Dear editor:

We thank you for the opportunity to revise our manuscript. The editor and reviewers have provided helpful suggestions. We’ve outlined below how we addressed every one of the comments. We’ve placed the original text in italics and our replies in bold.

Sincerely,

Frederick Boehm and Xiang Zhou

*Editor and Reviewer comments:*

*With pleasure I read this manuscript that compares methods for Mendelian randomization (MR). I think the authors did a*

*lot of work in making such an extensive review. However, I do have some comments:*

*-I think the current manuscript is somewhere in between guiding people who are new to MR and giving a complete*

*overview of all methods. I think adding a standard MR dag would be beneficial to the first type of reader. This could be*

*part of Fig 3 perhaps.*

**We completely agree. We’ve added this DAG to Figure 3.**

*-On page 13, the authors write 'This can happen, for instance, by using a noncausal SNP that is in high LD with a causal*

*SNP. Second, because many traits are polygenic or omnigenic, multiple causal SNPs may be*

*in high LD together. LD clumping is likely to omit one or more of the causal SNPs, which candiminish statistical power in*

*MR analysis.' (p13). I think this is not too much of a concern, as long as there is strong correlation between these SNPs,*

*because the GWAS estimate of a single variant also takes into account it's LD structure with other SNPs. Hence, it is not*

*really only the effect of that specific SNP that is measured and hence not much information should be lost due to*

*clumping.*

**We agree. We’ve omitted these sentences in our revised manuscript.**

*-The current section 'Applications of MR in GWAS' seems quite random why these specific studies were chosen. To me*

*as a reader I wonder why are these specific studies chosen.*

**We agree. To shorten the manuscript, we’ve omitted this section.**

*-I think the manuscript could give more guidance to readers on what methods should be used or not. This could easily*

*extend Figure 4. Currently it is unclear how different these methods really are and when they will give different results.*

**Thank you for the opportunity to clarify this. To discuss this further, we’ve added a section “Practice recommendations”.**

*-I think the manuscript would improve if it would say something on future prospects (this is somewhat done in the section summary and outlook, but is currently a bit underwhelming). E.g. what are currently open challenges?*

**Thank you for the opportunity to address this issue. We’ve extended the summary and outlook section to discuss current and future prospects, including open challenges.**

*Minor remarks:*

*-Please beware that Mendelian randomization should be written with capital M (e.g. caption Figure 1).*

**Thank you for pointing this out. We’ve corrected this in the updated manuscript.**

*-mathematical symbols sometimes difficult to read (\hat{} command often overlap)*

**Thank you for bringing this to our attention. We’ve fixed this in the updated manuscript.**

*-I find the graphical abstract unclear.*

**Thank you for the opportunity to revise the graphical abstract. We have included the new graphical abstract with the revised manuscript.**