Dear Dr. Gialluisi,

We are pleased to inform you that, after preview by the Editorial Office and peer review as well as CrossCheck and Google plagiarism detection, we believe that the academic quality, language quality, and ethics of your manuscript (Manuscript NO.: 73108, Letter to the Editor) basically meet the publishing requirements of the *World Journal of Psychiatry*. As such, we have made the preliminary decision that it is acceptable for publication after your appropriate revision.

Upon our receipt of your revised manuscript, we will send it for re-review. We will then make a final decision on whether to accept the manuscript or not, based upon the reviewers' comments, the quality of the revised manuscript, and the relevant documents.

Please follow the steps outlined below to revise your manuscript to meet the requirements for final acceptance and publication.

Dear Editor,

We thank you and the Reviewers for the sensible comments, which allowed us to improve the quality of the manuscript. Please find below a point-by-point reply to the observations of Reviewer #1 (no critical objections were made by Reviewer #2).

Should there be any further observations, please do not hesitate to contact us.

Regards,

Alessandro Gialluisi (on behalf of the corresponding author, Prof Dr Licia Iacoviello)

Department of Epidemiology and Prevention,

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Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

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.

We agree with the reviewer that checking both directions of causality would be the most appropriate approach with such a poorly known disease like Covid-19. Since the effect of the health conditions investigated here on Covid-19 risk was already tested in the original GWAS paper (https://doi.org/10.1038/s41586-021-03767-x), this analysis would have represented a duplication. Therefore, we focused on testing Covid-19 as an exposure in a MR setting, which had not been done in the original work.

#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)

We thank the reviewer for this insightful observation, which we now include as a potential limitation of our analysis. However, we believe this bias should be quite reduced, if ever, since the same work suggests that for case-control outcomes

"…if risk factor measurements are only included for the control participants, unbiased estimates are obtained even in a one-sample setting." (Burgess et al., 2016)

Indeed, they found that

"With IV–risk factor associations estimated in the controls only, there was no detectable bias in the IV estimates even with extremely weak instruments, nor was there any inflation of Type 1 error rates"

While we cannot rule out the presence of AD/GAD cases in Covid-19 cases tested in the GWAS by the COVID-19 Host Genetics, the relatively low prevalence of these disorders (especially for AD) in the general population suggests the real bias introduced by sample overlap may be very close to zero.

#3. Population stratification may be another limitation. The COVID-19 datasets (round 6) are meta-analyses in the mixed 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.

We agree with the reviewer and reported this as a potential limitation. Following his/her suggestion, we carried out a sensitivity analysis using COVID-19 round 5 datasets of European ancestry and observed a significant evidence of causality between hospitalized Covid-19 forms and increased AD risk (OR = 1.018 [1.000-1.036], $p < 0.05$; Table 1a, b, c), while only a trend of association was observed for increased AD risk vs the other Covid-19 exposures ($p<0.2$). With regard to anxiety risk, no significant evidence of causality was detected although severe Covid-19 slightly increased the risk of generalized GAD by 0.6% ($p = 0.09$; Table 1a, b, c). Overall, effect sizes between MR analyses using round 6 and round

5 (only EUR) data were very similar, corroborating the bounty of our main analysis. The lack of significance in most of the sensitivity MR analyses is probably due to the notable reduction in the number of IVs used (ranging from 3 to 10), implied by the lower number of independent genome-wide significant loci detected in the round 5 meta-analysis. Therefore, caution is suggested in the interpretation of these data and further analyses based on large datasets of pure European ancestry are warranted.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

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.

No replies required.