Research Letter

An example of how immortal time bias can reverse the results of an observational study

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Bias and confounding can distort findings from observational studies; adjustment or correction for these sources of error rarely dramatically change the results. Immortal time bias, which is included in the follow-up period during which the study outcome by design cannot occur, is a potential source of bias in longitudinal studies.[1-3] Researchers often assume that immortal time bias has, if anything, a negligible effect on results. In this research letter, we illustrate that the effect can sometimes be drastic.

The present re-analysis involves our recently published study that sought to quantify the extent to which quitting smoking might reduce the risk of work disability.[4] We used a non-randomized nested pseudo-trial design comparing the work disability risk of two groups, smokers at Time 1 (T1) and at Time 2 (T2, four years later) and quitters who were smokers at T1 but reported quitting smoking at T2. The measurement of smoking at T1 and T2 involved only those at work, corresponding to other studies in which exposure to smoking is measured from people who were eligible for work disability.

In our published study, the start of follow-up for work disability was T2 for both quitters and smokers.[4] Here we consider three additional time points for the start of work disability follow-up. The alternative options for the start were the following: the reported year of quitting between T1 and T2 for quitters and the average time-to-quit since T1 among quitters for smokers (Option 1); the year of quitting for quitters and T2 (Option 2); or T1 (Option 3; originally suggested by the reviewer of our paper) for smokers.

As the measurements of smoking were from people who were at work at both time points, all three alternative options actually include some "immortal time" when the participant could not have had the outcome (disability pension) due to the study design. This is the period before T2.

Figure 1 shows results from the analysis of the published study and the three alternative options in two independent cohorts and summary estimates from fixed-effect meta-analyses (total N=10 094, see **Appendix** for other details of study population, measurements, and statistical analysis). In the published analysis,[3] the pooled hazard ratio for quitting smoking versus continuing smoking was 0.91 (95% CI 0.81-1.02). This suggests that quitting smoking is associated with a 9% reduction of disability risk during the mean follow-up of 5 to 9 years. Starting the follow-up as defined in Option 1 resulted in a similar hazard ratio; quitting smoking resulted in a 12% decrease in risk of work disability. In contrast, the longer immortal time for those quitting smoking in Option 2 exaggerated the benefits from non-smoking, suggesting a 20% reduction in disability risk, whereas the immortal time from T1 to T2 for smokers in Option 3 completely reversed the association. According to this option, quitting smoking is associated with a 34% increase in the risk of work disability.

It has been suggested that immortal time bias has become more common in studies given the increased use of complex designs.[1] The data presented in this research letter demonstrate that a different immortal time between the exposure and reference groups can bias results in either direction and lead to completely incorrect conclusions. The option with longer immortal time for the "treatment group" (here quitting smoking) than the reference overestimated the benefits of the treatment. A longer immortal time for the reference group not only led to underestimation of the treatment benefits but actually made the treatment appear harmful (Option 3).

We hope this empirical illustration helps epidemiologists understand why immortal time bias should not be ignored in the analysis.

References

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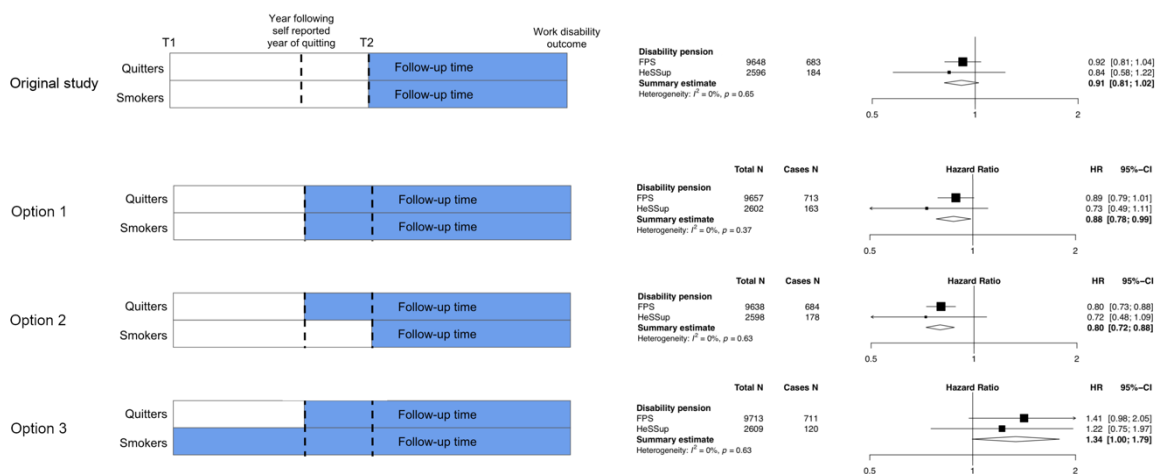
Figure 1. Cox regression analysis of the association between quitting smoking and the risk of work disability in four study designs. All study-specific and pooled hazard ratios were adjusted for age, sex, socioeconomic status, obesity, physical activity, alcohol consumption, and chronic diseases.