Reviewer’s report

Title: Reducing bias through directed acyclic graphs

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Reviewer: Jay Kaufman

Reviewer’s report:

Comments on revision of Shrier:

Abstract: Not clear why this is restricted to “clinical research”. Can we say “biomedical research”?

Introduction:

The authors write:

“For the purposes of this manuscript, we define it in counterfactual terms: “Had the exposure not been present at that time, the outcome would have differed”, where outcome may be dichotomous (e.g. occurrence/disappearance of disease) or continuous (e.g. a different value of blood pressure compared to the non-exposed condition).

But if the variable is continuous, like blood pressure, then I don’t know what it means for the variable to “not be present at that time”. Can blood pressure be “not present” at some time? Why not also refer to the exposure differing instead of being present/absent?

The authors write:

“Therefore, researchers are limited to causal inference at the population level (e.g. comparative risks)”

Since risk can be defined at the individual level (see Greenland AJE 1987, for example), maybe better to say “e.g., comparing average risks”.

On page 9, it might add to the original contribution of this paper to come up with a new example rather than Pearl’s sprinkler and wet grass, since that heuristic device is not in any way biomedical in nature. If the point of this article is to adapt the Pearl algorithm (as described in the 2000 book) for a biomedical audience, then it may be useful to come up with a more compelling illustrative example in this case, too.

At the bottom of page 10 the authors write:

If there is no uninterrupted series of lines through nodes from X to the outcome, then within this specific causal DAG, there is no non-causal structural association between X and the outcome.
But it doesn’t seem that the authors ever define exactly what they mean by “uninterrupted”. Pearl does so by using the specific criterion of “d-separation”, which the current authors avoid, but I am not sure that this is clear to the reader, since, for example, colliders (not defined until the glossary) will block a backdoor path as long as the collider is not in the adjustment set.

On page 15, I am still uncomfortable with the assertion:

“[a DAG analysis] will allow users of traditional stratification and regression techniques to reduce the probability of obtaining a biased estimate.”

I would say instead that it can reduce the magnitude of confounding bias, but I would not expect that any real analysis would achieve zero bias, since there will always be unmeasured or mismeasured covariates (among other improprieties). Thus, no matter the method employed in an observational study, the “probability of obtaining a biased estimate” is always 1. The same concern applies again at the bottom of page 15 where the authors say that an “unbiased estimate” is produced. It should perhaps read “a less biased estimate is produced”.

Overall, I am still concerned by the use of terms that are never defined (e.g. X being “dissociated” from the outcome) and also by some hand-waiving. For example, the authors reiterate the usual prohibition against adjusting for variables affected by exposure. But this is inappropriate only when one wants to estimate TOTAL effects. In effect decomposition analyses, one will often legitimately adjust for variables affected by exposure. I understand that the authors are premising the entire article on the estimation of TOTAL AVERAGE causal effects, but the failure to be clear about such assumptions is somewhat of a concern for a methodologic article. Or, to give another example, the authors define “Conditional Association” in the glossary by saying that “A conditional association is an association that occurs between two covariates if and only if one includes a common effect in the model.” First of all, what is “a common effect”? An “effect” is some kind of contrast, so this makes no sense to me. Do they mean a common descendent? But more fundamentally, why would the authors assert that variables that are conditionally associated must be marginally independent? I see no reason why variables that have a conditional association could not also have a marginal association. I recognize that the authors are aiming for a paper that will be as simple and as readable as possible, but many subtle issues are thus glossed over in such a way that much confusion could be generated. It is not easy to write a simple didactic article, so I am sympathetic to this dilemma, but where terms or assumptions remain undefined or poorly defined, I still worry that readers could become confused, frustrated or mislead.