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SARS-CoV-2 infection and COVID-19 outcomes across mental disorders and the role of sex: A register-based study from Catalonia

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ABSTRACT

Introduction: This study investigated the risk of SARS-CoV-2 infection and severe COVID-19 outcomes among different mental health diagnoses and the role of sex in these associations.
Methods: Using electronic records from Catalonia, we identified adults receiving mental health care from 2017–2019 with diagnoses of non-affective psychosis (NAP), bipolar disorder (BD), depressive disorder (DEP), stress-related disorders, neurotic/somatoform disorders (NSD), and substance misuse (SUB) (exposed). The outcomes assessed were SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19-related death, compared to matched individuals without these mental disorders (unexposed). Adjusted logistic regression analyses were conducted.
Results: 785,378 adults were included (70.3% < 65 years old; 57.1% women). Compared to unexposed, those with NAP, BD, DEP, and SUB had a lower risk of SARS-CoV-2 infection, while those with NSD had an increased risk. Infected individuals with DEP, NSD, and SUB had a lower risk of hospitalization but a higher risk of COVID-19-related death. Higher COVID-19-related death was also observed in individuals with NAP and BD. Sex-stratified analysis revealed that women with NSD were especially vulnerable to infection, and women with DEP and NSD had a higher risk of COVID-19-related death.
Conclusions: These findings emphasize the need for tailored public health strategies to reduce excess mortality risk among individuals with certain mental disorders, while accounting for sex differences.

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1. Introduction

People with pre-existing mental disorders are particularly vulnerable to the impact of the COVID-19 disease, as this population experiences worse COVID-19 outcomes and subsequent health complications following infection (Bertolini et al., 2023; Schultebraucks et al., 2023). However, it is unclear if this vulnerability is present in all mental disorder groups. Types of mental disorders differ in behavioural factors (e.g. stress response, cognitive impairment) (Zorn et al., 2017), biological factors, and health behaviours (e.g. smoking, sleeping habits) (Firth et al., 2020; Zhang et al., 2023). For instance, the prevalence of smoking is not equal across disorders, being higher in individuals with bipolar and drug misuse disorders, while different mental disorders exhibit distinct clusters of altered inflammatory markers (Smith et al., 2020; N. Yuan et al., 2019). In addition, mental disorders differ in clinical factors such as medication patterns or the prevalence of physical comorbidities (Jürisson et al., 2021). Given that most of these factors directly influence the risk of infection and COVID-19 severity (Hamer et al., 2020; Smadi et al., 2023; Zheng et al., 2022), the impact of COVID-19 disease might not be equal across mental disorders. Understanding the individual risks of SARS-CoV-2 infection and severe COVID-19 outcomes among mental health diagnoses is important to mitigate health disparities across people with mental disorders (Lawrence & Kisely, 2010) and to develop targeted interventions and public health strategies.

To date, several studies have analysed the association between specific mental health diagnoses and SARS-CoV-2 infection and severe COVID-19 outcomes, but results are inconsistent for most diagnostic groups. Current literature suggests an increased risk of COVID-related death in people with pre-existing psychotic and drug misuse disorders compared to individuals without mental disorders, but the results are diverse regarding their risk of infection (Bertolini et al., 2023; Molero et al., 2023). Likewise, the association between other mental disorders such as depression, anxiety or neurodevelopmental disorders and SARS-CoV-2 infection and mortality is unclear (Molero et al., 2023), while evidence is limited for some mental disorders such as stress-related disorders. One potential reason for the divergence of results across studies is the heterogeneity in grouping of mental disorders. For instance, one umbrella review including nine systematic reviews reported an increased COVID-19 mortality in people with mood disorders (which included both depression and bipolar depression into a single category) (Bertolini et al., 2023). Yet, results from other studies in which such disorders were examined individually showed that people with bipolar disorder faced an elevated risk of COVID-19-realted death (Fond et al., 2023), while results were mixed for depression (Kostev et al., 2023; Schultebraucks et al., 2023), with some studies suggesting a lower risk of COVID-19 mortality (Kostev et al., 2023).

Another factor that has the potential to play a significant role in these divergent findings is sex. Studies from the general population revealed that men had higher odds of SARS-CoV-2 infection, a severe course of the disease and COVID-19-related death than women. (Pijls et al., 2021) In addition, women and men present differences both in the manifestation and prevalence of several mental disorders (Tesic et al., 2019). This is mainly caused by disparities in brain structure and function, stress response, socio-cultural norms and sex hormones (Altemus et al., 2014). Some of these factors, such as sex hormones, have been reported to contribute to the risk of severe COVID-19 (Cai et al., 2022). However, we have only identified one study from the United States showing different risks of COVID-related outcomes between men and women across different pre-existing mental disorders (Wang et al., 2021). This study found that women with ADHD, depression, bipolar disorder, and schizophrenia had an increased risk of SARS-CoV-2 infection when compared to men, while COVID-19 hospitalization and death rates remained higher in men with any mental disorder than in women. However, the role of sex in the risk of COVID-19 hospitalization and COVID-19 death was not explored in the different diagnostic groups (Wang et al., 2021). Therefore, further studies from diverse countries are required to better understand the prognosis of individuals with COVID-19 according to their psychiatric diagnosis and sex.

This study used health registers from the region of Catalonia (Spain) to assess the association between several types of mental disorders (i.e., non-affective psychosis, bipolar disorder, depression, stress-related disorders, neurotic/somatoform disorders and substance misuse) and risk of SARS-CoV-2 infection, hospitalization and COVID-19-related death. Importantly, analyses were also stratified for sex to explore whether there are sex-specific patterns in the aforementioned associations.

2. Methods

2.1. Study design and population

An observational retrospective matched cohort study was performed using anonymized data from electronic health records from Catalonia, Spain. Data were retrieved from the Health Quality and Assessment Agency of Catalonia (AQuAS), which is responsible and manages the Public Data Analysis for Health Research and Innovation Programme (PADRIS) (Gencat, n.d.). Clinical information on users of the Catalan public health system, serving a population of 6358,740 inhabitants older than 18 years in the first semester of 2021, were here collected (Institut d'Estadística de Catalunya, 2021). These registers used the 9th and 10th versions of the International Classification of Diseases (ICD-9/ ICD-10) (Annex 1).

We selected all adults $\geq$ 18 years in 2017 and still alive on 31st of December 2019, that received specialized inpatient or outpatient mental health care between January 1, 2017, and December 31, 2019, for the following mental disorders: non-affective psychosis, bipolar disorder, depressive disorder, stress-related disorders, neurotic/somatoform disorders, and substance misuse (ICD-10 codes in Annex 1). For patients having more than one diagnosis of mental disorder, we used the following hierarchical order based on DSM-V to classify them (American Psychiatric Association, 2022): non-affective psychosis > bipolar disorder > depressive disorder > stress-related disorders > neurotic/somatoform disorders > substance misuse. That is, those having any diagnosis of non-affective psychosis were classified as "non-affective psychosis"; participants without a diagnosis of non-affective psychosis but a diagnosis of bipolar disorder were classified as "bipolar disorder"; individuals without non-affective psychosis or bipolar disorder but diagnosed with depressive disorder were classified as "depressive disorder", and so on.

Each individual with one of the mental disorders of interest (exposed) was matched to a random individual from the Catalonia health registry who did not receive specialized inpatient or outpatient mental health care for the mental disorders of interest between January 1, 2017, and December 31, 2019, according to sex, 3-years age band and living area (unexposed).

According to the current regulation for the use of registry-based health data, informed consent was not required. This study was approved by the ethics committee of Fundació Sant Joan de Déu (PIC-160–21).

2.2. SARS-CoV-2 infection and COVID-19 outcomes

The primary outcomes of our study were SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19-related death. These data were retrieved from February 25, 2020 (the date of the first official reported case of COVID-19 in Catalonia) up to December 31, 2020 (before the vaccination campaigns began). SARS-CoV-2 infection was defined by a positive PCR/antigen test or a clinical diagnosis of COVID-19. None of the individuals included had a SARS-CoV-2 reinfection during the study period. COVID-19 hospitalization was defined by admissions caused by the following ICD-10 diagnosis: COVID-19, coronavirus infection, coronavirus causing other diseases and other viral pneumonia (Annex 1). COVID-19-related deaths were ascertained using mortuary records.

Dichotomous variables were created for the outcomes (yes/no).

2.3. Covariates

We included the number of physical diagnoses and nursing home/sheltered accommodation stay as covariates in all the analyses. Data on physical diseases was obtained from primary care registries between 1997 and 2018, since no more recent data was accessible at the time of data extraction. Physical diseases included asthma, cardiovascular diseases, chronic pulmonary disease, diabetes, dyslipidaemia, heart failure, hypertension, ischemic heart disease, malignant neoplasia and obesity (ICD-10 codes in Annex 1), which have been related to severe COVID-19 outcomes (Izcovich et al., 2020). Following previous studies, a 3-level variable was created: 0, 1, ≥2 (Russell et al., 2023). We also accounted for individuals who stayed in nursing homes (irrespective of the duration) throughout the study period encompassing the pandemic (February 25, 2020, to December 31, 2020). This is because they experienced a unique environment, which could potentially lead to distinct implications for their health outcomes and risk factors. Thus, a dichotomous variable for those who were admitted to nursing homes (yes/no) was created.

2.4. Statistical analysis

Categorical variables were summarized by frequency tables. In addition, chi-squared tests were used to assess differences in clinical characteristics between exposed and unexposed. Then, we employed multivariable logistic regression analysis to assess the association between the presence of mental disorders and SARS-CoV-2 infection while adjusting for physical diseases and nursing homes stay. Analyses were not adjusted by sex or age because we matched the exposed and unexposed groups by these variables. We further employed multivariable logistic regression analysis in a sub-cohort containing only those individuals who had tested positive for COVID-19 to test the association between each mental health diagnosis and COVID-19 hospitalization and COVID-19-related death. These analyses were adjusted for age, sex, number of physical diseases and nursing homes stay. Sensitivity analysis including the whole sample (i.e. not restricting to infected individuals) were also conducted. Furthermore, multivariable logistic regression analyses were conducted separately for men and women to assess the association between the six mental disorder groups and COVID-19 infection, hospitalization, and COVID-19-related death, while accounting for potential sex-specific effects.

The level of statistical significance was set at *alpha* level of 0.05. All analysis were performed in R, version 4.3.1.

3. Results

3.1. Sample characteristics

Between the 1st of January 2017 and the 31st of December 2019, 392,689 people were diagnosed with a mental disorder of interest. After the 1:1 matching procedure, the total sample size for this study comprised 785,378 individuals. In both groups, 70.3% were younger than 65 years old and 57.1% were women. The demographic characteristics of the study population are shown in Table 1. Compared to unexposed, people with diagnoses of mental disorders had a higher prevalence of more than one physical diagnosis (35.5% vs 28.9% in unexposed) and were more likely to be staying in nursing homes (2.6% vs 1.6% in unexposed). The proportion of individuals infected with SARS-CoV-2 was similar between groups. The proportion of COVID-19 hospitalizations among individuals with a SARS-CoV-2 infection was lower in exposed than in unexposed (10.7% vs 11.5%), while COVID-19-related death was significantly higher in exposed (4.4% vs 3.3%).

3.2. Mental disorders and risk of SARS-CoV-2 infection and COVID-19 outcomes

Results from multivariable logistic regression analysis are shown in Table 2. Our results showed that people with non-affective psychosis, bipolar disorder, depression and substance misuse had a significant reduced risk of SARS-CoV-2 infection compared to unexposed [OR (95% CI): 0.84 (0.80–0.88); 0.80 (0.75–0.86); 0.97 (0.94–1.00); 0.81 (0.78–0.84), respectively], although in the case of depression the effect size was small. Conversely, individuals with neurotic/somatoform disorders exhibited a slightly elevated risk of infection [OR (95%CI): 1.03 (1.01–1.06)]. No significant differences were found in people with stress-related disorders.

Among those who tested positive for COVID-19, we explored differences in the risk of COVID-19 hospitalization and COVID-19-related death across the six groups of mental disorders (Table 2). We observed that individuals with depression, neurotic/somatoform disorders, and

Table 1
Sociodemographic characteristics of the study population.

N (%)		Total(n = 785,378)	Exposed(n = 392,689)	Unexposed(n = 392,689)	p-value[2]
Sex	**Men**	336,646 (42.9%)	168,323 (42.9%)	168,323 (42.9%)	-
	Women	448,732 (57.1%)	224,366 (57.1%)	224,366 (57.1%)	
Age	**18 - 64**	552,278 (70.3%)	283,917 (72.3%)	268,361 (68.3%)	-
	≥ 65	233,100 (29.7%)	108,772 (27.7%)	124,328 (31.7%)	
Mental disorder	**Non-affective psychosis**	26,665 (3.4%)	26,665 (6.8%)	-	-
	Bipolar disorder	15,000 (1.9%)	15,000 (3.8%)	-	
	Depressive disorder	98,434 (12.5%)	98,434 (25.1%)	-	
	Stress-related disorders	51,944 (6.6%)	51,944 (13.2%)	-	
	Neurotic and somatoform disorders	103,048 (13.1%)	103,048 (26.2%)	-	
	Substance misuse	97,598 (12.4%)	97,598 (24.9%)	-	
Nursing homes stay	**Non-user**	768,641 (97.9%)	382,315 (97.4%)	386,326 (98.4%)	<0.001
	User	16,737 (2.1%)	10,374 (2.6%)	6363 (1.6%)	
Physical comorbidities	**0**	348,153 (44.3%)	157,672 (40.2%)	190,481 (48.5%)	<0.001
	1	184,225 (23.5%)	95,694 (24.4%)	88,531 (22.5%)	
	≥2	253,000 (32.2%)	139,323 (35.5%)	113,677 (28.9%)	
SARS-CoV-2 infection	**No**	738,842 (94.1%)	369,429 (94.1%)	369,413 (94.1%)	0.942
	Yes	46,536 (5.9%)	23,260 (5.9%)	23,276 (5.9%)	
COVID-19 hospitalization[1]	**No**	41,368 (88.9%)	20,764 (89.3%)	20,604 (88.5%)	0.012
	Yes	5168 (11.1%)	2496 (10.7%)	2672 (11.5%)	
COVID-19 related death[1]	**No**	44,738 (96.1%)	22,230 (95.6%)	22,508 (96.7%)	<0.001
	Yes	1798 (3.9%)	1030 (4.4%)	768 (3.3%)	

[1] Sample size restricted to COVID-19 positive cases (n = 46,536). [2]P-values were calculated using 20,000 Monte Carlo simulations of the χ^2 test facing exposed and unexposed.

Table 2
Logistic regression analysis for risk of SARS-CoV-2 infection, COVID-19 hospitalization and COVID-19-related death.

		SARS-CoV-2 infectionAOR (95% CI)	COVID-19 hospitalizationAOR (95% CI)[1]	COVID-19-related deathAOR (95% CI)[1]
Physical diseases	1	1.08 (1.05, 1.11) p <0.001	1.14 (1.04, 1.24) p = 0.006	1.00 (0.84, 1.19) p = 0.999
	≥2	1.26 (1.23, 1.29) p <0.001	1.44 (1.33, 1.55) p <0.001	1.18 (1.03, 1.36) p = 0.021
Nursing homes stay	yes	7.90 (7.63, 8.18) p <0.001	0.83 (0.75, 0.91) p <0.001	0.93 (0.82, 1.06) p = 0.277
Mental disorder	Non-affective psychosis	0.84 (0.80, 0.88) p <0.001	1.08 (0.93, 1.26) p = 0.307	1.68 (1.34, 2.12) p <0.001
	Bipolar disorder	0.80 (0.75, 0.86) p <0.001	1.00 (0.81, 1.24) p = 0.957	2.02 (1.50, 2.73) p <0.001
	Depression	0.97 (0.94, 1.00) p = 0.030	0.90 (0.82, 0.98) p = 0.014	1.23 (1.07, 1.41) p = 0.003
	Stress-related disorder	1.02 (0.98, 1.06) p = 0.315	0.92 (0.80, 1.06) p = 0.245	0.94 (0.69, 1.28) p = 0.695
	Neurotic and somatoform disorder	1.03 (1.01, 1.06) p = 0.026	0.86 (0.78, 0.95) p = 0.004	1.26 (1.07, 1.48) p = 0.006
	Substance misuse	0.81 (0.78, 0.84) p <0.001	0.83 (0.75, 0.91) p <0.001	1.48 (1.24, 1.71) p <0.001

Analysis were adjusted for number of physical diseases and nursing home stay. [1] Sample size restricted to COVID-19 positive cases (n = 46,536), analysis were adjusted by age, sex, number of physical diseases, and nursing home stay. OR: Odd ratio, CI: Confidence Interval, p: p-value.

substance misuse disorders had a lower risk of COVID-19 hospitalization compared to unexposed [OR (95%CI): 0.90 (0.82–0.98); 0.86 (0.78–0.95); 0.83 (0.75–0.91), respectively], while no significant differences were found for non-affective psychosis, bipolar disorder, and stress-related disorders. Regarding COVID-19-related death, we found that all mental health groups (with the exception of stress-related disorders) had a greater risk of COVID-19-related death when compared to unexposed [OR_{NAP} (95%CI): 1.68 (1.34–2.12); OR_{BIP}: 2.02 (1.50–2.73); OR_{DEP}: 1.23 (1.07–1.41); OR_{NSD}: 1.26 (1.07, 1.48); OR_{SUB}: 1.48 (1.24, 1.71)]. These results were maintained in the sensitivity analysis with the whole sample (Annex 2).

3.3. Mental disorders and risk of SARS-CoV-2 infection and COVID-19 outcomes stratified by sex

Among COVID-19 outcomes, sex differences were only observed for depression and neurotic/somatoform disorders (Fig. 1, Annex 3). As regards to the risk of SARS-CoV-2 infection, only men with depression showed a lower risk of SARS-CoV-2 infection [AOR: 0.90 (95%CI 0.85–0.95), $p < 0.001$] when compared to unexposed men. Moreover, only women with neurotic/somatoform disorders presented an increased risk of SARS-CoV-2 infection [AOR: 1.07 (95%CI 1.03–1.11), $p < 0.001$] when compared to their unexposed counterparts. No differences within sexes were found in terms of COVID-19 hospitalization. Regarding COVID-19-related death, people with depression and neurotic/somatoform disorders had a significant increased risk of COVID-related death when compared to unexposed, but this was only significant for women [AOR_{DEP}: 1.24 (95%CI 1.05–1.47), p = 0.013; AOR_{NEU}: 1.26 (95%CI 1.02–1.54), p = 0.029].

4. Discussion

This study is the largest population-based study from Europe examining the risk of infection and severe COVID-19 outcomes across various mental disorders. While we identified different risks of SARS-CoV-2 infection and hospitalization among those with pre-existing mental disorders, almost all groups presented a higher risk of COVID-19-related death. Additionally, this study is among the few that explored the role of sex in the association between diverse psychiatric conditions and COVID-19 outcomes.

Our results showed that people with pre-existing non-affective psychosis, bipolar disorder, depression, and substance misuse had a lower risk of SARS-CoV-2 infection, which is in line with prior studies (Djuric et al., 2021; Egede et al., 2023). This reduced risk could be explained by social factors such as the decreased social activity observed in individuals with mental disorders, particularly in individuals with severe mental illnesses like schizophrenia or bipolar disorder (Richter & Hoffmann, 2019). Alternatively, the use of psychotropic drugs such as antidepressants or antipsychotics, which have been reported to reduce the risk of SARS-CoV-2 infection, could also explain these findings (Fred et al., 2022). Importantly, it should be noted that other studies reported a heightened risk of infection for these population groups (Dai et al., 2022; Jeon et al., 2021; Wang et al., 2021). One potential factor that could explain divergences across studies might be that, due to their life circumstances, people with pre-existing mental disorders, and especially those with severe mental illness, are more prone to be living in nursing homes, therapeutic communities, or hospitals, where infections can spread more rapidly (Shinn & Viron, 2020). However, none of the prior studies accounted for the fact of staying in these facilities. Thus, the increased risk of infection reported in some studies might be biased by the higher rate of people staying in mental health facilities or hospitals.

Conversely, we found a modest increased risk of SARS-CoV-2 infection in people with neurotic/somatoform disorders compared to unexposed, which is in line with findings of an umbrella review reporting a higher risk of infection in people with anxiety (Bertolini et al., 2023). The increased risk of COVID-19 (and other infectious diseases) (Coughlin, 2012) reported in people with anxiety disorders might be due to a compromised immune system (Vieira et al., 2010), caused by the impact of anxiety-related factors such as high psychological stress or sleep insufficiency on the immune system (Coughlin, 2012; Nami et al., 2020). Alternatively, this increased risk of infection could actually mean a greater inclination towards getting tested due to an exacerbated response to stress (Taylor et al., 2020).

Among those that were infected, we further examined whether there were differences in the risk of COVID-19 hospitalization and COVID-19-related death. We found that, compared to unexposed, people with pre-existing depression, neurotic/somatoform disorder, and substance misuse disorder had a lower risk of COVID-19 hospitalization, but a higher risk of COVID-related death. This decreased risk of hospitalization found in these populations might be explained by a neglect in seeking medical treatment due to a lack of energy, social withdrawal, feelings of hopelessness, and lower self-worth (Can & Tanriverdi, 2015; Marx et al., 2023; Pathare et al., 2018), what would ultimately lead to an increased mortality. Notably, the increased risk of COVID-19-related death was not exclusive to these diagnostic groups, since we also observed a higher risk of COVID-19-related death in people with

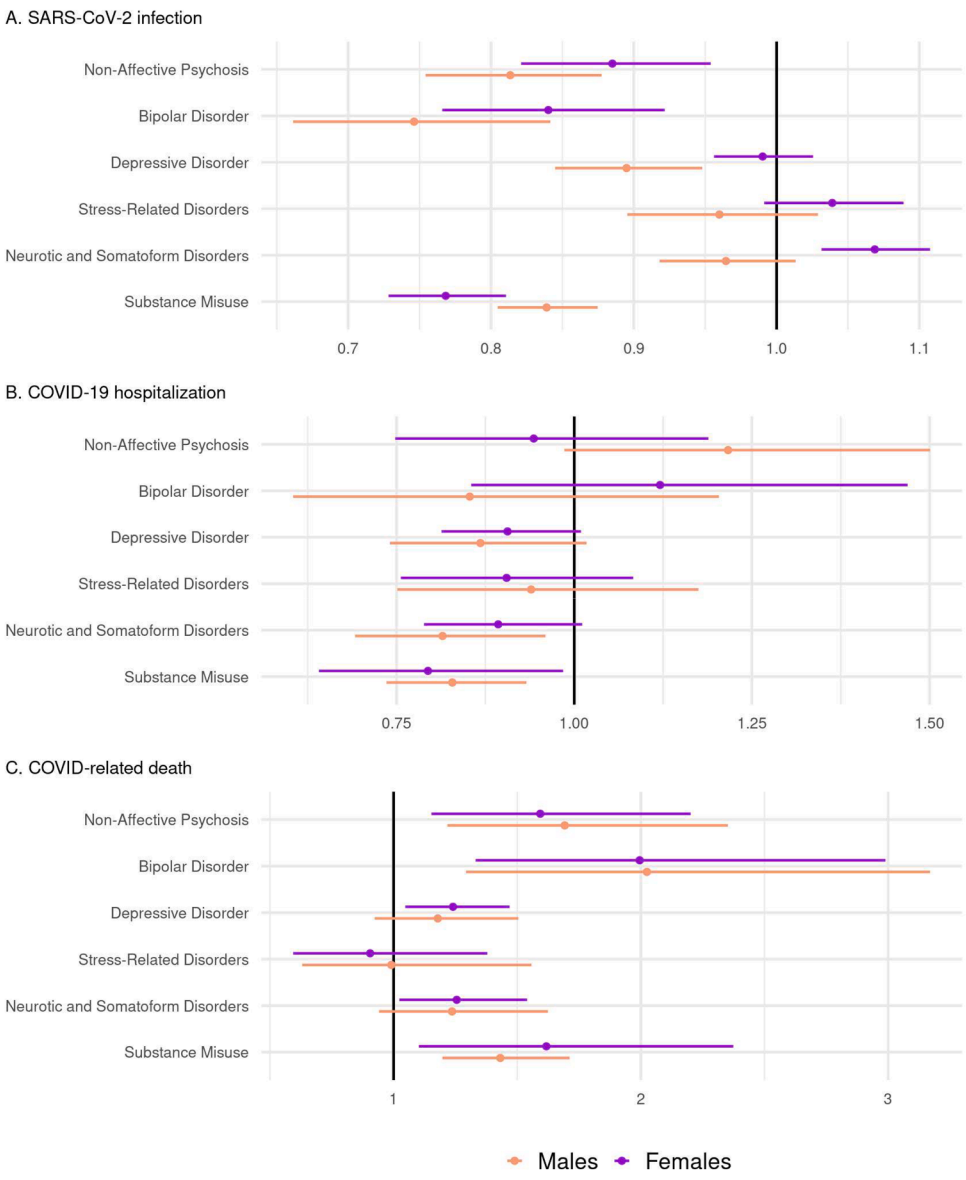

Fig. 1. Sex-stratified Forest plots of the association between mental disorder groups and SARS-CoV-2 infection, COVID-19 hospitalization and COVID-19-related death. Figure shows model coefficients in its odd ratio (OR) form. Models were adjusted for physical diseases and nursing homes stay (A) and for age, physical diseases and nursing homes stay (B,C).

non-affective psychosis and bipolar disorder when compared to unexposed. Overall, the increased COVID-19 mortality of people with these mental disorders has been widely reported in literature (Ceban et al., 2021; Molero et al., 2023; Vai et al., 2021), with numerous factors contributing to these associations, including a poor socioeconomic status (Riou et al., 2021), poor lifestyle habits such as smoking or unhealthy diet (Hamer et al., 2020; S. Yuan et al., 2020), and increased prevalence of comorbid medical conditions (Afzal et al., 2021; Teixeira et al., 2022). Interestingly, all these factors converge to a higher pro-inflammatory state (Hamer et al., 2020; Muscatell et al., 2020; Teixeira et al., 2022), which seems to be the baseline reason for the increased COVID-19-related death reported in people with these mental disorders (Hamer et al., 2020; N. Yuan et al., 2019). Conversely, the increased risk of COVID-19-related death observed for those with neurotic/somatoform disorders in our study contradicts prevailing evidence (Bertolini et al., 2023), which indicates that people with pre-existing anxiety face a similar risk of COVID-19-related death than unexposed individuals. As previously mentioned, anxiety disorders have been related to a compromised immune system (Vieira et al., 2010), caused in part by the effects of stress on the immune system (McEwen et al., 2012). Chronic stress can lead to both pro-inflammatory and immunosuppressive processes, so people with neurotic/somatoform disorders might have a highly heterogeneous immunological dysregulation (Dhabhar, 2014). A pro-inflammatory environment could lead to higher inflammation levels, what could explain the increased risk of COVID-19-related death found in people with neurotic/somatoform disorders in our study (Michopoulos et al., 2017). Furthermore, anxiety has been associated to acute respiratory distress syndrome resulting from viral respiratory infections, which is a risk factor for COVID-19 mortality (Coughlin, 2012; Davydow et al., 2008; Powers, 2022). Nevertheless, the divergence of results across studies suggest that further research is needed in order to elucidate the link between neurotic/somatoform disorders and the risk of COVID-19-related death, as well as the biological pathways behind them.

Finally, we explored the role of sex in the associations between the six mental disorders of interest and SARS-CoV-2 infection, COVID-19 hospitalization, and COVID-19-related death. Our results showed a higher vulnerability to SARS-CoV-2 infection in women, but not men,

with pre-existing neurotic/somatoform disorders, while the decreased risk of infection observed in people with depression was only present in men. The higher risk of infection found in women with depression and neurotic/somatoform disorders could be explained by a greater inclination of women towards getting tested, what is supported by studies suggesting greater health care-seeking behaviours among women than among men. (Thompson et al., 2016) Furthermore, we found that women with depression and neurotic/somatoform disorders had a significantly higher risk of COVID-19-related death compared to unexposed women, while no significant differences were identified for men. The increased vulnerability to COVID-19-realted death found in women with affective disorders might be influenced by ovarian hormones. Ovarian hormones fluctuations influence susceptibility to stress and inflammatory responses in women, both of which contribute to the risk of affective disorders and COVID-19 (Cai et al., 2022; Slavich & Sacher, 2019). For instance, oestrogens dysregulations have been reported in women with affective disorders, which have been reported to stimulate the production of pro-inflammatory cytokines in low concentrations (Slavich & Sacher, 2019). Moreover, psychological stress can strongly upregulate inflammatory pathways (Slavich & Sacher, 2019). Indeed, several studies have reported higher inflammation levels in women with depression than men (Kropp & Hodes, 2023), and inflammation is crucial in depression onset in women but not in men (Hiles et al., 2015). Thus, the higher risk of COVID-19 death found in women with depression and neurotic/somatoform disorders than in unexposed women might be related to higher inflammation levels, which are directly linked to a higher COVID-19 mortality. Nevertheless, it worth mentioning that our results could be influenced by the smaller sample size of men with depression and neurotic/somatoform disorders compared to women. Thus, further studies including a sex-perspective are needed in order to determine whether women with affective disorders present a higher risk of COVID-19-related death, and the underlying factors of this association.

The main strength of the present study is the use of a large database of electronic health records from Catalonia. The use of electronic health records offers the opportunity to generate reliable real-world evidence reflecting routine clinical practice, without being affected by selective participation or recall biases. However, our results should be interpreted in light of several limitations, also related to the data source. First, the data used primarily captures information from individuals accessing public healthcare services. As a result, some cases of infection or mental disorders may not have been recorded, particularly for individuals who exclusively utilized private healthcare services, were not considered in the public health system (i.e., undocumented migrants), or did not seek medical care. This is especially relevant for less severe cases that might not have required specialized mental health care or testing for COVID-19. Second, mental disorders were identified using ICD-9/10 codes for individuals who received specialized inpatient or outpatient mental health care between 2017 and 2019. As a result, we lacked information on the current symptomatology or severity of the mental disorders, and individuals classified as unexposed during the 2017–2019 period could have developed a mental disorder and become exposed in 2020. Third, given that our analysis focus on the first wave of the pandemic, hospitalization was defined by ICD-10 codes based on viral respiratory diseases, and not only COVID-19, so misclassification is possible. Nevertheless, it is improbable that this has impacted our results, given the decline in the occurrence of non-COVID-19 respiratory infections throughout the pandemic (Tanislav & Kostev, 2022). Forth, we had no information regarding the use of psychotropic drugs, which have been reported to have a protective effect against infection and severe COVID-19 (Fred et al., 2022; Schultebraucks et al., 2023). Fifth, we could not include data on lifestyle factors such as smoking, which is a known risk factor for COVID-19 mortality (Reddy et al., 2021) and is strongly associated to some mental disorders (S. Yuan et al., 2020). Sixth, the associations between pre-existing mental disorders and COVID-19 outcomes are complex and it is likely that multiple genetic factors, social variables and clinical decisions not assessed in the current study may also be important determinants of the disease progression. Finally, it is important to emphasize that our data reflect the circumstances from the early stages of the pandemic, a period when COVID-19 was more lethal due to the absence of vaccines, widespread natural immunity, and effective treatments. Consequently, future studies are essential to validate our findings in the later phases of the pandemic.

Despite the abovementioned limitations, our results suggest different COVID-19 risk profiles across mental disorders. Nevertheless, an increased risk of COVID-19-realted death was found for almost all mental health diagnoses. Moreover, we found that sex influenced the risk of COVID-19 in some psychiatric groups, with women with depression and neurotic/somatoform disorders being especially vulnerable to the disease. Therefore, our results suggest that the type of mental disorder should be considered when addressing the impact of COVID-19 and potential future epidemics on individuals with mental disorders, and highlights the need for tailored public health strategies and medical interventions for individuals with specific mental disorders. Finally, given the complexity of these findings, further research including data from different countries is needed to understand the specific mechanisms linking mental disorders and infectious diseases, also taking into account sex perspectives.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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CRediT authorship contribution statement

Anna Monistrol-Mula: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **Iago Giné-Vázquez:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Giulia Caggiu:** Writing – review & editing. **Claudia Conflitti:** Writing – review & editing. **Katalin Gemes:** Writing – review & editing. **Irwin Hecker:** Writing – review & editing. **Roberto Mediavilla:** Writing – review & editing. **Matteo Monzio Compagnoni:** Writing – review & editing, Methodology. **Irene Pinucci:** Writing – review & editing. **Jutta Stoffers-Winterling:** Writing – review & editing. **Anke B. Witteveen:** Writing – review & editing. **Pierre Smith:** Writing – review & editing. **Henrik Walter:** Writing – review & editing. **Jose Luis Ayuso-Mateos:** Writing – review & editing. **Maria Melchior:** Writing – review & editing, Project administration. **Ellenor Mittendorfer-Rutz:** Writing – review & editing, Supervision. **Marit Sijbrandij:** Writing – review & editing, Project administration, Funding acquisition. **Josep Maria Haro:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Mireia Felez-Nobrega:** Writing – review & editing, Validation, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2024.116325.

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