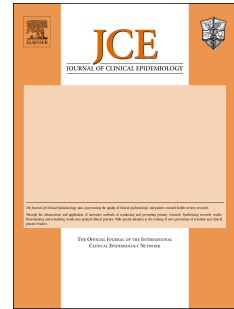# Journal Pre-proof

Author's reply : "The importance of properly specifying your target trial emulation: commentary on Mésidor et al."

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Title : Author's reply : "The importance of properly specifying your target trial emulation: commentary on Mésidor et al."

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Letter to Editor

Dear Editor,

We read with interest the commentary by Schaffer and Hulme[1] regarding our recent article titled " Effect of statin use for the primary prevention of cardiovascular disease among older adults: a cautionary tale concerning target trials "[2]. We are grateful to have an opportunity to respond.

The principal concern raised by these authors pertains to the potential misalignment of the time zero, the specification of the eligibility criteria, as well as the treatment assignment, which could have introduced an immortal time bias. As outlined in the supplementary material of our paper, the follow-up period begins after assignment to the treatment strategy, i.e. after the 3-month window required to determine statin persistence. As such, the follow-up does not start at the date of statin initiation, which would be a misalignment between time zero and treatment assignment and could indeed lead to immortal time bias, as suggested by Schaffer and Hulme[1]. However, such misalignment does not occur in our study.

Schafer and Hulme[1] further raise concerns regarding our exclusion of individuals who experienced the outcome within 30 days of the index date. These exclusions were performed to address a protopathic bias. This approach is commonly employed in the literature[3,4] and is considered the most effective way to mitigate a potential protopathic bias. Of note, a protopathic bias arises when a treatment is administered for an early manifestation of a disease that has not yet been diagnosed[4]. As reported in our paper, we have further used a causal graph depicting, under our hypothesis, that exposure does not affect early events. This approach does not introduce a selection bias and may help control for unmeasured confounders.

We appreciate the opportunity to clarify these issues regarding our analysis and hope that our explanation provides greater transparency of our methods.

References

1.   Schaffer SL HW. The importance of properly specifying your target trial emulation: commentary on Mésidor et al. *Journal of Clinical Epidemiology*. 2025;Under review

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Highlights

Not applicable

Declaration of interests

☒ 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.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: