Reviewer’s report

Title: Combining Directed Acyclic Graphs and the change-in-estimate procedure as a novel approach to adjustment-variable selection in epidemiology

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Reviewer: Hsin-Yi Weng

Reviewer’s report:

In this manuscript, the authors proposed a novel approach of using the observations in empirical data to assist in examining and revising the prior DAG. This brings up an immediate logical concern about whether it is appropriate to use samples to test the assumptions about the underlying population where the samples are from. After reviewing the manuscript I am still not fully convinced by the authors that their approach is appropriate. This is mainly because the authors did not critically discuss how the implications of sampling variation may affect their approach. For example, a non-confounding variable (in the population) may cause a change in estimates (or vice versa) in a sample by chance alone. The empirical example presented in this manuscript, which included only 17 cases in the PKD group, is a good example to illustrate this concern. The concern might be exacerbated by increased number of covariates to be considered or by weak confounders. I do not agree that empirical data from a single sample can be used to make decision on complex causal assumptions that may involve a set of confounding variables and different biases.

My second major concern is about their procedure of starting with only a single preferred working DAG. This is conflict (or confusing to a reader like me) with their suggestion of “The researcher should also list the main uncertainties when preparing the DAG”. I will suggest that instead of preparing only a single prior DAG, the researchers should prepare a group of prior DAGs each presenting different prior assumptions. Then they start with the simplest DAG (i.e., the one contains the least number of covariates in the minimally sufficient variable set or contains the covariates that can be best measured) or the most preferred (if any) DAG. The three main reasons to do so are: 1) DAGs are the best means to explicitly present prior assumptions, 2) It is not uncommon that two or more DAGs are equally good or possible, and 3) the results from empirical data should be used to evaluate only within this group of prior DAGs, thus it may help prevent the problem of researchers trying to revise DAG to fit the observed data. Point number two is particularly troubling me. Based on the proposed approach, users will report the results based on two DAGs, the working (prior) DAG and the revised DAG (based on data). Why limited to only these two sets of causal assumptions if all prior assumptions are equally plausible?

My third main concern is the title of the manuscript, which is “Combining Directed Acyclic Graphs and the change-in-estimate procedure as a novel approach to adjustment-variable selection in epidemiology”. I feel it is not reflecting their
objectives accurately as the main objective of the proposed approach was to use data to assist in reviewing the prior DAG.

The authors ambitiously tried to convey some very complex concepts to the audiences in this manuscript. But who are their target audiences? Those who are expert in DAGs or with only little knowledge? The current manuscript does not suit both groups of audiences well. This comment is especially for the subsection of DAGs and minimally sufficient adjustment variable sets in Methods. The authors may leave the whole subsection out by targeting only those whom have sufficient knowledge of DAGs or they should provide more details so the readers can follow the contents better. For example, by adding “A<-B->C represents a backdoor path from A to C through B” and using this example to explain what children and parents are would make the manuscript more readable. In addition, for their example of A->B<-C, explain that B is the collider. Given the complexity of this manuscript, I will suggest the authors to target audiences who already have sufficient knowledge of DAGs and focus on their approaches, however. Similar comment also applied to the appendix, particularly the appended table, which I found to be difficult to follow. It might help if the authors could provide more detailed description of each column title in the table.

The following are additional minor comments:

1. Abstract; Background: remove quotations for expert-knowledge.
2. Abstract; Background: change “change-in-coefficient” to “change-in-estimate”.
3. Please use the same numbering: such as i. in page 6 or (i) in abstract.
4. I don’t understand the wordings describing the two conditions for a sufficient variable set to adjust for confounding in pages 6 and 7. Please revise the wording.
5. Page 7, Using minimally sufficient adjustment sets to compare a DAG with data: check the wording of the first sentence.
6. Page8: are not mediators (or ancestors or descendants)...or colliders (or descendants): what are the ancestors and descendants referred to?
7. Page 9, Defining a “meaningful” change: 10% change is not an obvious “meaningful” threshold at all it is (for most) only a conventional value people use. Why adding quotations to meaningful?
8. Page 12: remove the parentheses for “Following [39], we define C* as the measured variable, and UC as representing all factors affecting measurement of C.” Make the c in UC subscript.
9. Page 14, Empirical example, spell PKD out
10. Page 14: we also show a 10% change in the estimate of what? RD?

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable
**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.