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Insight into potential long COVID effects: Antidepressant use in post SARS-CoV-2 Infection scenarios. A multiregional nested case-control study

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ABSTRACT

This study aimed to investigate the impact of previous SARS-CoV-2 infection and the role of vaccination in the onset of neuropsychiatric conditions, evaluated through antidepressant prescriptions. This case-control study evaluated the risk of new antidepressant prescriptions in relation to previous exposure to SARS-CoV-2 infection and vaccination. It was conducted in three Italian Regions on adults who did not receive antidepressant prescriptions in the year preceding the study period. Individuals with newly prescribed antidepressants (cases) were matched by sex and age to non-users of antidepressants (controls). Pooled estimates of regional Odds Ratios (ORs) were obtained through a meta-analysis. Findings showed that individuals previously infected with SARS-CoV-2 had a higher risk of receiving a new prescription of antidepressants. Moreover, this association was stronger among subjects hospitalized due to infection, and SARS-CoV-2 vaccination may have acted as an effect modifier by reducing that risk. In fact, the pooled OR for receiving a new antidepressant prescription was higher for unvaccinated individuals than for those vaccinated. The results of this study confirm the role of SARS-CoV-2 infection as a risk factor for the onset of neuropsychiatric symptoms. Antidepressant treatment initiation was much more likely after severe COVID-19 infection but vaccination reduced such a risk.

1. Introduction

Long COVID is a widely recognized illness defined by the persistence of signs or symptoms 4–12 weeks (according to the different definitions) after acute SARS-CoV-2 infection. (Center for Disease Control and Prevention., 2022; National Institute for Heath and Care Excellence., 2020; World Health Organization., 2021) This condition can affect subjects of any age and with different severity of the acute disease, with prevalence estimates ranging from 5 % to 50 % of all COVID-19 cases. (Bull-Otterson et al., 2022; Groff et al., 2021; Perlis et al., 2022; Wulf Hanson et al., 2022)

Long COVID has multisystemic aspects, and patients can show, beyond the period of acute infection with SARS-CoV-2, a very heterogeneous spectrum of symptoms, which may significantly impact their quality of life (Al-Aly et al., 2021; O'Mahoney et al., 2023; Parotto et al., 2023) and impose a relevant burden on healthcare systems in terms of utilization of services and use of medications. (Castriotta et al., 2024; Koumpias et al., 2022; Tartof et al., 2022; Tene et al., 2023)

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Neuropsychiatric symptoms are frequent manifestations of Long COVID. In studies assessing the prevalence of symptoms 3–12 months after the acute COVID-19 diagnosis, depressive symptoms were present in a proportion varying from 8 to 42 % (Aziz et al., 2023; Michelen et al., 2021; Premraj et al., 2022) of patients, and in a recent systematic review and meta-analysis (Fernandez-de-las-Peñas et al., 2024), 18 % of subjects who had been infected by SARS-CoV-2 still presented depressive symptoms at two years. Such symptoms, that generally require medical treatment, may be of new occurrence or represent recurrences of pre-existing diseases triggered by COVID-19. The proposed pathophysiological causes underlying their occurrence following SARS-CoV-2 infection include abnormal or persistent inflammatory responses and a possible cerebrovascular damage secondary to systemic endothelial damage. (Butler et al., 2022)

Neuropsychiatric symptoms, however, could be not only directly associated with SARS-CoV-2 infection, but could also represent indirect effects caused by concomitant factors, such as isolation and traumatic stress. (Salari et al., 2020) In one meta-analysis the estimated prevalence of anxiety and depression in the general population (independently of COVID-19 status) during the pandemic exceeded 30 %, (Salari et al., 2020) and the Global Burden of Disease 2020 study (COVID-19 Mental Disorders Collaborators., 2021) estimated that the COVID-19 pandemic had led to a 27.6 % increase in cases of major depressive disorder. Consistent with the above findings, other studies showed an increase in antidepressant prescriptions during the COVID-19 pandemic and in individuals infected by SARS-CoV-2. (Nobili et al., 2023; Rosolen et al., 2024) However, disease severity and the role of vaccination have been rarely taken into consideration in these studies.

In the attempt to fill this gap, we assessed the association between new prescriptions of antidepressant drugs and a previous SARS CoV-2 infection, taking into account its severity. In addition, given the potential role of SARS-COV-2 vaccination in reducing the risk of long-term effects of COVID-19 (Long COVID) (Al-Aly et al., 2022; Kuodi et al., 2022; Lundberg-Morris et al., 2023; Richard et al., 2023), we also assessed the potential protective role of vaccination on new use of antidepressants. The aim of this study is to contribute to a better definition and quantification of the impact of previous SARS-CoV-2 infection and vaccination on the onset of neuropsychiatric conditions, indirectly evaluated through antidepressant use. Additionally, it aims to provide a basis for pharmacoeconomic evaluations and facilitate more oriented planning of prevention and healthcare services.

2. Methods

2.1. Framework

This research is part of the project titled 'Analysis and Response Strategies for the Long-Term Effects of COVID-19 Infection (Long-COVID)', which was financially supported by the National Centre for Diseases Prevention and Control under the Italian Ministry of Health (Castriotta et al., 2024). The project, under the coordination of the Italian National Institute of Health (ISS), was designed to enhance our understanding of Long-COVID and establish nationwide standards for managing this condition. The project involves three distinct Regions of Italy: Friuli Venezia Giulia (FVG), Tuscany, and Apulia, covering an overall population of about 6·7 million individuals.

2.2. Ethics

The research protocol was approved by the Italian National Ethics Committee (AOO-ISS – 19/04/2022 – 0,015,066 Class: PRE BIO CE 01.00).

2.3. Data sources and inform consent

The data underlying the findings of this study were derived from regional electronic health databases. Information of interest to the study included data on: age, sex, residency history, comorbidity status (determined via hospital discharge diagnoses and drug prescriptions), results of laboratory molecular and antigenic tests for the diagnosis of SARS-CoV-2 infection (swabs), vaccination against SARS-CoV-2 and drug prescription. Data on drug prescriptions are limited to medications charged to Italian National Healthcare Service and dispensed by hospital based or community pharmacies.

2.4. Study population

For all the three Regions involved, the study population consisted of adults continuously resident from January 1, 2015 to February 28, 2020, and with no prescriptions of antidepressant drugs (AD), identified using the Anatomical Therapeutic Chemical code N06A, between March 1, 2019 and February 28, 2020.

2.5. Study design

A case-control design was adopted. In each Region, individuals with at least an AD prescription recorded in the regional databases, during the study period, namely from February 29, 2020 to December 31, 2022 for FVG and Apulia and from February 29, 2020 to December 31, 2021 for Tuscany, but without AD prescriptions in the 12 months before, were defined as cases (AD users). Controls (AD non-users) were selected from the same study population from which the cases arose, using the 'Incidence density sampling' method (Richardson, 2004) with a 1:1 cases to controls ratio. Cases and controls were matched by sex and age. Every selected control was alive, resident in the Region at the case's date of AD prescription (index date). All controls were eligible to also become cases if AD was prescribed later during the study period.

2.6. Exposure

Exposure was defined as the positive result of a diagnostic swab for SARS-CoV-2 infection, according to the surveillance policy of regional and national authorities. (Italian Ministry of Health, 2021a, 2021b) Starting from the index date, defined as the first antidepressant prescription in the observation period, in order to define exposure, swabs positivity was searched among cases and matched controls, considering two different periods separately: (a) within 365 days before the index date (primary analysis); (b) within 180 days before the index date (sensitivity analysis).

The exposure was further differentiated based on the severity of infection in the acute phase, classifying exposed individuals into (a) infected but non-hospitalized and (b) infected and hospitalized. In case of SARS-CoV-2 infection and reinfection during the study period, the assigned severity level corresponded to the most severe level achieved.

Criteria adopted to identify SARS-CoV-2 infection-related hospitalizations are presented in the supplementary materials.

2.7. Covariates

The following covariates were considered in the present research: province of residence, comorbidities, SARS-CoV-2 vaccination status, and residence in a nursing home for the elderly. Province of residence was considered on February 29, 2020; comorbidities were assessed in the period from January 1, 2015 to February 28, 2020 and the Multisource Comorbidity Score (MCS) (Corrao et al., 2017) was calculated. The MCS is a risk adjustment tool based on hospital discharge diagnoses and drug prescriptions that measures the one-year risk of death. The higher the score, the higher the one-year risk of death. The MCS score was grouped into the following categories: 0–4, 5–9, 10–14, 15–19 and 20.

SARS-CoV-2 vaccination status and residence in a nursing home for the elderly were considered at the index date. With respect to SARS-CoV-

2 vaccination status, individuals were classified into two categories: (a) unvaccinated, an individual who did not received any dose of vaccine or who received the first dose in the 14 days preceding the positive swab; (b) vaccinated, a person who received at least the first dose and, in case of a subsequent positive swab, this arrived at least 15 days after the first dose.

2.8. Statistical analysis

2.8.1. Statistical analysis per region

Frequency and percentage distributions of the matching variables, sex and age, in the study population and in AD users (cases) were computed. Age in years, calculated on February 29, 2020, was grouped in the following classes: 18–24, 25–34, 35–44, 45–54, 55–64, 65–74 and 75 and over.

Furthermore, frequency and percentage distribution of the main characteristics of cases and controls were calculated. The association between AD prescription and previous exposure to SARS-CoV-2 infection was studied by applying (i) simple conditional logistic regressions, (ii) multiple conditional logistic regression (full model) adjusted for all the covariates (except vaccination status), and (iii) multiple conditional logistic regression, adjusted for all the covariates, stratified for SARS-CoV-2 vaccination status (stratified model). The odds ratios (ORs) and 95 % confidence intervals (95 % CI) were reported for each Region.

2.8.2. Pooled statistical analysis

Inverse variance-weighted random-effects analyses, based on the DerSimonian-Laird method, were performed to compute pooled estimates of the Regional ORs of the previous SARS-CoV-2 exposures obtained from the fully and stratified models.

Analyses were performed with STATA (StataCorp. 2021. Stata Statistical Software: Release 17. College Station, TX: StataCorp LLC.) and SAS software (version 9.4 SAS Institute INC., Cary, N.C., USA).

2.8.3. Sensitivity analysis

As sensitivity analysis, for each of the three Regions involved, a further case-control study has been nested in a population which consisted of adults with no prescriptions of AD in the period between March 1, 2015 and February 28, 2020. The association between AD prescription and previous exposure to SARS-CoV-2 infection was studied by applying the same models described in the previous paragraph: (i) simple conditional logistic regressions, (ii) multiple conditional logistic regression (full model) and (iii) multiple conditional logistic regression (stratified model).

3. Results

The overall study population included 6658,840 individuals, distributed as follows: 933,763 from FVG, 2566,925 from Tuscany and 3158,152 from Apulia. In this population 50.4 % were women and 13.9 % were 75 years of age or older. AD users (cases) identified during the study period were 324,554 (4.9 % of the overall study population; 4.6 % in both FVG and Apulia and 5.4 % in Tuscany). Among the cases, these percentages were 63.2 % and 31.3 %, respectively, with a significantly different distribution from that of the general population by both sex ($p < 0.001$) and age ($p < 0.001$) (Table 1). These significant differences were also observed in each individual Region (Table S1).

For each Region, frequency and percentage distributions of the main characteristics of cases and controls and the ORs and 95 % CI obtained from the simple conditional logistic regressions are reported in Table S2. In Fig. 1 the overall (all Regions combined) results from the analysis of fully adjusted models are presented, considering a SARS-CoV-2 infection occurred in the 365 days before the index date. Heterogeneity among regions was found for the relation between AD prescription and infected non-hospitalized people (I^2=90.1 %, $p < 0.001$), where the ORs for the association between AD prescription and previous SARS-CoV-2 infection were 1.29 (95 % CI=1.23–1.35) in FVG, 1.23 (95 % CI=1.19–1.26) in Apulia and 1.39 (95 % CI=1.33–1.46) in Tuscany. When the analysis was limited to SARS-CoV-2 infection associated with hospitalization, no heterogeneity among Regions was found (I^2=0.0 %, $P = 0.524$) and the overall OR was 2.93 (95 % CI= 2.73–3.15). The analysis conducted considering SARS-CoV-2 infections that occurred in a shorter period of time before the index date, namely in the previous 180 days, showed consistent results (Figure S1).

Table 1
Frequency and percentage distributions of sex and age group of people included in the overall population and in cases.

Main characteristics	Overall Population			
	Population[a] (n = 6658,840)		Cases[b] (n = 324,554)	
	n	%	n	%
Sex				
Female	3355,072	50.4	205,229	63.2
Male	3303,768	49.6	119,325	36.8
P-value[c]		<0.0001		
Age groups (years)				
18–24	536,760	8.1	11,577	3.6
25–34	800,215	12.0	18,398	5.7
35–44	1016,945	15.3	30,007	9.2
45–54	1300,317	19.5	49,816	15.3
55–64	1143,696	17.2	53,945	16.6
65–74	936,663	14.1	59,131	18.2
≥75	924,244	13.9	101,680	31.3
P-value[c]		<0.0001		

[a] Sum of the target populations of each Region, consisting of people (aged 18 and over on February 29, 2020) continuously resident in the Region in the period from January 1, 2015 to February 28, 2020, alive and resident in the Region on February 29, 2020, and for whom no antidepressant medication prescriptions were recorded during the period from March 1, 2019 to February 28, 2020.

[b] Sum of cases detected in each Region, defined as with a new prescription of antidepressants in the period from February 29, 2020 to December 31, 2022 for Friuli Venezia Giulia and Apulia and in the period from February 29, 2020 to December 31, 2021 for Tuscany.

[c] Chi-square test.

Table S3 presents for each Region: (i) the frequency and percentage distributions of a previous SARS-CoV-2 infection in the 365 and 180 days before the index date in cases and controls stratified by vaccination status and (ii) ORs and 95 % CIs of multiple conditional logistic regressions stratified by vaccination status.

Fig. 2 displays the ORs for the association between AD prescription and previous SARS-CoV-2 infection, in the 365 days preceding the index date, stratified by SARS-CoV-2 vaccination status. No heterogeneity among regions was found. Among individuals non-hospitalized during acute SARS-CoV-2 infection, the overall OR for unvaccinated individuals was 1.60 (95 % CI=1.53–1.69) and the one for vaccinated was 1.15 (95 % CI=1.09–1.20); among individuals hospitalized during acute SARS-CoV-2 infection, the overall OR for unvaccinated individuals was 3.68 (95 % CI=2.99–4.54) and the one for vaccinated was 2.42 (95 % CI=2.10–2.78). Consistent results were obtained from the analysis that considered a previous SARS-CoV-2 infection in the 180 days before the index date (Figure S2). The interaction between SARS-CoV-2 vaccination status and the exposure was studied through multiple conditional logistic regression models and showed statistically significant results (Table S3). These results suggest that SARS-CoV-2 vaccination acts as effect-measure modifier of the exposure, on a multiplicative scale.

Results observed in sensitivity analysis were consistent with those reported in the present research (data not shown).

4. Discussion

In this analysis of three population-based case-control studies

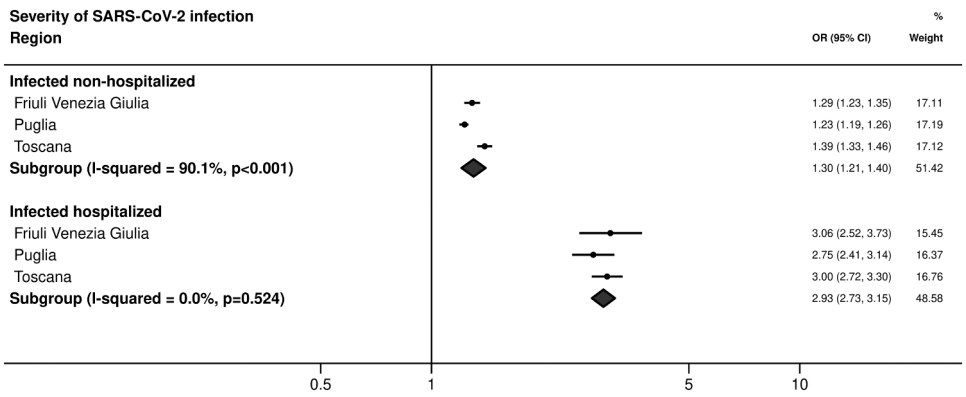

Fig. 1. Meta-analysis of multiple conditional logistic regressions studying the association between the first antidepressant prescription and a previous exposure to SARS-CoV-2 infection in the 365 days prior to the index date.
Multiple conditional logistic regressions were adjusted for province of residence, MCS and residence in a nursing home for the elderly at the index date
Abbreviations: OR – Odds Ratio, CI – Confidence Interval, MCS – Multisource Comorbidity Score.

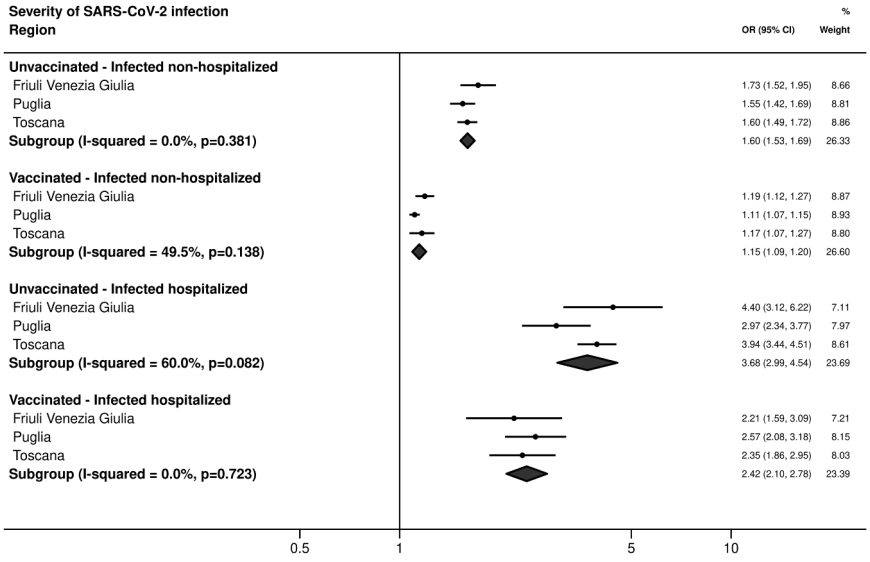

Fig. 2. Meta-analysis of multiple conditional logistic regressions studying the association between the first antidepressant prescription and a previous exposure to SARS-CoV-2 infection in the 365 days prior to the index date, stratified by vaccination status at the index date.
Multiple conditional logistic regressions were adjusted for province of residence, MCS and residence in a nursing home for the elderly at the index date
Abbreviations: OR – Odds Ratio, CI – Confidence Interval, MCS – Multisource Comorbidity Score.

performed using regional electronic databases, we identified a proportion of approximately 5 % of new AD users in the general population during the study period. A higher frequency of women and of people older than 75 years was found in the group of AD users compared to the general population, consistent with the observations that antidepressant drug administration is more frequent in these sex and age categories. (Frangou et al., 2023; Pazzagli et al., 2022)

A significant association was observed between a new prescription of antidepressant drugs and exposure to SARS-CoV-2 infection within the past 6 months, a pattern that was consistent across the three Regions involved. These findings are in line with the results of other studies showing an impact on mental health for Long COVID patients, generally dependent on severity of disease, but significant also for patients who needed only home treatment. Previous research found that, three months after COVID-19 diagnosis, patients had an approximately doubled risk of being diagnosed with a psychiatric disorder, and that the risk was dependent on the severity of the disease (Taquet et al., 2021). In a study conducted in Milan, a substantial proportion of patients still suffered from anxiety (29 %) and depression (11 %) symptoms one to three months after viral clearance. (Tomasoni et al., 2021). A cohort study in the US (Xie et al., 2022) demonstrated that post-COVID patients (after 30 days of SARS-CoV-2 positivity) had an increased risk of mental health disorders, including anxiety disorders and depressive disorders, and an increased use of antidepressants.

Another important finding, consistent with previous research (Magnúsdóttir et al., 2022; Walker et al., 2024), is that individuals who were hospitalized during SARS-CoV-2 infection appear to have a higher risk of developing mental disorders compared to those who were not hospitalized. From a biological point of view, the negative impacts of SARS-CoV-2 infection on mental health can be attributed to the infection's role in triggering an increase in pro-inflammatory cytokines. (Song et al., 2020) These cytokines are crucial in regulating the stress response and may contribute significantly to the development of depression in COVID-19 patients. (Mohammadkhanizadeh and Nikbakht, 2021) Furthermore, among patients exposed to SARS-CoV-2, those who were hospitalized show the greatest inflammatory response. (Song et al., 2020) Other factors including elevated cortisol levels, alterations in the HPA axis, mitochondrial damage, vitamin D3 deficiency, and malnutrition are among the factors are involved in the development of depression following SARS-CoV-2 infection. (Mohammadkhanizadeh

and Nikbakht, 2021) Social isolation and prolonged Long COVID symptoms may also have contributed to the higher prevalence of depression in hospitalized individuals. (Magnúsdóttir et al., 2022) Our results remain consistent whether infection occurred within 6 months or 1 year, aligning with previous research reporting that the adverse effects on mental health may persist for several months after SARS-CoV-2 infection. (Magnúsdóttir et al., 2022; Nobili et al., 2023; Walker et al., 2024) However, these results should be interpreted considering that several studies have reported an increase in neuropsychiatric symptoms and in mental health disorders, as well as an associated use of antidepressant drugs, in the pandemic period. This increase has been attributed to social life modifications, movement restrictions, and the possible financial problems caused by the pandemic. A survey conducted in Italy (Mazza et al., 2020) showed that in 2020 a significant proportion of people were affected by anxiety and depression irrespective of COVID infection, and in the Friuli Venezia Giulia Region (Pazzagli et al., 2022) antidepressant use in the general population was on average 20 % higher in each month of 2020 when compared with the same calendar months of 2015–2019. Both in France (De Bandt et al., 2024) and in Israel (Frangou et al., 2023) studies have reported an increase in the volume of antidepressants dispensed starting March 2020, independently of SARS-CoV-2 infection. Pandemic-associated stress was also thought to be responsible for the higher-than- expected dispensing of antidepressants found in children and in adolescents in a study performed in Canada following the pandemic. (Antoniou et al., 2023)

Another important finding of our study is that COVID-19 vaccination may provide a protective effect on mental health, potentially reducing the likelihood of receiving a new antidepressant prescription after SARS-CoV-2 infection in both hospitalized and non-hospitalized individuals. This appears consistent with findings from other observational studies (Chen et al., 2022; Rosolen et al., 2024; Walker et al., 2024), including a large cohort study in England, which observed a lower incidence of mental disorders, such as depression, in vaccinated individuals compared to unvaccinated ones in the weeks following infection. (Walker et al., 2024) There are several mechanisms that could explain the potential protective role of vaccination on mental health. One possible explanation is that vaccinated individuals, after symptomatic SARS-CoV-2 infection, generally exhibit lower levels of most cytokines compared to unvaccinated individuals (Zhu et al., 2023) which - as mentioned above - are key in the pathophysiology of depression (Raison et al., 2006). Additionally, the sense of protection provided by COVID-19 vaccination may have reduced levels of anxiety and depression, thereby contributing to this pattern. (Chen et al., 2022; Coley et al., 2023; Koltai et al., 2022; Nguyen, 2021; Souliotis et al., 2022).

As mentioned, results appear consistent across the Regions, even though the I^2 statistic related to non-hospitalized subjects, without distinction by vaccination status, might indicate the presence of heterogeneity for both analyses related to subjects with a previous exposure to SARS-CoV-2 infection in the 180 (Figure S1) or 365 days prior to the index date (Fig. 1).

Heterogeneity was also observed for unvaccinated infected hospitalized without a previous SARS-CoV-2 in the prior 180 days (Figure S2). However, the I^2 should be interpreted with caution when studies are few in number (Deeks et al., 2011). Furthermore, if the confidence intervals for the results of individual studies have little overlap, this could lead to statistical heterogeneity (Deeks et al., 2011). In some circumstances, this can be misleading; indeed, in our study, although the results of the individual Regions are consistent, the confidence intervals have little overlap. This can be noted for infected non-hospitalized (Fig. 1), where the Regional ORs are very close and the intervals calculated on large numbers are narrow.

Strengths of this study include the use of population data, the large amount of information available, and the involvement of three Italian Regions from the three main geographical areas of the country, with consistent findings across Regions. Further, the analyses were adjusted for different potential confounders by including the Multisource Comorbidity Score in the regression models, allowing a more unbiased measurement of the association between the exposure and the outcome. Moreover, our results may also allow pharmacoeconomic evaluations and help policy makers in planning prevention and care actions. Our results may help a comprehensive evaluation of the economic burden of COVID-19, since the direct costs associated with treating neuropsychiatric symptoms, including medications, hospitalizations, and outpatient visits, contribute to the overall cost of managing COVID-19 and its long-term sequelae. Additionally, the indirect costs, such as loss of productivity due to illness and the long-term care needs of patients with persistent symptoms, further exacerbate the economic impact.

The main limitations of this study derive from the use of administrative data and the lack of clinical information including signs, symptoms, diagnostic tests, and medication use, which may not allow the specific diagnostic context for antidepressant use to be distinguished. Our study did not account for some factors related to COVID-19 and medication use. First, socioeconomic status during the COVID-19 pandemic is an important factor affecting mental health, as financial stress and lifestyle changes (e.g., sedentary behavior, lack of physical activity, and insufficient sleep) may exacerbate anxiety, insomnia, and depressive symptoms (You, 2024; You et al., 2024b). Additionally, numerous studies have shown that physical activity levels, sleep quality, and nutrition intake also have a significant impact on mental health (You et al., 2024a, 2024c). The lack of inclusion of these key lifestyle variables in the analysis may lead to biased results, and future studies should consider a more comprehensive assessment of these potential confounders to better understand their impact on medication use. Nevertheless, it should be considered that our study was conducted in a large population and the relationship between SARS-CoV-2 infection and AD use was adjusted using a comorbidity score (Corrao et al., 2017), which can be reasonably associated with the previously mentioned potential confounders (Delpino et al., 2022; Gariballa and Forster, 2007; Hung et al., 2021; Nistor et al., 2023; Pathirana and Jackson, 2018), as well as with depression (Lin et al., 2021; Read et al., 2017).

Since AD are prescribed not only for depressive symptoms but also for other conditions (i.e. obsessive-compulsive disorders, social phobia, panic disorders, generalized anxiety disorders, eating disorders, chronic pain, post-traumatic stress disorders) that may also occur as a consequence of COVID-19 disease and represent Long COVID manifestations, it was not possible to link any specific diagnosis to the prescriptions and assess the appropriateness of the prescriptions. Although having information on the diagnostic context that led to the AD prescription would have enabled us to estimate a more specific association between AD prescription and Long COVID, it would likely have reduced sensitivity. This is because Long COVID is a syndrome with an evolving understanding, characterized by uncertain boundaries and a highly heterogeneous spectrum of symptoms (Center for Disease Control and Prevention., 2022; Onder G et al., 2021). Moreover, the Long COVID diagnosis rate likely underrepresented the true incidence of this condition, especially in the early stages of the pandemic. (Hedberg et al., 2023) Although our findings suggest that vaccination may provide a protective effect on mental health, it should be considered that low income and educational level are both associated with vaccine hesitancy (Primieri et al., 2023) and increased risk of depression (Bjelland et al., 2008; Patria, 2022; Sareen et al., 2011), and therefore unvaccinated individuals could be at higher risk of mental illness. Also, COVID-19 patients might be more likely to attend clinical visits and that therefore depressive symptoms could be more likely to be diagnosed and treated. We were also unable to perform analyses, among hospitalized patients, differentiating those admitted to ICU from those not admitted, because of the low numbers. Albeit with some limitations, our study contributes to the growing body of evidence highlighting the negative impact of SARS-CoV-2 infection on mental health. Therefore, despite evidence that the incidence of mental health disorders has increased in the adult population during the pandemic (Mazza et al., 2020), we were able to disentangle the effect of the pandemic from the consequences of

SARS-CoV-2 infection, showing that COVID-survivors were at higher risk of mental disorders compared to their uninfected contemporary counterparts.

In conclusion, in this meta-analysis of three population-based cohort studies involving Italian adults who had not received antidepressant treatment for at least one year, SARS-CoV-2 infection was linked to a heightened risk of starting antidepressant therapy in both hospitalized and non-hospitalized individuals. Our findings suggest that vaccination may help mitigate the negative impact of the virus on mental well-being. The present findings, providing evidence of increased risk of mental health disorders following SARS-CoV-2 infection, may support health policy makers in defining Long COVID care strategies.

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Data sharing statement

The Italian Ministry of Health holds the ownership of the data used for analysis and therefore can be made available with the legal permission of the Italian Ministry of Health. Anonymized data can only be shared if there is no potential for the reidentification of individuals (https://www.garanteprivacy.it). Thus, the data underlying this study are available on request once collapsed. Data access requests should be addressed to the corresponding author.

CRediT authorship contribution statement

Valentina Rosolen: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Yvonne Beorchia:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Conceptualization. **Luigi Castriotta:** Writing – review & editing, Supervision, Methodology, Formal analysis, Conceptualization. **Caterina Fanizza:** Writing – review & editing, Software, Methodology, Formal analysis, Conceptualization. **Francesco Profili:** Writing – review & editing, Software, Methodology, Formal analysis, Conceptualization. **Marco Floridia:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Marina Giuliano:** Writing – review & editing, Writing – original draft, Methodology, Conceptualization. **Flavia Pricci:** Writing – review & editing, Methodology, Conceptualization. **Marika Villa:** Writing – review & editing, Project administration, Conceptualization. **Tiziana Grisetti:** Writing – review & editing, Project administration, Conceptualization. **Tiziana Grassi:** Writing – review & editing, Methodology, Conceptualization. **Dorina Tiple:** Writing – review & editing, Methodology, Conceptualization. **Andrea Silenzi:** Writing – review & editing, Supervision. **Paolo Francesconi:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Lucia Bisceglia:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Fabio Barbone:** Writing – review & editing, Validation, Supervision, Methodology. **Silvio Brusaferro:** Writing – review & editing, Validation, Supervision, Funding acquisition. **Graziano Onder:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

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