio.			
Model 1: unadjusted, Model 2: adjustment on sociodemographic variables, Model 3: Model 2 + history of psychotic disorders, Model 4: Model 3 + characteristics of the reference hospitalization			
Significant associations are in bold.			

## Discussion

In this nationwide French study, the 12-month risk of hospitalization *for* a psychotic disorder (i.e., principal diagnosis only) after discharge from hospital for COVID-19 during the first wave of the pandemic was lower than the risk after discharge after hospitalization for another reason. This was consistent for acute and chronic psychotic disorders.

Two points are important to highlight to explain these results. First, we need to make an important distinction between principal and associated diagnoses: the former represents the reason for hospitalization (i.e., patient is hospitalized *for* a psychotic disorder), while the latter represents a comorbidity at the time of hospitalization (i.e., patient is hospitalized *with* a psychotic disorder). Accordingly, associated diagnoses may reflect to a large extent patients who are not hospitalized in a psychiatric ward (i.e., hospitalization *with* a diagnosis of psychotic disorders). In the present study, we were interested in the risk of FEP or psychotic relapse following severe COVID-19 disease. This is why the main finding of this study is the lower rate of hospitalization for a psychotic disorder among patients previously hospitalized for COVID-19 than in patients previously hospitalized for another reason.

Second, we cannot conclude that hospitalization for COVID-19 is a protective factor against hospitalization for psychotic disorders, given that the control group (i.e., hospitalized for another reason) was a vulnerable sample and not the general population. Indeed, the 12-month rate of hospitalization with or for psychotic disorders in those previously hospitalized for a reason other than COVID-19 was high (0.95% considering principal or associated diagnosis, 0.51% considering principal diagnosis only). In comparison, these rates were of the same order of magnitude as the prevalence of psychotic disorders in the general population (0.46%) according to a French urban-area based study [38]), and the majority of those with psychotic disorders in that study was not hospitalized.

With regard to patients with a history of psychotic disorders, hospitalization for non-psychiatric reasons (i.e., for COVID-19 or another reason) was a major risk factor for psychotic relapse, as hospitalization represents a major stressful event [39]. Moreover, during hospitalization in non-psychiatric wards, these patients' psychotropic (including antipsychotics) treatments are often stopped or modified because of their side effects [40–42]; this too constitutes a major risk factor for psychotic relapse [43].

The rate of hospitalization for acute psychotic disorders can be considered a proxy for the rate of incidence of psychotic disorders in the population of patients hospitalized given the majority of subjects with FEP are hospitalized in France [44]. Note however that this proxy is approximate, as in our study, the rate of patients with acute disorders with a history of psychotic disorders was 44.86% (while this rate was 74.39% in patients with chronic disorders). According to this hypothesis, the rates of FEP were also high (COVID-19 patients: 0.05% considering hospitalization *with* acute psychotic disorders, 0.02% considering hospitalization *for* acute psychotic disorders; non-COVID-19 patients: 0.11% and 0.08%). The only recent incidence study of psychotic disorder in France took place in two areas, one urban and one rural, and found lower rates (0.036% and 0.017%, respectively) [44]. This confirms that hospitalization, irrespective of the reason (i.e., COVID-19 or another reason), is a risk factor for FEP, but not specifically COVID-19 hospitalization. This contrasts with what was initially feared about the role of this diseases as a risk factor for psychotic disorder [3–5].

In an Australian study in early psychosis intervention services, O'Donoghue *et al.* found a higher rate of hospitalization of FEP during the pandemic than the pre-pandemic period (this difference was not significant: incidence rate ratio = 1.14, 95% CI [0.92–1.42]) [45]. Longitudinal studies with longer follow-up durations, especially for children with a history of COVID-19, are necessary to investigate the role of COVID-19 as a putative risk factor for FEP. Indeed, the associated risk may increase over time, as is the case for other infections. Interestingly, in the study by Taquet *et al.*, among the 14 neuro-psychiatric outcomes studied, psychotic disorders were the only psychiatric disorders whose risk was still higher after 2 years of follow-up [31]. In contrast, in an English cohort study of more than 8 million subjects focusing on the incident

psychotic disorders after initial hospitalization for COVID-19 or for severe acute respiratory infection hospitalizations, Clift *et al.* found non-significant differences between rates for the two types of hospitalization. [32].

Crude hospitalization rates in non-psychiatric wards were also very high in our study (hospitalization rate for or with a diagnosis of a psychotic disorder: 0.95%, including 0.49% for hospitalization in psychiatric wards and 0.46% in non-psychiatric wards). This confirms that psychotic disorders are major risk factors (and therefore very comorbid) for non-psychiatric diseases (with high associated mortality rates) [46–49]. These high rates of hospitalization must be interpreted in the context of the beginning of the COVID-19 pandemic when the use of hospitalization for non-COVID-19 pathologies was greatly reduced in France – both in psychiatric and non-psychiatric wards – because of bed availability issues [50–54].

In terms of adjustment variables, as expected, having a history of psychotic disorders was a major determinant of the risk of hospitalization *with* and *for* a psychotic disorder (aOR = 115.79 for principal or associated diagnosis, and 127.71 for principal diagnosis only, respectively), as reflected by the number of cases of hospitalization with an acute psychotic disorder (3,075 / 27,614, *i.e.*, only 11.1% of subjects hospitalized for a psychotic disorder had an acute psychotic disorder). Accordingly, the role of the history of psychotic disorder variable was much greater than that of the type of initial hospitalization (*i.e.*, COVID-19 or another reason). Moreover, male sex was associated with a higher risk of subsequent hospitalization for psychotic disorders, which is consistent with the fact that males present more severe forms of psychotic disorders than females [55]. Likewise, the young age group was associated with a higher risk of psychotic disorders, which also reflects the literature [56, 57].

A comparison of our results with the literature is difficult, as studies on the role of severe COVID-19 are very rare. Taquet *et al.* studied larger and international samples in several studies [29–31]; one of these can be compared to our present work [29]. Contrary to our results, the risk of psychotic disorders post-COVID-19 (with or without hospitalization) in that study was higher in comparison to influenza (HR = 2.03, 95% CI [1.78–2.31]), and other respiratory infections (HR = 1.66, 95% CI [1.53–1.81]). Interestingly, the authors compared COVID-19 with and without hospitalization, and found an even greater risk for patients requiring hospitalization (HR = 2.22, 95% CI [1.92–2.57]). This finding further increases the discrepancy with the present study. Moreover, their analyses of ICU care were consistent with this last association (HR = 1.48, 95% CI [1.14–1.92]). However, once again, their choice of specific health control events (*i.e.*, other respiratory infections), and their sample – which was very different (over 81 million patients in different countries, primarily in the USA) from the present study – make the comparison difficult. Elsewhere, Clift *et al.* found less inconsistent results [32]. In that study, which examined psychotic relapse in a register database of more than 8 million subjects, the rates of relapse were not different between persons previously hospitalized for COVID-19 and those previously hospitalized for a severe acute respiratory infection, although they were both higher than in the general population (HR = 3.05 95% CI [1.58–5.90] for COVID-19; 3.63 95% CI [1.88–7.00] for severe acute respiratory infection).

There are several putative explanations for the lower risk of hospitalization for psychotic disorders after COVID-19 hospitalization which we found, in comparison to hospitalization for another reason. The first regards the control population. COVID-19 hospitalization may have represented less severe reason than the other reasons (especially during the first wave of the pandemic), thereby leading to a lower risk of subsequent hospitalization for psychotic disorders. This phenomenon is particularly plausible given the lower rate of hospitalization for all the other diseases during this period in comparison to the pre-pandemic period [52, 53]. However, contrary to this hypothesis, subjects hospitalized for COVID-19 had a higher level of care and longer hospital stays. A second explanation is that hospitalization for a reason other than COVID-19 may have concerned patients with diseases that were more chronic than COVID-19, and who therefore had a higher and/or longer lasting vulnerability to relapse. Another explanation is that vulnerability to psychotic disorders may have been associated with reduced access to hospitalization for COVID-19 – especially admission to an ICU – during the first wave of the pandemic [13]. This hypothesis is consistent with the negative association which we found between hospitalization for psychotic disorders and previous admission to an ICU ward compared to non-ICU wards. Finally, patient mortality may have been higher in subjects hospitalized with COVID-19 than in those hospitalized for another reason; this could partially explain their lower rate of subsequent hospitalization for or with a psychotic disorder. Nevertheless, contrary to – but without excluding – this hypothesis, a recent French nationwide study highlighted that non-COVID-19 mortality increased more among patients with psychotic disorders than among controls during 2020 in comparison to 2019 (aOR = 1.18, 95% CI [1.11–1.25]) [58].

Several study limitations must be underlined. The control population (discussed in detail elsewhere [33]) was not specific (different ward types, a wide variety of indications). Contrary to Taquet *et al.*, we were not able to study different durations after the first hospitalization [31]. Moreover, in terms of FEP, given the etiology of psychotic disorders – where risk factors are involved years (or even decades) before the onset of the disease – our follow-up duration (12 months) was relatively short. Any conclusions concerning the putative influence of COVID-19 on the risk of FEP incidence must therefore be interpreted with caution. Finally, we had no information on patients that left the study (*i.e.*, patients that died or moved outside of metropolitan France).



Despite these limitations, the study has several strengths. The first is the exhaustiveness of the data which covered all hospitalizations in metropolitan France, thereby limiting selection and memory biases, and ensuring analyses with good statistical power. Second, the study of both principal and associated diagnoses of psychotic disorders enabled us to distinguish the reasons for hospitalization. Moreover, by studying acute vs. chronic psychotic disorders separately, we were able to study to what degree severe COVID-19 is a risk factor for FEP.

Overall, during the first wave of the COVID-19 pandemic in France, the risk of hospitalization for psychotic disorders in the 12 months following discharge from hospital for severe COVID-19 was lower than the risk following discharge after hospitalization for another reason. This was true for psychotic disorders as a whole, for acute and chronic psychotic disorders taken separately, and for schizophrenia. These findings contradict the hypothesis that the risk of psychotic disorders after hospitalization for COVID-19 is higher than that after hospitalization for another reason. Other studies on this topic with longer follow-up duration, and which integrate COVID-19 vaccination data are necessary. Indeed, vaccination may modify the consequences of COVID-19, including the rate of hospitalization or the risk of further psychotic disorders.

Finally, this study confirms that hospitalization for non-psychiatric reasons (*i.e.*, COVID-19 or another reason) is a major risk factor for psychotic relapse; this finding should encourage clinicians to provide greater care to patients with psychiatric disorders during hospital stays and after discharge.

## Declarations

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### CONFLICT OF INTEREST

Prof. Lemogne reports personal fees and non-financial support from Otsuka Pharmaceutical outside the submitted work. Prof. Messika received congress reimbursement fees from Biotest and CSL Behring. The other authors have no conflicts of interest to declare.

### AUTHORS' CONTRIBUTIONS

Baptiste Pignon:

Substantial contribution to the conception and design of the research presented;

Data interpretation;

Drafting the manuscript;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Valentina Decio:

Substantial contribution to the conception and design of the research presented;

Acquisition, analysis, and interpretation of data for the work;

Drafting the manuscript;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Philippe Pirard:

Substantial contribution to the conception and design of the research presented,;

Data interpretation;

Drafting the manuscript;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Olivier Bouaziz:

Substantial contributions to the conception or design of the work;

Interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Emmanuelle Corruble:

Substantial contributions to the conception or design of the work;

Interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Viviane Kovess-Masfety:

Substantial contributions to the conception or design of the work; interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Marion Leboyer:

Substantial contributions to the interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Cédric Lemogne

Substantial contributions to the interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Jonathan Messika:

Substantial contributions to the conception or design of the work; interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Vittorio Perduca:

Substantial contributions to the conception or design of the work; interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Franck Schürhoff:

Substantial contributions to the interpretation of data for the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Nolwenn Regnault:

Substantial contributions to the conception or design of the work;

Revising the work critically for important intellectual content;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

Sarah Tebeka:

Substantial contributions to the conception and design of the work;

Acquisition, analysis, and data interpretation for the work;

Drafting the manuscript;

Final approval of the version to be published;

Agrees to be accountable for all aspects of the research presented and ensures that questions related to the accuracy and integrity of all parts of the research will be appropriately investigated and resolved.

DATA AVAILABILITY STATEMENT

The SNDS (National French administrative healthcare database) comprises a set of strictly pseudonymized databases. By law, *Santé Publique France*, the French agency for public health, has permanent regulatory access to SNDS data for the performance of its missions (article L.1461-3 and R1461-13 and following of the French public health code [37]). Access to personal data in these systems for research purposes is subject to obtaining authorization from the CNIL (National Commission on Information Technology and Civil Liberties), after approval from the *Comité éthique et scientifique pour les recherches, les études et les évaluations dans le domaine de la santé* (CESREES, Ethics and Scientific Committee for Research, Studies and Evaluation in the field of health).

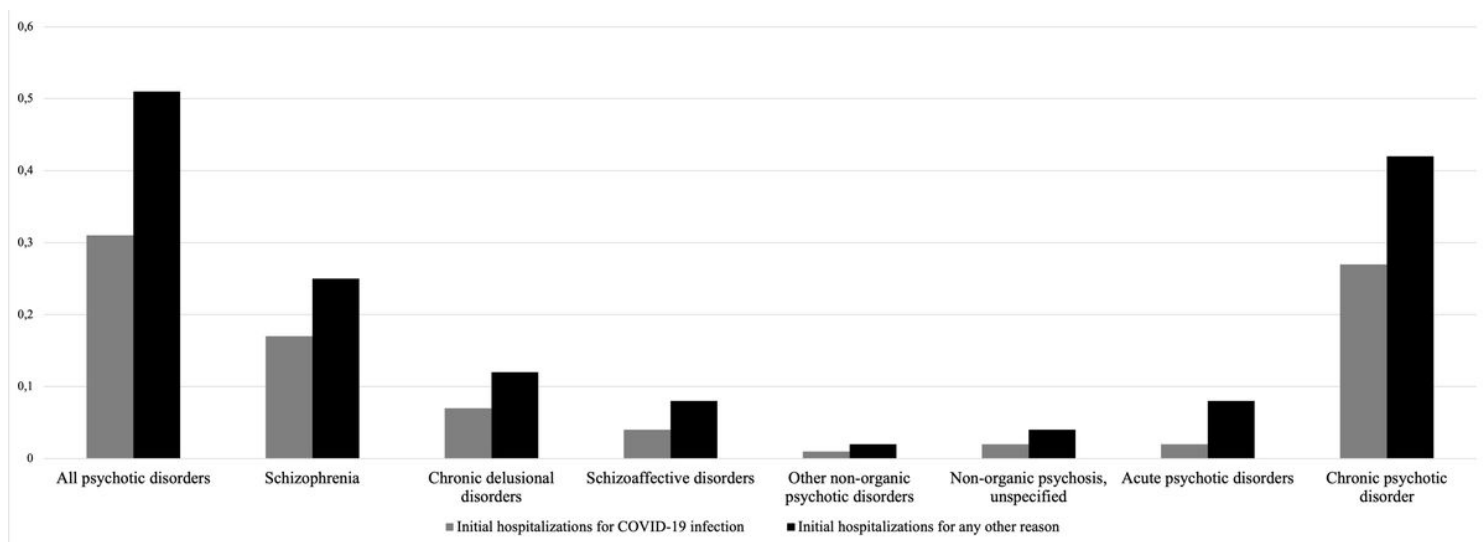
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## Figures



**Figure 1**

Rate of hospitalization for psychotic disorders (principal diagnoses) after hospitalization during the first wave of the COVID-19 pandemic in metropolitan France (%; denominator: patients hospitalized during the 6 first months of 2020)

## Supplementary Files

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