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LETTER TO THE EDITOR

The importance of properly specifying your target trial emulation: commentary on Mésidor et al

We read with interest the paper "Effect of statin use for the primary prevention of cardiovascular disease among older adults: a cautionary tale concerning target trials emulation" by Mésidor et al [1]. Using administrative health data from Québec, the investigators estimated large effects for statin use for primary prevention of cardiovascular events and mortality that were biologically implausible and inconsistent with previous studies. A range of sensitivity analyses did not alter this finding. Investigators present this work as a "cautionary tale concerning target trial emulation" (TTE) [1], concluding that their use of TTE was not able to deal fully with confounding. While we agree this study is a cautionary tale, we disagree on why this is so.

A properly specified TTE substantially reduces the risk of bias due to improperly defined eligibility, exposure status, and follow-up, and the authors are correct that residual confounding is still possible [2]. Indeed, a claimed advantage of TTE is that when correctly applied, it "eliminates other common sources of bias so attention can be focused on confounding" [3], rather than addressing confounding directly.

A common cause of TTE failure is "when the time zero, the specification of the eligibility criteria, and the treatment assignment are not synchronized." [2] While we are uncertain as to exactly how time zero (start of follow-up) and exposure were defined in this study, based on the available information we hypothesize that these time points were misaligned, and therefore the target trial was improperly specified. This misalignment is likely to be a greater contributor to the implausible findings than residual confounding.

In this study, treatment was defined as persistence to statins (yes or no) among people newly prescribed statins. This was not defined at time zero, but rather using the first 3 months of follow-up. Similarly, one of the exclusion criteria was experiencing the outcome within the first month of follow-up. Relying on future information to define patient status retrospectively often introduces immortal time bias [2], leading to spurious findings, and should be avoided. Like in a hypothetical trial, eligibility and treatment assignment should be based solely on information available at time zero. To their credit, the investigators used this approach to attempt to reduce the risks of confounding by indication and protopathic bias, by selecting a comparable control group and excluding early events. However, more appropriate approaches are available to minimize these biases [4].

Observational studies of medicine effectiveness and safety are challenging, and time-related biases are common despite their harms [5]. The key advantage of TTE is that—when correctly implemented—it helps avoid these self-inflicted biases so that only unavoidable biases, like confounding, remain. The importance of temporal alignment of eligibility, treatment assignment, and time zero cannot be understated, and a design that does not successfully achieve this cannot reasonably be called a TTE.

Lastly, had the authors shared their analytic code, we would have more certainty as to the potential causes of the observed results. We encourage all authors to share their code and/or detailed methods to encourage reproducibility and replicability [6].

CRediT authorship contribution statement

Andrea L. Schaffer: Conceptualization, Writing – original draft, Writing – review & editing. **William J. Hulme:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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