

No significant association between COVID-19 diagnosis and the incidence of depression and anxiety disorder? A retrospective cohort study conducted in Germany

Running title: COVID-19 diagnosis, depression, and anxiety disorder

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Abstract

Little is known about the effects of coronavirus disease 2019 (COVID-19) on mental health compared with other respiratory infections. Thus, the aim of this retrospective cohort study was to investigate whether COVID-19 diagnosis is associated with a significant increase in the incidence of depression and anxiety disorder in patients followed in general practices in Germany compared with acute upper respiratory infection diagnosis. This study included all patients diagnosed with symptomatic or asymptomatic COVID-19 for the first time in 1,198 general practices in Germany between March 2020 and May 2021. Patients diagnosed with acute upper respiratory infection were matched to those with COVID-19 using propensity scores based on sex, age, index month, and Charlson Comorbidity Index. The index date corresponded to the date on which either COVID-19 or acute upper respiratory infection was diagnosed. Differences in the incidence of depression and anxiety disorder between the COVID-19 and the acute upper respiratory infection group were studied using conditional Poisson regression models. This study included 56,350 patients diagnosed with COVID-19 and 56,350 patients diagnosed with acute upper respiratory infection (52.3% women; mean [SD] age 43.6 [19.2] years). The incidence of depression (IRR=1.02, 95% CI=0.95–1.10) and anxiety disorder (IRR=0.94, 95% CI=0.83–1.07) was not significantly higher in the COVID-19 group than in the upper respiratory infection group. Compared with acute upper respiratory infection diagnosis, COVID-19 diagnosis was not associated with a significant increase in the incidence of depression and anxiety disorder in patients treated in general practices in Germany.

Keywords: COVID-19 diagnosis; depression; anxiety disorder; general practices; Germany

Introduction

Coronavirus disease 2019 (COVID-19), a viral disorder caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Hu et al., 2021), emerged in China in December 2019 and has spread rapidly across the world (Sanyaolu et al., 2021). COVID-19 is a systemic disease associated with pulmonary and extra-pulmonary complications (e.g., gastrointestinal, cardiovascular and neurologic) (Gupta et al., 2020; Konturek et al., 2020). On March 11, 2020, the World Health Organization declared COVID-19 a pandemic (Sanyaolu et al., 2021). Since December 2019, around 269 million people have been diagnosed with COVID-19 worldwide, while approximately five million individuals have died as a result of the disease (World Health Organization, 2021). Countries have therefore adopted public health measures to reduce the transmission of COVID-19, including mandatory mask-wearing, school closures, lockdowns, and vaccination (Ayouni et al., 2021).

Previous research has shown overwhelmingly that the ongoing COVID-19 pandemic is having deleterious effects on mental health (Ettman et al., 2020; Gasteiger et al., 2021; Winkler et al., 2020; Zhao et al., 2021). For example, one study of more than 3,000 non-institutionalized adults in the Czech Republic revealed that the prevalence of at least one psychiatric disorder increased significantly from 20.0% in November 2017 to 29.6% in May 2020 (Winkler et al., 2020). Another study including 681 participants living in New Zealand found that depression and anxiety levels were significantly higher during the first 10 weeks of the COVID-19 pandemic than during the pre-COVID-19 era (Gasteiger et al., 2021). A substantial body of literature has also investigated the potential impact of COVID-19 diagnosis on mental health, and most

of these studies have shown that COVID-19 diagnosis increases the risk of subsequent psychiatric disorders (Deng et al., 2021, p. 19; Huang et al., 2021; Klaser et al., 2021; Ma et al., 2020; Mazza et al., 2020; Paz et al., 2020; Poyraz et al., 2021; Taquet et al., 2021a, 2021b; Zhang et al., 2021). Although these studies have advanced the field, they are subject to a number of limitations that need to be acknowledged. First, the majority of the studies mentioned above were conducted during the first few months of the COVID-19 pandemic and it is possible that the effects of COVID-19 diagnosis on mental health have evolved over time and with the amount of scientific evidence accumulated on this viral disease. Second, apart from two studies (Taquet et al., 2021a, 2021b), this literature failed to compare the impact of COVID-19 on psychiatric disorders with the impact of other common respiratory conditions. This limitation is of particular concern because it may be possible that the deleterious effects of the COVID-19 pandemic on mental health are predominantly driven by social disruption rather than by the neuropsychiatric sequelae of the infection. Third, most of these studies had small sample sizes, limiting the generalizability of their findings to the population as a whole. Taking these limitations together, it is clear that more recent data are needed on the relationship between COVID-19 diagnosis and the subsequent occurrence of common psychiatric disorders.

Therefore, the aim of this retrospective cohort study was to investigate whether COVID-19 diagnosis is associated with a significant increase in the incidence of depression and anxiety disorder in patients followed in general practices in Germany compared with acute upper respiratory infection diagnosis. Given that COVID-19 mortality (Fan et al., 2021; Jones et al., 2021) and complications (Doidge et al., 2021) have decreased since the beginning of the pandemic, and a substantial proportion of

COVID-19 infections are asymptomatic (Oran and Topol, 2021), it was hypothesized that COVID-19 diagnosis is not significantly associated with incident depression and anxiety disorder compared with acute upper respiratory infection diagnosis.

Material and methods

Database

Data from the Disease Analyzer database (IQVIA) were used for the present retrospective cohort study. This database has been described extensively in the literature (Rathmann et al., 2018). Briefly, the Disease Analyzer database contains demographic, diagnosis, and prescription data obtained from general and specialized practices in Germany. Around 3% of all practices in Germany are included in the Disease Analyzer database, and the database has been found to be a representative sample of general and specialized practices in this country.

Study population

This retrospective cohort study included all patients aged ≥ 18 years diagnosed with symptomatic or asymptomatic COVID-19 (German version of the International Classification of Diseases, 10th revision [ICD-10]: U07.1 [virus identified]) in 1,198 general practices in Germany between March 2020 and May 2021 (index date). To be included in the study, patients had to have had no diagnosis of COVID-19 (ICD-10: U07.1, U08.9, U09.9, and U99.0!), depression (ICD-10: F32 and F33) or anxiety disorder (ICD-10: F41) within 365 days prior to the index date. After applying the same inclusion criteria, patients diagnosed with acute upper respiratory infection (ICD-10: J00-J06; index date) were matched to those with COVID-19 using propensity scores

based on sex, age, index month, and Charlson Comorbidity Index. The selection of study patients is displayed in **Figure 1**.

Depression and anxiety disorder (outcomes)

Outcomes included depression (ICD-10: F32 and F33) and anxiety disorder (ICD-10: F41). The incidence of depression and anxiety disorder was investigated separately in the COVID-19 and acute upper respiratory infection groups.

Statistical analyses

Baseline characteristics (i.e., sex, age, index month, and Charlson Comorbidity Index) were compared for patients with COVID-19 and those with acute upper respiratory infection using McNemar tests for categorical variables and Wilcoxon signed-rank tests for continuous variables. The incidence of depression and anxiety disorder in the COVID-19 and acute upper respiratory infection groups were estimated as the number of cases per 1,000 person-years. In addition, differences in the incidence of depression and anxiety disorder between the COVID-19 and the acute upper respiratory infection group were studied using conditional Poisson regression models. These models were applied to the overall population and further stratified by sex and age. The results of the Poisson regression analyses are displayed as incidence rate ratios (IRRs) with 95% confidence intervals (CIs) and p-values. All analyses were performed using SAS 9.4.

Results

This study included 56,350 patients diagnosed with COVID-19 and 56,350 patients diagnosed with acute upper respiratory infection. In total, 52.3% of patients were women, and the mean (standard deviation) age was 43.6 (19.2) years (**Table 1**). The incidence of depression was 88.6 cases per 1,000 person-years in the COVID-19 group and 86.5 cases per 1,000 person-years in the acute upper respiratory infection group (IRR=1.02, 95% CI=0.95-1.10, and p-value=0.526; **Table 2**). There was no significant association between COVID-19 diagnosis and the incidence of depression in all sex and age subgroups. With regard to anxiety disorder, the incidence of this psychiatric condition was 30.1 cases per 1,000 person-years in individuals with COVID-19 and 31.9 cases per 1,000 person-years in those with acute upper respiratory infection (IRR=0.94, 95% CI=0.83-1.07, p-value=0.338). The relationship between the diagnosis of COVID-19 and the subsequent incidence of anxiety disorder was also found to be non-significant in the different sex and age subgroups.

Discussion

Main findings

This retrospective study including more than 112,000 adults followed in general practices in Germany between March 2020 and May 2021 showed that the incidence of depression and anxiety disorder was not significantly higher in those diagnosed with COVID-19 than in those diagnosed with acute upper respiratory infection. This lack of significant association between COVID-19 diagnosis (versus acute upper respiratory infection diagnosis) and the incidence of depression and anxiety disorder was

corroborated in the analyses stratified by sex and age. To the best of the authors' knowledge, this is one of the first studies to have compared the effects of the diagnosis of COVID-19 on mental health with the effects of the diagnosis of other respiratory infections.

Interpretation of findings

A substantial body of research has recently focused on the impact of COVID-19 diagnosis on mental health. For example, a study of 413,148 participants surveyed between February and April 2021 revealed that the prevalence of depression and anxiety was higher in those who tested positive for SARS-CoV-2 (30.4%) than in their counterparts who tested negative (26.1%) (Klaser et al., 2021). However, only a few studies have analyzed the effects of COVID-19 diagnosis on psychiatric disorders compared with the effects of the diagnosis of other respiratory infections (Taquet et al., 2021a, 2021b). In a US retrospective cohort study conducted between January and August 2020, it was observed that participants with COVID-19 were more likely to be subsequently diagnosed with psychiatric illnesses such as mood, anxiety, and psychotic disorders than their counterparts with influenza and other respiratory tract infections (Taquet et al., 2021b). These findings were corroborated in another US study of 236,379 patients diagnosed with COVID-19 in 2020 and 236,038 patients diagnosed with any respiratory tract infection that same year, which found that COVID-19 was associated with a significant increase in the risk of psychiatric diseases compared with any respiratory tract infection (Taquet et al., 2021a).

There are several hypotheses that may explain the discrepancy in the findings between the literature mentioned above and the present study. First, COVID-19 mortality (Fan

et al., 2021; Jones et al., 2021) and complications (Doidge et al., 2021) have decreased since the beginning of the pandemic. A study including data from 53 countries or regions found that the case fatality rate (i.e., the number of COVID-19 deaths divided by the total number of cases) was lower during the second wave of the pandemic in 43 countries than it was during the first (Fan et al., 2021). This decline in mortality may have resulted in a decrease in fear and poor mental health outcomes following the diagnosis of COVID-19. Second, the proportion of asymptomatic cases is slightly higher for COVID-19 than for other acute upper respiratory infections such as influenza. A systematic review of 61 studies showed that more than one-third of SARS-CoV-2 infections are asymptomatic (Oran and Topol, 2021), whereas another systematic review and meta-analysis including 30 studies estimated the proportion of asymptomatic influenza virus infections at around 16% (Leung et al., 2015). Given that major respiratory symptoms and syndromes may play a substantial role in the triggering of psychiatric disorders (Bienvenu et al., 2018), these data could explain, at least partially, why COVID-19 diagnosis was not associated with a significant increase in the incidence of depression and anxiety disorder compared with acute upper respiratory infection diagnosis. Third, COVID-19 media coverage, which was particularly high at the beginning of the pandemic (Krawczyk et al., 2021) and was associated with poor mental health outcomes (Bendau et al., 2021; Nekliudov et al., 2020), may have decreased over time. Indeed, previous research has shown that weekly newspaper articles about COVID-19 decreased globally from around 60,000 in March 2020 to around 30,000 in November 2020 (Pearman et al., 2021). This may have caused the diagnosis of COVID-19 to have stronger deleterious effects on mental health than the diagnosis of other acute upper respiratory infections in early 2020 but not in late 2020 or 2021. Fourth, one should bear in mind that COVID-19 patients with

depression or anxiety disorder may not have visited their general practitioner because of self-isolation and quarantine, and thus the incidence of these two psychiatric conditions may have been underestimated in the COVID-19 group.

Public health implications and directions for future research

Based on the findings of this study conducted in Germany, patients followed in general practices who were diagnosed with COVID-19 were not at a significantly increased risk of depression and anxiety disorder compared with their counterparts who were diagnosed with other acute upper respiratory infections. Although these preliminary data are reassuring, general practitioners and other health professionals should regularly assess the potential presence of depressive and anxiety symptoms in patients newly diagnosed with COVID-19. Furthermore, social support should be promoted, as it may play an important role in preventing the occurrence of psychiatric disorders in COVID-19 patients. This social support may include phone calls with relatives and friends, and online services specifically dedicated to individuals in self-quarantine (Brooks et al., 2020). In terms of future research, further studies comparing the effects of the COVID-19 on mental health with those of other acute upper respiratory infections are needed to corroborate or invalidate the present findings in other countries. Besides, more research is warranted on the incidence of other psychiatric conditions (e.g., post-traumatic stress disorder and psychotic disorder) as well as neurologic diseases following the diagnosis of COVID-19.

Strengths and limitations

Two major strengths of this study are the large sample size and the inclusion of patients diagnosed with COVID-19 in 2020 and 2021. However, these results should be

interpreted in the light of several limitations. First, no data were available on COVID-19 symptoms and it was therefore not possible to conduct sensitivity analyses based on symptoms. In particular, there was a lack of information on persistent symptoms, while the occurrence of psychiatric diseases may be favored by the presence of symptoms lasting more than a few weeks. Second, depression and anxiety disorder were diagnosed using the ICD-10 classification alone, and more information on these psychiatric conditions would have allowed for more detailed analyses. Third, a substantial proportion of patients with depression or anxiety disorders may have displayed fatigue only, and the incidence of these conditions may have therefore been underestimated. Fourth, since this study did not include individuals with depression or anxiety disorder in the year prior to the index date, we were unable to analyze the potential effects of COVID-19 diagnosis on pre-existing psychiatric conditions. Fifth, given that this study only included patients followed in general practices, the study findings may not be generalizable to those diagnosed with COVID-19 in specialized practices or hospitals. Sixth, psychiatric conditions other than depression and anxiety disorder were not sufficiently documented, and it was therefore not possible to investigate their incidence in the present study.

Conclusions

This study including around 113,000 patients followed in general practices in Germany between 2020 and 2021 found that the diagnosis of COVID-19 was not associated with a significant increase in the incidence of depression and anxiety disorder compared with the diagnosis of acute upper respiratory infections. Taking together, these findings suggest that the decrease in the mental well-being of the general population observed since the beginning of the COVID-19 pandemic is related to factors other than the

infection itself (e.g., decreased physical activity and social disruption). Finally, further research is warranted to corroborate or invalidate these reassuring preliminary data in other regions of the world and in other settings.

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Tables and Figures

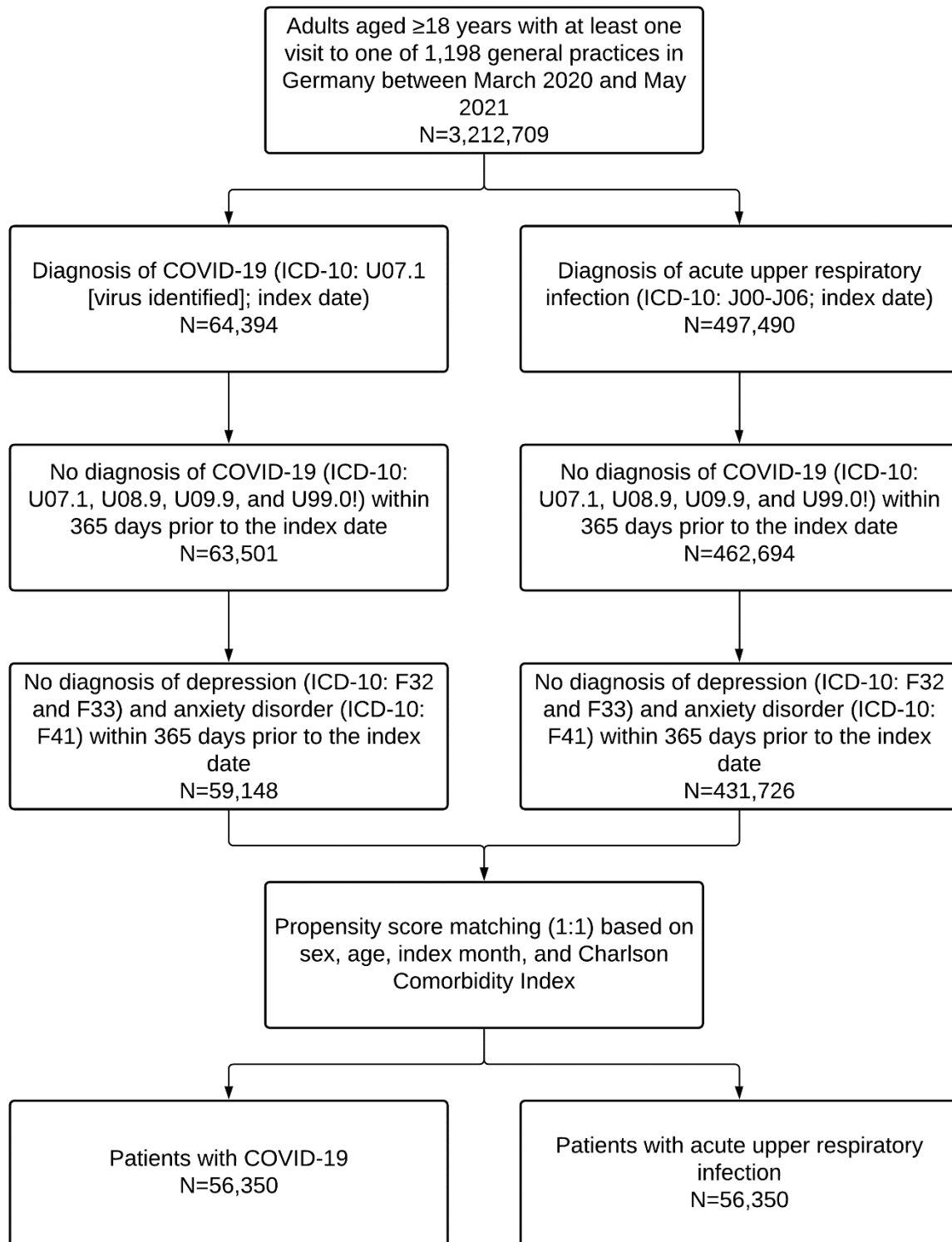


Figure 1. Selection of study patients

Abbreviation: COVID-19 coronavirus disease 2019; ICD-10 International Classification of Diseases, 10th revision.

Table 1. Baseline characteristics of study patients after 1:1 matching

Variable	Patients with COVID-19 (N=56,350)	Patients with AURI (N=56,350)	P-value
<i>Sex</i>			
Female	29,457 (52.3)	29,444 (52.3)	0.938
Male	26,893 (47.7)	26,906 (47.7)	
<i>Age (in years)</i>			
Mean (SD)	43.6 (19.2)	43.6 (19.2)	1.000
18–30	15,931 (28.3)	15,931 (28.3)	1.000
31–40	9,835 (17.5)	9,835 (17.5)	
41–50	9,461 (16.8)	9,461 (16.8)	
51–60	10,838 (19.1)	10,838 (19.1)	
61–70	5,399 (9.6)	5,399 (9.6)	
>70	4,886 (8.7)	4,886 (8.7)	
<i>Index month</i>			
March 2020	391 (0.7)	411 (0.7)	0.980
April 2020	1,552 (2.8)	1,560 (2.8)	
May 2020	888 (1.6)	890 (1.6)	
June 2020	654 (1.2)	657 (1.2)	
July 2020	831 (1.5)	836 (1.5)	
August 2020	1,335 (2.4)	1,341 (2.4)	
September 2020	1,350 (2.4)	1,356 (2.4)	
October 2020	4,227 (7.5)	4,229 (7.5)	
November 2020	8,803 (15.6)	8,796 (15.6)	
December 2020	10,115 (18.0)	10,094 (17.9)	
January 2021	6,661 (11.8)	6,645 (11.8)	
February 2021	3,476 (6.2)	3,469 (6.2)	
March 2021	5,490 (9.7)	5,491 (9.7)	
April 2021	6,958 (12.3)	6,956 (12.3)	
May 2021	3,619 (6.4)	3,619 (6.4)	
Charlson Comorbidity Index, mean (SD)	0.8 (1.2)	0.8 (1.2)	1.000

Abbreviations: COVID-19 coronavirus disease 2019; AURI acute upper respiratory infection; SD standard deviation.

Data are absolute numbers (percentages) unless otherwise specified.

Table 2. Association between COVID-19 diagnosis and the subsequent incidence of depression and anxiety disorder in patients followed in general practices in Germany

Population	Incidence per 1,000 person-years in patients with COVID-19	Incidence per 1,000 person-years in patients with AURI	IRR (95% CI)	P-value
<i>Depression</i>				
Overall	88.6	86.5	1.02 (0.95–1.10)	0.526
Female sex	108.0	102.1	1.06 (0.96–1.16)	0.234
Male sex	65.5	68.4	0.96 (0.84–1.09)	0.504
Age 18–30 years	70.5	68.9	1.02 (0.86–1.21)	0.799
Age 31–40 years	94.5	92.3	1.02 (0.86–1.23)	0.796
Age 41–50 years	99.2	102.6	0.97 (0.82–1.15)	0.698
Age 51–60 years	93.5	99.7	0.94 (0.81–1.09)	0.415
Age 61–70 years	90.1	77.4	1.16 (0.93–1.46)	0.188
Age >70 years	89.2	78.6	1.14 (0.90–1.44)	0.287
<i>Anxiety disorder</i>				
Overall	30.1	31.9	0.94 (0.83–1.07)	0.338
Female sex	34.6	40.0	0.86 (0.74–1.01)	0.066
Male sex	24.6	22.6	1.09 (0.88–1.35)	0.417
Age 18–30 years	28.6	31.6	0.90 (0.70–1.17)	0.447
Age 31–40 years	31.0	40.1	0.77 (0.57–1.04)	0.089
Age 41–50 years	34.5	32.1	1.07 (0.80–1.44)	0.629
Age 51–60 years	30.4	31.0	0.98 (0.80–1.29)	0.894
Age 61–70 years	29.7	28.3	1.05 (0.72–1.54)	0.801
Age >70 years	24.3	25.9	0.94 (0.62–1.42)	0.757

Abbreviations: COVID-19 coronavirus disease 2019; AURI acute upper respiratory infection; IRR incidence rate ratio; CI confidence interval.

The association between COVID-19 diagnosis (compared with AURI diagnosis) and the subsequent incidence of depression and anxiety disorder was studied in the overall population and also differentiated by sex and age using conditional Poisson regression models.