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PEER-REVIEW REPORT

Name of journal: *World Journal of Psychiatry*

Manuscript NO: 73108

Title: Does COVID-19 increase the risk of neuropsychiatric sequelae? Evidence from a mendelian randomization approach

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04686139
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Portugal

Author's Country/Territory: Italy

Manuscript submission date: 2021-11-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-12 14:35

Reviewer performed review: 2021-11-14 16:18

Review time: 2 Days and 1 Hour

Scientific quality	[Y] Grade A: Excellent [ ] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Dear Author Abstract includes introductory statement that outlines the background and significance of the study. Introduction summarizes relevant research to provide context and clearly state the problem. The topics are well developed and confronted to other publications. Methods are sufficient explained to replicate the research. The interpretation of the results is correct. Discussion is well balanced and adequately supported by the data.

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Title: Does COVID-19 increase the risk of neuropsychiatric sequelae? Evidence from a mendelian randomization approach

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 04122814
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Japan

Author's Country/Territory: Italy

Manuscript submission date: 2021-11-12

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-11-15 07:30

Reviewer performed review: 2021-11-25 02:39

Review time: 9 Days and 19 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

I would like to thank the editor and the authors for giving me the opportunity to review this interesting manuscript. The MR study indicated that Alzheimer's disease (AD) and GAD risks increased COVID-19 severity risk. These findings will be helpful for a further understanding of relationships between neuropsychiatric diseases and COVID-19. I have been able to obtain almost exactly the same results as the authors. For example, regarding AD risk on COVID-19 severity: method nsnp b 1 Inverse variance weighted (fixed effects) 20 0.01046501 2 Inverse variance weighted (multiplicative random effects) 20 0.01046501 se pval lo_ci up_ci or or_lci95 1 0.003522298 0.002967599 0.0035613056 0.01736871 1.010520 1.0035677 2 0.003160772 0.000929955 0.0042698963 0.01666012 1.010520 1.0042790 or_uci95 1 1.017520 2 1.016800 Therefore, I believe that the statistical methods are sound. My comments (#1-#3) to the authors are as follows: #1. To validate the causal direction further, bi-directional MR analysis (AD as exposure, COVID-19 as outcome) may be useful. I suppose that, although the dataset of GAD (ukb-d-20544_15) includes only one SNP at P = 5E-08, the dataset of AD (AD_sumstats_Jansenetal_2019sept.txt) includes dozens of genome-wide significant SNPs. #2. I think that sample overlap between exposure and outcome datasets is one of limitations. Both datasets include UK Biobank study and the overlap can cause some biases. (Burgess S, Davies NM, Thompson SG. Bias due to participant overlap in two-sample Mendelian randomization. Genet Epidemiol. (2016) 40:597–608. doi: 10.1002/gepi.21998) #3. Population stratification may be another limitation. The COVID-19 datasets (round 6) are meta-analyses in the mixed

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population, while AD and GAD datasets are in the European population. The authors may be able to conduct a sensitivity analysis using COVID-19 round 5 datasets of European ancestry.