

Mental health conditions and COVID-19 vaccine outcomes: a scoping review

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Abstract

Background: The COVID-19 pandemic has had a profound impact on the mental health of people worldwide. Mental health also impacts on physical health. In the context of viral illnesses, viral challenge studies have shown that indices of mental health are associated with susceptibility to viral infections, including coronaviruses. Research conducted during the pandemic has shown that people with a history of mental health conditions were at increased risk of infection, hospitalisation, and mortality. However, the relationship between mental health conditions and vaccine outcomes such as vaccine intentions, uptake, and vaccine breakthrough is not yet well-understood.

Methods: We conducted a systematic search on the topics of COVID-19 vaccine intentions, vaccine uptake, and vaccine breakthrough, in relation to mental health conditions, in four databases: PubMed, MEDLINE, SCOPUS, and PsychINFO, as well as the publication lists of Clinical Practice Research Datalink (CPRD), The Health Improvement Network (THIN), OpenSAFELY, and QResearch. Inclusion criteria focus on studies reporting either of the aforementioned COVID-19 vaccine outcomes among people with mental health conditions.

Results: Thirty-three out of 251 publications met our inclusion criteria for this review.

Overall, the evidence is inconclusive regarding the level of intention to accept the COVID-19 vaccine among people with mental health conditions. However, people with mental health conditions were more likely to have lower uptake of the COVID-19 vaccine, compared to people without. Common barriers to COVID-19 vaccine uptake include concerns about the safety, effectiveness, and side effects of the vaccines. Limited evidence also suggests that vaccine breakthrough may be a particular risk for those with substance use disorder.

Conclusions: Our findings revealed a possible intention-behaviour gap for receiving the COVID-19 vaccine among people with mental health conditions, yielding interventions to

encourage vaccine uptake in this population. There is also the need to enhance our understanding of COVID-19 vaccine breakthrough in people with mental health conditions.

Keywords: COVID-19, mental health, vaccination

Introduction

The COVID-19 pandemic resulted in more than 700 million cases and 6 million deaths globally (WHO, n.d.). Vaccines against SARS-CoV-2 were developed to reduce the spread of the virus and morbidity and mortality caused by COVID-19. The UK was the first country to approve a COVID-19 vaccine and started a vaccine roll-out program in December 2020 (Authority of the House of Commons, 2022). By autumn 2022, approximately 151 million vaccinations were given to the UK population (Majeed et al., 2022). However, while the mass vaccination roll-out was necessary in the pandemic, certain factors determine whether vaccines can realise their full potential. Arguably, the two most salient of these are vaccine uptake i.e., an individual's willingness to be vaccinated and vaccine effectiveness i.e., the ability for vaccines to protect against infection and adverse outcomes.

One factor that may influence both vaccine uptake and vaccine effectiveness is mental health. Pre-pandemic the evidence suggested that people with mental illness might be less likely to engage in preventive healthcare such as blood pressure monitoring and vaccinations, compared with people without mental illness (Lord et al., 2010). Evidence during the pandemic seems to show a mixed picture. For example, a study in early 2021 found higher COVID-19 vaccine uptake (i.e., receiving at least one dose) among people with mood disorders (e.g., major depression and bipolar disorder) in certain areas in the UK, but lower COVID-19 vaccine uptake among individuals with psychotic disorders (e.g., schizophrenia), compared with people without mental illness (Hassan et al., 2022). Another study, conducted in the same year, found that the vaccination rate among people with mental health conditions (11%) was lower than the vaccination rate among other residents (40%) in Wuhan area (Huang et al., 2021). Reviews of the literature on vaccine hesitancy appear to confirm that the relationship between vaccine uptake and mental health varies according to the nature of the

mental health problem (Farcas et al., 2022). However, attempts to review and synthesise this evidence have been limited to studies capturing the intention (or not) to be vaccinated, rather than actual uptake.

There is also potential for mental health to influence the effectiveness of COVID-19 vaccines. Mental health can dysregulate the immune system and thus can impair the immune response to vaccination (Cohen, 2021; O'Connor et al., 2021; Vedhara et al., 1999). For example, viral and vaccine challenge studies have shown that depression and stress are associated with poorer antibody responses to vaccinations, as well as increased risk of infection and symptomatic illness (Cohen, 2021; Cohen et al., 1998; Phillips et al., 2006; Vedhara et al., 1999).

Evidence from the pandemic suggests that this relationship between mental health and impaired responses to respiratory infections may also occur in the context of COVID-19. For example, observational data have shown that greater psychological distress was significantly associated with subsequent self-reported SARS-CoV-2 infection, together with an increased number of, and more severe, symptoms (Ayling et al., 2022). Similarly, Yang and colleagues reported that people with previous mental health conditions were more likely to get SARS-CoV-2 infection, be hospitalised, and to die from COVID-19 (Yang et al., 2020). However, no study, to our knowledge, has reviewed current evidence on the association between mental health conditions and COVID-19 vaccine breakthrough (i.e., evidence of SARS-CoV-2 infection after vaccination).

Thus, in summary, there is evidence to suggest that mental health conditions are associated with greater vaccine hesitancy, impaired immune responses to vaccination and greater risk of

respiratory infections. In the context of COVID-19, the emerging evidence suggests that the relationship with vaccine hesitancy may vary between different mental health conditions; the relationship with vaccine uptake is less clear and while poorer COVID-19 outcomes have been associated with mental health conditions, the evidence on the relationship with vaccine effectiveness is limited. In an effort to bring this literature together, we present here results from a scoping review in which we have examined the evidence exploring the relationship between indices of mental health (past and current) and vaccine hesitancy (i.e., behavioural intentions), vaccine uptake (behavioural response) and vaccine effectiveness as measured by vaccine breakthrough i.e., evidence of infection following vaccination. An understanding of this literature will help to inform whether and in what ways people with mental health conditions need to be supported to reduce their risk of COVID-19 infection.

Methods

Population

The population of interest was people with mental health conditions. Consistent with previous work, mental health conditions included depression, anxiety, stress-related disorder, substance misuse, psychotic disorders, schizophrenia, and bipolar disorder (Thompson et al., 2022; Yang et al., 2020). We included studies involving people with a history of mental health difficulties as well as those arising during the pandemic. No restrictions were made for other characteristics, including age, gender, health conditions etc.

Outcomes

The outcomes of interest were intention to accept or decline a COVID-19 vaccination when offered, COVID-19 vaccine uptake, and COVID-19 vaccine breakthrough. A COVID-19 vaccine breakthrough infection is defined according to CDC: “the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person ≥ 14 days after receipt of all recommended doses of an FDA-authorized COVID-19 vaccine” (Birhane et al., 2021).

Search strategy

Searches for relevant studies were conducted in PubMed, MEDLINE, SCOPUS, and PsychINFO. To include potentially eligible population-based studies, the CPRD, The Health Improvement Network (THIN), OpenSAFELY, and QResearch lists of publications were also searched. To include articles that may be under review, the electronic pre-print service MedRxiv was also searched. The search paradigm was based on the following combination: (*mental, major* [MeSH terms]) AND (*COVID-19 vaccine* [MeSH terms]). To ensure our searches were comprehensive, the term *mental* was replaced with psychiatric, schizophrenia, psychotic, bipolar disorder, mood disorder, major depressive disorder, anxiety disorder, personality disorder, eating disorder, alcohol abuse, alcohol misuse, substance abuse, and substance misuse. We limited our searches to publications in English language. We did not limit the searches by time period.

Eligibility criteria

Only observational studies were included. Eligible studies had to report at least one of the following: (1) intentions towards COVID-19 vaccine (i.e., intended willingness to accept or decline a vaccination when offered) among people with mental health conditions, and in comparison with people without mental health conditions where applicable; (2) COVID-19 vaccine uptake rate among people with mental health conditions, and in comparison with people without mental health conditions where applicable; (3) COVID-19 vaccine breakthrough (i.e., evidence of SARS-CoV-2 infection after vaccination) among people with mental health conditions. For mixed-method studies, only the observational part of the study was included. Only articles reporting results from original observational studies were included. Qualitative studies, reviews, protocols, commentary or opinion pieces, editorial letters and posters were excluded.

Barriers to COVID-19 vaccine uptake

We were also interested in the potential predictors to COVID-19 vaccine intention, and vaccine uptake. However, predictors of COVID-19 vaccine intention have been systematically reviewed in previous work (see Farcas et al., 2022; Terry et al., 2022; Q. Wang et al., 2021). Demographic predictors (e.g., age, gender, ethnicity, education, socioeconomic status, etc) of vaccine uptake in general have also been reviewed previously (see Galanis et al., 2021). Therefore, in the current review, where studies reported on psychological barriers to COVID-19 vaccine uptake (e.g., beliefs, trust, etc.), we summarised these findings.

Results

Selection of studies

The database search was conducted on 9th November 2022 and returned 251 initial results. Of these, 197 studies were excluded after title and abstract screening and 21 studies were excluded after full-text screening (Figure 1). The main reasons for exclusion include the article being a comment piece or review of literature or intervention etc. (k=51, 23%); studies not conducted among people with mental health conditions (k=42, 28%), and not investigating the outcomes of interest (k=16, 8%). Therefore, 33 studies were included in this scoping review.

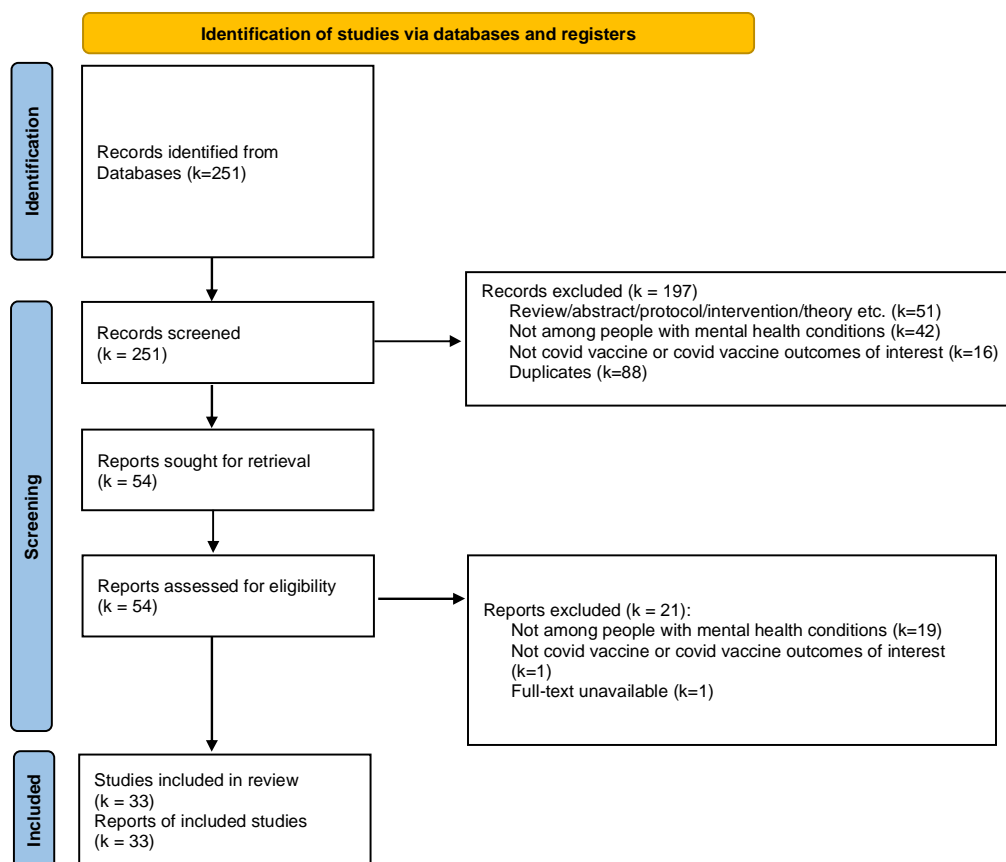


Figure 1 Flow diagram for the scoping review

Overview of study characteristics

The 33 studies included in this review were conducted across 13 countries and regions including North America (e.g., Canada and the United States), Europe (e.g., United Kingdom, Belgium, France, Denmark), Asia (e.g., Mainland China, Japan, India, Taiwan), and the Middle East (e.g., Israel and Qatar). Of the 33 studies, 22 used survey designs including 6 longitudinal survey studies. Ten studies collected data from electronic health or registration records, including one study linking survey and electronic health record data. Two studies

examined vaccine outcomes among patients within psychiatric hospitals through healthcare screening and assessment. Populations investigated by these studies included the general public or population-representative cohorts, and more specific cohorts for instance veterans, psychiatric patients, adolescents with attention-deficit/hyperactivity disorder (ADHD), and youth who are 2-spirit, lesbian, gay, bisexual, transgender, queer, and questioning (2SLGBTQ+) and experiencing homelessness, etc. One study investigated the intentions to vaccinate children with ADHD among their caregivers (Tsai et al., 2022). The sizes of the studies range from 62 to 57.9 million.

Measurement of mental health conditions

Twenty-one of the 33 reviewed studies identified patients with mental health conditions through clinical diagnoses obtained from medical records (Bai et al., 2021; Cai et al., 2022; Curtis, Inglesby, MacKenna, et al., 2022; Curtis, Inglesby, Morton, et al., 2022; Eyllon et al., 2022; Gibbon et al., 2021; Hassan et al., 2022; Jepsen et al., 2021; Mazereel et al., 2021; Moeller et al., 2021; Nilsson et al., 2022; Nishimi, Neylan, et al., 2022; Qin et al., 2022; Raffard et al., 2022; Ren et al., 2021; Shkalim Zemer et al., 2022; Sullivan et al., 2022; Tsai et al., 2022; Tzur Bitan et al., 2022; Uvais, 2022; L. Wang et al., 2022).

The recorded mental health conditions included depressive disorder, bipolar disorder, schizophrenia, ADHD, PTSD, generalized anxiety disorder, and substance use disorder, etc. One study used records of prescription of psychotropic drugs (i.e., anxiolytics, antipsychotics, hypnotics, and antidepressants) as an indication of patients' mental health conditions (Murphy et al., 2022). Six studies asked participants to self-report whether they have been diagnosed with mental health conditions (Afifi et al., 2021; Balut et al., 2021; Dvorsky et al., 2022; Huang et al., 2021; Paul & Fancourt, 2022; Roberts et al., 2022). Five other studies measured self-reported anxiety, depression, substance use, and posttraumatic stress disorder

(PTSD) through surveys such as the Physician Health Questionnaire (PHQ-9, Kroenke et al., 2010), the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7, Spitzer et al., 2006), and the 20-item posttraumatic stress disorder Checklist-5 (PCL-5, Blevins et al., 2015; Abramovich et al., 2022; Khaled et al., 2021; Nguyen et al., 2022; Nishimi et al., 2022; Sekizawa et al., 2022).

Mental health conditions and COVID-19 vaccine intentions

Eighteen of the 33 reviewed studies reported on the association between the presence of mental health conditions and willingness or hesitancy to accept the COVID-19 vaccine or booster vaccine (Abramovich et al., 2022; Afifi et al., 2021; Bai et al., 2021; Cai et al., 2022; Dvorsky et al., 2022; Eyllon et al., 2022; Huang et al., 2021; Jepsen et al., 2021; Khaled et al., 2021; Nguyen et al., 2022; Nishimi, Borsari, et al., 2022; Paul & Fancourt, 2022; Qin et al., 2022; Ren et al., 2021; Roberts et al., 2022; Sekizawa et al., 2022; Sullivan et al., 2022; Tsai et al., 2022). The sizes of the studies range from 92 to 77104 (see Table 1). Participants in these studies were asked to indicate their intentions once the COVID-19 vaccines became available. Seventeen of the 18 studies reported on people with current mental health conditions. In the remaining study, no distinction was made between current and history of mental health conditions (Roberts et al., 2022). Therefore, we do not distinguish between current and history of mental health conditions in the following reporting.

Across the 18 studies, the intended willingness to accept a COVID-19 vaccination was between 44% and 93% among people with mental health conditions.

Differences between people with and without mental health conditions

When compared with people without mental health conditions, the majority of studies (i.e., 12/18) found no differences in vaccine hesitancy between people with and without mental health conditions. Specifically, 5/18 studies reported that people with mental health

conditions were less willing or more hesitant to accept the COVID-19 vaccine. In general, the degree of hesitancy varied significantly between the studies with rates of hesitancy as low as 15.2% through to 53% (Abramovich et al., 2022; Dvorsky et al., 2022; Eyllon et al., 2022; Jepsen et al., 2021; Sekizawa et al., 2022). Three out of the five studies reported that the levels of hesitancy were significantly higher in patients with mental health conditions including major depressive disorder, bipolar disorder, anxiety disorder, ADHD, PTSD, substance use disorder (0.78-2.74 times, Abramovich et al., 2022; 0.65-1.68 times, Eyllon et al., 2022; 4.7%, Jepsen et al., 2021). Only 1/18 studies reported the contrary: individuals with anxiety or depression were 1.13 times (95% CI: 1.08–1.19) more likely to intend to get a vaccine than those without these conditions (Nguyen et al., 2022). Six of the 18 studies found no differences in vaccine hesitancy between people with and without mental health conditions. Specifically, one reported that having depression or anxiety symptoms was not associated with willingness to have a COVID-19 vaccine (Khaled et al., 2021). One reported that having a mental health condition was not associated with uncertainty or unwillingness to accept a COVID-19 booster vaccine (Paul & Fancourt, 2022). One reported that PTSD symptom clusters were not associated with COVID-19 vaccine hesitancy in the investigated cohort (Nishimi, Borsari, et al., 2022). The other three of the nine studies reported similar levels of willingness to accept a COVID-19 vaccine between participants with and without mental health conditions (Afifi et al., 2021; Mazereel et al., 2021; Roberts et al., 2022).

Differences between different mental health conditions

Three of the 18 studies reported findings in relation to patients' different diagnosis and treatment conditions. Bai et al., (2021) did not find any significant difference in vaccine hesitancy across major depressive disorder, bipolar disorder, and schizophrenia. However, they reported that community-dwelling psychiatric patients had a higher incidence of COVID-19 vaccination hesitancy (49%) compared to hospitalised patients (31%). Mazereel

et al., (2021) also reported no effect of different psychiatric diagnosis on vaccine acceptance. Eyllon et al., (2022) reported that, after adjusting for other sociodemographic characteristics and physical comorbidities, patients with substance use disorders had 68% higher odds for vaccine hesitancy while bipolar disorder was associated with 35% lower odds for vaccine hesitancy.

Overall, these findings suggest that most studies fail to find evidence of significantly greater hesitancy in people with mental health conditions, with only five studies reporting greater hesitancy among people with mental health conditions. The evidence on the association between different mental health diagnosis and vaccine intentions is limited and, therefore, not conclusive. The available evidence suggests that patients with substance use disorder might have higher risks of COVID-19 vaccine hesitancy, compared with other mental health conditions.

Mental health conditions and COVID-19 vaccine uptake

Seventeen of the 33 reviewed studies reported on the association between mental health conditions and the uptake of the COVID-19 vaccine or booster vaccine (Table 2, Balut et al., 2021; Curtis, Inglesby, MacKenna, et al., 2022; Curtis, Inglesby, Morton, et al., 2022; Gibbon et al., 2021; Hassan et al., 2022; Huang et al., 2021; Mazereel et al., 2021; Moeller et al., 2021; Murphy et al., 2022; Nguyen et al., 2022; Nilsson et al., 2022; Qin et al., 2022; Raffard et al., 2022; Sekizawa et al., 2022; Shkalim Zemer et al., 2022; Tzur Bitan et al., 2022; Uvais, 2022). Sizes of the studies ranged from N=62 to 57.9 million. Nine of the 17 studies measured COVID-19 vaccine uptake using participants' health or medical records (Balut et al., 2021; Curtis, Inglesby, MacKenna, et al., 2022; Curtis, Inglesby, Morton, et al., 2022; Hassan et al., 2022; Moeller et al., 2021; Murphy et al., 2022; Nilsson et al., 2022; Shkalim Zemer et al., 2022; Tzur Bitan et al., 2022), five of the 17 studies asked participants

to self-report their vaccine status (Huang et al., 2021; Nguyen et al., 2022; Raffard et al., 2022; Sekizawa et al., 2022; Uvais, 2022), and two of the 17 studies recorded the number of patients in hospital accepting the COVID-19 vaccine when offered (Gibbon et al., 2021; Mazereel et al., 2021). One of the 17 studies did not clearly describe how vaccine uptake was measured (Qin et al., 2022). 13 of the 17 studies reported on people with current mental health conditions (Balut et al., 2021; Gibbon et al., 2021; Huang et al., 2021; Mazereel et al., 2021; Moeller et al., 2021; Murphy et al., 2022; Nguyen et al., 2022; Qin et al., 2022; Raffard et al., 2022; Sekizawa et al., 2022; Shkalim Zemer et al., 2022; Tzur Bitan et al., 2022; Uvais, 2022). Four of the 17 studies reported on people with either current or history of mental health conditions, but no distinction was made between current and history of mental health conditions (Curtis, Inglesby, MacKenna, et al., 2022; Curtis, Inglesby, Morton, et al., 2022; Hassan et al., 2022; Nilsson et al., 2022). Therefore, we did not distinguish between current and history of mental health conditions in the following reporting.

In the 17 studies, the reported uptake of COVID-19 vaccines (including boosters) ranged from 2% to 93%, among patients with mental health conditions. One study was conducted early in the pandemic when the COVID-19 vaccines were not widely available (October 2020 – May 2021), thus their reported COVID-19 vaccine uptake rates were low (2-3%, Sekizawa et al., 2022). After excluding this study, other studies reported an uptake of 11-93% among patient with mental health conditions.

Differences between people with and without mental health conditions

Thirteen of the 17 studies compared COVID-19 vaccine uptake among people with mental health conditions with uptake among people without these conditions. Eight of these 13 studies observed that uptake was lower in people with mental health conditions (Curtis, Inglesby, MacKenna, et al., 2022; Curtis, Inglesby, Morton, et al., 2022; Murphy et al., 2022;

Nguyen et al., 2022; Nilsson et al., 2022; Qin et al., 2022; Raffard et al., 2022; Tzur Bitan et al., 2022). The reported vaccine uptake was between 3-21% lower among people with mental health conditions. Five of the 13 studies observed that the vaccine uptake was up to 1.19 times higher among patients with mental health conditions, compared with people without (Balut et al., 2021; Hassan et al., 2022; Mazereel et al., 2021; Moeller et al., 2021; Shkalim Zemer et al., 2022). However, among these five studies, two further reported significantly higher rates of declining the COVID-19 primary or booster vaccines among people with mental health conditions, compared with people without (Hassan et al., 2022; Shkalim Zemer et al., 2022). Two of the 17 studies reported the uptake of booster vaccines. Shkalim Zemer et al., (2022) reported higher uptake of the booster vaccine among adolescents with ADHD aged 16-17 (46%) compared with non-ADHD adolescents of the same age (43%), and similar uptake of the booster vaccine among adolescents with ADHD aged 12-15 and non-ADHD adolescents of the same age (1.2% vs 1.4%). Tzur Bitan et al., (2022) reported significantly lower booster vaccine uptake among patients with schizophrenia (75%) compared with people without (78%).

Differences between different mental health conditions

Two of the 17 studies compared vaccine uptake across different psychiatric diagnoses but reported different observations. One reported that 51% of patients with schizophrenia were vaccinated, which was lower (significance levels unreported) than those with other psychiatric disorders: bipolar disorder, 74%; depression disorder, 74%; anxiety disorder, 66%; obsessive-compulsive disorder, 85%; sleep disorder, 80%; other psychiatric disorders, 65% (Qin et al., 2022). Another study, however, did not find significant effects of psychiatric diagnosis on vaccine uptake (Mazereel et al., 2021).

Barriers to COVID-19 vaccine uptake among people with mental health conditions

We also extracted results on barriers to the COVID-19 vaccine uptake among people with mental health conditions from these studies. Five of the 17 studies reported results on this (Huang et al., 2021; Nguyen et al., 2022; Qin et al., 2022; Raffard et al., 2022; Uvais, 2022). Four of the five studies reported that, among people with mental health conditions, unvaccinated individuals were more likely to report greater concerns about the safety, effectiveness, and side effects of the COVID-19 vaccine than vaccinated people (Huang et al., 2021; Nguyen et al., 2022; Raffard et al., 2022; Uvais, 2022). Lack of trust in the vaccine, development of the vaccine, and the government was reported among unvaccinated people with mental health conditions in two studies (Nguyen et al., 2022; Raffard et al., 2022). One study reported that the vaccination rate was higher among patients who had the intention to be vaccinated (78%), compared with those who were unwilling to be vaccinated (21%) or those who were uncertain about the vaccination (13%, Qin et al., 2022). One study reported that recommendation for vaccination from health care providers was positively associated with vaccine uptake in people with mental health conditions (Uvais, 2022).

Overall, the observed uptake of COVID-19 vaccines among people with mental health conditions varied between studies. The results were mixed, with 8/13 studies reporting lower vaccine uptake in people with mental health conditions and 5/13 studies reporting no differences. Although with limited evidence, patients with schizophrenia might have lower COVID-19 vaccine uptake, compared with people without mental health conditions and people with other mental health conditions. Among people with mental health conditions, the most common barriers to COVID-19 vaccine uptake include concerns about the safety, effectiveness, and side effects of the COVID-19 vaccine.

Mental health conditions and COVID-19 vaccine breakthrough

Only two out of 33 studies reported outcomes related to breakthrough infection following vaccination in people with mental health conditions (Table 3, Nishimi, Neylan, et al., 2022; Wang et al., 2022). Both studies defined a COVID-19 vaccine breakthrough infection as “a positive SARS-CoV-2 test record occurring in the medical records ≥ 14 days after their final SARS-CoV-2 vaccine dose”, in line with the CDC definition (Birhane et al., 2021). Wang et al., (2022) included patients with current substance use disorders, while Nishimi, Neylan, et al., (2022) included patients who had psychiatric disorder diagnoses within the past five years. The observation period was from February 2020 to November 2021 in Nishimi, Neylan, et al., (2022), and from December 2020 to August 2021 in Wang et al. (2022).

Both studies reported that people with mental health conditions were at increased risk of breakthrough infections for COVID-19. Specifically, Nishimi, Neylan, et al., (2022) reported that patients with any psychiatric disorder were 7% more likely to experience a breakthrough infection (95% CI, 1.05-1.09; $P < .001$), compared with patients without psychiatric disorders, after adjusting for potential confounders (e.g., age, ethnicity, vaccine type, time since vaccine, etc.). These patients were still at 3% increased risk of experiencing breakthrough infection (95% CI, 1.01-1.05; $P < .001$), compared with patients without psychiatric disorders, after further adjusting for medical comorbidities (e.g., diabetes, cardiovascular diseases etc.) and smoking status. Nishimi, Neylan, et al., (2022) also reported that when considering specific psychiatric disorder diagnoses (i.e., major depressive disorder, PTSD, anxiety disorder, adjustment disorder, alcohol use disorder, substance use disorder, bipolar disorder, and other psychiatric disorder) the highest relative risk was observed for adjustment disorder (relative risk= 1.13; 95% CI: 1.10-1.16, $P < .001$) and substance use disorders (relative risk=1.16; 95% CI: 1.12-1.21, $P < .001$), after adjusting for

confounders, medical comorbidities, and smoking status and there were no significant increases for psychotic disorder (relative risk=1.05; 95% CI, 0.99-1.11; $P = .09$).

The other study, Wang et al., (2022), reported that among patients with substance use disorders, the risks for breakthrough infections were 7% for tobacco use, 7% for opioid use, 7% for alcohol use, 8% for cocaine use, and 8% for cannabis use, all significantly higher than that in matched cohorts without substance use disorder (2-4%, $P < 0.001$). The modest but higher risks of breakthrough infection among patients with substance use disorder remained significant after controlling for age, gender, ethnicity and vaccine types, for all but tobacco use disorder. However, after controlling for socioeconomic determinants of health (e.g., problems related to education, employment, occupational risk factors, and housing and economic circumstances) and physical comorbidities, the risks for breakthrough infection no longer differed between patient with substance use disorder and matched cohorts for all but cannabis use disorder. Patients with cannabis use disorder remained at increased risk (hazard ratio=1.55, 95% CI: 1.22-1.99) compared with matched cohorts without cannabis use disorder. When looking at severe outcomes of vaccine breakthrough infections (i.e., COVID-19 hospitalisation and death), the risk of hospitalization was 22.5% for patients with substance use disorders who experienced breakthrough infections and 1.6% for patients without breakthrough infections. The risk of death was 1.7% for patients with substance use disorders who experienced breakthrough infections and 0.5% respectively. When looking at the type of vaccines patients with substance use received, the risk for breakthrough infection was higher in patients who received the Pfizer than the Moderna vaccine (hazard ratio=1.49, 95% CI: 1.31-1.69).

Findings from these two studies suggest that patients with mental health conditions, especially those with substance use disorder, might be at a slightly increased risk of experiencing breakthrough infection after being vaccinated against COVID-19.

Discussion

This review highlights the evidence and gaps in research concerning mental health conditions and three COVID-19 vaccine outcomes: vaccine intentions, vaccine uptake, and breakthrough infection. Overall, the evidence was mixed regarding the level of intention to accept the COVID-19 vaccine among individuals with mental health conditions, compared with those without. This finding largely agrees with previous reviews, where a scarcity of evidence of vaccine hesitancy among people with mental health conditions was reported (Kafadar et al., 2022; Payberah et al., 2022). This is possibly due to the levels of vaccine hesitancy or willingness varying across different mental health conditions, which was not considered in previous reviews. In this scoping review, we further differentiated the levels of vaccine hesitancy between different mental health conditions. We found evidence reporting that patients with substance use disorders had higher odds for vaccine hesitancy, while patients with bipolar disorder had lower odds for vaccine hesitancy (Eyllon et al., 2022). Another study included in this review also reported that community-dwelling patients had a higher proportion of COVID-19 vaccination hesitancy compared to hospitalised patients (Bai et al., 2021). Therefore, combining people with different mental health conditions, or combining hospitalised patients and community-dwelling patients together in such investigations might lead to different results. Future research should divide patients into subgroups of different mental health conditions or diagnoses to understand the association between different conditions or diagnoses and vaccine willingness and hesitancy.

Intention versus behaviour

One unique contribution of this review is that we also summarised evidence on the actual uptake of COVID-19 vaccines among people with mental health conditions, and did not rely on data on vaccine intentions. One of the reviewed studies reported results on the intention-behaviour association: the vaccination rate was higher among patients who were willing to be vaccinated compared with those who were unwilling or uncertain about the vaccination. This result implies that vaccine hesitancy (intention) is a valuable target for interventions to address low vaccine uptake. However, although tackling vaccine hesitancy among people with mental health conditions is important, it might not be sufficient to encourage vaccine uptake in this population. According to the Theory of Planned Behaviour (TPB), attitude towards the behaviour, subjective norm, and perceived behavioural control are three determinants of a behavioural intention, which then lead to a behaviour. The behavioural intention is an “immediate antecedent of behaviour” (Ajzen & Manstead, 2007). Therefore, although intention is a key contributor to behaviour, it might not necessarily translate into a certain behaviour directly. A meta-analysis on the efficacy of TPB examined to what extent behavioural intentions predicted actual behaviours (Armitage & Conner, 2001). They reported that, intention accounted for only 25% variance in behaviours, and the correlation between intention and behaviour was 0.47. This intention-behaviour discordance has been reported in previous literature and in other contexts. For example, a meta-analysis focusing on physical activity found that 36% of people who intended to engage in physical activity failed to do so (Rhodes & de Bruijn, 2013). In a more recent study where TPB was used as the theoretical model to explore the associations between intention and the behaviour of receiving Human papillomavirus (HPV) vaccines using TPB, intention accounted only for 9.6% of the variance in behaviour, while moral norm (i.e., the perceived moral correctness of a behaviour) and intention together accounted for 14.1% of the variances in behaviour (Juraskova et al., 2012).

In the context of vaccine hesitancy, it was also pointed out in literature that there might be circumstances where vaccine hesitancy is not the sole or main contributor to low vaccine uptake (MacDonald, 2015). In this review, the evidence on COVID-19 vaccine intentions and uptake among people with mental health conditions also seems to suggest a discordance between the two. Although the reported uptake of the COVID-19 vaccine varied across studies, depending on the timings, settings, and populations under investigation, most of the studies suggested that people with mental health conditions were more likely to decline the vaccine when offered. Especially when looking at studies (k=8 of 17) using electronic health records with large sample sizes (n>4000), the reported rate of COVID-19 vaccine uptake among people with mental health conditions ranged from 47% to 90% (Balut et al., 2021; Curtis, Inglesby, MacKenna, et al., 2022; Curtis, Inglesby, Morton, et al., 2022; Hassan et al., 2022; Murphy et al., 2022; Nilsson et al., 2022; Shkalim Zemer et al., 2022; Tzur Bitan et al., 2022). Five out of these eight studies reported that people with mental health conditions had significantly lower uptake of the COVID-19 vaccine, compared with people without mental health conditions (Curtis, Inglesby, MacKenna, et al., 2022; Curtis, Inglesby, Morton, et al., 2022; Murphy et al., 2022; Nilsson et al., 2022; Shkalim Zemer et al., 2022; Tzur Bitan et al., 2022), while three reported the opposite (Balut et al., 2021; Hassan et al., 2022; Shkalim Zemer et al., 2022). The nature of this intention-behaviour gap, and other barriers (e.g., other systematic-level barriers) that contribute to low vaccine uptake, need further understanding. Interventions targeting at other aspects of vaccine delivery may also be considered, for example, making vaccines available at psychiatric clinics, providing psychiatrists with sufficient information about the vaccines, providing more support for patients with mental health conditions to receive vaccines at GPs, having engagement campaigns and activities

tailoring to people with mental health conditions and their carers, etc (Mazereel et al., 2021; Payberah et al., 2022).

Understanding barriers to vaccine hesitancy and uptake in people with mental health conditions

According to the WHO's "3Cs" model of vaccine hesitancy, confidence, complacency, and convenience are the three main determinants of vaccine hesitancy (Sage Working Group on Vaccine Hesitancy, 2014). The "confidence" element mainly includes trusts in the vaccines (e.g., safety, effectiveness, the delivery system, the government, etc.). The "complacency" element mainly includes the perceived risks of vaccine-preventable diseases. Both the "confidence" and "complacency" elements reflect more on the individual-level barriers. The "convenience", on the other hand, mainly reflects systematic-level barriers around the availability, affordability, and accessibility of the vaccine and vaccine services. Both individual-level barriers and system-level barriers may contribute to the lower vaccine uptake in people with mental health conditions (Warren et al., 2021). We also summarised findings regarding these barriers. Our findings suggest that people with mental health conditions are more likely to experience barriers related to the "confidence" (i.e., concerns about the safety, effectiveness, and side effects of the COVID-19 vaccine) and "convenience" (e.g., whether people with mental health conditions received recommendations from health care providers) of the COVID-19 vaccines. These findings suggest studies and interventions should aim to tackle both the individual-level and system-level barriers, especially targeting vaccine "confidence" and "convenience", to encourage the uptake of vaccines in people with mental health conditions. For example, outreach by mental health care providers may be a strategy to improve COVID-19 vaccine uptake in this population. A pilot trial found that when psychiatric providers were actively engaged in addressing concerns about the COVID-19 vaccine with patients with severe mental illness during outpatient visits, the vaccination rate

among outpatients was higher (84%) than estimated (62.1% - 77.3%; Lim et al., 2022). Other strategies such as identifying leaders in the communities to promote vaccination outreach (Sullivan et al., 2022), transparent communication concerning the safety and effectiveness of the COVID-19 vaccines (Eyllon et al., 2022; Jefsen et al., 2021; Sullivan et al., 2022) may also be helpful. Another observation from this review was that, two of the five studies reporting higher or comparable vaccine uptake in people with mental health conditions were conducted among adolescents or children (Moeller et al., 2021; Shkalim Zemer et al., 2022), while all other studies were conducted in adult populations. It is possible that their caregivers' opinions determined vaccine uptake in this group (Shkalim Zemer et al., 2022). Caregiver-related barriers and facilitators to vaccine uptake should also be considered in future studies investigating vaccine uptake in people, especially children or adolescents, with mental health conditions.

Vaccine breakthrough in people with mental health conditions

Another contribution of this review is the summary on the association between mental health conditions and COVID-19 vaccine breakthrough. Only two published studies were identified and they both suggested that vaccine breakthrough may be a particular risk for those with substance use disorder (Nishimi, Neylan, et al., 2022; L. Wang et al., 2022). Wang et al. (2022) further reported that these patients were also at risk of more adverse outcomes, including hospitalisation and death, following a breakthrough infection, compared with non-breakthrough infections. These results suggest that psychological stressors may influence the susceptibility to COVID-19. However, both studies were conducted in the US. There is no other evidence that can support generalisability of these findings in other countries and populations. In general, findings from both studies echo evidence from prior to the COVID-19 pandemic that both psychological and social factors affect vulnerability to viral infections and also vaccine effectiveness. For example, the series of viral challenge studies by Sheldon

Cohen and colleagues, where they found that individuals with higher levels of psychological stress or experiencing chronic stressors were at significantly increased risk of acute infectious respiratory illness when exposed to respiratory viruses (e.g., rhinovirus type 2, 9, or 14, respiratory syncytial virus, coronavirus type 229E, rhinovirus RV39, Hanks; Cohen et al., 1991, 1998). Other observational and interventional studies have also shown a consistent pattern in which poorer mental health (e.g., exposure to more stressful life events, bereavement, chronic stress) is associated with sub-optimal vaccine responses (Gallagher et al., 2008; Phillips et al., 2006; Vedhara et al., 1999). The evidence together shows that mental health is associated with an increased risk of illness from viral infection, and increased risk of impaired protection following vaccination over time. This again emphasises the need to encourage people with mental health conditions to receive vaccinations to protect them from increased risks of infections and subsequent illnesses. However, there is need to investigate the risks of vaccine breakthrough in people with mental health conditions in other countries or regions, to allow comparison of the impact of different healthcare systems.

Limitations

This scoping review did not assess the quality of the studies or quantitatively assess the relationships between mental health and COVID-19 vaccine outcomes using meta-analysis. For studies concerning COVID-19 vaccine willingness or hesitancy, settings (e.g., in hospital or in community) and populations varied between studies which may limit the generalisability of the findings. In addition, 90% of these studies measured vaccine willingness or hesitancy using different self-reported item(s) where self-report biases may be present (Johnson & Fendrich, 2005). For studies concerning COVID-19 vaccine uptake and breakthrough, studies did not distinguish between people who were experiencing current mental health conditions and who had previous mental health diagnosis. It is unclear whether current or previous mental health conditions would have any impact on vaccine uptake or

breakthrough. Only two studies reported results concerning COVID-19 vaccine breakthrough among people with mental health conditions, suggesting that evidence on this topic is currently limited.

Future directions

Urgent research effort is needed to investigate the risks of COVID-19 vaccine breakthrough and severe COVID-19 outcomes among people with mental health conditions, and associated risk factors. Future studies should also be encouraged to distinguish between the different mental health conditions and also the impact of current or previous mental health conditions on COVID-19 vaccine outcomes. The nature of barriers to vaccine uptake, and the intention-behaviour gap in vaccinations also need further investigation.

Conclusions

This is the first review, to our knowledge, focusing on the three COVID-19 vaccine outcomes (i.e., intention, uptake, and vaccine breakthrough) among people with mental health conditions. We found that the evidence regarding the level of vaccine intentions in this population was inconclusive. However, the majority of evidence seemed to suggest that the level of vaccine uptake among people with mental health conditions was lower than people without. There might be an intention-behaviour gap among people with mental health conditions, in the context of COVID-19 vaccination. Future studies may investigate both the nature of this intention-behaviour gap, and strategies to encourage vaccine uptake in this population. Limited evidence seemed to also suggest that people with mental health conditions may be at increased risk of COVID-19 vaccine breakthrough. Future work may also investigate the scale of this issue, and possible consequences.

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Conflict of interest

None.

Table 1 Summary of studies investigating the association between mental health conditions and COVID-19 vaccine intention

Author	Region	Data source	Population	Size	Mental health measure	Mental health condition	Vaccine intention measure	Results
Abramovich et al. (2022)	Canada	Survey	2SLGBTQ+ youth (average age = 20 years) experiencing homelessness. The majority were White 61% (n = 56); identified their gender identity as transgender or gender diverse (n = 53; ~58%); and their sexual	92	Self-reported survey	Anxiety, depression, substance use	"Do you plan on receiving the COVID-19 vaccine?" (Yes or No/Unsure)	Participants who scored mild/moderate or moderately severe/severe on the PHQ-9 depression scale had less confidence in the COVID-19 vaccine compared to those with minimal depression. Those with moderate/severe anxiety had more confidence in the COVID-19 vaccines compared to those with mild/moderate anxiety.

			orientation as bisexual or pansexual (n = 40; ~ 43%).					Participants who scored in the range of problematic substance use had less confidence in the COVID-19 vaccine compared to those scoring in the nonproblematic substance use range.
Afifi et al. (2021)	Canada	Longitudinal survey	Young people between the age of 14-17 years (male=45%, female=55%).	1000 at baseline (2016-2017), 747 at wave 2 (2019) and 664 in wave 3 (664)	Self-reported current mental health conditions “Do you currently have a long-term health condition that is	Mental health conditions included depression, bipolar disorder, anxiety disorder, obsessive–compulsive disorder, posttraumatic	"If a COVID-19 vaccine was available would you get it?" (Yes/No/Maybe/I don't know)	Having a mental health conditions were not related to willingness to get a COVID-19 vaccine. Among people reporting having current mental health conditions, willingness to get a COVID-19 vaccine were: 67% yes, 9% no, 25%

					<p>expected to last or has lasted 6 months or more and has been diagnosed by a medical doctor or other health care professional?</p> <p>”</p>	<p>stress disorder, attention-deficit/hyperactivity disorder, eating disorder, alcohol problems, drug problems, oppositional defiant disorder, and conduct disorder.</p>		<p>unsure. Among those without current mental health conditions, willingness were 65% yes, 9% no, 26% unsure.</p>
Bai et al. (2021)	Mainland China	Survey	Community-dwelling and hospitalised patients with severe mental illness	1853 (27% male)	Clinical diagnosis according to the International Classification	Major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ)	"Do you intend to be vaccinated against COVID-19 in the future?" (No/Not having vaccination temporarily/Yes)	The proportion of COVID-19 vaccination hesitancy was 45.3%, with 45.3% in major depressive disorder, 43.6% in bipolar

					n of Diseases, Tenth Revision (ICD-10), obtained from medical records			disorder, and 47.4% in schizophrenia subgroups. The proportion of COVID-19 vaccination hesitancy was 49.2% in community-dwelling patients, and 31.3% in hospitalized patients. No significant difference in vaccine hesitancy was found across the three major psychiatric disorders.
Cai et al., (2022)	Mainland China	Survey	Patient with depression	1149 (male=842, female=307)	Clinical diagnosis according to the International Classificatio	Depressive disorder	“Do you intend to be vaccinated against COVID-19 in the future?” (“I would be vaccinated against COVID-19”/ “I would not accept COVID-19 vaccination	A total of 617 depressed patients (53.7%) reported they would accept a future COVID-19 vaccination while 435 patients (37.9%) reported

					n of Diseases, Tenth Revision (ICD-10), obtained from medical records		temporarily”/ “I would refuse to accept a COVID-19 vaccination”)	they would not accept COVID-19 vaccination temporarily, and 97 patients (8.4%) stated they would refuse to accept a COVID-19 vaccination.
Dvorsky et al. (2022)	US	Survey	Adolescents in 11th and 12th grade	196 (male=87, mean age=17.5)	Self-reported clinical diagnosis	Attention-deficit/hyperactivity disorder (ADHD)	"If a vaccine that could prevent COVID-19 were made available to you, would you accept it for yourself?" (No/Maybe/Yes/Already vaccinated)	Only 61.8% of adolescents with ADHD reported vaccine acceptance, compared to 81.3% of adolescents without ADHD. Adolescents with ADHD were significantly less likely to report intent to accept the COVID-19 vaccine, than adolescents

								without ADHD.
Eyllon et al. (2022)	US	Survey and electronic health record	Patients registered at a group medical practice	14365 (male=38%, female=63%)	Clinical diagnosis according to the International Classification of Diseases, Tenth Revision (ICD-10), obtained from medical records	Major depressive disorder, generalized anxiety disorder, other anxiety disorders, posttraumatic stress disorder (PTSD), attention deficit and hyperactivity disorder (ADHD), alcohol use disorder (AUD), and substance use disorder (SUD).	Participants were asked if they had received at least one dose of a COVID-19 vaccine. For those who had not yet received a vaccine, they were asked about their intention to be vaccinated (Yes/Unsure/I don't know/Probably would not/Definitely would not)	Vaccine hesitancy was significantly more prevalent among participants with substance use (29.6%), attention deficit and hyperactivity (23.3%), posttraumatic stress (23.1%), bipolar (18.0%), generalized anxiety (16.5%), major depressive (16.1%), and other anxiety (15.5%) disorders, and tobacco use (18.6%). After adjustment for sociodemographic characteristics and

								physical comorbidities, SUD conferred 68% higher odds for vaccine hesitancy. Bipolar disorder was associated with 35% lower odds for vaccine hesitancy. Nicotine dependence/tobacco use was associated with vaccine hesitancy.
Huang et al. (2021)	Mainland China	Survey	Outpatients and inpatients at a psychiatric speciality hospital	906 (male=39%, female=61%)	Self-reported clinical diagnosis	Psychotic disorders, mood disorders, anxiety disorders, other disorders	"Are you willing to take a COVID-19 vaccine?" (Yes/No/Unsure)	Among 906 participated patients, 526 (58.1%) reported that they were willing to take the vaccine, and 282 (31.1%) were hesitant to take the vaccine (17.1% unwilling and 14.0% unsure).

Jefsen (2021)	Denmark	Longitudinal survey	Randomly selected patients with mental illness from the psychiatric services of the Central Denmark Region and one targeting the general Danish population	Mental illness patients = 992, general Danish population = 2458	Clinical diagnosis obtained from medical records	Not described	"Have you been offered vaccination against coronavirus? (Yes/No/Do not wish to answer). For those answered Yes: "Have you accepted this offer?" (Yes/No/Do not wish to answer). For those answered otherwise: "Will you accept vaccination against coronavirus, once it is offered to you? (Yes/No/Do not wish to answer)	Vaccine willingness was high in both groups, but slightly lower amongst patients with mental illness (84.8%), compared with the general population (89.5%).
Khaled (2021)	Qatar	Survey	Nationally representative sample of the population recruited from the community	1038 (male=67%, female=33%)	Self-reported survey: the Physician Health Questionnaire (PHQ-9)	moderate-to-severe symptoms of depression or anxiety	"I am willing to get coronavirus vaccine if it became available for me" (5-point Likert Scale: 1 = Strongly agree, 2 = Somewhat agree, 3 = Neutral, 4 =	The three vaccine willingness groups (accepting, hesitant, vaccine-resistant) differed significantly on the presence of current

				and the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7)	Some what disagree, 5 = Strongly disagree). Responses were collapsed into three groups: vaccine accepting (strongly agree), vaccine resistant or refusers (strongly disagree) and vaccine hesitant (somewhat agree, neutral, somewhat disagree)	anxiety or depression. In the accepting group, 94% were people without current anxiety or depression, 6% were people with current anxiety or depression. In the vaccine hesitant group, 90% were people without current anxiety or depression, 10% were people with current anxiety or depression. In the vaccine-resistant group, 86% were people without current anxiety or depression, 14% were people with current anxiety or depression.
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Mazereel et al. (2021)	Belgium	Healthcare assessment	Patients at a psychiatric hospital who were offered a COVID vaccine	1151 patients (male=41%, female=59%)	Clinical diagnosis obtained from medical records	Cognitive disorder, psychotic disorder, bipolar disorder, depressive disorder, developmental disorder, anxiety disorder, personality disorder, substance use disorder, eating disorder, adjustment disorder, etc.	Patients' acceptance of the COVID-19 vaccine when offered.	1070 (93%) patients accepted the COVID-19 vaccine they were offered. Logistic regression did not show any effect of diagnosis on vaccination status. This rate was not lower than that in the general population: by July 19, 2021, 88.9% of the adult population in the same area had received their first vaccine dose, and 61.6% were fully vaccinated.
Nguyen et al. (2022)	US	Longitudinal survey	Nationally representative	77104 adults (30% had	Self-reported survey: the	Anxiety and depression	"Have you received a COVID-19 vaccine?" (yes/no) For	Adults with anxiety or depression were more

			sample of the population recruited from the community	anxiety symptoms, 25% had depression symptoms, 35% had symptoms of either disorder)	two-item Patient Health Questionnaire (PHQ-2) and the two-item Generalized Anxiety Disorder (GAD-2) scale		people who answered no, they were asked “Once a vaccine to prevent COVID-19 is available to you, would you...definitely/probably/probably not/or definitely not get a vaccine.”	likely to intend to get a vaccine than those without these conditions.
Nishimi et al. (2022)	US	Longitudinal survey	The sample included community-dwelling US adults with high levels of pre-pandemic trauma	544 (male=21%, female=77%, other=3%)	Self-reported survey: 20-item posttraumatic stress disorder (PTSD)	posttraumatic stress disorder (PTSD)	“Have you received at least one shot of COVID-19 vaccine?” (yes/no) For people who answered no, they were asked “Once a vaccine to prevent COVID-19 is available to you, would	PTSD symptom clusters were not associated with COVID-19 vaccine hesitancy in the full sample. Total PTSD symptoms were also not associated with receiving

			and trauma-related distress based on sample recruitment.		Checklist-5 (PCL-5)		you...definitely/probably/not sure/probably not/or definitely not get a vaccine.”	the COVID-19 vaccine or with hesitancy versus acceptance among unvaccinated individuals (n = 368), or with odds of being unsure versus those who would probably or definitely not getting vaccinated among vaccine-hesitant individuals (n = 148). Increasing PTSD symptom severity from baseline to follow-up was marginally associated with higher odds of COVID-19 vaccine hesitance.
Paul and	UK	Longitudin	Fully vaccinated	22139 adults	Self-reported	Depression,	"How likely do you think you	Having a mental health

Fancourt (2022)		al survey	adults recruited from the community	(weighted: male=49%, female=51%)	mental health diagnosis (yes/no)	anxiety, or other psychiatric diagnosis	are to get a COVID-19 vaccine when one is approved?" (1, very unlikely - 6, very likely) "How likely do you think you are to get a COVID-19 booster vaccine if/when you are offered one?" (1, very unlikely - 6, very likely)	condition was not associated with uncertainty or unwillingness to accept a COVID-19 booster vaccine.
Qin (2022)	Mainland China	Survey	Psychiatric patients who have previously been diagnosed with bipolar disorders, depressive disorders, anxiety disorders, obsessive compulsive disorders, sleep disorders, sleep	1328 patients (male=34%, female=66%)	Clinical diagnosis obtained from medical records	Bipolar disorders, depressive disorders, anxiety disorders, obsessive compulsive disorders, sleep disorders, schizophrenia, and other mental disorders	Not reported	85.5% of patients were willing to be vaccinated.

			disorders, schizophrenia, and other mental disorders					
Ren et al. (2021)	Mainland China	Survey	Psychiatric patients who have previously been diagnosed with schizophrenia, bipolar disorder, major depression disorder, generalized anxiety disorder or other mental disorders.	229 patients and 143 family caregivers	Clinical diagnosis obtained from medical records	Schizophrenia, bipolar disorder, major depression disorder, generalized anxiety disorder or other mental disorders	"Would you like to be vaccinated if COVID-19 vaccines become available?" (Yes/No)	77.7% (n=178) of patients and 100% of the family caregivers said they intended to receive vaccination once the COVID-19 vaccine became available on the market.
Roberts et al. (2022)	US	Survey	Individuals with mental illness or substance use	332 individuals with mental	Self-reported diagnosis of mental	Not described	"How willing would you be to receive a vaccine [specify the stage of vaccine approval]" (1-	Participants with mental illness and no illness responded similarly on

			disorder	illness (male=47%, female=52%) , 328 individuals with no illness (male=64%, female=36%)	illness (yes/no)		7: 1 = “Not at all willing”; 4 = “Somewhat willing”; 7 = “Extremely willing”)	willingness to accept a COVID-19 vaccine.
Sekizawa et al. (2022)	Japan	Longitudinal survey	Community sample	11846 (male=50%, female=50%) participants. 1705 participants reported moderate-to-	Self-reported survey: Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7	Depression, anxiety	"Are you going to receive a vaccine against COVID-19?" (Willing to be vaccinated/Unwilling to be vaccinated/Undecided)	46% of participants with moderate-to-severe depression symptoms at wave 1 were willing to accept a vaccine, 38% were undecided, and 13% were unwilling. 45% of participants with moderate-to-severe

			<p>severe depression symptoms at wave 1, 1751 participants reported at wave 3. 1021 participants reported moderate-to-severe anxiety symptoms at wave 1 and 1057 reported at wave 3.</p>	<p>scale (GAD-7)</p>			<p>depression symptoms at wave 3 were willing to accept a vaccine, 38% were undecided, 14% were undecided. 45% of participants with moderate-to-severe anxiety symptoms at wave 1 were willing to accept a vaccine, 38% were undecided, and 14% were unwilling. 44% of participants with moderate-to-severe anxiety symptoms at wave 3 were willing to accept a vaccine, 37% were undecided, 16% were undecided. After</p>
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								adjusting for other factors, those who were moderate-severely depressed, and severely depressed were more likely to be undecided than those who were not depressed. After adjusting for other factors, those who were mildly depressed at wave 1, moderately depressed at wave 3, and moderate-severely anxious at wave 3 were significantly more likely to be unwilling to be vaccinated.
Sullivan et al. (2022)	US	Survey	People with opioid use	109 (female=56)	Clinical diagnosis	Opioid use disorder (OUD)	Participants were asked to select which best described	32.1% of the participants reported willingness to

			disorder (OUD) enrolled in a methadone maintenance program	(%)	obtained from medical records		their COVID-19 vaccination intentions (Willing/Unwilling/Conditionally willing)	use a safe and partially effective vaccine against COVID-19. 47.7% endorsed willingness to be vaccinated only if safe and highly effective. 20.1% of the participants were unwilling to be vaccinated in either scenario.
Tsai et al. (2022)	Taiwan	Survey	Caregivers of children with Attention-deficit/hyperactivity disorder (ADHD)	252 caregivers (male=21%, female=79%)	Clinical diagnosis obtained from medical records	Attention-deficit/hyperactivity disorder (ADHD)	“When a COVID-19 vaccine becomes available, will you be willing to vaccinate your child?” (Definitely not willing/Not sure/If my doctor recommends it, I would let my children receive it/Definitely willing). “Please rate your current willingness to let your	Regarding caregivers’ intentions to vaccinate their children, 91 (36.1%) caregivers reported the willingness to let their child take vaccine shots against COVID-19, 117 (46.4%) would let their child take

						<p>child receive a COVID-19 vaccine.” (Definitely not willing/Not sure/If my doctor recommends it, I would let my children receive it/Definitely wiling)</p>	<p>vaccine shots under their doctors’ recommendation, 40 (15.9%) felt hesitant about vaccination, and 4 (1.6%) definitely refused to vaccinate their children. The proportion of caregivers who were willing to vaccinate their children definitely or under doctors’ recommendation increased from 62.8% in the first wave of the study to 82.5% in the second wave of the study.</p>
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Table 2 Summary of studies investigating the association between mental health conditions and COVID-19 vaccine uptake

Author	Region	Population	Size	Mental health measure	Vaccine uptake measure	Mental health condition	Barrier to vaccine uptake	Results
Balut et al., (2021)	US	Veterans experiencing homelessness	83528 (male=90%, female=10%)	Self-reported mental health diagnosis (yes/no)	Electronic health records	Alcohol use disorder, drug use disorder, posttraumatic stress disorder, psychotic disorders, depression, anxiety, schizophrenia, or bipolar disorder	NA	Veterans with any mental health conditions (47.2% vs. 38.3%) were more likely to get vaccinated.
Curtis et al., (2022)	UK	All patients registered with a general practice in England	57.9 million	Clinical diagnosis (yes/no), obtained from medical records	Electronic health records	Severe mental illness	NA	Presence of a severe mental health condition was associated with lower vaccination rates (71% vs 85% in those without severe mental health conditions) and more declines (5% vs 3% in those without severe mental health

								conditions) being recorded, and a similar but less divergent pattern was seen in those with a learning disability.
Curtis et al., (2022)	UK	All patients registered with a general practice in England	57.9 million	Clinical diagnosis (yes/no), obtained from medical records	Electronic health records	Severe mental illness	NA	Vaccination coverage was substantially lower among those living with severe mental illness (89.5%).
Gibbon et al., (2021)	UK	In-patients within a medical secure psychiatric hospital	85	Clinical diagnosis obtained from medical records	Survey	Not described	NA	68 (80.0%) consented and 17 (20.0%) declined to consent to the COVID-19 vaccine.
Hassan et al., (2022)	UK	All patients registered with a	1152831 adults with and without severe	Clinical diagnosis obtained from	Electronic health records	Schizophrenia or related psychotic disorders, bipolar disorder, and recurrent	NA	Compared to matched controls, vaccination rates were highest among people with recurrent

		<p>general practice in England</p>	<p>mental illness: exclusive groups of individuals with schizophrenia or related psychotic disorders (N=46,859), bipolar disorder (N=3,461), and recurrent major depressive disorder (N=134,661), and a 10%</p>	<p>medical records</p>		<p>major depressive disorder, and a 10% sample of individuals with diagnoses of other depressive disorders, excluding all previously mentioned diagnoses.</p>		<p>major depression (77.1%), followed by bipolar disorder (75.7%), other depressive disorders (75.1%), and psychotic disorders (69.6%). The prevalence of vaccination among all controls was 68.4%. The proportion of individuals recorded as having declined vaccination by June 30, 2021 among all controls was 2.0%. Rates of having been recorded as declining vaccination were significantly higher across all mental disorders examined, with psychotic disorder diagnoses highest (5.0%), followed by bipolar disorder (3.8%), recurrent major</p>
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			sample of individuals with diagnoses of other depressive disorders, excluding all previously mentioned diagnoses (N=45,586).					depression (2.9%) and other depressive disorders (2.8%).
Huang et al., (2021)	Mainland China	Outpatients and inpatients at a psychiatric speciality hospital	906 (male=39%, female=61%)	Self-reported clinical diagnosis	Survey	Psychotic disorders, mood disorders, anxiety disorders, other disorders	Compared to vaccine-hesitant persons, vaccine-recipients were more likely to have a college-	98 (10.8%) patients had taken the vaccine at the time of this survey,

								level education or above, be married, remarried, or cohabiting, rate their family financial status as “good”, agree that the preventive effect of vaccines is good, believe that at least half of vaccine- recipients would be	
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							immune to COVID-19, believe that vaccines are safe, be not worried about the side effects of vaccines, be outpatients, have mental disorders other than psychotic, mood, and anxiety disorder, and be not depressed	
Mazereel et al.	Belgium	Healthcare assessment	Patients at a psychiatric	1151 patients (male=41%,	Clinical diagnosis	Cognitive disorder, psychotic disorder, bipolar	NA	1070 (93%) patients accepted the COVID-19 vaccine they

(2021)			hospital who were offered a COVID vaccine	female=59%)	obtained from medical records	disorder, depressive disorder, developmental disorder, anxiety disorder, personality disorder, substance use disorder, eating disorder, adjustment disorder, etc.		were offered. Logistic regression did not show any effect of diagnosis on vaccination status. This rate was not lower than that in the general population: by July 19, 2021, 88.9% of the adult population in the same area had received their first vaccine dose, and 61.6% were fully vaccinated.
Moeller et al., (2021)	US	Patients at a academic child and adolescent psychiatric hospital	174 (male=35%, female=66%)	Clinical diagnosis obtained from medical records	Healthcare assessment	Attention-deficit/hyperactivity disorder, adjustment disorder, anxiety disorder or trauma-related disorder, autism spectrum disorder, disruptive mood dysregulation disorder,	NA	29.8% of adolescent inpatients with mental illness screened for the COVID-19 vaccine requested and consented to vaccination. 30.5% of adolescent patients have already received one dose of the vaccine before admission.

						major depressive disorder/suicidal ideations, others		This is comparable to the national average on June 30, 2021, with 30.9% of adolescents aged 12–15 years having at least one dose of the vaccine.
Murphy et al., (2022)	Northern Ireland	Patients registered with the Northern Ireland National Health Authority Information System	1433814 individuals (male=49%, female=51%). 267 049 (19%) individuals had received psychotropic medication in both 3-month periods before the vaccination programme	Prescription of psychotropic drugs obtained from medical records	Electronic health records	Recipients of anxiolytics, antipsychotics, hypnotics, and antidepressant.	NA	After adjusting for sociodemographic, socioeconomic and physical health factors, individuals in receipt of anxiolytics, on antipsychotics and hypnotics were less likely to receive the COVID-19 vaccination. Antidepressant use was not associated with vaccination.

			started, of which 33% had been prescribed antidepressants, 3% had been prescribed hypnotics and anxiolytics, and 2% had been prescribed antipsychotics.					
Nguyen et al., (2022)	US	Nationally representative sample of the population recruited	77104 adults (30% had anxiety symptoms, 25% had depression	Self-reported survey: the two-item Patient Health Questionnaire (PHQ-2) and the	Longitudinal survey	Anxiety and depression	Among those who did not get vaccinated but probably will later, concerns about	A lower proportion of adults with anxiety (39.9%), depression (37.7%), and either disorder (40.2%) received at least 1 dose of the COVID-19 vaccine compared to adults

		from the community	symptoms, 35% had symptoms of either disorder)	two-item Generalized Anxiety Disorder (GAD-2) scale			side effects and uncertainty about whether the vaccine will work were higher among people with anxiety or depressive symptoms than those without any symptoms (56.9% compared to 47.1%, and 19.6% compared to 13.5%,	without any symptoms (52.9%). Adults with anxiety or depression were less likely to receive COVID-19 vaccination than those without these conditions.
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							respectively). Among those who did not get vaccinated and probably will not get vaccinated, both a lack of trust in COVID-19 vaccines and in the government were higher among people with anxiety or depression compared to people without	
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							these disorders. Among people who did not get vaccinated and definitely will not get a vaccine, dislike of vaccines was higher among those with anxiety or depression compared to those without either disorder (24.4% compared to	
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							16.2%, respectively).	
Nilsson et al., (2022)	Denmark	All Danish residents being alive and living in Denmark on Dec 27, 2020 (i.e. first date of vaccination against SARS- CoV-2 infection in Denmark) and aged at least 15	4935344 individuals, accounting for 2560981 person-years under observation for two doses of vaccines against SARS- CoV-2 infection.	Clinical diagnosis obtained from medical records	Electronic health records	Substance abuse, supported psychiatric housing, psychiatric hospital admission, and severe mental illness (schizophrenia, bipolar disorder, or depressive disorder)	NA	The vaccine uptake for people with psychiatric exposures were lower than in the nonexposed individuals. Among the psychiatric groups, highest cumulative vaccine uptake was found for severe mental illness and lowest uptake for substance abuse.

		years on the day of inclusion.						
Qin et al., (2022)	Mainland China	Psychiatric patients who have previously been diagnosed with bipolar disorders, depressive disorders, anxiety disorders, obsessive compulsive disorders,	1328 patients (male=34%, female=66%)	Clinical diagnosis obtained from medical records	Survey	Bipolar disorders, depressive disorders, anxiety disorders, obsessive compulsive disorders, sleep disorders, schizophrenia, and other mental disorders	Only finishing junior middle school was associated with lower vaccination rates compared to graduating from universities. Patients who were willing to be vaccinated were more likely to get inoculated	69.4% of patients had been vaccinated at the time of the survey, which was lower than their family members (89.8%)

		sleep disorders, schizophrenia, and other mental disorders					(77.5%) and patients who were unwilling (20.8%) and uncertain (12.5%) about vaccination were less likely to be inoculated compared to those who were indifferent (43.2%) about vaccines.	
Raffard et al., (2022)	France	Patients with diagnosis	100 patients (female=38%) and 72 family	Clinical diagnosis obtained from	Survey	Schizophrenia	Non-vaccinated individuals	A statistical trend was noted with respect to the proportion of vaccinated participants,

		of schizophrenia	caregivers (female=26%)	medical records			had higher negative attitudes towards vaccine benefit, unforeseen future effects of the vaccine, and commercial profiteering of the vaccine, and had higher preference for natural immunity. Non- vaccinated	showing lower rates of vaccination in patients (64%), compared to controls (77.8% of n=72, p = 0.07, Phi = 0.15).
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							individuals had lower levels of trust in institutions than did the vaccinated participants.	
Sekizawa et al., (2022)	Japan	Community sample	11846 (male=50%, female=50%) participants. 1705 participants reported moderate-to-severe depression symptoms at wave 1, 1751	Self-reported survey: Patient Health Questionnaire-9 (PHQ-9), Generalized Anxiety Disorder-7 scale (GAD-7)	Longitudinal survey	Depression, anxiety	NA	2% of participants with moderate-to-severe depression symptoms at wave 1 were already vaccinated at wave 3, 3% of participants with moderate-to-severe depression symptoms at wave 3 were already vaccinated at wave 3. 3% of participants with moderate-to-severe anxiety symptoms at wave 1 were already vaccinated at wave 3,

			participants reported at wave 3. 1021 participants reported moderate-to-severe anxiety symptoms at wave 1 and 1057 reported at wave 3.					3% of participants with moderate-to-severe anxiety symptoms at wave 3 were already vaccinated at wave 3.
Shkalim Zemer et al., (2022)	Israel	Adolescents diagnosed with attention-deficit/hyperactivity disorder	46511 adolescents aged 12-17 years (n=8241 with ADHD, 18%)	Clinical diagnosis obtained from medical records	Survey	Attention-deficit/hyperactivity disorder (ADHD)	NA	In total, 52.5% of adolescents with ADHD were vaccinated, compared with 47.8% of adolescents without ADHD. 1.2% of adolescents with ADHD aged 12-15 years received the booster dose, which was comparable to 1.4%

		(ADHD)						of adolescents with non-ADHD aged 16-17 years. A total of 45.8% of adolescents with ADHD aged 16-17 years received the booster dose, higher than 42.5% of adolescents with non-ADHD aged 16-17 years.
Tzur Bitan et al., (2022)	Israel	Patients with schizophrenia	4797 individuals (male=60%) with schizophrenia and 34797 matched controls (male=60%)	Clinical diagnosis obtained from medical records	Electronic health records	Schizophrenia	NA	20.7% of individuals with schizophrenia were completely unvaccinated, compared with 14.5% of matched control participants. Once vaccinated, no significant differences were observed in the uptake of the second vaccine. Gaps emerged again with the booster vaccine, with 74.7% of individuals with schizophrenia completing the

								booster, lower than 77.9% in the control group.
Uvais, N.A., (2022)	India	Patients with severe mental illness	62 patients (male=69%, female=31%)	Clinical diagnosis obtained from medical records	Survey	Bipolar affective disorder, schizophrenia, psychosis, obsessive-compulsive disorder, depressive disorder	Respondents in the vaccinated group perceived the vaccine to be more effective in preventing COVID-19 infection than those in the unvaccinated group. Vaccinated respondents were also less in agreement	Only 27.9% of the respondents received the first dose of COVID-19 vaccination, and 59.7% were recommended for vaccination from a healthcare provider.

							with the statement about the risk of COVID-19 vaccine worsening mental illness. Both vaccinated and unvaccinated respondents tended to disagree with the statement about COVID-19 vaccines can cause COVID-19 infection,	
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							COVID-19 vaccines can cause mental illness, or it is harmful to take COVID-19 vaccination while taking medications for mental illness. Apart from age, recommendati on for vaccination from health care providers was significantly	
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							and positively associated with vaccination.	
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Table 3 Summary of studies investigating the association between mental health conditions and COVID-19 vaccine breakthrough

Author	Region	Data source	Population	Size	Mental health measure	Mental health condition	Res:breakthrough
Nishimi et al., (2022)	US	Electronic health records	Patients who accessed Veterans Affairs (VA) health care during the study period, had at least 1 SARS-CoV-2 test recorded in the electronic health record, had no	263697 patients (male=90.8%)	Clinical diagnosis obtained from medical records	Depressive, posttraumatic stress, anxiety, adjustment, alcohol use, substance use, bipolar, psychotic, attention-deficit/hyperactivity, dissociative, and	51.4% of the fully vaccinated patients had at least 1 psychiatric disorder diagnosis, and 14.8% developed a breakthrough infection. A diagnosis of any psychiatric disorder was associated with increased incidence of breakthrough infection, both in models adjusted for potential confounders and additionally adjusted for medical

			record of SARS-CoV-2 infection prior to vaccination, and had completed a full SARSCoV-2 vaccination regimen 14 days or more prior.			eating disorders.	comorbidities and smoking. Most specific psychiatric disorder diagnoses were associated with an increased incidence of breakthrough infection, with the highest relative risk observed for adjustment disorder and substance use disorders.
Wang et al., (2022)	US	Electronic health records	Fully vaccinated patient with substance use disorders (SUD)	579,372 individuals (30,183 with a diagnosis of SUD and 549,189 without such a diagnosis) who were fully vaccinated between	Clinical diagnosis obtained from medical records	Substance use disorder (SUD)	Among SUD patients, the risk for breakthrough infection ranged from 6.8% for tobacco use disorder to 7.8% for cannabis use disorder, all significantly higher than the 3.6% in non-SUD population. Breakthrough infection risk remained significantly higher after controlling for demographics (age, gender, ethnicity) and vaccine types for all SUD subtypes, except for tobacco use disorder, and was

				<p>December 2020 and August 2021, and had not contracted COVID-19 infection prior to vaccination</p>		<p>highest for cocaine and cannabis use disorders. When matching patients with SUD and non-SUD individuals for lifetime comorbidities and adverse socioeconomic determinants of health, the risk for breakthrough infection no longer differed between these populations, except for patients with cannabis use disorder, who remained at increased risk. The risk for breakthrough infection was higher in SUD patients who received the Pfizer than the Moderna vaccine. In the vaccinated SUD population, individuals with breakthrough infections had higher risk for hospitalisation and death, compared to non-breakthrough infections.</p>
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