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:** Please provide your response for Point 1. (in red)

**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:** Please provide your response for Point 2. (in red)

**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:** Please provide your response for Point 2. (in red)

**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:** I would like to thank the reviewer for their formatting suggestions. I 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. I hope this improves the readability. Text has been added to page 1 of the Appendix to reflect the additional figure (text in blue).

**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 "\( \epsilon \)"?

**Response 5:** Thank you for highlighting the formatting errors. Decimal separators have all been changed to “.” in the Appendix Tables.

Appendix 1: AppendixTable1EpigraphDBIVWresults.xlsx. EpiGraphDB data downloaded to produce Figure 2.

Appendix 2: AppendixTable2StudyCharacteristics.xlsx.

SNP-level information on all 10 studies analyzed needed to reproduce analyses of these 10 studies. to supplementary scatter plots, leave-one-out plots, and Figures 3-5 and supplementary figures.

Appendix 3: AppendixTable3MRAnalysisResults.xlsx. Summary level results for each of the 10 MR analyses, including leave-one-out statistics, MR-Egger statistics, and all MR statistics. Used to produce supplementary scatter plots, leave-one-out plots, and Figures 3-5 and supplementary figures.

Appendix 4: AppendixTable4ConfounderGraph.xlsx.

Statistics downloaded from EpiGraphDB needed to reproduce figures 6 and 7.

\textcolor{blue}{Appendix 5: AppendixFigure7: A2 size PDF of Figure 6 for on-screen viewing.}