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Severe mental illness is associated with increased mortality and severe course of COVID-19

Running title: Outcome of COVID-19 in psychiatric disorders

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Abstract

Objective: Psychiatric disorders have been associated with unfavorable outcome following respiratory infections. Whether this also applies to coronavirus disease 2019 (COVID-19) has been scarcely investigated.

Methods: Using the Danish administrative databases, we identified all patients with a positive real-time reverse transcription-polymerase chain reaction test for COVID-19 in Denmark up to and including January 2, 2021. Multivariable Cox regression was used to calculate 30-day absolute risk and average risk ratio (ARR) for the composite endpoint of death from any cause and severe COVID-19 associated with psychiatric disorders, defined using both hospital diagnoses and redemption of psychotropic drugs.

Results: We included 144,321patients with COVID-19. Compared with patients without psychiatric disorders, the standardized ARR of the composite outcome was significantly increased for patients with severe mental illness including schizophrenia spectrum disorders 2.43 (95% confidence interval [CI], 1.79-3.07), bipolar disorder 2.11 (95% CI, 1.25-2.97), unipolar depression 1.70 (95% CI, 1.38-2.02), and for patients who redeemed psychotropic drugs 1.70 (95%

CI, 1.48-1.92). No association was found for patients with other psychiatric disorders 1.13 (95% CI, 0.86-1.38). Similar results were seen with the outcomes of death or severe COVID-19. Among the different psychiatric subgroups, patients with schizophrenia spectrum disorders had the highest 30-day absolute risk for the composite outcome 3.1% (95% CI, 2.3-3.9%), death 1.2% (95% CI, 0.4-2.0%) and severe COVID-19 2.7% (95% CI, 1.9-3.6%).

Conclusion: Schizophrenia spectrum disorders, bipolar disorder, unipolar depression and psychotropic drug redemption are associated with unfavourable outcomes in patients with COVID-19.

Keywords: Covid-19; respiratory infection; schizophrenia; bipolar disorder; depression; unfavourable outcome

Significant Outcome

- In this nationwide cohort including 144,321 patients with coronavirus disease 2019 (COVID-19), we found that a medical history of severe mental illness (i.e. schizophrenia spectrum disorders, bipolar disorder or unipolar depression) or a psychiatric disorder requiring active medical treatment is associated with an unfavourable outcome in patients with COVID-19. This was not the case for other psychiatric disorders.

Limitations

Considering its observational nature, the study only reports associations and does not allow conclusions of causality. Likewise, the risk of residual confounding is always a potential limitation in observational studies.

A positive real-time reverse transcription-polymerase chain reaction test for COVID-19 was necessary to be included in the study. As patients with psychiatric disorders often avoid seeking medical help, selection bias may have influenced the results.

Data availability statement

The data and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure.

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) which has infected more than 126 million people worldwide and claimed more than 2.7 million lives, as of March 28, 2021.[1]

Infectious diseases, especially from the respiratory tract system, contribute markedly to the excess mortality of patients with psychiatric disorders compared with the general population.[2,3] Notably, previous studies have documented a 2-to 7-fold higher mortality following respiratory infections in patients with psychiatric disorders.[4–7]

Several risk factors associated with severe COVID-19 outcome are common among patients with psychiatric disorders such as chronic obstructive pulmonary disease (COPD), obesity, diabetes, cardiovascular disease, substance abuse and low socioeconomic status.[8–10] Moreover, a previous diagnosis of a mental disorder has been associated with increased risk for COVID-19 infection.[11] However, few studies have investigated whether different psychiatric disorders are associated with unfavourable COVID-19 outcomes.[11–13]

Aims of the Study: The aim of the study was to evaluate possible differences in the risk of severe Coronavirus disease 2019 and death from any cause between patients with and without psychiatric disorders in a large Danish cohort of patients with Coronavirus disease 2019. Considering clinical differences among various psychiatric disorders, five subgroups were analyzed separately: schizophrenia spectrum disorders, bipolar disorder, unipolar depression (severe mental illness - SMI), other psychiatric disorders, and patients who redeemed psychotropic medications within 90 days prior to index date without having a hospital psychiatric diagnosis.

Methods

Data sources and definitions

In Denmark, nationwide administrative registries hold complete information on various health care-related and administrative variables. The unique and permanent civil registration number

allows cross-linkage of the registries at an individual level.[14] The Danish Civil Registration System includes information on sex, vital status and migration. The Danish National Patient Register holds information on in- and out-patient hospital contacts and surgical procedures.[14] The Danish Psychiatric Central Research Register is a nationwide registration of all psychiatric hospitalizations and ambulatory contacts.[15] In these two registries, the diagnoses are recorded according to the International Classification of Diseases (ICD), the 8th revision (ICD-8) until 1994 and the 10th revision (ICD-10) from 1994. From the Danish National Prescription Registry,[16] we retrieved data on claimed drug prescriptions from all Danish pharmacies. Medications are classified according to the international Anatomical Therapeutic Chemical Classification System (ATC). Information on patient income and educational status was collected from the Danish registers on personal income and transfer payments and the Danish Education Registers, respectively.[17,18]

Study population

We included all patients in Denmark aged between 16 and 80, who were diagnosed with COVID-19 from February 27, 2020 until January 2, 2021.[19]

Diagnosis was confirmed by a positive real-time reverse transcription-polymerase chain reaction test for COVID-19 obtained from the Danish Microbiology Database.[19,20] Moreover, for patients diagnosed for COVID-19 in a hospital setting, we used ICD-codes (ICD-10 codes B342A, B972, and B972A) from the Danish National Patient Registry. These codes were created for the COVID-19 pandemic by the Danish Ministry of Health in accordance with the definition established by the World Health Organization and have been validated with a positive predictive value of 98%.[21]

We excluded patients with dementia (previous hospital diagnosis identified by ICD-10 codes: F00-F03, G30, G311, G312 or redemption of a prescription for anti-dementia drugs [N06D] within 180 days prior to index date) and those >80 years of age (Figure 1) as that they are often deemed ineligible for intensive support.[22]

Exposure of interest

Patients with psychiatric disorders were identified by either an inpatient or outpatient hospital diagnosis from the Danish Psychiatric Central Research Register any time prior to the day of diagnosis of COVID-19 (index date), and/or redemption of prescription for a psychotropic drug from the National Prescription Register up to 90 days prior to index date. The following patient

groups were identified: schizophrenia spectrum disorders, bipolar disorder, unipolar depression, other psychiatric disorders encompassing psychiatric diagnoses not included in the previous groups; and lastly, patients who redeemed psychotropic medications (antipsychotics, lithium, antidepressants and psychostimulants) within 90 days prior to index date without having a hospital psychiatric diagnosis (i.e. patients treated for their psychiatric disorder only in the primary sector, not reported in the hospital-based registries).[23,24]

If more than one diagnosis was present, the patient was assigned to the most severe group in accordance with the diagnostic hierarchical order in ICD-10, as done previously.[23,25] The ICD and ATC codes used to define psychiatric disorders are listed in Supplemental table 1.

Explanatory covariates

The ICD- and ATC-codes used to identify baseline comorbidities are listed in Supplemental table 2. The use of psychotropic drugs (antipsychotics, lithium, antidepressants and psychostimulants) was defined as the redemption of these medications within 90 days prior to index date.[23,24] Socioeconomic status was defined according to the average household income in the year prior to index date and grouped into quartiles. Household income was weighted in accordance with the number of people living in the household by the Organization for Economic Co-operation and Development- (OECD) modified scale, as done previously.[26] Educational status was defined according to the highest completed educational level in agreement with the International Standard Classification of Education (ISCED).[26]

Outcome

The primary outcome was a composite of death from any cause or severe COVID-19 (defined as ICD-10 diagnosis code B972A designating COVID-19 with SARS or intensive care unit [ICU] admission), as done previously.[21,27] Also, the two outcomes were analysed separately. In the analyses where the outcome was severe COVID-19, death without severe COVID-19 was considered a competing risk.

Statistics

We used multivariable Cox regression to examine the association between outcomes and the psychiatric subgroups.[21,27] The results were presented as 30-day absolute risks of outcomes standardized to the risk factor distribution of all patients in the sample with related average risk

ratios (ARR). Moreover, we calculated unadjusted and adjusted hazard ratios (HRs) with 95% confidence interval (CI).[21]

The following variables were included in the models: age, sex, highest obtained education, income, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, hypertension, diabetes, asthma, COPD, substance abuse, and malignancy.

The following supplementary analyses were performed:

1) reducing the exposure-window to one year, i.e. identifying patients with hospital psychiatric diagnoses (schizophrenia spectrum disorders, bipolar disorder, unipolar depression and other psychiatric disorders) during the year prior to index date;

2) stratifying patients with a hospital psychiatric diagnosis according to the redemption of psychotropic drugs within 90 days prior to index date (two categories: no redemption or redemption of ≥ 1 drug);

3) stratifying the whole psychiatric population by the number of drugs redeemed within 90 days prior to index date, classified as follows: (1) patients not taking psychotropic drugs, (2) taking only one drug, (3) taking two drugs and (4) taking three or more drugs;

4) including only individuals prescribed psychotropic medications for mental disorders.

Data management and statistical analyses were performed using the SAS Version 9.4 (SAS Institute Inc., Cary, NC, USA) and R version 3.6.1.

Ethics

In Denmark, registry-based studies do not require ethical committee approval or patient consent if the study is conducted for the sole purpose of statistics and scientific research as defined in The Data Protection Act. Approval to use the data sources for research purposes was granted by the data responsible institute in the Capital Region of Denmark in accordance with the General Data Protection Regulation (Approval number: P-2019-191).

Results

We included 144,321patients with COVID-19, of these 984 (0.7%) had a schizophrenia spectrum disorder, 485 (0.3%) bipolar disorder, 3764 (2.6%) unipolar depression, 7328 (5.1%) other psychiatric disorders and 4479 (3.1%) were in treatment with psychotropic drugs without having a hospital psychiatric diagnosis (Figure 1). Compared with patients without psychiatric disorders, patients from all five psychiatric groups had a general higher burden of comorbidity, lower income

and lower educational level (Table 1). Patients who redeemed psychotropic drugs were older compared to those in the other groups.

Absolute risks and average risk ratio

Composite outcome

By 30 days, 1.2% of COVID-19 positive patients without psychiatric disorders experienced the composite outcome. In comparison, 4.9% of COVID-19 positive patients with schizophrenia spectrum disorders, 4.1% of patients with bipolar disorder, 2.1% of patients with unipolar depression, 1.0% of patients with other psychiatric disorders, and 5.4% of patients who redeemed psychotropic drugs experienced the composite outcome (Table 2). Patients with schizophrenia spectrum disorders had the highest 30-day standardized absolute risk (SAR) for the composite outcome: 3.1% (95% CI, 2.3-3.9%).

The standardized ARR was significantly increased for patients with schizophrenia spectrum disorders 2.43 (95% CI, 1.79-3.07), bipolar disorder 2.11 (95% CI, 1.25-2.97), unipolar depression 1.70 (95% CI, 1.38-2.02) and those who redeemed psychotropic drugs 1.70 (95% CI, 1.38-2.02) (Table 2), but not for patients with other psychiatric disorders 1.13 (95% CI, 0.86-1.38).

Death

Among the different psychiatric subgroups, COVID-19 positive patients with schizophrenia spectrum disorders had the highest 30-day SAR (1.2% [95% CI 0.4-2.0%]). Compared with COVID-19 positive patients without psychiatric disorders, patients with schizophrenia spectrum disorders (2.29 [95% CI, 1.36-3.22]), bipolar disorder (1.87 [95% CI, 1.12-3.12]), unipolar depression (1.92 [95% CI, 1.39-2.44]) and those who redeemed psychotropic drugs (2.14 [95% CI, 1.77-2.51]) were associated with a significantly increased standardized ARR (Table 3A).

Severe COVID-19

Among the different psychiatric subgroups, COVID-19 positive patients with schizophrenia spectrum disorders had the highest 30-day SAR of severe COVID-19 disease (2.7% [95% CI, 1.9-3.6%]). Patients with schizophrenia spectrum disorders (2.82 [95% CI, 1.96-3.67]), bipolar disorder (2.26 [95% CI, 1.16-3.37]) and unipolar depression (1.47 [95% CI, 1.11-1.83]) were associated with significantly increased standardized ARR of severe COVID-19 disease compared with patients without psychiatric disorders (Table 3B).

Hazard ratios

The fully adjusted HRs reflect the results of the main analyses for all three tested outcomes (Supplementary table 3). We observed that the adjustment considerably reduced the association between the outcomes and the different psychiatric disorders, especially for the subgroup of patients who redeemed psychotropic drug.

Supplementary analyses

We observed similar results when only including patients with a recent (within past year) diagnosis of a mental disorder (Supplementary table 4).

In the analysis stratified by the redemption of psychotropic drugs, for all four considered psychiatric diagnoses (schizophrenia spectrum disorders, bipolar disorder, unipolar depression and other psychiatric disorders), higher estimates were seen for the subgroups receiving treatment with one or more drugs (Supplementary table 5). Similarly, when the whole psychiatric population was stratified according to the number of redeemed psychotropic drugs, we observed a trend towards an increasing risk for the composite outcome with increasing number of drugs (Supplementary table 6). The adjusted 30-day SAR went from 1.5% (95%CI, 1.2-1.8%) in patients with psychiatric disorders who did not redeem any drugs to 2.9% (95%CI, 2.4-3.4%) in patients who redeemed ≥2 psychotropic drugs.

The 4479 patients who were receiving treatment with psychotropic drugs but without having a hospital psychiatric diagnosis redeemed in total 8775 prescriptions. Of these, 4476 (51.0%) prescriptions included information on the indication. In 7.8% of the cases (349 out of 4476 prescriptions, corresponding to 231 patients), the indication was not a mental disorder. Repeating the analysis for the composite outcome, excluding these 231 patients, did not change the results: SAR 2.1% (95% CI, 1.8-2.4%) and ARR 1.63 (95% CI, 1.40-1.85), respectively.

Discussion

This nationwide study had two major findings: firstly, in COVID-19 positive patients, schizophrenia spectrum disorders, bipolar disorder, unipolar depression and psychotropic drug

redemption – but not other psychiatric disorders - were associated with an increased risk of death and severe COVID-19; secondly, the number of redeemed psychotropic drugs was (non-significantly) correlated with an higher risk of death and severe COVID-19, suggesting an association between illness severity and unfavorable COVID-19 outcomes.

Differences in the risk of unfavourable outcome in diverse psychiatric disorders

Two recent studies have suggested an association between psychiatric disorders and severe clinical outcomes in COVID-19 patients in United States and South Korea.[11,13] In a larger and unselected cohort of COVID-19 patients from Denmark, our study expanded these findings showing differences in the risk of unfavourable outcome associated with diverse mental disorders. Moreover, we showed an increased risk of severe COVID-19 outcome even in patients not having a hospital psychiatric diagnosis but whose mental disorder is severe enough to require active medical treatment. This implies that a thorough monitoring is also needed in COVID-19 patients with mental disorders handled in the primary sector.

Our data suggested an association between mental illness severity and unfavourable COVID-19 outcomes. For example, patients with schizophrenia spectrum disorders had the highest 30-day absolute risk for all the three outcomes. Similarly, in the analysis stratified by the number of redeemed psychotropic drugs, the risk of the composite outcome increased with higher psychotropic drug use.

This may have different explanations. A more severe mental illness often implies a more unhealthy lifestyle and a related higher burden of somatic disease.[2,28] Furthermore, SMI per se[29] as well as different drugs such as alcohol, marijuana and cocaine have been associated with dysregulation of the immune system[30] and may predispose these patients to a more severe infection or bacterial super-infection.

Cognitive impairment, lack of communication skills, limited comprehension of medical advices and poor self-awareness typically worsen, as the mental illness progresses.[31] Likewise, stigmatization of mental disorder and "diagnostic overshadowing" may aggravate social isolation of patients with psychiatric disorders and complicate the diagnosis of COVID-19.[4,31] All these factors may lead to a late request for medical advice during the course of the infection, thereby limiting treatment options.[25,31]

Factors underlying the association with unfavourable COVID-19 outcomes

We found an overall higher burden of somatic comorbidity in all psychiatric groups compared with patients without psychiatric disorders. Cardiometabolic and respiratory diseases such as diabetes and COPD are particularly common among patients with psychiatric disorders.[2] These somatic comorbidities have been proven to influence the development of acute respiratory distress syndrome and death in patients with COVID-19.[9] Therefore, the increased risk of unfavourable outcome that we observed may be explained, at least partly, by a higher comorbidity burden. Correspondingly, adjusting for comorbidities markedly reduced this association.

Both antipsychotics and antidepressants seem to affect the immune system.[32–34] Furthermore, several studies have hypothesized a direct link between antipsychotics use and risk of pneumonia and pneumonia-related mortality. Sedation, impairment of swallowing and cough reflexes, hypersalivation and changes in pharyngeal and laryngeal muscle tone are among the possible underlying mechanisms.[32,33]

A low socioeconomic status and educational level were also more common among patients with psychiatric disorders in our cohort. It has been demonstrated that both factors negatively impact the post-infection course primarily because of an association with unhealthy lifestyle and lower access to medical help.[8] Moreover, as a result of economic and social disadvantage, patients with psychiatric disorders, especially those with more severe disorders,[35] more often live in nursing homes, congregate settings or homeless shelters. The characteristics of these settings such as poor hygienic conditions and overcrowding may pose an increased risk to these patients of being infected by SARSCoV-2 and exposure to a higher viral load, which correlates with disease severity and mortality.[11]

Clinical implications of the study

The association between psychiatric disorders and unfavourable COVID-19 outcomes may thus be mediated by somatic comorbidities and severity of the mental disorder. Hence, an important first step in the prevention of unfavourable COVID-19 outcomes in these patients would be an optimal management of their pulmonary, metabolic and cardiovascular diseases.[8,9] However, the management of patients with psychiatric disorders may be particularly challenging in the course of a pandemic,[36] for example because of a low treatment-adherence.[31] Therefore, during the present recurrence of COVID-19 outbreak, improvements in management policy including special prevention measures, active surveillance and prompt treatment as well as prioritization in

vaccination strategies should be considered in patients with psychiatric disorders to tackle their higher risk of unfavourable COVID-19 outcome.

Limitations

Firstly, due to the observational nature of the study, no conclusions of causality can be drawn. Secondly, the Danish registries lack important clinical parameters such as smoking habits and BMI, which have been shown to influence outcome in COVID-19 patients.[8,37] As tobacco use and overweight are particularly common among patients with psychiatric disorders,[28] we cannot rule out the possibility that our results were mainly driven by unmeasured confounders.

Thirdly, selection bias must be acknowledged. As patients with psychiatric disorders often seek help late in the course of a disease [25] and considering that this phenomenon would be expected to be proportional to the severity of the mental disorder[31], it is possible that the association with unfavorable outcomes is the result of a delayed diagnosis of COVID-19.

Fourthly, information about the indication for drug prescription is poorly reported in the Danish registries. Some psychotropic drugs are prescribed for conditions other than mental disorders. However, repeating the analysis but excluding tricyclic antidepressants - the antidepressants most used in non-psychiatric condition – and excluding patients with a registered non-psychiatric indication for their psychotropic drugs did not alter the results.

Fifthly, treatment nonadherence is particularly high among patients with psychiatric disorders, especially among those with SMI.[38,39] Therefore, in the analyses based on the number of redeemed drugs, the group of patients without psychotropic drugs may be composed of a mix of patients with a milder disorder, perhaps not requiring treatment, and patients with a more severe disorder, not redeeming well-indicated drugs. This could have fictively increased the association with unfavorable outcome in this group (and reduced the association in the groups of patients redeeming ≥1 drugs). However, both the analyses based on redeemed drugs and those based on diagnoses were consistent in showing a trend towards an increasing risk of the composite outcome in the patients with a more severe psychiatric disorder.

Lastly, the study was conducted in Denmark and this could weaken the generalizability of our findings, considering differences in health care systems, handling of pandemic and screening strategies in different countries.

Conclusions

A medical history of schizophrenia spectrum disorders, bipolar disorder or unipolar depression or a psychiatric disorder requiring active medical treatment may represent a substantial risk factors for an unfavourable outcome in patients with COVID-19.

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Table 1: Baseline characteristics of the study population divided according to the psychiatric disorders.

Characteristics	Patients without psychiatric disorders*	Patients with schizophrenia spectrum disorders	Patients with bipolar disorder	Patients with unipolar depression	Patients with other psychiatric disorders	Patients who redeemed psychotropic drugs
Total number of patients, n (%)	127,281 (88.2)	984 (0.7)	485 (0.3)	3764 (2.6)	7328 (5.1)	4479 (3.1)
Median duration of the psychiatric disorder, years (IQR)**	NA	9.1 (3.8-16.7)	6.8 (3.2-12.6)	7.6 (3.7-13.2)	7.2 (3.3-12.9)	NA
Sex Male, n (%)	63,241 (49.7)	480 (48.8)	181 (37.3)	1161 (30.8)	3137 (42.8)	1714 (38.3)
Median age, years (IQR)	40.5 (26.2, 54.3)	40 (28.5, 53.6)	45.3 (31.4, 58.6)	44 (31.1, 54.8)	32.6 (23.6, 47.1)	53.5 (41.5, 64.7)
Living alone, n (%)	38773 (30.5)	590 (60.0)	252 (52.0)	1607 (42.7)	3347 (45.7)	1570 (35.1)
Ethnic group, Native Danish, n (%)	95,830 (75.3)	675 (68.6)	422 (87.0)	2,640 (70.1)	5,488 (74.9)	3,607 (80.5)
Immigrant, n (%)	23170 (18.2)	240 (24.4)	46 (9.5)	1014 (26.9)	1345 (18.4)	784 (17.5)
Descendant from immigrant, n (%)	8281 (6.5)	69 (7.0)	17 (3.5)	110 (2.9)	495 (6.8)	88 (2.0)
Comorbidities						
Ischemic heart disease ***, n (%)	2240 (1.8)	19 (1.9)	9 (1.9)	120 (3.2)	132 (1.8)	178 (4.0)

Heart failure, n (%)	796 (0.6)	15 (1.5)	4 (0.8)	32 (0.9)	35 (0.5)	83 (1.9)
COPD, n (%)	7066 (5.6)	90 (9.1)	38 (7.8)	329 (8.7)	548 (7.5)	598 (13.4)
Asthma, n (%)	2480 (1.9)	30 (3.0)	15 (3.1)	142 (3.8)	231 (3.2)	137 (3.1)
Diabetes mellitus, n (%)	5384 (4.2)	120 (12.2)	28 (5.8)	301 (8.0)	354 (4.8)	507 (11.3)
Malignancy, n (%)	3020 (2.4)	19 (1.9)	13 (2.7)	107 (2.8)	126 (1.7)	250 (5.6)
Cerebrovascular disease, n (%)	1653 (1.3)	28 (2.8)	8 (1.6)	83 (2.2)	107 (1.5)	237 (5.3)
Substance abuse, n (%)	1709 (1.3)	126 (12.8)	58 (12.0)	234 (6.2)	383 (5.2)	206 (4.6)
Hypertension, n (%)	10561 (8.3)	96 (9.8)	53 (10.9)	424 (11.3)	428 (5.8)	982 (21.9)
Chronic kidney disease, n (%)	1156 (0.9)	20 (2.0)	10 (2.1)	66 (1.8)	80 (1.1)	111 (2.5)
Number of redeemed psychotropic drugs						
0, n (%)	127,281 (100.0)	533 (54.2)	161 (33.2)	2375 (63.1)	5859 (80.0)	0 (0.0)
1, n (%)	0 (0.0)	243 (24.7)	127 (26.2)	978 (26.0)	1170 (16.0)	3880 (86.6)
≥2, n (%)	0 (0.0)	208 (21.1)	197 (40.6)	411 (10.9)	299 (4.1)	599 (13.4)
Socioeconomic status, income quartile						
-Lowest, n (%)	17,556 (13.8)	101 (10.3)	21 (4.3)	252 (6.7)	1264 (17.2)	187 (4.2)
- Middle low, n (%)	33,079 (26.0)	585 (59.5)	226 (46.6)	1481 (39.3)	3009 (41.1)	1286 (28.7)

-Middle high, n (%)	36,094 (28.4)	235 (23.9)	135 (27.8)	1322 (35.1)	1964 (26.8)	1591 (35.5)
-Highest, n (%)	40,552 (31.9)	63 (6.4)	103 (21.2)	709 (18.8)	1091 (14.9)	1415 (31.6)
Highest obtained educational level						
-ISCED 0-2, n (%)	33,718 (26.5)	491 (49.9)	137 (28.2)	1172 (31.1)	3150 (43.0)	1181 (26.4)
-ISCED 3, n (%)	48,153 (37.8)	296 (30.1)	179 (36.9)	1425 (37.9)	2378 (32.5)	1791 (40.0)
-ISCED 5-6, n (%)	28,853 (22.7)	124 (12.6)	109 (22.5)	829 (22.0)	1269 (17.3)	1030 (23.0)
-ISCED 7-8, n (%)	13,736 (10.8)	52 (5.3)	56 (11.5)	261 (6.9)	410 (5.6)	375 (8.4)
-missing, n (%)	2821 (2.2)	21 (2.1)	4 (0.8)	77 (2.0)	121 (1.7)	102 (2.3)

†Patients without prior hospital psychiatric diagnoses and who did not redeem psychotropic drugs within 90 days prior to index date.

‡ Defined as the time from the first hospital contact for the specific disorder to index date as a proxy for the duration of the psychiatric disorder

§ Acute myocardial infarction included

IQR, interquartile range; ISCED, International Standard Classification of Education

Table 2: Standardized 30-Day Absolute Risks and average risk ratio for Composite of Death or Severe COVID-19 in different subgroups of patients with psychiatric disorders

Composite Outcome	Total number of patients	Events n (%)	30-day absolute risk, % (95% CI)[†]	Standardized average risk ratio [95% CI]
No psychiatric disorders‡	127,281	1551 (1.2)	1.3 (1.2-1.4)	Ref.
Schizophrenia spectrum disorders	984	48 (4.9)	3.1 (2.3-3.9)	2.43 (1.79-3.07)
Bipolar disorder	485	20 (4.1)	2.7 (1.6-3.8)	2.11 (1.25-2.97)
Unipolar depression	3764	102 (2.7)	2.2 (1.7-2.6)	1.70 (1.38-2.02)
Other psychiatric disorders	7328	73 (1.0)	1.4 (1.1-1.8)	1.13 (0.86-1.38)
Psychotropic drug redemption [§]	4479	242 (5.4)	2.1 (1.9-2.4)	1.70 (1.48-1.92)

† Cox models included age, sex, highest obtained education, income, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, hypertension, peripheral artery disease, diabetes, chronic obstructive pulmonary disorder, asthma, substance abuse, and malignancy

‡ patients without prior psychiatric diagnoses and who did not redeem psychotropic drugs within 90 days prior to index date.

§ within 90 days prior to index date without having a hospital psychiatric diagnosis.

COVID-19, coronavirus disease 2019; CI, confidence interval.

Table 3: Standardized 30-Day Absolute Risks and average risk ratio for Death and Severe COVID-19 in different subgroups of psychiatric disorders				
A - Death	Total number of patients	Events n (%)	30-day absolute risk (95% CI)†	Standardized average risk ratio [95% CI]

	Total number of patients	Events n (%)	30-day absolute risk (95% CI)[1]	Standardized average risk ratio [95% CI]
No psychiatric disorders‡	127,281	632 (0.5)	0.5 (0.2-0.8)	Ref.
Schizophrenia spectrum disorders	984	20 (2.0)	1.2 (0.4-2.0)	2.29 (1.36-3.22)
Bipolar disorder	485	8 (1.7)	1.0 (0.3-1.8)	1.87 (1.12-3.12)
Unipolar depression	3764	49 (1.3)	1.1 (0.4-1.6)	1.92 (1.39-2.44)
Other psychiatric disorders	7328	28 (0.4)	0.6 (0.2-1.1)	1.24 (0.75-1.65)
Psychotropic drug redemption§	4479	159 (3.5)	1.1 (0.5-1.8)	2.14 (1.77-2.51)
B - Severe COVID-19	Total number of patients	Events n (%)	30-day absolute risk (95% CI)[1]	Standardized average risk ratio [95% CI]
No psychiatric disorders‡	127,281	1197 (0.9)	0.9 (0.1-1.0)	Ref.
Schizophrenia spectrum disorders	984	39 (4.0)	2.7 (1.9-3.6)	2.82 (1.96-3.67)
Bipolar disorder	485	15 (3.1)	2.2 (1.1-3.3)	2.26 (1.16-3.37)
Unipolar depression	3764	65 (1.7)	1.4 (1.1-1.8)	1.47 (1.11-1.83)
Other psychiatric disorders	7328	52 (0.7)	1.0 (0.7-1.3)	1.04 (0.76-1.33)
Psychotropic drug redemption §	4479	127 (2.8)	1.3 (1.1-1.5)	1.27 (0.91-1.52)

†Cox models included age, sex, highest obtained education, income, ischemic heart disease, congestive heart failure, cerebrovascular disease, chronic kidney disease, hypertension, peripheral artery disease, diabetes, chronic obstructive pulmonary disorder, asthma, substance abuse, and malignancy

‡ patients without prior psychiatric diagnoses and who did not redeem psychotropic drugs within 90 days prior to index date.
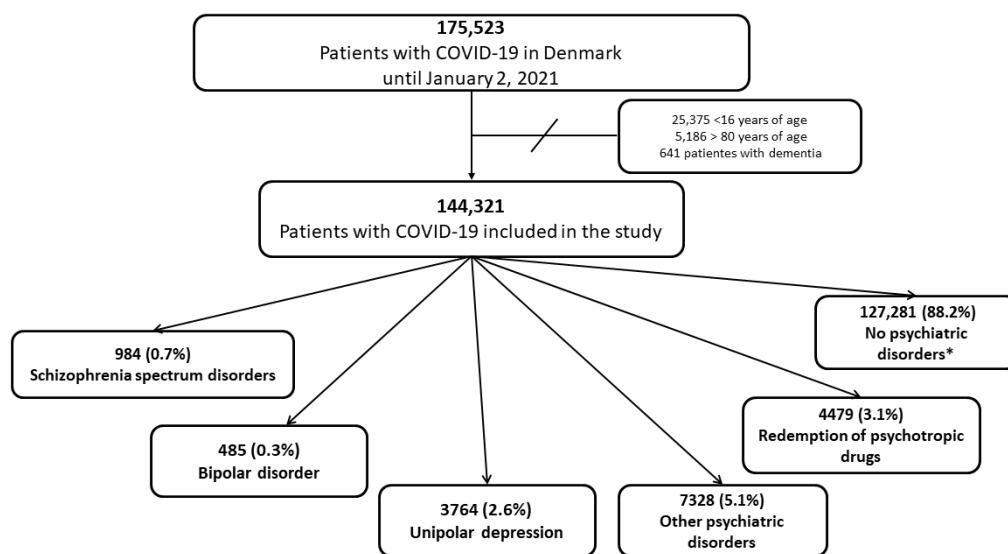
§ within 90 days prior to index date without having a hospital psychiatric diagnosis.

COVID-19, coronavirus disease 2019; CI, confidence interval.

Figure legends

Figure 1: Selection of the study population. COVID-19, coronavirus disease 2019

*patients without prior hospital psychiatric diagnoses and who did not redeem psychotropic drugs within 90 days prior to index date.

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