To

The Editor
Dr. Rona Strawbridge

Special Issue "Genetic Studies of Mood Disorders and Comorbidities"

Dear Dr. Stawbridge,

Thank you and the reviewers for your time in reviewing our paper and providing valuable feedback and welcome comments. Your time and effort helped improve the work, both in helping the science and explanations of analytic choices become clearer but helping to improve the communication of the results. We have done our best to address the concerns of both reviewers, and we welcome any further feedback as needed. We hope these corrections, which are addressed to Reviewer 1, improve the manuscript and highlight the collaborative nature of good science. Reviewer 2 did not provide detailed corrections, though their comments were noted and appreciated. Corrections to the text appear as blue in the manuscripts.

We found an additional correction in the author submission that should be addressed if we are fortunate enough to make it to copy editing – one author, Victor Roth Cardoso, had one of this names entered in lowercase.

Thank you again for your consideration,

John Williams (On behalf of other authors)

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Response to Reviewer 1 Comments

I would like to thank Reviewer 1 for their very helpful and insightful comments. For their convenience, changes to the text indicated in blue in the main text and the appendix.

Point 1: The authors' analysis workflow begins with candidate GWAS selection from EpiGraphDB, and two studies "ukb-a-11 Morning/evening person (chronotype)" and "ebi-a-GCST003837 (Chronotype)" are selected as exposures and basis of further analyses. I wonder if the authors could further comment on why a particular GWAS is selected amongst the multiple curated studies of the same trait?

Response 1: The EpiGraphDB database contains two curated studies with the "Chronotype" exposure trait, and two with the "Morning/evening person (chronotype)" trait. Of the studies investigating morning/eveningness (as reported), ukb-a-11 has 13 reported significant (5e-8) findings using the fixed effects IVW method, while the ukb-b-4956 has 5. Both of these studies use public, unpublished GWAS summary data from the UK Biobank, so one was selected. The other two studies each reported 51 associations, again from the UK Biobank. Changes in GWAS methods and the use of imputed GWAS data explain the increased associations. The ebi-a-GCST003837 study has been previously published, while ieu-a-1087 used a subset of the UK Biobank enriched for smoking. Because smoking may be a confounding variable in analysing the effect of chronotype on cardiometabolic traits, thus GCST003837 was selected.

Point 2: In the first stage the authors re-analysed pre-computed MR results of the data source on the identified exposures and outcomes, and then in the second stage examined the statistical findings with additional pre-computed results regarding confounders, intermediates, etc from the data source. As the authors have suggested in the manuscript, differences with methods could lead to results that do not agree with each other. As found in the documentation of EpiGraphDB, pairwise and confounder MR results are from this study (https://doi.org/10.1101/173682), and therefore I think the authors should have further discussions comparing the original method to the steps they took.

Response 2: Thank you for the opportunity to clarify and discuss the methods we used. We have discussed this further, starting on line 287 (additions in blue). One correction of note, we accidentally wrote "Fixed Effect" instead of "Random Effect" when reporting the results in text – this did not change the analysis, results, or reporting in the Appendix, but did explain some of the different p-values observed between our replication and the pre-calculated results found online. Other discrepancies are due to method choice (IVW, Egger, etc) and SNP inclusion, which is discussed in the text, while the repository's choice for any individual analysis is not apparent.

Point 3: Regarding Figure 2, outcome study labels are hard to read, and exposure studies don't show trait labels so I would suggest some formatting to improve readability.

Response 3: Thank you for the suggestion to improve Figure 2. We have added the trait labels, enlarged the font, and made the figure landscape in orientation to give enough room for more easy readability.

Point 4: The colourscheme in Figure 6 and Figure 7 is not very suitable for reading in a document with white background, especially the lines in yellow, and for Figure 6 it might be worth having a separate version in supplementary as it is still difficult to read in detail.

Response 4: We would like to thank the reviewer for their formatting suggestions. We have included an A2-sized vector graphic (PDF) of Figure 6 in the Appendix that can be zoomed in without loss of resolution, and have updated the colourscheme of Figures 6 and 7. We hope this improves the readability. Text has been added to page 1 of the Appendix to reflect the additional figure (text in blue). Changes occurred in the Figure 6 and Figure 7 legend text to reflect colour updates

Point 5: The authors obviously need to thoroughly correct the various typesetting errors in cross-referencing tables (e.g. line 160, line 245, etc), and typos (e.g. "White nodes [are] potential confounding variables" in Figure 6's legend). I also noted that the results reported by authors do not have a consistent use of decimal separators, i.e. in the main text it is "." and the in the supplementary it is a mixed use of "," and "." (Appendix Table 1). In addition, I was confused the text in lines 105-106, where the authors wrote "I is an error term" and I think they meant "ϵ"?

Response 5: Thank you for highlighting the formatting errors and typos. These have been addressed (in blue where noted). Decimal separators have all been changed to "." in the Appendix Tables. Cross-referencing has been made consistent in each line given (blue), and in one case the phrase "supplemental table" changed to appendix table. We have changed the error term in the equation.