Published in final edited form as:
Am J Epidemiol. 2007 November 1; 166(9): 1003–1004. doi:10.1093/aje/kwm230.

Petersen et al. Respond to "Effect Modification by Time-varying Covariates"

Maya L. Petersen and **Mark J. van der Laan**
From the Division of Biostatistics, School of Public Health, University of California, Berkeley, CA.

We thank Robins et al. (1) for their thoughtful commentary on our article (2). Before responding, we wish to point out that they altered our notation slightly, using *m* rather than *j* to refer to the baseline time point.

Robins et al. distinguish between two types of history-adjusted marginal structural models (HA-MSMs), those that consider an outcome at a fixed time point ("group 1," or those with multiple baseline time points for a single time-point-specific outcome) and those that consider a moving outcome ("group 2," or those that still use multiple baseline time points but use no more than a single baseline for each time-point-specific outcome). They raise the issue of model incompatibility and make the point that "only MSMs in group 1 can be incompatible and thus lead to logical inconsistencies" (1, p. 996). We concur with their discussion of the pitfalls that can be involved in modeling group 1 HA-MSMs and appreciate their emphasis on this issue.

We make two major points in response. 1) As Robins et al. state explicitly (1), the pitfalls regarding model incompatibility do not apply to group 2 HA-MSMs. However, we discuss only group 2 HA-MSMs in our article (2). Therefore, we would like to clarify that the issue of model incompatibility raised in the commentary does not apply to the method outlined in our paper. 2) We feel that the method outlined in our paper for estimation of group 2 HA-MSMs constitutes a significant practical contribution, for the reasons stated below.

First, as Robins et al. mention (1), group 2 HA-MSMs allow pooling of data across time and can thereby enhance the efficiency of the resulting estimators. Second, this approach provides insight into how effect estimates differ across strata defined by covariates measured at different time points. Our data example illustrates this application: Effect estimates at later time points following loss of viral suppression differed less between subjects with different CD4 T-cell counts than such estimates at earlier time points. We agree that this type of effect modification by time-dependent covariates is different from the effect modification in a group 1 HA-MSM, but we suggest that it is nonetheless both interesting and interpretable. Third, although the issue was beyond the scope of our article, group 2 HA-MSMs can be used to identify interesting dynamic treatment rules, in which treatment assignment is updated over time in response to changes in patient covariates (3).

Correspondence to Dr. Maya L. Petersen, Division of Biostatistics, School of Public Health, University of California, Berkeley, Earl Warren Hall #7360, Berkeley, CA 94720-7360 (e-mail: mayaliv@gmail.com).

We appreciate Robins et al.'s focus on the confounding/ selection bias that can result from the way in which treatment prior to baseline was assigned. We agree that this is an important issue in the interpretation of HA-MSMs and their application to dynamic treatment rules, and we discuss it in more detail elsewhere (3,4). Inclusion in $V(j)$ (or $V(m)$ in Robins et al.'s notation) of covariates sufficient to control confounding of past treatment guarantees that the parameter estimated is only a function of the distribution of the counterfactuals, whereas if this condition is not met, one estimates a causal effect for a selected subpopulation in which the selection was ruled by the treatment mechanism. For example, in our paper (2), we point out the potential role played by changes over time in the composition of the population remaining on nonsuppressive therapy. This issue can also arise in standard baseline-adjusted MSMs if the baseline history includes time-dependent covariates.

Finally, Robins et al. raise an interesting philosophical question. They reason that the group 1 HA-MSM parameter, in spite of the fact that it is well-defined and identifiable, is not well-suited for modeling. One might argue in response that difficulty in modeling a specific parameter should be regarded as a welcome challenge by statisticians, rather than a motivation to avoid the parameter altogether. In the case of group 1 HA-MSMs, however, we wonder whether the issue is less that the parameter is difficult to model and more that in many instances it is not in fact the causal effect of interest. We look forward to future work exploring these issues.

Acknowledgments

Conflict of interest: none declared.

REFERENCES

1. Robins JM, Hernán MA, Rotnitzky A. Invited commentary: effect modification by time-varying covariates. Am J Epidemiol 2007;166:994–1002. [PubMed: 17875581]
2. Petersen ML, Deeks SG, Martin JN, et al. History-adjusted marginal structural models for estimating time-varying effect modification. Am J Epidemiol 2007;166:985–993. [PubMed: 17875580]
3. Petersen ML, Deeks SG, van der Laan MJ. Individualized treatment rules: generating candidate clinical trials. Stat Med. 2007 Apr 20; (Epub ahead of print).
4. van der Laan MJ, Petersen ML, Joffe MM. History-adjusted marginal structural models and statically-optimal dynamic treatment regimens. Int J Biostat 2005;1 article 4. (http://www.bepress.com/ijb/vol1/iss1/4).