A meta-analysis: The mortality and severity of COVID-19 among patients with mental disorders

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ABSTRACT

Several observational studies investigated the relationship between pre-diagnosis with mental disorders and COVID-19 outcomes. Thus, we have decided to conduct this meta-analysis to explore this relationship. We complied to the PRISMA guidelines in conducting this meta-analysis. PubMed, ScienceDirect, Google Scholar and medRxiv were searched until the 15th of February, 2021. We used the Random effect model in Meta XL, version 5.3 to pool the included studies. Statistical heterogeneity was assessed using Cochran's Q heterogeneity test and I^2. This meta-analysis included 634,338 COVID-19 patients from 16 studies. Our findings revealed that pre-diagnosis with mental disorders increased the risk of COVID-19 mortality and severity. This increase in the risk of COVID-19 mortality and severity remained significant in the model that only included the studies that adjusted for confounding variables. Furthermore, higher mortality was noticed in the included studies among schizophrenia, schizotypal and delusional disorders patients compared to mood disorders patients. In this meta-analysis we provided two models which both reported a significant increase in the risk of COVID-19 severity and mortality among patients with mental disorders, and with the upcoming COVID-19 vaccines, we recommend to give this category the priority in the vaccination campaigns along with medical health providers and elderly.

1. Introduction

On December, 31, 2019 an outbreak of atypical pneumonia caused by the 2019 novel coronavirus (2019-nCov) was announced.(Wu et al., 2020) Since then, this virus resulted in large numbers of cases and deaths worldwide causing public health emergencies and threatening pandemic.(Palacios Cruz et al., 2020)

Coronavirus infectious disease 2019 (COVID-19) pandemic has a serious impact on emotional and social aspects of individuals with negative consequences that have been widely predicted but not specifically estimated yet.(Pfefferbaum and North, 2020; Taquet et al., 2020)

The World Health Organization (WHO) has defined mental health as "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his community".(Vigo et al., 2016) According to the statistics this state of well-being is disturbed in one of four individuals (Ginn and Horder, 2012; Steel et al., 2014) and the evidence that mental diseases shorten life expectancy is also well established.(Happell et al., 2017) However, the global burden of mental illnesses is markedly underestimated.(Vigo et al., 2016) It is reviewed that this global burden accounts for 32.4% of years lived with disability (YLDs) and 13.0% of disability-adjusted life-years (DALYs).These percentages place mental illness as the first in global burden of disease in terms of YLDs, and equivalent to cardiovascular and circulatory diseases in terms of DALYs.(Vigo et al., 2016) In addition to its physical burden, mental diseases are associated with large economic load.(Doran and Kinchin, 2019)

The risk of developing several medical conditions among patients with mental disorders can be attributed to the fact that these disorders affect lifestyle, daily habits, and socioeconomic status.(Momen et al., 2020) A study conducted in South Korea found that being tested positive for COVID-19 did not increase among people with mental disorders, while the severity and mortality did.(Lee et al., 2020b)

Furthermore, people with mental disorders have a worse prognosis compared to the general population as they have higher risk to develop other diseases and higher mortality rates of any disease, and they are less

likely to get tested for general comorbidities.(Erlangsen et al., 2017; Momen et al., 2020) Similarly, higher mortality due to infections was noticed among patients with severe mental disorders; depending on the type of the infection, the variability of the risk after hospitalization was 27% for sepsis and 161% for central nervous system (CNS) infection. (Ribe et al., 2015) It was found that the innate immunity affects the resilience of the (CNS), the local microenvironment and synaptic refinement throughout the brain progression which shows that there is a relationship between neurological and psychiatric disorders pathogenetically. The genetic anomalies trigger pro-inflammatory pathways by impairing the phagocytic capacity and changing the synaptic pruning of the microglial cells, or by favoring protein aggregation and degradation deficits.(Novellino et al., 2020) The relationship between neuropsychiatric disorders and inflammation is bidirectional; for example, depression facilitates and is promoted by inflammatory reactions.(Bauer and Teixeira, 2019b)

The occurrence of comorbid psychiatric disorders like; anxiety, depression and bipolar was found to be highly related to Autism Spectrum Disorder (ASD).(Hossain et al., 2020) Additionally, The predisposition of infection was genetically correlated with the diagnosis of mental disorders.(Nudel et al., 2019)

Several observational studies (An et al., 2020; Batty et al., 2021; Cavallaro et al., 2020; Collaborative, 2021; Cummins et al., 2021; Fond et al., 2020; Giannoglou et al., 2020; Hirashima et al., 2021; Jeon et al., 2020; Lee et al., 2020a; Lee et al., 2020b; McKeigue et al., 2020; Nemani et al., 2021 Wang et al., 2020; Yang et al., 2020; Yanover et al., 2020) investigated whether people with mental disorders have poorer COVID-19 outcomes or not, thus we have decided to conduct this meta-analysis that aims to investigate the relationship between pre diagnosed psychiatric illness and COVID-19 mortality and severity suggesting that people with mental disorders might have worse outcome of COVID-19.

2. Methods

2.1. Registration and protocol

We complied to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in conducting this meta-analysis (Moher et al., 2010). This meta-analysis was pre-registered in the PROSPERO database (CRD42020225330).

2.2. Search strategy

The search was conducted on the 11th, updated on the 19th of December, 2020 and updated again on the 15th of February, 2021 by AAT and HBA independently by searching PubMed, ScienceDirect, Google Scholar and medRxiv. The following keywords; Mental Disorder, COVID-19 and Outcome and their related MeSH terms were used; Mental Illness, Behavioral Disorders, Psychiatric Disorders, Psychiatric Diseases, Psychiatric Illnesses and Psychiatric Diagnosis for Mental Disorders keyword and SARS-CoV-2 Infection, SARS Coronavirus 2 Infection, 2019 Novel Coronavirus Disease, 2019 Novel Coronavirus Infection, 2019-nCoV Disease, 2019-nCoV Infection, COVID-19 Pandemic, COVID-19 Pandemics, COVID-19 Virus Disease, COVID-19 Virus Infection, COVID19, Coronavirus Disease 2019, Coronavirus Disease-19 for COVID-19 keyword. Then the search results were cross checked and any discrepancy was solved by discussion.

2.3. Study selection

The included studies were chosen if they were cohort or case-control in design, included patients clinically diagnosed with mental disorders and compared the mortality and severity of COVID-19 infection among patients with and without mental disorders. The COVID-19 mortality and severity were defined as death, intensive care unit (ICU) admission
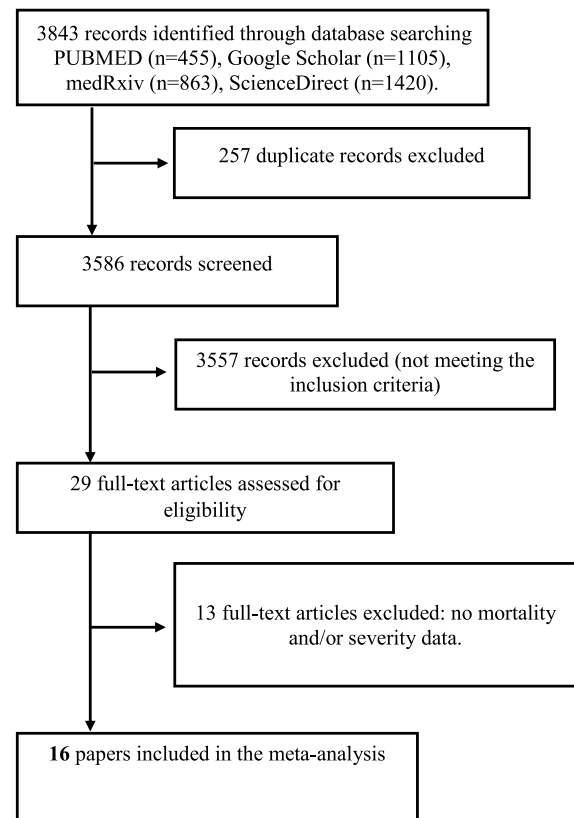
and the need of mechanical ventilation. The selection of the studies was done by AAT and HBA independently and any difference in the included studies was solved by discussion. Furthermore, the exposure of interest was the diagnosis with mental disorders which include any mental illness while the outcome of concern was COVID-19 mortality and severity which was defined as ICU admission and/or the use of mechanical ventilation.

2.4. Data extraction

The variables of interest that were extracted from the included studies were; country, design, number of participants, age, number of participants with mental disorders, comorbidities, number of participants who developed the outcome, the adjusted and non-adjusted odds ratio (OR), confounding variables and outcome of interest by AAT and HBA independently then checked by RBA and RHA and any discrepancy was solved by discussion. The extracted data was entered into a table then was analyzed. The quality of the included studies was assessed using Newcastle Ottawa Scale (NOS) for observational studies (Wells et al., 2000) by AAT and HBA independently then checked by RBA and RHA and any difference in the scoring was solved by discussion.

2.5. Analysis

The analysis was done by creating two models; one for pooling all the included studies (non-fully adjusted model). The other one was for pooling only the studies that were adjusted for confounding variables by matching between their participants or using analytic adjustment models (fully adjusted model). Furthermore, an additional subanalysis was done by pooling the studies that were conducted in the same health care system. We used Cochran's Q heterogeneity test and I^2 statistic to assess statistical heterogeneity. Additionally, a funnel plot was used to detect publication bias. Meta XL, version 5.3 (EpiGear International,

Fig. 1. PRISMA Flow Chart.

The flow chart contains the following boxes:
- 3843 records identified through database searching PUBMED (n=455), Google Scholar (n=1105), medRxiv (n=863), ScienceDirect (n=1420).
- 257 duplicate records excluded
- 3586 records screened
- 3557 records excluded (not meeting the inclusion criteria)
- 29 full-text articles assessed for eligibility
- 13 full-text articles excluded: no mortality and/or severity data.
- **16** papers included in the meta-analysis

Table 1
Characteristics of the included studies.

Study	Country	Design	Age (Median)	Number of Participants	Number of participants with mental disorders. (%)	Type of Mental Health Disorders (%)	Number of participants with mental disorders who developed the outcome. (%)	Number of participants without mental disorders who developed the outcome. (%)	Number of participants with Schizophrenia, Schizotypal and delusional disorders who developed the outcome. (%)	Number of participants with mood disorders who developed the outcome. (%)	Adjusted OR for all mental disorders (LLCI-ULCI).	Non-Adjusted OR for all mental disorders (LLCI-ULCI).	Adjustment for Confounding variables.	Outcome of interest.	Score
(Wang et al., 2020)	USA	Case Control	18-65 years: 71%	9,660	3,430/9,660 (35.5)	Depression= 1,460/3430 (42.6)	290/3,430 (8.5)	293/6,230 (4.7)			-	1.87 (1.58-2.21)	-	Death	7
(Lee et al., 2020 b)	South Korea	Retrospective Cohort	-	2,640	1,320/2,640 (50.0)	-	128/1,320 (9.7)	109/1,320 (8.3)			1.27 (1.01–1.66)	-	Age, gender region of residence and Comorbidities (2).	Severity (1)	9
							89/1,320 (6·7)	71/1,320 (5.4)			1.38 (1.00–1.95)	-		Death	9

Table 1 (*continued*)

(Fond et al., 2020)	France	Retrospective Cohort	Above 80: 31.7%	50,750	823/50,750 (1.6)	Schizophrenia= 823/823 (100)	211/823 (25.6)	10,854/49,927 (21.7)	211/823 (25.6)	-		1.30 (1.08–1.56)	1.25 (1.05–1.49)	Sociodemographic data (age, sex, social deprivatio), clinical data at baseline, stay data, hospital data, (3) and geographical areas of hospitalization.	Death	9
							195/823 (23.7)	14,156/49,927 (28.4)	195/823 (23.7)	-		0.75 (0.62–0.91)	0.78 (0.65–0.94)		Severity (4)	9
(Yanover et al., 2020)	Israel	Retrospective Cohort	35	4,353	578/4,353 (13.3)	-	53/578 (9.1)	120/3,775 (3.2)	-		-	3.07 (2.20-4.30)	-	Severity (5)	7
(Giannoglou et al., 2020)	Greece	Retrospective Cohort	60.4±18.2	512	103/512 (20.1)	-	18/103 (17.5)	63/409 (15.4)	-		-	1.16 (0.65–2.07)	-	Death	7

4

Table 1 (*continued*)

(Cavallaro et al., 2020)	UK	Retrospective Cohort	70	13,954	84 (0.6)	-	-	-			-	1.09 (0.63-1.82)	-	Age, sex, pregnancy, admission day, Ethnicity and comorbidities (6). .	Death	9
						-	-	-	-	-	-	2.58 (1.50-4.46)	-		Severity (7)	9
(McKeigue et al., 2020)	Scotland	Case-control	-	18,738	656/18,738 (3.5)	-	120/656 (18.29)	825/18,082 (4.81)	-			-	4.68 (3.80-5.78)	-	Severity (8)	7
(Jeon et al., 2020)	South Korea	Retrospective Cohort	56.4± 16.5	3,608	734/3,551 (20.7)	Schizophrenia, schizotypal and delusional disorders= 159/734 (21.7)	27/734 (3.5)	49/2,865 (1.9)	6/159 (3.8)	12/273 (4.4)	1.99(1.15–3.43)	-	Insuranc, residential area, comorbidities (9) ,age, sex, Charlson Comorbidity Index and co-	Death	9

Table 1 (*continued*)

						-12/-9 Mood Disorders=273/734 -17/-9 (37.2)	32/734 (4.4)	98/2,817 (3.5)	10/159 (6.3)	12/273 (4.4)	1.15(0.73–1.82)	-	medications.	Severity (10)	9
(Hirashima et al., 2021)	Japan	Retrospective cohort	47.51	61	2/61 (3.3)	-	0/2	16/59 (27.1)				0.53 (0.02 - 11.57)	-	Severity (11)	7
(Yang et al., 2020)	UK	Prospective cohort	67.8±8.12	1,951	442/1,951 (22.7)	Depression=231/442 (52.3) Anxiety = 165/442 (37.3) Stress Related Disorder=10/442 (2.3) Substance Misuse=212/442	120/442 (27.1)	256/1,509 (17.0)		68/231 (29.4)	2.03 (1.59 −2.59)	-	Year, sex, race or ethnicity, Townsend deprivation index, educational attainment, annual household income, body-mass index, smoking status, and co-morbidities(12).	Death	9

Table 1 (*continued*)

					(50.0) Psychotic Disorders=19/442 (4.3)									
(Lee et al., 2020 a)	South Korea	Retrospective cohort	-	781	236/781 (30.21%)	Depressive Disorder=228/497 (45.9) Anxiety=205/497 (41.2) Bipolar Disorder= 72/497 (14.5) Psychotic Disorder=62/497 (12.5) Schizophrenia=4	30/236 (12.7)	37/545 (6.8)	-		-	2.00 (1.20 - 3.32)	Age, sex, and index month	Death 7

Table 1 (*continued*)

					1/497 (8.2) Substance Use Dis Related Diseases =18/497 (3.6)										
(An et al., 2020)	South Korea	Retrospective Cohort	50-60: 18.4%	10,237	497/10,237 (4.9)	-	58/497 (11.7)	170/9,740 (1.7)	-		-	7.44 (5.44-10.17)	-	Death	7
(Cummins et al., 2021)	UK	Retrospective Cohort	50-69: 35.8%	1,781	301/1,781 (16.9)	Depression= 216/301 (71.8)	54/301 (17.9)	346/1,480 (23.3)	-	14/216 (6.5)	-	0.72 (0.52-0.98)	-	Death	7
							22/301 (7.3)	130/1,480 (8.7)	-	36/216 (13.9)	-	0.82 (0.51-1.31)		Severity (2)	7

Table 1 (*continued*)

(Nemani et al., January 2021 in JAMA psychiatry)	USA	Retrospective cohort	-	7,003	654/7,003 (9.3)	Schizophrenia=46/654 (7.0) Anxiety=234/654 (35.8) Mood Disorders=374/654 (57.2)	121/654 (18.5)	701/6,349 (11.0)	12/46 (26.1)	80/374 (21.4)	-	1.83 (1.48-2.26)	-	Death	7
(Batty et al., 2021)	UK	Prospective cohort	-	502,655	57,681/502,655 (11.5)	-	56/57,681 (0.1)	348/444,974 (0.1)			-	1.24 (0.94-1.65)	-	Death	7
(Collaborative, 2021)	UK	Retrospective Cohort	More than 80: 36.4%	5,711	482/5,711 (8.4)	-	124/482 (25.7)	1472/5,229 (28.1)			-	0.88 (0.71-1.09)	-	Death	7

1. Admission to the intensive care unit, invasive ventilation, or death.
2. ICU admission.
3. Clinical Data (smoking status, overweight and obesity, Charlson Comorbidity Index), Stay Data (origin of the patient) and Hospitalization Data (hospital category, number of hospital stays for COVID-19)
4. History of diabetes, cardiovascular disease, cerebrovascular disease, chronic obstructive pulmonary disease, asthma, hypertension, or chronic kidney disease; and Charlson comorbidity index.
5. Deteriorated to moderate or severe (at any point in time), admitted to the intensive care unit, or died.
6. Type-1 diabetes, chronic liver, serious mental illness, chronic renal disease, chronic neurological condition, chronic heart disease, hypertension, and asthma.
7. ICU Admission.
8. Critical care or death within 28 days or death certificate.
9. Diabetes, hypertension, heart failure, stroke, MI, asthma, COPD, renal disease, liver disease, cancer, and pneumonia.
10. Intensive care unit (ICU) admission, use of mechanical ventilation, and acute respiratory distress.
11. Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, lung infiltrates >50%, Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
12. History of chronic cardiac disease, diabetes, chronic pulmonary disease, chronic kidney disease, and asthma.

Queensland, Australia) was used in the data analysis.

3. Results

Our search yielded 3843 articles, 257 of them were duplications. The remaining 3586 articles were screened, 3464 were excluded because they were cross-sectional in design, reviews, editorials, commentaries or assessed mental health outcomes not COVID-19 outcomes. Of the lasting 122 articles, 93 were excluded because they didn't include any patient with mental disorders. Finally, 29 articles have been reviewed in their full text form, where 13 of them were excluded because they did not contain data about COVID-19 mortality or severity and 16 articles of them have been included in our meta-analysis (Fig. 1). According to NOS, all of the included articles got a score of 7 or more.

The total number of COVID-19 patients was 634,338 and 10.7% of them were diagnosed with mental disorders before being tested positive to COVID-19 (68,023/634,338). In the studies that provided data about types of mental disorders, 43.1% of the patients suffered from mood disorders (2,854/6,620) and 16.1% suffered from schizophrenia, schizotypal and delusional disorders (1,069/6,620). Furthermore, 22.3% of patients who suffered from schizophrenia, schizotypal and delusional disorders died (229/1,028) while only 15.9% of patients with mood disorders died (174/1,094). The characteristics of the included studies are described in (Table 1). Among COVID-19 patients in the studies that included data about comorbidities with mental disorders, 24.5% were diabetic (764/3,113), 35.4% were hypertensive (727/2,054), 11.5% with history of cardiovascular diseases (332/2,877), 9.1% with history of cerebrovascular diseases (261/2,877) and 9.6% with history of chronic kidney disease (220/2,290). In comparison among COVID-19 patients without mental disorders, 28.8% were diabetic (15,684/54,300), 28.9% were hypertensive (1,196/4,137), 22.2% with history of cardiovascular diseases (12,009/54,064), 6.2% with history of cerebrovascular diseases (3,359/54,064), 10.3% with history of chronic kidney disease 480/4,682. Co-morbidities among patients with and without mental disorders are described in (Table 2).

Our pooled analysis in the non-fully adjusted model revealed that pre-diagnosis with mental disorders significantly increased the risk of COVID-19 severity and mortality (Fig. 2: OR=1.76; 95% CI: 1.29-2.41). This significant increase in mortality and severity among patients with mental disorders remained significant in the fully adjusted model (Fig. 3: OR=1.52; CI: 1.20-1.93). In both models the heterogeneity across the studies was significant. Nevertheless it was lower in the fully adjusted one than the non-fully adjusted one (I2=63%; P-value=0.03, I2=94%; P-value <0.001) respectively. Moreover, the funnel plot for publication bias showed visual asymmetry (Fig. 4).

3.1. Subgroup analysis

In the subgroup analysis of each health care system, the pooling of the studies that were conducted in the United Kingdom revealed insignificant association between the diagnosis with mental disorders and COVID-19 severity and mortality (Fig. 5: OR=1.12; CI:0.76-1.65; I2=89%; P-value=0.00). On the other hand, the two models that pooled studies that were conducted in South Korea (Fig. 6: OR=2.5; CI:1.02-6.11; I2=95%; P<0.001) and United States of America (Fig. 7: OR=1.85; CI:1.63-2.12; I2=0; P<0.001) resulted that diagnosis with mental disorders increased the risk of COVID-19 severity and mortality.

4. Discussion

This analysis provides evidence suggesting that the need of mechanical ventilation, ICU admission and mortality is higher among COVID-19 patients who were diagnosed with mental disorder by the provided odds ratio by 63.8% (OR= 1.76, 95% CI=1.29-2.41).(An et al., 2020; Batty et al., 2021; Cavallaro et al., 2020; Collaborative, 2021; Cummins et al., 2021; Fond et al., 2020; Giannoglou et al., 2020;

Table 2
Comorbidities among patients with and without mental disorders.

| Study	Country	Design	Co-morbidities among people with mental disorders(%)					Co-morbidities among people without mental disorders(%)				
			Diabetes	Hypertension	Cardiovascular disease	Cerebrovascular disease	Chronic Kidney Disease	Diabetes	Hypertension	cardiovascular disease	Cerebrovascular disease	Chronic Kidney Disease
(Lee et al., 2020b)	South Korea	Retrospective Cohort	320/1,320 (24.2)	517/1,320 (39.2)	169 /1,320 (12.8)	162 /1,320 (12.3)	73/1,320 (5.5)	314/1,320 (23.8)	492/1,320 (37.3)	146/1,320 (11.1)	132/1,320 (10.0)	60/1,320 (4.5)
(Fond et al., 2020)	France	Retrospective Cohort	208/823 (25.3)	-	148 /823 (18.0)	63 /823 (7.7)	-	14,903/49,927 (27.8)	-	11,770/49,927 (23.6)	3,128/49,927(6.3)	-
(Jeon et al., 2020)	South Korea	Retrospective Cohort	139 /734 (18.9)	210 /734 (28.6)	15/734 (2.3)	36 /734 (4.9)	4 /734 (0.5)	398 /2,817 (14.1)	704 /2,817 (25.0)	93/2,817 (3.3)	99 /2,817 (3.5)	25/2,817 (0.9)
(Lee et al., 2020a)	South Korea	Retrospective cohort	97/236 (41.2)	-	-	-	143/236 (56.7)	69/236 (29.3)	-	-	-	395/545 (72.5)
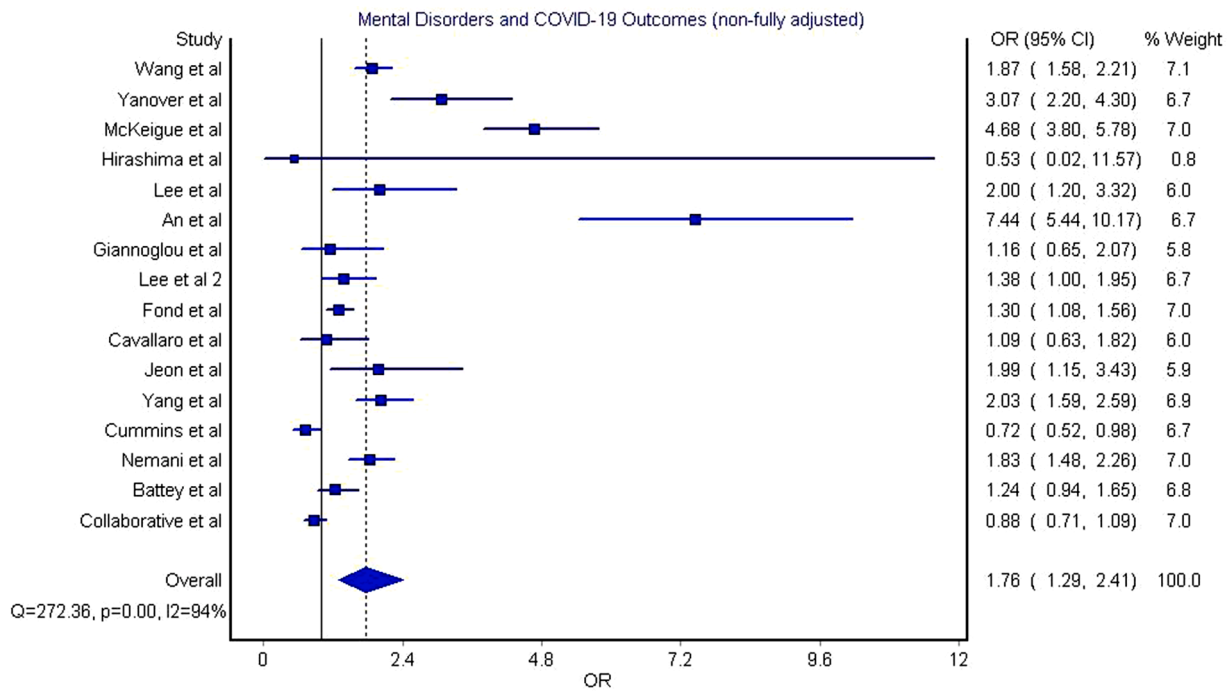
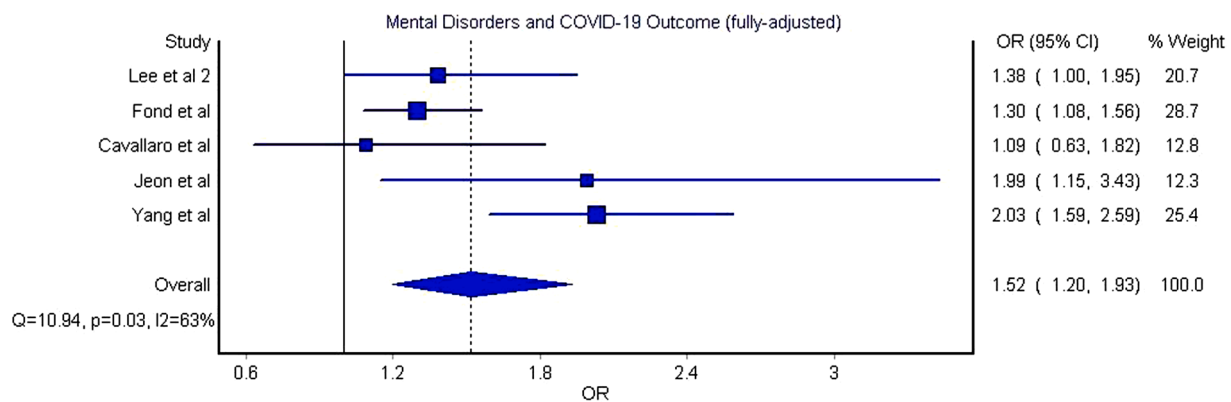**Fig. 2.** Mental Disorders and COVID-19 Outcomes (non-fully adjusted).

Fig. 3. Mental Disorders and COVID-19 Outcomes (fully-adjusted).

Hirashima et al., 2021; Jeon et al., 2020; Lee et al., 2020a; Lee et al., 2020b; McKeigue et al., 2020; Nemani et al., 2021; Wang et al., 2020; Yang et al., 2020; Yanover et al., 2020) This was also suggested in the fully adjusted as patients with mental disorders had 60.3% higher risk (OR=1.52, 95% CI= 1.20-1.93).(Cavallaro et al., 2020; Fond et al., 2020; Jeon et al., 2020; Lee et al., 2020b; Yang et al., 2020)

In the subanalysis of our study, variation of the effects of COVID-19 outcomes has been noticed across the nations. The pooling of the studies that were conducted in the UK (Batty et al., 2021; Cavallaro et al., 2020; Collaborative, 2021; Cummins et al., 2021; Yang et al., 2020) resulted in insignificant association between mental disorders and COVID-19 outcomes (OR=1.12; CI:0.76-1.65; I2=89%; P-value=0.00). While the 2 models which analyzed the studies that were conducted in South Korea (An et al., 2020; Jeon et al., 2020; Lee et al., 2020a; Lee et al., 2020b) and USA (Nemani et al., 2021; Wang et al., 2020) separately showed significant harmful effect of being diagnosed with mental disorders and COVID-19 outcomes (South Korea: OR=2.5; CI:1.02-6.11; I2=95%; P<0.001 and USA: OR=1.85; CI:1.63-2.12; I2=0%; P<0.001).

Among the included studies in the non-fully adjusted model six studies (Batty et al., 2021; Cavallaro et al., 2020; Collaborative, 2021;

Giannoglou et al., 2020; Hirashima et al., 2021; Lee et al., 2020b) showed insignificant effect for mental disorders on COVID-19 outcomes, where one of them showed protective effect (Cummins et al., 2021) and the rest showed harmful effect. The other nine studies included in this model showed a significant harmful effect of mental disorders on COVID-19 mortality and severity.(An et al., 2020; Fond et al., 2020; Jeon et al., 2020; Lee et al., 2020a; McKeigue et al., 2020; Nemani et al., 2021; Wang et al., 2020; Yang et al., 2020; Yanover et al., 2020) On the other hand, all the studies included in the fully-adjusted model showed a negative effect for mental disorders on COVID-19 outcomes.(Cavallaro et al., 2020; Fond et al., 2020; Jeon et al., 2020; Lee et al., 2020b; Yang et al., 2020)

This can be attributed to the fact that these disorders come with abnormal thinking, delusions, or hallucinations which can impair cognition; resulting in not seeking for care or treatment, and difficulty getting health care.(Lee et al., 2020b) They might be less likely to undergo testing for and being diagnosed with coexisting conditions. (Momen et al., 2020) In addition to that, it was found that loneliness and social isolation, which are both common features of psychiatric disorders, can decrease the efficiency of artificial immunization and thus
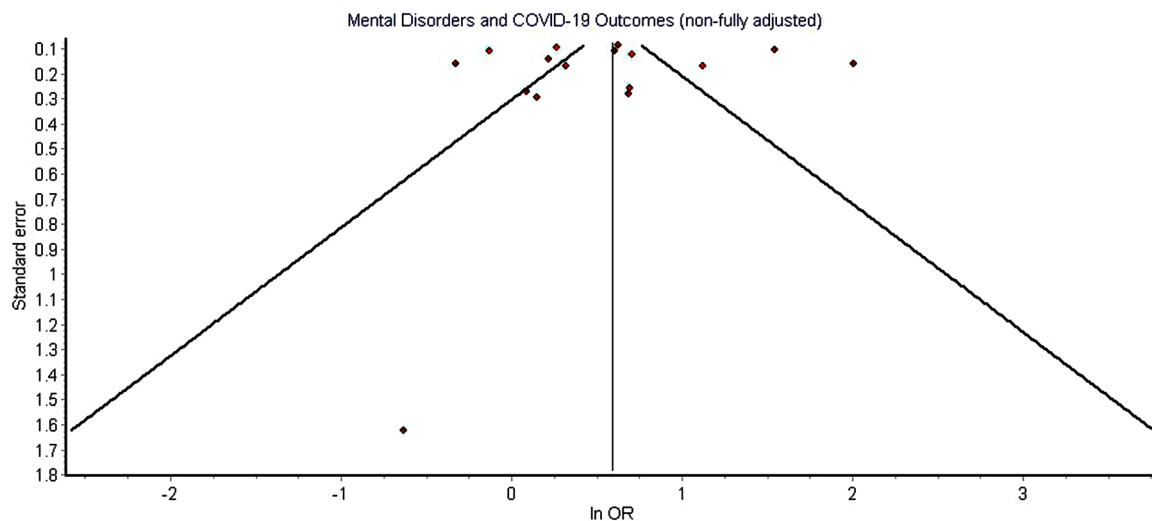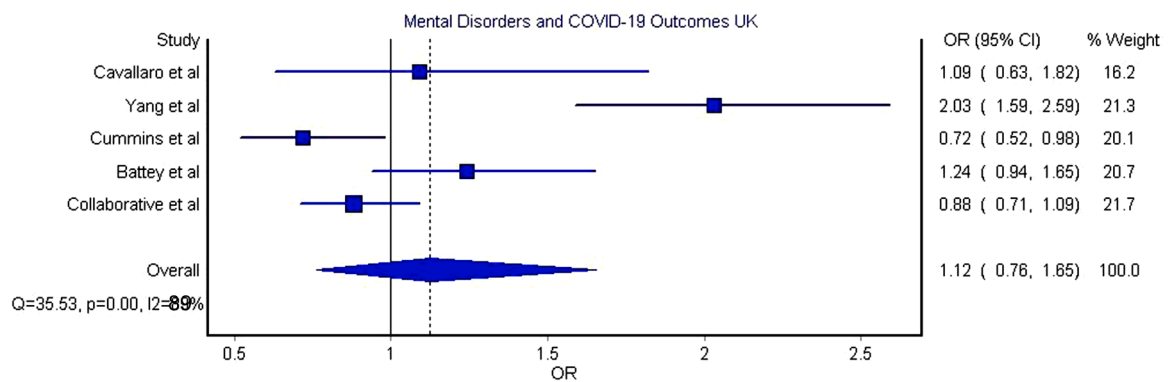
Fig. 4. Publication Bias Funnel Plot.

Fig. 5. Mental Disorders and COVID-19 Outcomes in UK.
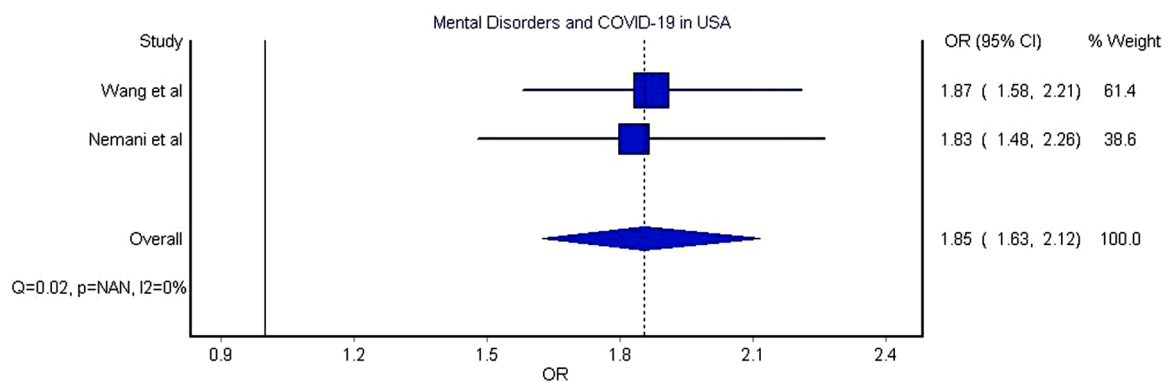

Fig. 6. Mental Disorders and COVID-19 Outcomes in USA.

increase the risk of catching infections.(Pressman et al., 2005) Attention deficit hyperactivity disorder (ADHD), for example, can place its patients in a risk of forgetting their face masks or maintaining social distancing due to their inattention.(Wang et al., 2020) Depression and other types of emotional stress were demonstrated damaging the immune system in a psychoneuroimmunological research.(Wada, 2000) Also, the amotivation among depressed patients might lead them to disregard protection or calling for medical help when needed.(Wang et al., 2020) Furthermore, people with mental disorders are at risk to live in environments where infections can spread easily, as their medical condition may require them to be admitted into crowded hospitals or even prisons, which might be due to the low socioeconomic status in some countries.(Shinn and Viron, 2020) On top of that, there is a possible drug-drug interaction between the treatments used for mental disorders like selective serotonin reuptake inhibitors (SSRIs) and COVID-19 medications, which might decrease the efficacy of the medication or increase the risk of toxicity.(Mohebbi et al., 2020) However, SSRIs showed early promising results in the randomized clinical trials as treatment for COVID-19.(Lenze et al., 2020)

It was reported in a meta-analysis that higher concentrations of pro-
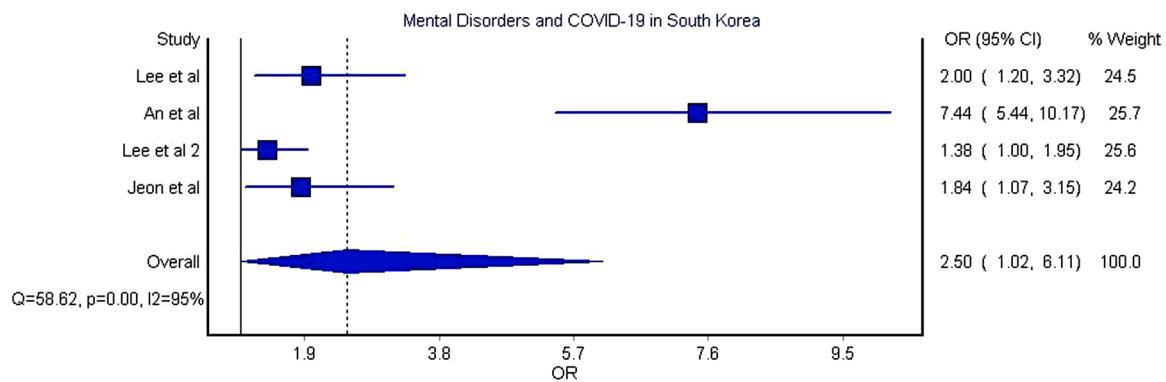
Fig. 7. Mental Disorders and COVID-19 Outcomes in South Korea.

inflammatory cytokines; interleukins-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) were found in depressed patients (Dowlati et al., 2010), which indicates that depression exacerbates inflammatory reaction.(Bauer and Teixeira, 2019a) Significant correlation between infections and mental disorders with odds ratio of 1.72 (OR=1.72) mediated by genetic factors was reported among a random Danish population sample. Moreover, psychological stress increases the susceptibility to life threatening infections,(Song et al., 2019) and upper respiratory infections for specific.(Pedersen et al., 2010)

This study, however, has few notable limitations. First of all, the substantial heterogeneity of 63% in the fully adjusted model (Fig. 3). Also, the considerable heterogeneity of 94% in the non-fully adjusted model (Fig. 2). This heterogeneity means that there is a high variation in study outcomes between the included studies which can be explained by the fact that we only included studies with COVID-19 patients and assessed for pre-diagnosis with mental disorders. Second, data about the types of mental disorders were present in a few of the included studies rendering the ability to create models that assess the COVID-19 outcomes association with different types of mental disorders. This is a very important limitation as different mental illnesses may impact COVID-19 outcomes differently. In addition to, the lack of information about the severity of the mental illness and what medications the patients are on. Both of which are very important variables and may affect the relationship between mental disorders and COVID-19 outcomes. Third, few studies provided data about co-morbidities among COVID-19 patients with mental disorders which limits the ability to investigate the interaction of these variables with COVID-19 outcomes in the presented models. Fourth, although we have created models for 3 nations, we were not able to do a subanalysis for other nations as there was only one study for each country. Moreover, different societies define mental disorders in different ways, suffer from different degrees of stigma and provide different qualities for patients with mental disorders which could impact our results. Finally, due to the asymmetrical funnel plot (Fig. 4), publication bias can not be denied, which might overestimate the effect of mental disorders on COVID-19 outcome.

In conclusion, by providing two models which both reported a significant increase in the risk of COVID-19 severity and mortality among patients with mental disorders, and with the upcoming COVID-19 vaccines, we recommend to give this category the priority in the vaccination campaigns along with medical health providers and elderly, hence, consider them as at-high-risk of infection. As we also encourage healthcare providers and families to be more cautious in protecting patients with mental disorders by assuring mask wearing, continuous hygiene, and safe isolation.

Funding

Data Availability

The Data is Available in Table 1.

Contributors

AAT and RBA was involved in the conception and design of the study; AAT, RBA, HBA, RHA and SSA involved in the data acquisition and analysis of the study; AAT, RBA, HBA, RHA and SSA involved in the interpretation of the data of work; AAT, RBA, HBA and RHA involved in the drafting of the manuscript; SSA involved in revising it critically for important intellectual content; All the authors are involved in the final approval of the version of manuscript to be published.

Conflict of Interest

Declarations of interest: none.

Acknowledgment

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