Neuropsychiatric disorders as risk factors and consequences of COVID-19: A Mendelian randomization study

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Abstract

Background

More than 170 million cases of COVID-19 have been reported worldwide. It has been proposed that psychiatric disorders may be risk factors and/or consequences of COVID-19 infection. However, observational studies could be affected by confounding bias.

Methods

We performed bi-directional two-sample Mendelian randomization (MR) analysis to evaluate causal relationships between liability to COVID-19 (and severe/critical infection) and a wide range of neuropsychiatric disorders or traits. We employed the latest GWAS summary statistics from the COVID-19 Host Genetics Initiative. A variety of MR methods including those accounting for horizontal pleiotropy were used.

Results

Overall we observed evidence that liability to COVID-19 or severe infection may be causally associated with higher risks of post-traumatic stress disorder (PTSD), bipolar disorder (BD) (especially BD II), schizophrenia (SCZ), attention deficit hyperactivity disorder (ADHD) and suicidal thought (ST) when compared to the general population. On the other hand, liability to a few psychiatric traits/disorders, for example ADHD, alcohol and opioid use disorders may be causally associated with higher risks of COVID-19 infection or severe disease. In genetic correlation analysis, cannabis use disorder, ADHD, and anxiety showed significant and positive genetic correlation with critical or hospitalized infection. All the above findings passed multiple testing correction at a false discovery rate (FDR)<0.05. For pneumonia, in general we observed a different pattern of associations, with bi-directional positive associations with depression- and anxiety-related phenotypes.

Conclusions

In summary, this study provides evidence for tentative bi-directional causal associations between liability to COVID-19 (and severe infection) and a number of neuropsychiatric disorders. Further replications and prospective studies are required to verify the findings.

Introduction

The number of confirmed COVID-19 has exceeded 180 million and more than 3.9 million fatalities were reported at 25 Jun 2021. A number of risk factors have been identified for COVID-19 infection and severity of infection, mostly related to age, sex and cardiometabolic disorders or abnormalities (e.g. obesity, diabetes mellitus [DM], chronic renal disease etc.). However, there has been relatively limited evidence on whether psychiatric disorders may affect the risk or severity of COVID-19.

A recent study using electronic health records in US showed that patients with schizophrenia and depression had elevated risks for infection, and as a whole, patients with mental disorders showed higher hospitalization and mortality rates[1]. In another study in Korea[2], history of psychiatric disorders did not significantly affect the infection risk but was associated with a modest increase in the risk of severe disease (adjusted odds ratio (OR) of 1.27). Yet another recent study[3] on mortality reported that schizophrenia spectrum disorders were associated with higher mortality, but not mood or anxiety disorders. The main limitation is that confounding may create spurious associations and render causal inference difficult. For example, psychiatric disorders are frequently associated with (lower) socioeconomic status, mental/physical comorbidities and use of various medications, all of which may also be associated with infection risk or severity.

On the other hand, it is possible that neuropsychiatric disorders may develop as a consequence of the infection. A recent large-scale study[4] by Taquet et al. reported that COVID-19 infection is associated with higher incidence of a psychiatric diagnosis (new or recurrent) 14-90 days after a COVID-19 diagnosis. Conversely, history of psychiatric disorder within one year was associated with approximately 65% increased risk of COVID-19. Also, a study from China[5] revealed that numerous symptoms may persist after discharge; the most common symptoms included fatigue/muscle weakness, sleep problems and anxiety or depressive symptoms. Of note, neuropsychiatric sequelae are considered an important component of the 'long-COVID' syndrome[6], although studies on such consequences are still limited. Again a major limitation of these studies is that many factors may influence both the risk of infection and psychiatric disorders, leading to confounding. Also for some patients, it is possible that the psychiatric disorder remain undiagnosed until after more detailed follow-up post-infection, as a result reverse causality may also explain the association.

Here we employed Mendelian randomization (MR) to evaluate causal relationships between neuropsychiatric disorders and COVID-19 infection, including hospitalized and critical cases as subtypes. MR is much less prone to confounding and reverse causality when compared to observational studies. In addition, some of the psychiatric disorders may have relatively low incidence (e.g. schizophrenia) and may remain undetected with modest sample sizes and limited duration of follow-up. On the other hand, MR only requires summary statistics from genome-wide association studies (GWAS), which were usually of very large sample sizes (often >100,000). This could improve the statistical power to detect causal relationships of COVID-19 with neuropsychiatric disorders. Of note, prior to the outbreak of COVID-19, several studies have suggested

suiciinclude pneumonia as an exposure and outcome in this study, as pneumonia itself is also a major public health burden and the comparison with COVID-19 will be of interest.

Methods

GWAS data

COVID-19 data

We extracted GWAS summary statistics from the COVID-19 Host Genetics Initiative, release 5 (updated Jan 18 2021). Please also refer to ref[10], ref[11], and https://docs.google.com/document/d/16ethjgi4MzlQeO0KAW_yDYyUHdB9kKbtfuGW4XYVKQg/edit for details on samples and analytic methodologies.

We focused on three sets of GWAS results, including very severe/critically ill, hospitalized, and (any) COVID-19 cases compared against unscreened population controls (denoted as A2, B2, C2 respectively). Detailed definitions of these outcomes are given at https://docs.google.com/document/d/1okamrqYmJfa35ClLvCt_vEe4PkvrTwggHq7T3jbeyCI/edit. Very severe or critically ill cases are defined as hospitalized and laboratory-confirmed cases who required respiratory support or whose mortality was related to the infection. These three datasets were chosen mainly because the sample sizes were among the largest (A2: 5870 cases/1,155,203 controls; B2, 11,829 cases/1,725,210 controls; C2: 42,557 cases/1,424,707 controls). We selected the sets of GWAS summary statistics that did not contain the UK Biobank (UKBB) sample, to minimize the chance of sample overlap with GWAS of neuropsychiatric disorders.

Pneumonia

For pneumonia, we conducted a meta-analysis on the GWAS results from the UKBB (phecode 480) and Finngen (under the code J10_pneumonia). The combined results from meta-analysis were used as input for further MR analysis.

Neuropsychiatric disorders

The list of neuropsychiatric disorders or traits under study is presented in Table 1. For details, please refer to the references therein. In brief, we included a wide range of psychiatric disorders or traits which includes schizophrenia (SCZ), bipolar disorder (BPD) (including bipolar disorder I, II and combined), major depressive disorder (MDD) [including ordinary MDD[12], severe MDD requiring electroconvulsive therapy and melancholic depression from MDD-CONVERGE], other depression-related phenotypes (general depressive symptoms, number of depressive episodes, suicidal thoughts [ST], self-harm, suicide attempts[SA], insomnia), psychotic experience (PE), anxiety disorders (based on meta-analysis of PGC and UKBB samples conducted by us), general anxious symptoms (UKBB data field 1980), neuroticism (two studies), anorexia nervosa (AN), obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), attention deficit hyperactivity

disorder (ADHD) and substance-related disorders (alcohol dependence[ALD], cannabis use disorder[CUD], and opioid dependence[OD]). For OD, for comprehensiveness, we included several comparisons including OD vs subjects exposed or unexposed to opioids, and comparison of exposed vs unexposed individuals. We also included several neurological disorders including Alzheimer's disease, Lewy Body dementia and Parkinson's disease.

The majority of the samples are European in ancestry, but we also included meta-analysis of trans-ethnic samples for larger sample sizes. All GWAS summary statistics were corrected for population stratification.

Mendelian randomization analysis

Here we performed two-sample MR, in which the instrument-exposure and instrument-outcome associations were estimated in different samples.

We conducted MR with several different MR approaches, including (1) inverse-variance weighted (MR-IVW)[13] method; (2) Egger regression (MR-Egger)[14]; (3) weighted median (WM)[15]; (4) GSMR[16]; and (5) MR-RAPS[17]. We employed the "TwoSampleMR" R package for methods (1) to (3) and the GSMR R package for method (4). For method (5), the "mr-raps" package was used with default settings, allowing for overdispersion and shrinkage estimates. Briefly, MR-IVW is a widely used and standard approach for MR, based on meta-analysis of single-SNP MR results. The MR-Egger approach allows for imbalanced horizontal pleiotropy, and all the instruments can be invalid. The statistical power is however weaker. The weighted median method employed a median estimate which allows at most half of the instruments to be invalid. GSMR employed an 'outlier-removal' principle to exclude SNPs that are likely invalid instruments, and is similar to MR-IVW in principle with slight differences. The MR-RAPs method employed another approach that considers the measurement error in SNP-exposure effects and has been shown to be unbiased in the presence of many weak instruments. MR-RAPS allows both systematic and idiosyncratic pleiotropy.

Each of the above methods is based on different assumptions, and the statistical power also differs. However, it is hard to evaluate a priori which MR approach is the most optimal for a certain analysis. Hence we performed analyses with multiple methods; results supported by multiple MR approaches are considered to be relatively more robust. The false discovery rate (FDR) approach was used to correct for multiple testing.

One of the major concerns of MR is (imbalanced) horizontal pleiotropy, in which the genetic instruments have effects on the target phenotype through pathways not passing through the exposure. Except MR-IVW, the other four methods can account for such pleiotropy, given that corresponding assumptions are satisfied.

Inclusion of a larger number of SNPs as instruments

We note that the number of SNP instruments passing genome-wide significance (p<5e-8) is generally small (particularly for COVID-19 as exposure), which may limit the power to detect possible causal relationships. One approach is to increase the number of instruments by relaxing the p-value threshold. This will lead to

weak instrument bias, but the direction is towards the null for two-sample MR (i.e. conservative bias). A previous simulation study[18] showed that that type I error control (for null effect) is maintained for very weak instruments[18]. Another study[19] showed that type I error is controlled at the nominal rate when MR is conducted with up to ~900 SNPs which fell short of genome-wide significance. We have also conducted extensive simulations earlier[20] and have showed that relaxation of the p-value threshold (pthres) up to 0.01 does not lead to increased rate of false positive findings. Based on the above studies and recent advances, here we also considered more liberal pthres for instrument inclusion to improve power. To avoid the arbitrariness of setting particular thresholds, we considered a range of thresholds (p=5e-8, 1e-7, 1e-6, 1e-5, 1e-4, 1e-3, 1e-2) and corrected for multiple comparisons by FDR.

The other approach is to include SNPs in LD (correlated SNPs) [21] for MR analysis. The methodology to account for LD has been developed [21]. However, if the SNPs are too highly correlated, the resulting estimates may be unstable[21]. Simulation studies[21] showed that type I error was controlled at correct levels, for up to ~320 correlated SNPs (correlation ~0.4-0.6). To avoid unstable estimates, based on the above findings, we set an r^2 threshold of 0.2 and a threshold for number of SNPs at 350, for analysis involving correlated SNPs. Since there is no consensus for a particular r^2 cut-off for optimal results, we performed MR analysis with correlated SNPs at four levels of r^2 (0.05, 0.1, 0.15 and 0.2) and assessed the consistency of results. Multiple testing was accounted for by FDR[21]. The R packages "MendelianRandomization" and "gmsr" were used for MR-IVW and GSMR of correlated SNPs respectively.

Interpretation of MR causal estimate for binary exposure

For exposures that are binary, the MR estimate is equal to the change in the outcome per log-odds change of the exposure. The causal estimate reflects the change of outcome for every 2.72-fold increase in the odds of the exposure. For uncommon outcomes, the MR estimate is approximately equal to 2.72-fold increase in the probability of exposure, e.g. a change of disease/infection risk from 1% to 2.72%. [22].

Steiger test of directionality

In brief, this test examines whether the instrument SNPs explain more variance for exposure than for the outcome [23]. This serves to further confirm whether the causal direction is correct. The test is applicable to independent SNPs. We employed the mr_steiger function in "TwoSampleMR" for this test. We would primarily focus on results whose causal direction was indicated as "TRUE" by the function.

Multiple testing control by FDR

Multiple testing was controlled by the FDR approach, which controls the expected *proportion* of false positives among the rejected hypotheses.

In this study we set a FDR threshold of 0.05 to declare significance. Results with FDR<0.1 but >0.05 are considered 'suggestive' associations. FDR calculation was stratified by each psychiatric trait, which also enables average FDR (averaged across all subgroups) to be controlled[24].

Genetic correlation analysis

Genetic correlation analysis was performed using LD score regression [25] following default settings. The method evaluates genetic overlap between pairs of disorders using the entire GWAS panel of SNPs, although it is not designed for inferring causality.

Results

We will mainly present results that survive multiple testing correction at FDR<0.05 (considered as 'significant' associations in this study). Results are presented in Tables 2-9. Results of suggestive associations (0.05<FDR<0.1) are shown in Tables S1-S8 and Figures 1-2.

If significant results are observed across multiple p-value thresholds and/or r^2 thresholds, we would present findings corresponding to the smallest p-value threshold and lowest r^2 in the main tables. For space limits, we mainly present MR-IVW results as it is one of the most widely used approaches; full results can be found in main and supplementary tables.

MR with liability to COVID-19 as exposure and neuropsychiatric disorders (psyD) as outcome

Independent SNPs (r^2=0.001) as instruments

In the analysis with independent SNPs (r^2=0.001) as exposure, liability to COVID-19 and hospitalized/critical infection was found to be causally and positively associated with several psyD. At an FDR threshold of 0.05, most significant associations were observed when A2 (critical disease) or B2 (hospitalized cases) were considered as the exposure.

All the associations were in the positive direction (COVID-19 increasing the risks of psyD). The most consistent associations were observed for ADHD and Bipolar Disorder II (associations observed across multiple MR methods and pthres), but we also observed associations with other psychiatric traits/disorders including SCZ, PTSD and suicidal thoughts (ST). Associations with the above traits were more consistent at an FDR threshold of 0.1 (Table S1).

For ADHD, significant associations were observed across all MR methods and multiple pthres. With critical illness (A2) as exposure, the OR was 1.021 per log-odds increase in the liability to critical infection (roughly equivalent to every 2.72-fold increase in the exposure risk; same below) (MR-IVW, CI: 1.008-1.034; pthres=1e-3). The effect size estimates from other methods were similar but were generally attenuated with larger number of SNPs included. This may be due to weak instruments bias that bias towards the null. This may also be due to 'winner's curse'[26] that overestimates SNP-exposure effects, which in turn biases the MR estimate towards zero. We also observed that liability to hospitalized infection (B2) was associated with ADHD (MR-IVW, OR=1.052, CI: 1.022-1.083; pthres=1e-4).

As for bipolar disorder (BD), we observed primarily that liability to hospitalized infection (B2) was associated with bipolar II disorder (BD-II). The causal effect estimate by MR-IVW was 1.041 (CI:1.013 -1.070, pthres=1e-3). The associations were observed across multiple methods (MR-IVW, MR-Egger, Egger with SIMEX correction, MR-RAPS) and pthres. For SCZ, we observed associations when critical or hospitalized infection were treated as the exposure (analysis A2: MR-IVW, OR=1.049, CI 1.019-1.080, pthres=1e-6; analysis B2, MR-IVW, OR=1.019, CI 1.008-1.030, pthres=1e-2). We also observed evidence that liability to critical COVID-19 was casually associated with PTSD (MR-IVW: OR=1.020, CI 1.009-1.031, pthres=1e-3). We also observed associations of A2 and B2 with suicidal thoughts (ST) by GSMR and SIMEX. Besides, we observed that (genetically predicted) hospitalized infection (B2) and infection in general (C2) may be associated with opioid dependence (Table S1), yet the results did not pass Steiger test of directionality. This indicates the direction of causality may not be reliably inferred, however the significant results still implied genetic overlap between the exposure and outcome.

The results with FDR<0.1 are shown in Table S1. In general similar psychiatric traits were implicated, but more consistent associations were observed (especially with PTSD and ADHD). In addition, bipolar disorder (overall) also showed significant associations.

Correlated SNPs as instruments

With correlated SNPs as instruments, as expected, the power to detect associations is generally higher. We shall focus on the results that are significant (with FDR<0.05) across at least two p-value thresholds or two r2-clumping thresholds, for higher robustness. Most of the psychiatric traits/disorders implicated in independent-SNP analysis also showed significant associations with correlated instruments, including BD II, SCZ, PTSD and ST. For BD, we also observed several significant associations with overall BD (Analysis B2: MR-IVW, OR=1.043, CI 1.023-1.063, pthres=1e-4, r2=0.05). Besides, it was observed that liability to critical and hospitalized disease were causally associated with suicidal thoughts across multiple r^2 thresholds, using MR-Egger (analysis A2, OR=1.034, CI 1.010-1.059, pthres=1e-7, r2=0.15; analysis B2, OR 1.054, CI 1.016-1.094, pthres=1e-7, r2=0.05).

We also observed associations with several other neuropsychiatric disorders not found in independent-SNP analysis. For example, significant associations with OCD and anxiety disorders were detected by MR-Egger; however, we did not observe significant (FDR<0.05) associations using other MR methods. Since we conservatively restrict the number of SNPs to <350 and pthres<=1e-4 to avoid unstable causal estimates, some of the associations in independent-SNP analysis may not be observed in the correlated-SNP analysis.

At a more relaxed FDR threshold of 0.1, we observed several more psychiatric traits being associated with COVID-19 phenotypes (Table S2). Such traits/disorders included BD (overall), BD I, SCZ, ADHD and PTSD, among others. For instance, it was observed that liability to critical and hospitalized COVID-19 infection were causally associated with ADHD (Analysis A2: GSMR, OR=1.024, CI: 1.007-1.042, pthres=1e-4, r2 =0.05;

Analysis B2: GSMR, OR=1.030, CI:1.006-1.056; pthres=1e-4, r2=0.05). COVID-19 Infection in general (C2) was also associated with Alzheimer disease (AD) at FDR<0.1 (MR-IVW, OR=1.039, CI: 1.014-1.065, pthres=5e-8, r2=0.05).

COVID-19 severity and effects on psychiatric disorders

Overall speaking, most significant causal associations were observed when critical or hospitalized infection was considered as the exposure, suggesting that in general neuropsychiatric sequelae are more likely to be caused by severe rather than mild infections. Only a few phenotypes showed relatively consistent association with C2 (infection in general), such as ADHD and PTSD.

MR analysis with COVID-19 as outcome and liability to neuropsychiatric disorders as exposure

Independent SNPs (r^2=0.001) as instruments

We observed a smaller number of significant results compared to the case when psychiatric disorders were considered as the outcome. At an FDR threshold of 0.05, liability to ALD, OD and suicide were associated with increased risks or severity of COVID-19 (Table 4). Neuroticism was negatively associated with the disease across all three phenotypes, however they did not pass the Steiger test of directionality, implying that there is genetic overlap but the direction of causality cannot be reliably inferred from the data. At FDR<0.1 (Table S3), similar results were observed but we also found PTSD to be associated with increased risk of C2 (any infection).

Correlated SNPs as instruments

We observed more associations with correlated SNPs as instruments, presumably due to better power with larger number of instruments (Table 5). Again we focus on significant (FDR<0.05) exposure-outcome associations across at least two p-value thresholds or two r2-clumping thresholds. Liability to ADHD was causally associated with higher risks of hospitalized or critical infection compared to the general population (analysis A2, MR-IVW; OR=1.112, CI: 1.046-1.182, pthres=1e-4, r2=0.1; analysis B2, MR-Egger; OR=1.136, CI:1.069-1.206, pthres=1e-4, r2=0.05). There was also suggestive evidence (FDR<0.1) that liability to ADHD was associated with higher risks of being test-positive. As for other psychiatric disorders, ALD showed positive association with A2 using MR-Egger (OR=1.209, CI: 1.055-1.386, pthres=1e-4, r2=0.05); association was also observed with C2. Similar to findings from independent SNPs, liability to PTSD was associated with being infected (C2). Several psychiatric traits showed inverse associations with infection phenotypes. Anxious feeling (UKBB data field 1980) and neuroticism were both associated with lower risks of infection or severe illness compared to the population, and the associations were consistent across different methods and p-value thresholds. We also observed that AD was associated with lower risks of critical infection (A2). At FDR<0.1 (Table S4), the results were similar, except that we also observed that MDD was associated with higher risks of infection or severe infection.

MR analysis with liability to pneumonia as exposure and neuropsychiatric disorders as outcome

Full results for MR analysis with pneumonia can be found in Tables 6 and 7. Based on our MR analysis, we observed different patterns of neuropsychiatric complications of pneumonia, when compared to COVID-19. Figure 1 shows the pattern of significant causal associations in a 'heatmap'. Interestingly, there is little overlap between COVID-19 and pneumonia in terms of causal associations with neuropsychiatric complications. Overall, liability to pneumonia was casually associated with increased risks/levels of depressive symptoms, MDD, neuroticism, insomnia (at FDR<0.1), anxiety disorders and cannabis use disorder (CUD) (Table S5-S6).

MR analysis with liability neuropsychiatric disorders as exposure and pneumonia as outcome

Full results for MR analysis with liability to pneumonia as outcome are given in Tables 8 and 9. With independent SNPs as instruments, we observed that the liability to multiple PsyD were casually associated with higher risks of pneumonia across multiple pthres and r2-clumping thresholds. The associated disorders included for example ADHD (OR=1.115, MR-IVW, CI: 1.032-1.205, pthres=5e-8), CUD (OR=1.268, MR-IVW, CI:1.077-1.493, pthres=5e-8), depressive symptoms (beta=0.443, SE=0.143, pthres=1e-6), MDD (OR=1.140, MR-IVW, CI:1.022-1.271, pthres=1e-7) and anxiety disorders (OR=1.047, CI:1.014-1.080, pthres=1e-4). In addition, insomnia and neuroticism were also associated with elevated risk of pneumonia. On the other hand, BD I showed an inverse association with the risk of pneumonia. The above findings were largely consistent using SNPs in LD as instruments (Table 9). Figure 2 showed that the psyD leading to increased risks of pneumonia and COVID-19 were in general different without substantial overlap.

Genetic correlation (rg) by LD score regression

For genetic correlation analysis, most associations with COVID-19 did not pass multiple testing correction by FDR. Hospitalized COVID-19 infection showed significant rg with CUD (rg=0.340, FDR=2.82e-3), ADHD (rg=0.213, FDR=2.64e-2), and anxiety disorders (rg=0.362, FDR=2.64e-2) at FDR<0.05 (Table 10). Other traits showing at least nominal associations (i.e. p<0.05) with critical/hospitalized illness included psychotic experience (B2, rg=0.543), MDD (A2/B2, rg=0.106 and 0.130 respectively), insomnia (B2, rg=0.126), ADHD (A2, rg=0.146) and BD II (A2, rg = 0.191). Of note, all nominally significant results were related to critical/hospitalized infection (A2 or B2) only. For pneumonia, a large variety of psychiatric traits were found to have significant genetic correlations (Table 10), mostly positive (except OCD). For example, highly significant rg (FDR <1e-4) were observed for MDD, ADHD, insomnia, CUD, anxiety disorders and depressive symptoms.

Discussion

Overview

Overall speaking, we observed potential bi-directional causal associations between neuropsychiatric disorders and COVID-19 (including severe illness). We observed that liability to COVID-19 (especially critical or severe illness requiring hospitalization) may be causally linked to ADHD, BD (especially BD II), PTSD, SCZ and ST. Conversely, liability to a few psychiatric traits/disorders, for example ADHD, ALD, OD, PTSD and SA may be causally associated with higher risks of COVID-19 infection or severe disease. Interestingly, the patterns of causal associations with psychiatric traits appeared to be different when we compared COVID-19 to pneumonia.

Neuropsychiatric disorders as sequelae to COVID-19 infection

The current MR study provides support that COVID-19 may be casually linked to a number of neuropsychiatric sequelae. A few studies have attempted to examine neuropsychiatric consequences of COVID-19 to date, which will be highlighted below.

One of the largest observational studies was performed by Taquet et al.[4], who observed increased risks of mood disorders, anxiety disorders, insomnia and dementia as first psychiatric diagnoses within 3 months after the infection in a retrospective cohort. Psychotic disorders were also observed to be of higher incidence after infection if both new and recurrent diagnoses were counted. Based on further details provided in supplementary information (Table S8)[4], compared to influenza, the risks of bipolar disorder, depressive episode and PTSD all appeared to be increased in COVID-19 patients, with the latter two being statistically significant. A very recent further analysis[29] with a larger sample (*N*=236379) and longer (6-month) follow-up showed similar findings. Dementia, mood, anxiety, psychotic and substance use disorders were all significantly associated with COVID-19 infection compared to influenza or other respiratory tract infections, and the effects were generally larger for more severe cases.

These findings were largely consistent with our current MR analyses. Our results using MR suggests that the associations with some of the above psychiatric traits/disorders may be causal, and may not be fully explained by confounding factors alone. As stated by the authors, the previous study[4] was limited by possibility of (residual) confounding factors; in addition, socioeconomic factors, which is known to be associated with both infection risk/severity[30-34] and some other psychiatric disorders, were not modelled. It is also possible that some disorders (e.g. dementia) was undiagnosed but were detected during follow-up after the infection as a result of detailed assessments and monitoring for mental health problems, hence the disorder may not be a consequence of infection. Another related possible bias is that COVID-19 patients may have received more attention and follow-ups for mental health issues compared to flu or other RTI patients. The MR approach substantially reduces the risk of confounding (e.g. by socioeconomic status) or uncertainty about temporal sequence of events, and avoids possible bias of differential assessment after COVID-19 vs other comparison diseases.

With respect to specific disorders implicated in our MR study, we observed relatively consistent evidence of causal links with PTSD (especially at FDR<0.1). Several studies have reported on increased incidence of PTSD after COVID-19 infection. For example, it was reported that up to ~30% of patients developed PTSD after an acute infection[35, 36]. Other studies have also looked into the risk factors and clinical correlates of PTSD[37], showing that more severe disease may be associated with higher risks of PTSD.

BD (especially BD II) and SCZ were also implicated in our analysis as possible sequelae of infection. Tanquet et al.[4] reported that the incidence of both psychotic and mood disorders were significantly higher than influenza and other RTI from a US population, although data specifically on BD II and schizophrenia were not available. There were also a number of case reports on psychosis following COVID-19 infection[38, 39], but longer follow-up is required to delineate the course of the illness. However, there are otherwise very few studies on whether new-onset or recurrent BD and SCZ is a consequence of COVID-19, given that both disorders are of relatively low incidence and the available follow-up period is short.

As for suicidal thoughts (ST), as COVID-19 may be associated with a range of psychiatric disorders and physical symptoms, it has been suggested that there may be increased suicidal risk among COVID-19 survivors[40, 41]. A recent study on veterans showed[42] increased suicidal ideations in infected subjects. The possible mechanisms underlying heightened suicidal risks was summarized in a recent review[43].

For ADHD, although ADHD is generally a childhood-onset disorder, the current analysis may also be considered to reflect the effect of the exposure on the propensity to ADHD or the continuum of ADHD symptoms[44]. Of note, ADHD *symptoms* such as inattention and poor concentration are known to be associated with coronavirus infections[36] and are considered part of the 'long-COVID' syndrome[27]. The current MR analysis provides some support that COVID-19 may be causally related to ADHD symptoms. Finally, for OD, a recent study has shown that opioid analgesics are significantly more commonly received by COVID-19 survivors (HR=9.39) [28], which may be related to chronic pain symptoms.

Neuropsychiatric disorders as sequelae to pneumonia

We found that pneumonia may be a causal risk factor for depressive symptoms, MDD, neuroticism, insomnia (at FDR<0.1), anxiety disorders and CUD. It was reported that hospitalization for pneumonia was associated with higher odds of substantial depressive symptoms (OR = 1.63)[45]. However, there were few studies on the neuropsychiatric sequelae of pneumonia, which precludes a detailed comparison of the current findings to previous studies.

A number of studies have investigated whether psychiatric disorders may increase the risk or severity of COVID-19 infection. For example, Yang et al[46] showed that in general pre-existing psychiatric disorders were associated with higher risks of COVID-19 infection and mortality, based on the UKBB sample. Considering individual disorders, depression, anxiety, substance misuse and psychotic disorders were all associated at least one of the outcomes (COVID-19 infection, hospitalized infection or fatality)[46] in the above study. However,

the number of cases for stress-related disorders and some other disorders (e.g. psychosis) is relatively small, and the UKBB may not be representative of the underlying population due to 'healthy volunteer bias'[47]. Tanquet et al. also reported that patients with a psychiatric diagnosis within a year of the COVID-19 outbreak had ~65% higher risk of being infected compared to a matched cohort with matched physical risk factors. However, associations of individual psychiatric disorders with infection were not reported in the study. In another US study of electronic health records[1], ADHD, BD, MDD and SCZ were all associated with elevated risks of infection. On the other hand, Lee et al.[2] did not find an association of mental illness with infection but there was a modest association (adjusted OR of 1.27) with severity of infection. One important limitation of observational studies is the risk of residual confounding. For example, socioeconomic status is not controlled for by Tanquet et al., and incomplete data on some covariates may lead to inadequate control for confounders. In addition, the above studies typically focused on a few psychiatric disorders, and the coverage is not as comprehensive as the current study.

In this MR study, liability to AD, ADHD, ALD, OD, PTSD and SA were associated with increased risk and/or severity of COVID-19 infection/severity. As discussed above, there was evidence that ADHD[1] and substance use disorders[46] may be associated with heightened risk of COVID-19. There were no previous studies that directly addressed association of PTSD and history of suicide with susceptibility to infection. However, in Yang et al[46], stress-related disorders were associated with higher risks of infection, hospitalization and mortality, although the results were non-significant. Suicide attempts (SA) is linked to many psychiatric disorders (e.g. mood, anxiety and psychotic disorders) and previous studies have shown that prior psychiatric disorders as a whole were associated with COVID-19.

There have been relatively few studies on the associations of psychiatric disorders with risks/severity of pneumonia. A study using linked hospital records showed that the risk of pneumococcal disease was elevated for patients with SCZ, BD, anxiety or depression[8]. We found potential causal relationships of anxiety and depression phenotypes with pneumonia in this study. SCZ showed positive associations with pneumonia in MR-Egger analysis with correlated SNPs, but the association was less consistent than that observed for anxiety or depression. Unexpectedly, we observed negative associations of BD I with pneumonia, contrary to the finding of the above study. The underlying reason is unknown, but could be due to differences in the phenotype under study (BD in general vs BD I), heterogeneity of the study samples, differences in comorbidity patterns etc. A previous study has shown that lithium (which is commonly prescribed in BD) has protective effects against pneumonia[49], however antipsychotics may have the opposite effects (cite) so it is hard to conclude the direction of effect.

Another study showed that depression is associated with heightened risks of ICU admission, mechanical ventilation and mortality from pneumonia[50]. As for ADHD, a German study using claims data[51] revealed that ADHD may be associated with higher risks of multiple comorbidities including viral pneumonia. Another interesting finding was that cannabis use disorders was consistently associated with higher risk of pneumonia by MR. It has been proposed that cannabis is linked to various lung pathologies and may weaken the immune

response thus raising the risk of pneumonia[52, 53]. Another case-control study[54] showed that regular cannabis use was associated with higher pneumonia risks, regardless of tobacco co-use.

A recent bi-directional MR study by Luykx and Lin found that liability to BD and SCZ combined together (based on GWAS meta-analysis of BD and SCZ) may be associated with increased risk of COVID-19 infection[30]. However, the study did not reveal any other significant causal associations, either considering COVID-19 as outcome or exposure. Our reported findings are partially different which can be due to various reasons. For example, Luykx and Lin considered a stringent p-value threshold of 5e-8 and hence only a few instruments were included in each analysis, especially when COVID-19 phenotypes were considered as the exposure, which may lead to limited statistical power. Here we have employed more relaxed p-value thresholds, which have shown by several previous studies and our own simulations to maintain type I error control. Inclusion of larger number of instrumental SNPs in LD may also increase the power. In addition, we have also covered a much wider range of psychiatric traits/disorders than the previous study, and a number of psychiatric GWAS datasets we used were also different or more updated (hence of larger sample sizes) (see Table 1). We also included pneumonia as an outcome and exposure; to our knowledge, no previous studies have investigated causal relationship of psychiatric disorders with pneumonia.

Strengths and limitations

There are several limitations of this study. We have employed the latest and GWAS summary statistics to date for COVID-19, however heterogeneity (e.g. in disease severity, demographics) may be present across different constituent studies. It is also difficult to verify that the reason for hospitalization is due to (severe) COVID-19 symptoms, and the criteria for admission may differ across cohorts. The control population is composed of the general population, and asymptomatic patients and patients with mild symptoms may be missed. The sample sizes of severe and critical cases were still relatively modest, hence the statistical power to detect weaker associations may be limited. Similar limitations, such as heterogeneity across studies and modest sample sizes, are also present for many of the neuropsychiatric GWAS datasets. For example, the severity and presentation of MDD can be highly heterogeneous, yet they may be grouped under the same category. We have tried to include more well-characterized phenotypes (e.g. melancholic depression, severe MDD requiring ECT etc.), but such studies are usually of smaller sample sizes.

Many of our findings are supported by previous studies. However, for some associations supported by the literature, we were unable to verify their causal relationship in this MR study. For example, increased risks of depression and anxiety disorders after COVID-19 have been reported in observational studies[4], but our MR analysis did not support this observation. A number of possible reasons may explain this. As discussed above, statistical power may be insufficient to detect modest (causal) associations due to limited sample sizes of COVID-19 and/or the psychiatric GWAS datasets. Heterogeneity in inclusion/exclusion criteria and sample characteristics or definition of psychiatric outcomes may also explain the differences. On the other hand, it is possible that previously observed associations may be (partially) explained by confounding factors. For

example, low socioeconomic status (SES) and poor physical health are linked to both COVID-19 infection and depression/anxiety disorders. Some confounders may remain uncontrolled for or not adequately controlled for.

There are other limitations of the MR methodology. For more detailed discussions of the strengths and shortcomings of MR, please also refer to other papers[20, 55-57]. For example, horizontal pleiotropy (the instrumental SNP being associated with the outcome via another pathway not through the exposure) may affect the validity of results, which can be accounted for by some MR methods[58, 59]. Yet different MR method require different assumptions such as the InSIDE assumption[60] for MR-Egger, systematic and idiosyncratic pleiotropy for MR-RAPS and so on. We therefore have attempted multiple methods and results robust across different approaches may be more reliable for further studies. We also note that there is sample overlap between the pneumonia GWAS datasets and some other neuropsychiatric datasets (both included UKBB samples); as such results may bias towards the confounded estimate and should be interpreted with caution. However, we expect the bias to be relatively small as instrument strengths were generally strong. Also, the primary focus of this study is on COVID-19, and we have used COVID-19 summary statistics that did not contain UKBB samples.

Conclusions

To our knowledge, this is the most comprehensive MR study to date investigating *bi-directional* causal relationships between COVID-19 and neuropsychiatric disorders/traits. This is also the first MR study of neuropsychiatric disorders with pneumonia. We found tentative evidence of causal links between several psychiatric traits/disorders and COVID-19, especially for severe infections. The patterns of associations appeared to be different when compared to pneumonia. Further replications in larger and prospective cohorts are required, and the underlying mechanisms require further studies.

Figure legends

Figure 1 An overview of significant MR results (FDR<0.05) with COVID-19/pneumonia as exposure and neuropsychiatric disorders/traits as outcome. The color indicates the number of significant results for the specific exposure and outcome.

Figure 2 An overview of significant MR results (FDR<0.05) with neuropsychiatric disorders/traits as exposure and COVID-19/pneumonia as outcome. The color indicates the number of significant results for the specific exposure and outcome.

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Supplementary Information

All supplementary Tables and notes are available at the journal's website and at https://drive.google.com/drive/folders/18ZECXMeoDL1NRpweKsD0wYWGKm_y4QPa?usp=sharing

Conflicts of interest The authors declare no conflict of interest.

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Table 1 Description of GWAS data of neuropsychiatric disorders/traits used in this study.

Phenotype	abbr.	Source	data type	Cases	Controls	Total N	No. of SNPs	PMID/Links
Alcohol dependence 2018	alco2018	PGC	binary	11,476	23,080	34,556	7,939,164	PMID: 30482948
Alzheimer disease	ad	CTG lab	binary	71,880	383,378	455,258	13,367,299	PMID: 30617256
Anxiety disorders (UKBB phecode 300)	ukbb.anxiety	UKBB	binary	10,751	384,235	394,986	24,385,924	Pan-UKB
Anxiety disorder case control study (PGC)	pgc.anx.cc	PGC	binary	7,016	14,745	17,310	6,330,995	PMID: 26754954
Anxiety disorder Meta (PGC anxiety + ukbb.anxiety)	meta.anxiety	This study	binary	17,767	398,980	416,747	5,977,203	NA
Worrier / anxious feelings (UKBB data field 1980)	anx	UKBB	binary	213,808	162,603	376,411	10,579,925	PMID: 31427789
Attention Deficit Hyperactivity Disorder 2019	adhd2019	IPSYCH	binary	19,099	34,194	53,293	8,047,420	PMID: 30478444
Bipolar Disorder I PGC3 2021	bip.2021.i	PGC	binary	250,606	307,499	558,105	7,391,594	PMID: 34002096
Bipolar Disorder II PGC3 2021	bip.2021.ii	PGC	binary	6,781	273,693	280,474	7,188,236	PMID: 34002096
Bipolar Disorder PGC3 All	bip.2021.all	PGC	binary	41,917	371,549	413,466	7,608,183	PMID: 34002096
Cannabis Use Disorder 2020 Eur (Exclude related subjects)	cud.eur.exclude	PGC	binary	14,808	343,726	358,534	8,851,634	PMID: 33096046
Depressive Symptoms	dep.sym2016	SSGAC	continuous	---	---	161,460	6,524,474	PMID: 27089181
Eating Disorder (anorexia nervosa) 2019	ed2019	PGC	binary	16,992	55,525	72,517	8,219,102	PMID: 31308545
Ever contemplated self-harm (UKBB data field 20485)	ever.sh	UKBB	binary	5,099	112,634	117,733	12,075,153	Pan-UKB
Insomnia 2019	insom2019	UKBB&CTG	binary	109,389	277,144	386,533	10,862,567	PMID: 30804565
Lewy Body Dementia	dementia.lbd2020	Chia et al.	binary	2,591	4,027	6,618	7,843,595	PMID: 33589841
Major Depressive Disorder 2019	mdd2019	PGC	binary	170,756	329,443	500,199	8,483,301	PMID: 30718901
Major Depressive Disorder (severe MDD requiring ECT) 2021 Broad	mdd.2021.broad	PGC	binary	2,725	3,290	6,015	7,751,438	PMID: 33483693
Major Depressive Disorder (severe MDD requiring ECT) 2021 Narrow	mdd.2021.narrow	PGC	binary	1,796	3,290	5,086	7,750,957	PMID: 33483693
Major Depressive Disorder CONVERGE	mddco	PGC	binary	5,303	5,337	10,640	5,992,772	PMID: 26176920
Neuroticism (SSGAC)	neuroti.meta2016	SSGAC	continuous	---	---	170,991	6,524,432	PMID: 27089181
Neuroticism (UKBB 2018)	neuroti_eur_ukbb_2018	UKBB	continuous	---	---	293,006	13,584,548	PMID: 29942085
Number of depression episodes (UKBB phecode 4260)	no.dep	UKBB	continuous	---	---	45,695	13,356,624	Pan-UKB
Obsessive-Compulsive Disorder 2018	ocd2018	PGC	binary	2,688	7,037	9,725	8,409,516	PMID: 28761083
Opioid Dependence 2020 Case/Exposed Eur	od.case-exposed.eur	PGC	binary	3,272	2,876	6,148	4,213,977	PMID: 32099098
Opioid Dependence 2020 Case/Exposed Trans	od.case-exposed.trans	PGC	binary	4,503	4,173	8,676	4,002,503	PMID: 32099098
Opioid Dependence 2020 Case/Unexposed Eur	od.case-unexposed.eur	PGC	binary	2,712	10,540	13,252	4,889,007	PMID: 32099098
Opioid Dependence 2020 Case/Unexposed Trans	od.case-unexposed.trans	PGC	binary	3,594	15,895	19,489	4,012,235	PMID: 32099098
Opioid Dependence 2020 Exposed/Unexposed Eur	od.exposed-unexposed.eur	PGC	binary	2,876	25,022	27,898	5,989,497	PMID: 32099098
Opioid Dependence 2020 Exposed/Unexposed Trans	od.exposed-unexposed.trans	PGC	binary	4,173	31,820	35,993	7,435,111	PMID: 32099098
Parkinson Disease Meta5 (excluding 23andMe)	pd	IPDGC	binary	5,542	5,866	11,408	17,669,774	PMID: 25444595
Pneumonia UKBB	ukbb.pneumonia	UKBB	binary	14,507	423,632	438,139	25,852,522	Pan-UKB
Pneumonia Meta-analysis (used in our final analysis)	meta.pneumonia	This study	binary	70,115	97,305	573,777	10,996,219	NA
Pneumonia FinnGen r3 J10	finn.pneumonia	FinnGen	binary	15,771	119,867	135,638	16,948,862	FinnGen
Posttraumatic Stress Disorder Freeze 2 2019	ptsd2019	PGC	binary	32,428	174,227	206,655	8,659,506	PMID: 31594949
Psychotic Experiences 2019	psycho.experi	UKBB	binary	6,123	121,843	127,966	7,562,334	PMID: 31553412
Recent thoughts of suicide or self-harm (UKBB data field 20513)	st	UKBB	continuous	---	---	117,177	13,571,470	Pan-UKB
Schizophrenia Wave3 Public.v2	scz.wave3.v2	PGC	binary	67,390	94,015	161,405	7,481,682	Ripke, Stephan, et al.
Suicide Attempts with or without Mental Disorders	sa.ipsych	IPSYCH	binary	6,024	44,240	50,264	8,017,026	PMID: 30116032
Thoughts of death during worst depression (UKBB data field 20437)	st.dep	UKBB	binary	32,630	30,018	62,648	13,559,507	Pan-UKB

UKBB, UK Biobank; MDD, major depressive disorder; ECT, electroconvulsive therapy; Eur, European; Trans, trans-ethnic. For opioid dependence, case represents subjects with opioid dependence, exposed represents those exposed to opioids.

Table 2 MR results (FDR<0.05) with liability to COVID-19 as exposure and neuropsychiatric disorders as outcome (independent SNPs as instruments)

exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	p.adjust
B2	adhd2019	GSMR	136	0.047	0.014	1.048	1.019	1.079	1.10E-03	1.00E-04	3.26E-02
B2	adhd2019	IVW	136	0.051	0.015	1.052	1.022	1.083	5.58E-04	1.00E-04	3.26E-02
B2	adhd2019	MR-RAPS	136	0.056	0.017	1.058	1.024	1.093	7.02E-04	1.00E-04	3.26E-02
A2	adhd2019	SIMEX	401	0.025	0.007	1.025	1.011	1.039	6.83E-04	1.00E-03	3.26E-02
B2	adhd2019	SIMEX	136	0.053	0.016	1.054	1.022	1.087	1.05E-03	1.00E-04	3.26E-02
B2	adhd2019	Wt-median	136	0.069	0.021	1.071	1.028	1.116	1.12E-03	1.00E-04	3.26E-02
A2	bip.2021.ii	GSMR	30	0.071	0.027	1.074	1.019	1.131	7.67E-03	1.00E-05	4.88E-02
B2	bip.2021.ii	GSMR	840	0.036	0.011	1.036	1.014	1.060	1.50E-03	1.00E-02	1.69E-02
B2	bip.2021.ii	IVW	410	0.040	0.014	1.041	1.013	1.070	3.50E-03	1.00E-03	2.75E-02
B2	bip.2021.ii	MR Egger	840	0.123	0.032	1.131	1.063	1.204	1.15E-04	1.00E-02	5.59E-03
B2	bip.2021.ii	MR-RAPS	410	0.044	0.015	1.045	1.014	1.077	3.82E-03	1.00E-03	2.80E-02
A2	bip.2021.ii	SIMEX	30	0.084	0.028	1.088	1.031	1.148	4.91E-03	1.00E-05	3.24E-02
A2	ptsd2019	IVW	423	0.020	0.006	1.020	1.009	1.031	4.51E-04	1.00E-03	3.07E-02
A2	ptsd2019	SIMEX	423	0.023	0.006	1.024	1.011	1.036	1.71E-04	1.00E-03	2.85E-02
B2	scz.wave3.v2	GSMR	841	0.015	0.004	1.016	1.007	1.024	4.71E-04	1.00E-02	2.29E-02
A2	scz.wave3.v2	IVW	12	0.048	0.015	1.049	1.019	1.080	1.13E-03	1.00E-06	3.14E-02
B2	scz.wave3.v2	IVW	846	0.019	0.006	1.019	1.008	1.030	6.33E-04	1.00E-02	2.50E-02
B2	scz.wave3.v2	MR-RAPS	846	0.019	0.006	1.020	1.008	1.032	1.16E-03	1.00E-02	3.14E-02
B2	scz.wave3.v2	SIMEX	846	0.020	0.006	1.021	1.009	1.033	7.20E-04	1.00E-02	2.50E-02
A2	st	GSMR	11	0.007	0.002	---	0.003	0.011	2.85E-03	1.00E-06	4.27E-02
B2	st	GSMR	9	0.014	0.004	---	0.006	0.022	2.45E-04	1.00E-06	6.43E-03
A2	st	SIMEX	11	0.009	0.002	---	0.005	0.013	3.64E-03	1.00E-06	4.92E-02
B2	st	SIMEX	9	0.015	0.004	---	0.007	0.023	5.37E-03	1.00E-06	4.92E-02

Exp: exposure; out, outcome; nsnps, number of SNPs used as instruments for MR; b, MR effect estimate; se, standard error, OR, odds ratio, LCI/UCI, lower and upper 95% confidence interval for OR; pval, p-value of MR analysis; p_thres, p-value threshold for inclusion as instrument SNPs; p.adjust, FDR-adjusted *p* (corrected for multiple testing). Wt-median, weighted median approach. For abbreviations of the traits, please also refer to Table 1. For abbreviations/descriptions of the MR methods, please refer to the main text.

For each exposure-outcome-method combination, we only show at most one result (selecting the result with lowest p_thres and r2 threshold). Only results which passed the Steiger test of directionality are shown in main tables.

Note: od.cu.e: od.case_unexposed.eur; od.ce.e: od.case_exposure.eur;od.expu.e: od.case_exposed.eur; od.expu.t: od.exposed_unexposed.trans;

Table 3 MR results (FDR<0.05) with liability to COVID-19 as exposure and neuropsychiatric disorders as outcome (correlated SNPs as instruments)

exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	r2	p.adjust
B2	bip.2021.all	IVW	201	0.042	0.010	1.043	1.023	1.063	1.58E-05	1.00E-04	0.05	9.05E-04
A2	bip.2021.ii	GSMR	36	0.076	0.025	1.079	1.028	1.133	2.10E-03	1.00E-05	0.05	2.02E-02
A2	bip.2021.ii	IVW	36	0.088	0.024	1.092	1.042	1.143	2.09E-04	1.00E-05	0.05	5.59E-03
B2	bip.2021.ii	IVW	37	0.096	0.034	1.101	1.031	1.176	4.35E-03	1.00E-05	0.05	3.00E-02
B2	bip.2021.ii	MR Egger	199	0.160	0.044	1.173	1.076	1.279	3.00E-04	1.00E-04	0.05	5.59E-03
C2	meta.anxiety	MR Egger	156	0.286	0.074	1.331	1.151	1.539	1.16E-04	1.00E-04	0.1	1.14E-02
B2	ocd2018	MR Egger	202	0.237	0.067	1.267	1.112	1.444	3.78E-04	1.00E-04	0.05	4.91E-02
B2	ptsd2019	MR Egger	224	0.091	0.025	1.096	1.043	1.151	2.80E-04	1.00E-04	0.2	2.85E-02
B2	scz.wave3.v2	IVW	201	0.048	0.010	1.049	1.029	1.069	1.17E-06	1.00E-04	0.05	1.51E-04
B2	st	GSMR	9	0.014	0.004	---	0.006	0.022	2.45E-04	1.00E-06	0.05	6.43E-03
A2	st	MR Egger	8	0.034	0.012	---	0.010	0.058	5.01E-03	1.00E-07	0.15	4.92E-02
B2	st	MR Egger	6	0.053	0.019	---	0.016	0.090	5.21E-03	1.00E-07	0.05	4.92E-02

R2, LD-clumping threshold for inclusion as instruments. Note: neuroti_ukbb: neuroti_eur_ukbb_2018; od.expu.t: od.exposed_unexposed.trans.

Table 4 MR results (FDR<0.05) with liability to neuropsychiatric disorders as exposure and COVID-19 as outcome (independent SNPs as instruments)

exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	p.adjust
alco2018.beta	C2	GSMR	113	0.035	0.011	1.036	1.014	1.057	8.68E-04	1.00E-04	7.74E-03
alco2018.beta	C2	IVW	113	0.038	0.010	1.039	1.019	1.060	1.66E-04	1.00E-04	4.45E-03
alco2018.beta	C2	MR-RAPS	113	0.040	0.011	1.041	1.018	1.063	3.59E-04	1.00E-04	6.69E-03
alco2018.beta	C2	SIMEX	113	0.037	0.011	1.037	1.015	1.060	1.28E-03	1.00E-04	1.06E-02
od.cu.t	B2	IVW	654	0.001	0.000	1.001	1.000	1.002	3.95E-03	1.00E-02	2.16E-02
od.cu.t	C2	IVW	227	0.001	0.000	1.001	1.000	1.001	8.54E-03	1.00E-03	3.91E-02
od.cu.t	B2	MR-RAPS	654	0.003	0.001	1.003	1.001	1.006	3.54E-03	1.00E-02	2.16E-02
od.cu.t	C2	MR-RAPS	227	0.002	0.001	1.002	1.001	1.003	4.39E-03	1.00E-03	2.16E-02
od.cu.t	A2	SIMEX	652	0.003	0.001	1.003	1.001	1.005	3.39E-04	1.00E-02	5.43E-03
od.cu.t	B2	SIMEX	68	0.008	0.002	1.008	1.003	1.012	2.77E-03	1.00E-04	2.16E-02
od.cu.t	C2	SIMEX	15	0.017	0.005	1.017	1.008	1.027	3.39E-03	1.00E-05	2.16E-02
od.expu.e	C2	SIMEX	196	0.002	0.001	1.002	1.001	1.004	9.96E-05	1.00E-03	9.36E-03
ptsd2019	C2	MR Egger	994	0.051	0.016	1.053	1.021	1.086	1.16E-03	1.00E-02	4.40E-02
sa.ipsych	A2	IVW	326	0.061	0.019	1.063	1.025	1.104	1.18E-03	1.00E-03	3.87E-02
sa.ipsych	C2	MR Egger	350	0.045	0.014	1.046	1.018	1.075	1.35E-03	1.00E-03	3.87E-02
sa.ipsych	A2	MR-RAPS	326	0.069	0.021	1.071	1.028	1.116	1.01E-03	1.00E-03	3.87E-02
sa.ipsych	A2	SIMEX	326	0.069	0.020	1.071	1.029	1.115	8.04E-04	1.00E-03	3.87E-02

Note: od.cu.t: od.case_unexposed.trans; od.cu.e: od.case_unexposed.eur; od.ce.e: od.case_exposure.eur;od.expu.e: od.case_exposed.eur; od.expu.t: od.exposed_unexposed.trans; neuroti_eur: neuroti_eur_ukbb_2018;

Table 5 MR results (FDR<0.05) with liability to neuropsychiatric disorders as exposure and COVID-19 as outcome (correlated SNPs as instruments)

exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	r2	p.adjust
ad	A2	GSMR	87	-0.300	0.086	0.741	0.625	0.877	5.01E-04	1.00E-07	0.2	3.92E-02
ad	A2	IVW	301	-0.380	0.111	0.684	0.551	0.85	5.96E-04	1.00E-04	0.05	3.92E-02
ad	A2	MR Egger	301	-0.493	0.130	0.611	0.473	0.788	1.53E-04	1.00E-04	0.05	2.01E-02
adhd2019	A2	IVW	327	0.106	0.031	1.112	1.046	1.182	7.20E-04	1.00E-04	0.1	2.29E-02
adhd2019	A2	MR Egger	313	0.222	0.069	1.249	1.092	1.429	1.21E-03	1.00E-04	0.05	3.44E-02
adhd2019	B2	MR Egger	314	0.193	0.045	1.213	1.11	1.326	1.99E-05	1.00E-04	0.05	1.01E-03
alco2018.beta	C2	GSMR	153	0.032	0.009	1.032	1.014	1.051	6.25E-04	1.00E-04	0.05	6.69E-03
alco2018.beta	C2	IVW	153	0.044	0.009	1.045	1.027	1.064	1.06E-06	1.00E-04	0.05	4.30E-05
alco2018.beta	A2	MR Egger	153	0.190	0.070	1.209	1.055	1.386	6.41E-03	1.00E-04	0.05	4.57E-02
alco2018.beta	C2	MR Egger	153	0.085	0.025	1.089	1.038	1.143	5.28E-04	1.00E-04	0.05	6.69E-03
anx	B2	MR Egger	259	-0.671	0.194	0.511	0.349	0.747	5.31E-04	1.00E-05	0.05	2.49E-02
anx	C2	MR Egger	266	-0.378	0.089	0.685	0.575	0.816	2.23E-05	1.00E-05	0.05	1.34E-03
neuroti_eur	A2	GSMR	83	-0.913	0.200	---	-1.305	-0.521	4.73E-06	5.00E-08	0.05	1.23E-04
neuroti_eur	B2	GSMR	103	-0.333	0.133	---	-0.594	-0.072	1.26E-02	5.00E-08	0.1	3.58E-02
neuroti_eur	C2	GSMR	170	-4.159	0.386	---	-4.916	-3.402	5.00E-27	1.00E-07	0.15	7.35E-25
neuroti_eur	A2	IVW	83	-0.812	0.212	---	-1.228	-0.396	1.27E-04	5.00E-08	0.05	9.60E-04
neuroti_eur	A2	MR Egger	159	-1.863	0.555	---	-2.951	-0.775	7.97E-04	5.00E-08	0.2	4.19E-03
neuroti_eur	B2	MR Egger	85	-1.605	0.580	---	-2.742	-0.468	5.65E-03	5.00E-08	0.05	2.08E-02
od.cu.t	B2	IVW	75	0.004	0.001	1.004	1.001	1.006	4.09E-03	1.00E-04	0.05	2.16E-02
ptsd2019	C2	MR Egger	248	0.127	0.025	1.136	1.081	1.194	5.33E-07	1.00E-04	0.1	6.08E-05

Note: neuroti_eur: neuroti_eur_ukbb_2018; od.cu.t: od.case-unexposed.trans

Table 6 MR results (FDR<0.05) with liability to pneumonia as exposure and neuropsychiatric disorders as outcome (independent SNPs as instruments)

exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	p.adjust
FP	cud.eur.exclude	GSMR	854	0.066	0.022	1.068	1.023	1.115	2.67E-03	1.00E-02	1.22E-02
FP	cud.eur.exclude	IVW	103	0.132	0.052	1.141	1.031	1.262	1.11E-02	1.00E-04	3.96E-02
FP	cud.eur.exclude	MR Egger	855	0.140	0.047	1.150	1.050	1.261	2.83E-03	1.00E-02	1.22E-02
FP	cud.eur.exclude	MR-RAPS	389	0.080	0.031	1.083	1.019	1.151	1.04E-02	1.00E-03	3.96E-02
FP	cud.eur.exclude	SIMEX	389	0.097	0.029	1.102	1.040	1.167	1.02E-03	1.00E-03	5.54E-03
FP	dep.sym2016	GSMR	337	0.023	0.007	---	0.009	0.037	3.02E-04	1.00E-03	2.19E-03
FP	dep.sym2016	SIMEX	83	0.030	0.012	---	0.006	0.054	1.69E-02	1.00E-04	4.47E-02
FP	insom2019	GSMR	905	0.018	0.006	1.018	1.007	1.030	2.24E-03	1.00E-02	1.85E-02
FP	insom2019	IVW	905	0.021	0.006	1.021	1.009	1.033	4.96E-04	1.00E-02	7.69E-03
FP	insom2019	MR-RAPS	905	0.023	0.007	1.023	1.010	1.037	6.99E-04	1.00E-02	7.69E-03
FP	insom2019	SIMEX	421	0.024	0.009	1.024	1.007	1.041	5.73E-03	1.00E-03	3.78E-02
FP	mdd2019	GSMR	116	0.032	0.011	1.032	1.010	1.055	4.15E-03	1.00E-04	1.50E-02
FP	mdd2019	IVW	116	0.037	0.012	1.038	1.014	1.062	1.62E-03	1.00E-04	7.27E-03
FP	mdd2019	MR-RAPS	116	0.036	0.012	1.037	1.012	1.063	3.54E-03	1.00E-04	1.42E-02
FP	mdd2019	SIMEX	116	0.042	0.013	1.043	1.017	1.068	1.15E-03	1.00E-04	5.93E-03
FP	mdd2019	Wt-median	920	0.017	0.007	1.017	1.003	1.031	2.08E-02	1.00E-02	4.68E-02
FP	meta.anxiety	GSMR	76	0.107	0.040	1.113	1.029	1.204	7.32E-03	1.00E-04	1.97E-02
FP	meta.anxiety	IVW	310	0.103	0.024	1.108	1.057	1.162	2.14E-05	1.00E-03	1.84E-04
FP	meta.anxiety	MR-RAPS	310	0.110	0.027	1.117	1.060	1.177	3.51E-05	1.00E-03	2.16E-04
FP	meta.anxiety	SIMEX	76	0.129	0.042	1.138	1.048	1.235	2.85E-03	1.00E-04	8.76E-03
FP	meta.anxiety	Wt-median	310	0.101	0.033	1.106	1.037	1.180	2.12E-03	1.00E-03	7.02E-03
FP	neuroti_eur	GSMR	126	0.017	0.006	---	0.005	0.029	7.37E-03	1.00E-04	2.35E-02
FP	neuroti_eur	IVW	126	0.020	0.007	---	0.006	0.034	5.91E-03	1.00E-04	2.31E-02
FP	neuroti_eur	MR Egger	966	0.021	0.006	---	0.009	0.033	8.87E-04	1.00E-02	4.63E-03
FP	neuroti_eur	MR-RAPS	126	0.020	0.007	---	0.006	0.034	7.88E-03	1.00E-04	2.35E-02
FP	neuroti_eur	SIMEX	126	0.021	0.008	---	0.005	0.037	8.00E-03	1.00E-04	2.35E-02
FP	neuroti_eur	Wt-median	966	0.013	0.004	---	0.005	0.021	3.94E-03	1.00E-02	1.68E-02
FP	neuroti.meta2016	GSMR	83	0.026	0.011	---	0.004	0.048	1.77E-02	1.00E-04	4.70E-02
FP	neuroti.meta2016	IVW	83	0.029	0.011	---	0.007	0.051	8.03E-03	1.00E-04	2.60E-02
FP	neuroti.meta2016	MR-RAPS	83	0.030	0.012	---	0.006	0.054	1.04E-02	1.00E-04	2.92E-02
FP	neuroti.meta2016	SIMEX	83	0.030	0.011	---	0.008	0.052	7.44E-03	1.00E-04	2.60E-02

FP: FinnGen and UKBB meta-analysed Pneumonia GWAS data.

Table 7 MR results (FDR<0.05) with liability to pneumonia as exposure and neuropsychiatric disorders as outcome (correlated SNPs as instruments)

exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	r2	p.adjust
FP	cud.eur.exclude	IVW	129	0.157	0.045	1.170	1.071	1.278	5.12E-04	1.00E-04	0.05	4.40E-03
FP	dep.sym2016	GSMR	100	0.032	0.011	---	0.010	0.054	3.18E-03	1.00E-04	0.05	1.02E-02
FP	dep.sym2016	IVW	4	0.106	0.038	---	0.032	0.180	5.83E-03	1.00E-06	0.05	1.69E-02
FP	mdd2019	GSMR	148	0.023	0.010	1.024	1.004	1.044	1.88E-02	1.00E-04	0.05	4.51E-02
FP	mdd2019	IVW	17	0.057	0.024	1.059	1.009	1.110	1.88E-02	1.00E-05	0.05	4.51E-02
FP	meta.anxiety	GSMR	93	0.129	0.037	1.138	1.059	1.223	4.36E-04	1.00E-04	0.05	1.87E-03
FP	meta.anxiety	IVW	93	0.106	0.037	1.112	1.033	1.197	4.55E-03	1.00E-04	0.05	1.30E-02
FP	neuroti.meta2016	GSMR	100	0.028	0.010	---	0.008	0.048	6.70E-03	1.00E-04	0.05	2.60E-02
FP	neuroti.meta2016	IVW	100	0.031	0.009	---	0.013	0.049	1.02E-03	1.00E-04	0.05	6.53E-03

Note: FP: pneumonia.

Table 8 MR results (FDR<0.05) with liability to neuropsychiatric disorders as exposure and pneumonia as outcome (Independ SNPs as instruments)

exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	p.adjust
adhd2019	FP	GSMR	9	0.107	0.040	1.113	1.028	1.204	8.26E-03	5.00E-08	1.26E-02
adhd2019	FP	IVW	9	0.109	0.039	1.115	1.032	1.205	5.80E-03	5.00E-08	9.53E-03
adhd2019	FP	MR-RAPS	9	0.118	0.042	1.125	1.036	1.221	5.02E-03	5.00E-08	8.74E-03
adhd2019	FP	SIMEX	9	0.111	0.038	1.118	1.037	1.204	2.22E-02	5.00E-08	3.08E-02
adhd2019	FP	Wt-median	9	0.140	0.052	1.150	1.040	1.273	6.52E-03	5.00E-08	1.05E-02
bip.2021.i	FP	GSMR	37	-0.051	0.021	0.950	0.913	0.990	1.34E-02	5.00E-08	3.18E-02
bip.2021.i	FP	IVW	37	-0.053	0.022	0.948	0.908	0.990	1.49E-02	5.00E-08	3.44E-02
bip.2021.i	FP	MR-RAPS	37	-0.054	0.022	0.947	0.907	0.990	1.58E-02	5.00E-08	3.54E-02
bip.2021.i	FP	SIMEX	37	-0.059	0.024	0.943	0.900	0.988	1.90E-02	5.00E-08	3.86E-02
bip.2021.i	FP	Wt-median	37	-0.074	0.029	0.928	0.877	0.983	1.14E-02	5.00E-08	3.00E-02
cud.eur.exclude	FP	GSMR	6	0.133	0.048	1.143	1.040	1.256	5.57E-03	1.00E-07	1.75E-02
cud.eur.exclude	FP	IVW	2	0.237	0.083	1.268	1.077	1.493	4.35E-03	5.00E-08	1.75E-02
cud.eur.exclude	FP	MR-RAPS	2	0.239	0.093	1.270	1.059	1.522	9.91E-03	5.00E-08	2.66E-02
cud.eur.exclude	FP	SIMEX	6	0.135	0.041	1.145	1.057	1.240	2.98E-02	1.00E-07	4.68E-02
cud.eur.exclude	FP	Wt-median	6	0.130	0.060	1.139	1.013	1.281	2.95E-02	1.00E-07	4.68E-02
dep.sym2016	FP	GSMR	13	0.403	0.147	---	0.115	0.691	6.33E-03	1.00E-06	3.51E-02
dep.sym2016	FP	IVW	13	0.443	0.143	---	0.163	0.723	1.92E-03	1.00E-06	2.35E-02
dep.sym2016	FP	MR-RAPS	13	0.447	0.157	---	0.139	0.755	4.38E-03	1.00E-06	3.20E-02
dep.sym2016	FP	SIMEX	40	0.313	0.112	---	0.093	0.533	8.23E-03	1.00E-05	4.18E-02
insom2019	FP	GSMR	566	0.080	0.020	1.084	1.042	1.126	4.89E-05	1.00E-03	4.59E-04
insom2019	FP	IVW	273	0.076	0.025	1.078	1.027	1.133	2.57E-03	1.00E-04	1.75E-02
insom2019	FP	MR Egger	1000	0.100	0.038	1.105	1.025	1.190	8.98E-03	1.00E-02	4.81E-02
insom2019	FP	MR-RAPS	273	0.075	0.028	1.078	1.021	1.139	6.77E-03	1.00E-04	3.91E-02
insom2019	FP	SIMEX	273	0.082	0.026	1.086	1.033	1.142	1.48E-03	1.00E-04	1.11E-02
insom2019	FP	Wt-median	566	0.079	0.028	1.082	1.024	1.143	4.96E-03	1.00E-03	3.10E-02
mdd2019	FP	GSMR	43	0.124	0.056	1.132	1.013	1.264	2.80E-02	1.00E-07	4.89E-02
mdd2019	FP	IVW	43	0.131	0.056	1.140	1.022	1.271	1.86E-02	1.00E-07	3.66E-02
mdd2019	FP	MR-RAPS	43	0.138	0.059	1.148	1.022	1.290	2.00E-02	1.00E-07	3.85E-02
mdd2019	FP	SIMEX	91	0.166	0.045	1.181	1.082	1.289	3.62E-04	1.00E-06	1.11E-03
mdd2019	FP	Wt-median	346	0.094	0.037	1.099	1.021	1.182	1.14E-02	1.00E-04	2.45E-02
meta.anxiety	FP	IVW	114	0.046	0.016	1.047	1.014	1.080	4.26E-03	1.00E-04	1.41E-02
meta.anxiety	FP	MR-RAPS	114	0.050	0.017	1.051	1.016	1.087	4.22E-03	1.00E-04	1.41E-02
meta.anxiety	FP	Wt-median	395	0.038	0.014	1.039	1.010	1.069	7.99E-03	1.00E-03	2.40E-02
neuroti_eur	FP	GSMR	274	0.101	0.043	---	0.017	0.185	1.83E-02	1.00E-05	4.51E-02
neuroti_eur	FP	IVW	274	0.112	0.042	---	0.030	0.194	7.83E-03	1.00E-05	2.16E-02
neuroti_eur	FP	MR-RAPS	470	0.151	0.039	---	0.075	0.227	8.64E-05	1.00E-04	4.97E-04
neuroti_eur	FP	SIMEX	274	0.121	0.043	---	0.037	0.205	5.36E-03	1.00E-05	1.61E-02
od.case_unexposed.eur	FP	IVW	190	0.001	0.000	1.001	1.000	1.001	1.65E-03	1.00E-03	3.96E-02

Note: FP: pneumonia.

Table 9 MR results (FDR<0.05) with liability to neuropsychiatric disorders as exposure and pneumonia as outcome (correlated SNPs as instruments)

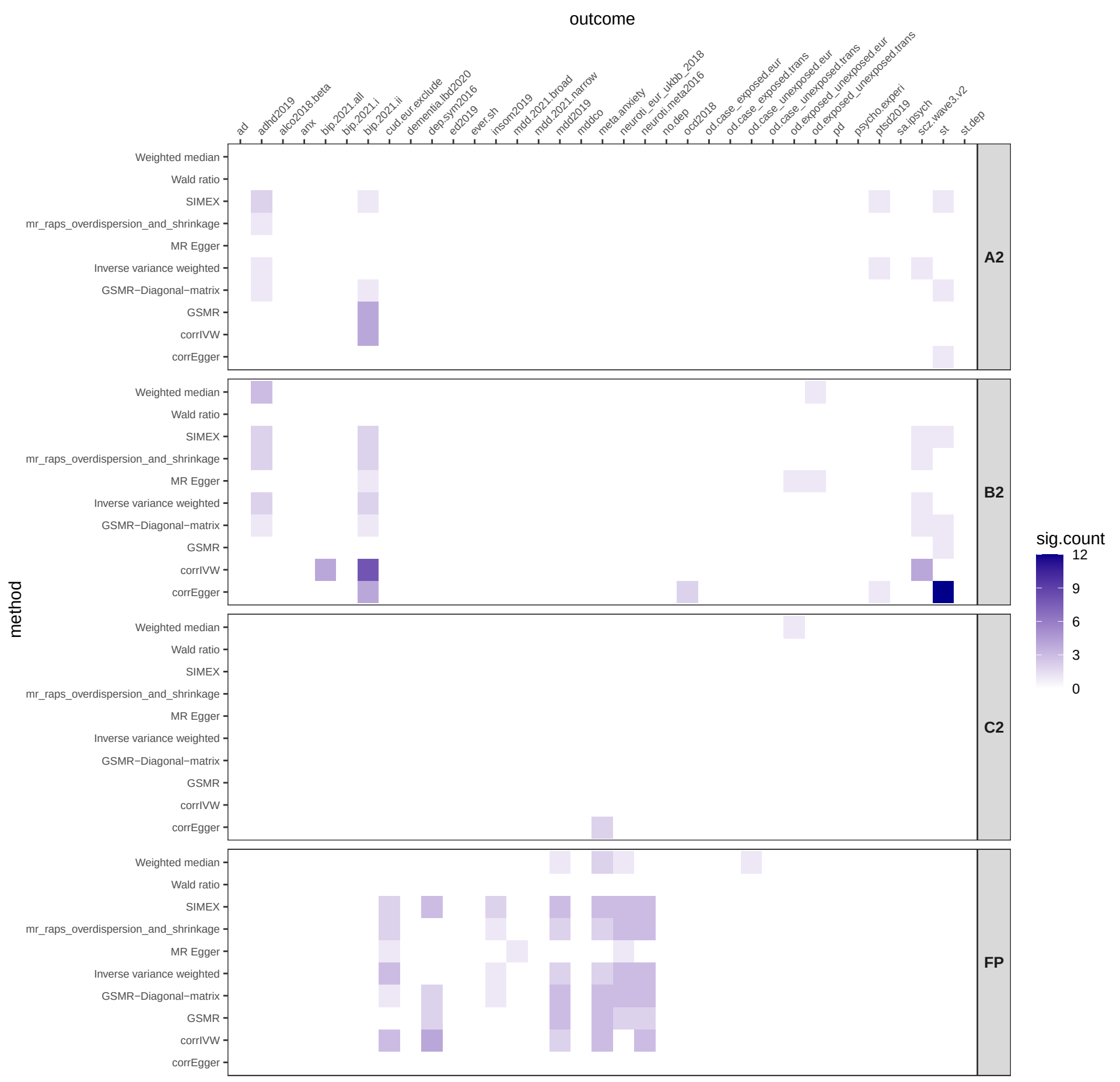
exp	out	method	nsnps	b	se	OR	LCI	UCI	pval	p_thres	r2	p.adjust
ad	FP	GSMR	104	1.134	0.063	3.109	2.746	3.521	2.01E-71	1.00E-07	0.2	1.75E-69
adhd2019	FP	GSMR	10	0.091	0.039	1.095	1.015	1.181	1.87E-02	5.00E-08	0.05	2.67E-02
adhd2019	FP	IVW	10	0.093	0.038	1.097	1.017	1.183	1.59E-02	5.00E-08	0.05	2.39E-02
bip.2021.i	FP	GSMR	41	-0.056	0.020	0.946	0.909	0.984	5.32E-03	5.00E-08	0.05	2.13E-02
bip.2021.i	FP	IVW	41	-0.052	0.019	0.949	0.913	0.986	6.95E-03	5.00E-08	0.05	2.40E-02
bip.2021.i	FP	MR Egger	119	-0.150	0.063	0.861	0.760	0.974	1.74E-02	1.00E-06	0.15	3.75E-02
cud.eur.exclude	FP	GSMR	6	0.133	0.048	1.143	1.040	1.256	5.57E-03	1.00E-07	0.05	1.75E-02
cud.eur.exclude	FP	IVW	2	0.237	0.084	1.267	1.076	1.493	4.61E-03	5.00E-08	0.05	1.75E-02
dep.sym2016	FP	IVW	14	0.421	0.144	---	0.139	0.703	3.45E-03	1.00E-06	0.05	3.20E-02
mdd2019	FP	GSMR	54	0.123	0.052	1.131	1.022	1.252	1.73E-02	1.00E-07	0.05	3.50E-02
mdd2019	FP	IVW	54	0.109	0.049	1.115	1.012	1.228	2.75E-02	1.00E-07	0.05	4.89E-02
mdd2019	FP	MR Egger	121	-0.354	0.138	0.702	0.535	0.921	1.05E-02	1.00E-06	0.05	2.38E-02
meta.anxiety	FP	GSMR	160	0.046	0.014	1.047	1.019	1.077	1.07E-03	1.00E-04	0.05	7.04E-03
meta.anxiety	FP	IVW	160	0.038	0.015	1.039	1.009	1.070	1.13E-02	1.00E-04	0.05	2.86E-02
neuroti_eur_ukbb_2018	FP	GSMR	145	0.139	0.053	---	0.035	0.243	8.35E-03	1.00E-07	0.1	2.22E-02
neuroti_eur_ukbb_2018	FP	IVW	91	0.193	0.068	---	0.060	0.326	4.51E-03	5.00E-08	0.05	1.41E-02
scz.wave3.v2	FP	MR Egger	251	0.117	0.037	1.124	1.045	1.208	1.60E-03	5.00E-08	0.05	4.57E-02
st	FP	GSMR	196	0.308	0.126	---	0.061	0.555	1.47E-02	1.00E-04	0.05	3.35E-02
st	FP	IVW	196	0.363	0.118	---	0.132	0.594	2.03E-03	1.00E-04	0.05	1.93E-02

Note: FP: pneumonia.

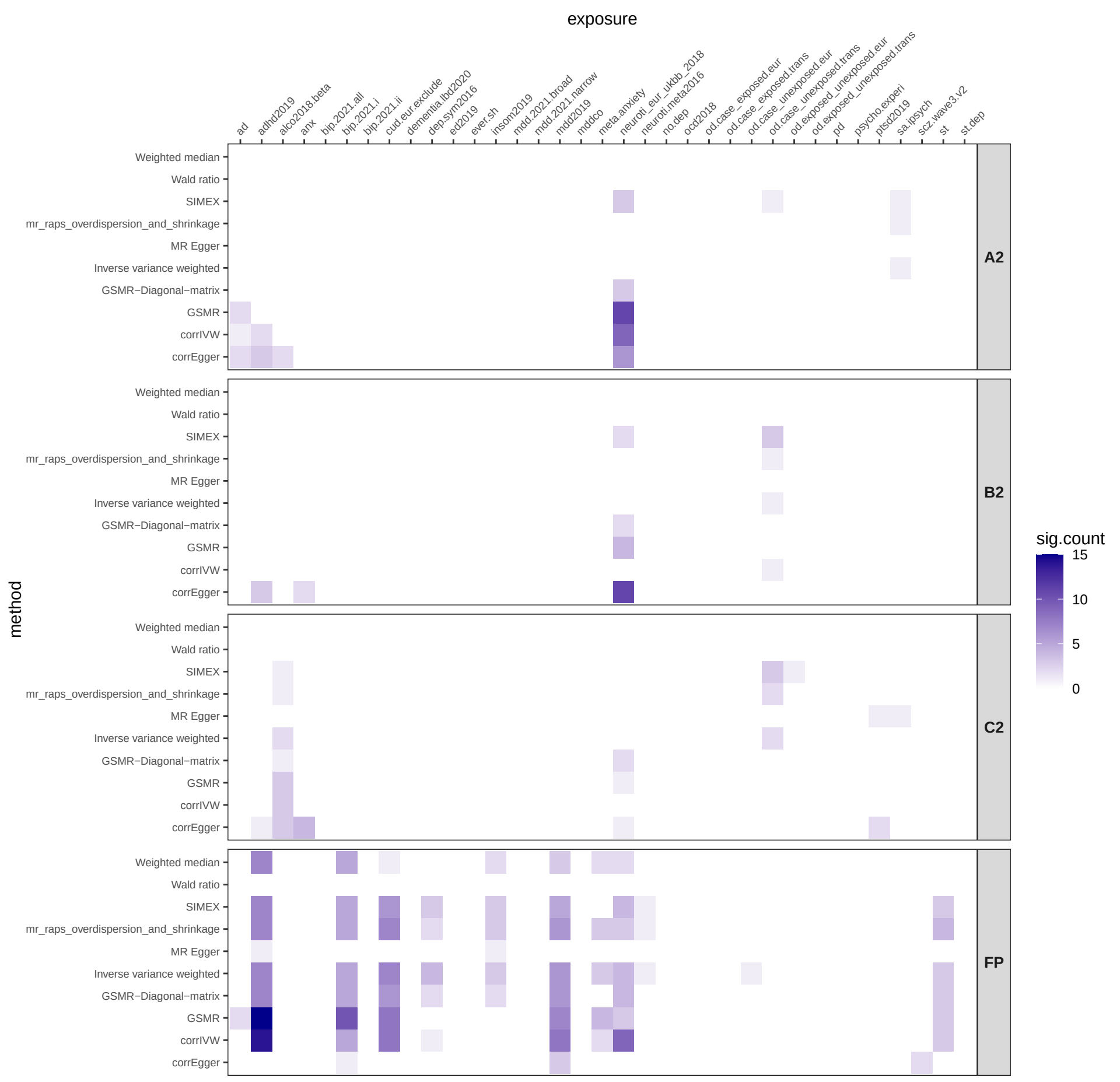
Table 10 Genetic correlation between COVID-19 and Pneumonia with PsyD.

p1	p2	rg	se	z	p	p.adjust	
B2	adhd2019	0.21	0.07	3.03	2.44E-03	2.64E-02	
B2	cud.eur.exclude	0.34	0.09	3.83	1.29E-04	2.82E-03	
B2	mdd2019	0.13	0.05	2.50	1.26E-02	7.98E-02	*
B2	psycho.experi	0.54	0.21	2.56	1.04E-02	7.91E-02	*
B2	meta.anxiety	0.36	0.12	2.99	2.78E-03	2.64E-02	
FP	adhd2019	0.46	0.07	6.12	9.28E-10	1.64E-08	
FP	anx	0.08	0.04	2.04	4.10E-02	6.11E-02	*
FP	bip.2021.all	0.14	0.05	2.91	3.60E-03	8.32E-03	
FP	bip.2021.ii	0.33	0.09	3.54	4.02E-04	1.35E-03	
FP	cud_eur	0.54	0.10	5.36	8.43E-08	6.23E-07	
FP	cud.eur.exclude	0.49	0.09	5.80	6.79E-09	6.28E-08	
FP	dep.sym2016	0.38	0.08	4.50	6.84E-06	3.62E-05	
FP	ever.sh	0.41	0.14	2.94	3.28E-03	8.08E-03	
FP	insom2019	0.39	0.06	6.06	1.33E-09	1.64E-08	
FP	mdd.2021.broad	0.21	0.10	2.09	3.64E-02	6.11E-02	*
FP	mdd.2021.narrow	0.26	0.12	2.23	2.56E-02	4.73E-02	
FP	mdd2019	0.32	0.05	6.34	2.29E-10	8.47E-09	
FP	neuroti_eur_ukbb_2018	0.15	0.05	2.88	3.96E-03	8.61E-03	
FP	neuroti.meta2016	0.18	0.07	2.58	9.83E-03	1.91E-02	
FP	ocd2018	-0.23	0.11	-2.01	4.49E-02	6.39E-02	*
FP	ptsd2019	0.51	0.12	4.11	3.97E-05	1.63E-04	
FP	sa.ipsych	0.43	0.21	2.06	3.96E-02	6.11E-02	*
FP	scz.wave3.v2	0.10	0.05	2.04	4.13E-02	6.11E-02	*
FP	st	0.79	0.19	4.17	3.04E-05	1.41E-04	
FP	st.dep	0.55	0.18	3.16	1.59E-03	4.20E-03	
FP	alco2018.beta	0.57	0.14	3.98	6.76E-05	2.50E-04	
FP	meta.anxiety	0.54	0.11	5.18	2.24E-07	1.38E-06	
FP	od.case_unexposed.eur	0.46	0.21	2.20	2.76E-02	4.87E-02	
FP	od.case_unexposed.trans	0.55	0.20	2.76	5.71E-03	1.17E-02	

*Represents results with 0.05< FDR-adjusted p<0.1. All other results have FDR-adjusted p<0.05.



Forward MR:
A2,B2,C2,FP (exposure) − Psychiatric disorder (outcome) − FDR <0.05



Reverse MR:
Psychiatric disorder (exposure) − A2,B2,C2,FP (outcome) − FDR <0.05