Subject: IJE Submission - IJE-2022-08-1030
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From: International Journal of Epidemiology
To: Matthew Lee

IJE-2022-08-1030
Systematic review and meta-analyses: What has the application of Mendelian randomization told us about the causal effect of adiposity on health outcomes?

07-Oct-2022

Dear Dr. Lee,

We have now had a chance to review the paper you submitted to the International Journal of Epidemiology. The paper has been refereed by at least one external reviewer and has also been read by an Editor or Associate Editor of the Journal.

I am afraid that we found that your submission was not suitable for publication in the International Journal of Epidemiology. This decision was made both in response to referee comments and also on the grounds of suitability with respect to the journal and priority in relation to the other submissions we have received. The decision is thus not solely influenced by the particular comments of referee(s).

We enclose a set of referee comments which we hope will be of use when revising your paper for submission elsewhere.

Thank you for your interest in the International Journal of Epidemiology.

Yours sincerely,

Stephen Leeder
Editor-in-Chief

Comments from Referees:

Referee: 1

Comments to the Author
Thank you for inviting me to review this manuscript and I want to firstly and importantly acknowledge the huge volume of work that has been undertaken. In general, this is well written and easy to follow. I do have some concerns regarding statements throughout that implicate MR is always a better source of evidence compared to other studies designs. Surely, for example, meta-analyses of observational data is also of value? My specific comments are below.

Key Messages: I suggest the authors edit the point “Evidence for the causal effects of adiposity and health outcomes has not been comprehensively evaluated.” A multitude of evidence (MR studies, observational studies, systematic reviews of observational studies etc) suggests that adiposity is casually associated with adverse health outcomes. What the current manuscript adds is further evidence to support this statement looking exclusively at MR studies – this certainly adds value but is not the only way to assess causality; hence to ‘comprehensively evaluate causality’ the authors would in fact need to expand the review to beyond just MR studies. This point applies throughout the text as well e.g., last sentence of 1st paragraph of the ‘Introduction’ and 1st sentence of “Strengths and limitations”.

I note the authors have considered as exposures several ‘adjusted’ factors for example, WHR, WC, HC etc adjusted for BMI. I am sure the authors are aware of the potential issues of examining these exposures in an MR context (see https://doi.org/10.1093/ije/dyaa266). Given the inherent bias in these associations why focus on

them and meta-analyse them together? I would argue that these exposures should be dropped (with an explanation as to why they were excluded). A meta-analysis of biased associations will be biased.

I suggest the authors reconsider the statement "These inconsistencies may reflect the robustness of MR estimates to unmeasured confounding between the exposure and outcome in comparison to observational studies or …." This is not entirely true, is it? Have the authors assessed pleiotropy in all included studies and only included in the meta-analyses studies which suggest that there is no pleiotropy? In any case, in both MR and observational studies one can never be completely confident in the assumption of 'no unmeasured confounding' and therefore MR is not (in my view) more robust to this assumption.

Some comments on (i) the variability of instruments used from study to study is warranted and (ii) the fact that non-linear associations were not considered in the literature is important to flag – because it is not just overweight that is a concern, but underweight is also a serious health problem.

Minor comments:
For clarity, can the authors confirm in lines 390-393, would results be biased towards the confounded observational estimate, or the observational estimate more generally?
Completely acknowledging the tediousness of referencing a manuscript, please double-check the reference library because at various places "(Error! Reference source not found.)" appears.
Figure 3 does not appear in the pdf (but does in the html version of the manuscript).

Referee: 2

Comments to the Author
Systematic review and meta-analyses: What has the application of Mendelian randomization told us about the causal effect of adiposity on health outcomes?

Matthew A L et al

In this study the authors performed a systematic review and meta-analysis of a series of outcomes previously associated with a causal effect of adiposity. Although a large number of relevant papers exist, the authors followed a well though procedure to select the most reliable evidence which they meta-analyse. The results confirm several suggested associations. An attempt to provide a narrative of studies not used in the meta-analysis was also attempted. This is an interesting idea that will help our identification of risk factors in the future but some limitations are obvious.

1) My main concern is the period reviewed. The authors state that they covered publications up to February 2019. Although I appreciate the effort and time that a systematic review requires, if this manuscript is to be published in IJE it will appear almost 4 years after the review time cut-off. This would have been OK for clinical trials that are few and take years to complete, but for a rapidly progressing topic as the causal impact of adiposity, I am afraid that this delay negatively impacts the work done. This is more of an issue if we consider that adiposity is a well-known factor of COVID-19 severity with different MRs recently published looking at the causal associations of related traits and outcomes.

2) The authors have included pre-prints in their sources, which is commendable. Though the authors restrict their search to bioRxiv and do not mention medRxiv, which also publishes MR studies.

3) Line 255: "The remaining 26 tests had positive effect estimates, 15 of which had CIs that did not span the null". This description can be misunderstood easily. If the CIs span the null, do we have evidence to say that the effect is positive or negative, or should we just describe it as indistinguishable from 0? In my view, under a frequentist setting suggesting that these associations have positive or negative effect can be problematic.

4) Line 29. Why three outcomes? The results provide analyses for many more.

5) Line 112: "If a study focused on adiposity alongside other exposures, the effect of each adiposity measure was reported separately if available. If it was not available, the joint effect was reported". I am not sure what the authors mean here. Have they done this in the manuscript? At which point?

6) Line 216: Some of the references in the copy I downloaded appear with an error.

7) Figure 3: The in-text Figure 3 does not render correctly. It is OK at the end of the manuscript.

8) In Figures 4 and 5 it will be good to add that the p-values are for the heterogeneity test.

9) Line 281: “BMI was the predominant exposure and was found to be associated with an increase in the risk of all cancers tested (colorectal, endometrial, lung, ovarian, and prostate”. This is not true for breast cancer. As CIs cross 0 it is not correct to describe an association with prostate cancer either. The correct statement is similar to: no evidence of association were observed with prostate cancer.

10) I am not convinced that the Narrative analysis adds any additional information to this work. I suggest that the authors remove this section.

11) Line 325: General statements on the association of adiposity to cancer are not taking into account the vast heterogeneity between cancer types and should be avoided.

12) Line 358: HDL and LDL are described as metabolites (from previous sentence). This is not correct. All studies used for HDL actually use HDL-C instead of the particle. For LDL, one study appears to use LDL as particle while the other LDL-C in which case the meta-analysis is not looking at the same outcome and should be revised.