

Original article

Implications of immortal person-time when outcomes are nonfatal

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ABSTRACT

Purpose: The amount of immortal time bias in studies with nonfatal outcomes is unclear. To quantify the magnitude of bias from mishandling of immortal person-time in studies of nonfatal outcomes.

Methods: We derived formulas for quantifying bias from misclassified or excluded immortal person-time in settings with nonfatal outcomes, assuming a constant rate of outcome. In the situation of misclassified or excluded immortal person-time, the quantification includes the immortal time and corresponding events mistakenly attributed to the exposed group (misclassified) or excluded from study (excluded) that must be attributed to the comparison group.

Results: With misclassified immortal person-time, the magnitude of bias varies according to the incidence rate ratio of immortal time and comparison group as well as the rate ratio of immortal time and exposed group: toward null for both ratios less than 1, no bias for both ratios equal to 1, away from null for both ratios greater than 1. For one ratio less than 1 and the other greater than 1, the direction and magnitude of bias can be obtained from the formula provided. With excluded immortal person-time, the magnitude of bias is associated with the incidence rate ratio of immortal time and comparison group: toward null for the ratio less than 1, no bias for the ratio equal to 1, and away from null for the ratio greater than 1.

Conclusions: Bias due to immortal person-time in studies with nonfatal outcomes can vary widely and can be quantified under assumptions that apply to many studies.

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Background

Immortal time is a period of follow-up in study during which death is impossible.¹ It may occur when person-time before initiation of treatment is mishandled in an epidemiologic study (participants who receive treatment are immortal before treatment, conditional on being alive to receive treatment). Mishandling of immortal time can bias estimates of effect when the outcome is death or is related to death.² Immortal-time bias results from the mishandling of the person-time between the beginning of follow-up and the date that study participants initiate the treatment of interest. Because the study participants initiate treatment subsequent to entering follow-up, the time between the beginning of follow-up and initiation of treatment is by definition, immortal (participants must live long enough to begin treatment). Moreover, because this time is unexposed, it belongs with the person-time of

the comparison group. When this time is excluded from the comparison group and when the density of the outcome is different (i.e., lower density of the outcome) in the immortal time than in the comparison time, the incidence rate of the outcome in the comparison group will be overestimated.³ An upwardly biased incidence rate in the comparison group will mean that the exposure being compared to it will artificially appear to have a relatively lower rate of the outcome. Similarly, when the immortal time is misclassified as exposed, the incidence of the outcome in the exposed group will also be biased lower.

The inadvertent mishandling of immortal person-time will result in bias that is most severe when the outcome of interest is death. However, when the outcome of interest is not fatal, bias can also occur during the immortal time with the magnitude of bias varying as a function of the density of the outcome of interest in the immortal time relative to the person-time of the comparison group. In this sense, immortal person-time in studies with fatal outcomes is a special case of immortal person-time in all studies, representing the most extremely biasing result (no outcomes occur in the mishandled person-time). On the other end of the spectrum, where the study

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outcome is never fatal, the mishandling will generally not result in bias (the mishandled person-time has a comparable incidence rate to the unexposed cohort) but could affect precision. When the misclassified or excluded person-time is not fully immortal relative to the comparison group, the bias varies. The immortal time will occur with nonfatal events when the outcome of interest is associated with death, such as when the outcome of interest results in death, but not uniformly. (We assume this particular meaning of the term “nonfatal” throughout the article). This phenomenon applies to nonfatal events whether recurrent (e.g., exacerbations of heart failure) or not recurrent (e.g., nonfatal cancer) when there is an association between the outcome and death.

These concepts of immortal time have received increasing attention in the literature in recent years, and the quantification of immortal time bias for the outcome of death has been reported previously.^{1,4,5} However, the issues of immortal time when outcomes are not fatal have rarely been discussed, and the magnitude of immortal time bias for nonfatal events had not been adequately addressed. In this study, we extended a pre-existing framework to quantify the magnitude of immortal time bias from mishandling immortal time in studies with nonfatal outcomes and apply it within a cohort study with a largely nonfatal outcome.

Quantification of immortal time bias with death as the outcome

Suissa¹ described three variant designs of cohort studies that result in immortal time bias because of the misclassification or exclusion of this time from the incidence rate calculation in the comparison group and provided formulas for quantifying the resulting bias. In “time-based” cohorts, cohort entry is usually defined by a seminal point in time (e.g., discharge from the hospital after an acute illness) with subjects followed from this date until the occurrence of the outcome or censoring. The person-time between cohort entry and the first exposure to study drug is misclassified as exposed and results in immortal time bias. In “event-based” cohorts, the start of follow-up is usually defined by a clinical event (e.g., diagnosis of diabetes) that precedes the initiation of treatment. Subjects are followed¹ from the earlier date of cohort entry until the occurrence of the study outcome or censoring. As a result, person-time before treatment in the exposure groups is immortal and misclassified as exposed when it is indeed unexposed. In “exposure-based” cohorts, cohort entry is preferentially defined by the first occurrence of the exposure of interest (e.g., a dispensing of a prescription drug), which, on average, is later than the time at which subjects fulfill the study’s eligibility criteria. As a result, eligible and unexposed person-time before initiation of treatment of interest is excluded from the study while it belongs among the person-time of the unexposed group. This excluded person-time is immortal because the subjects subsequently received the exposure of interest. This hierarchical selection of patients for cohort entry does not generally occur with prospective studies based on primary data collection but has been cited in studies using existing data, such as health insurance claims databases.^{1,2}

Formulas were derived to quantify the magnitude of immortal time bias under the different design variants and under different assumptions of survival distributions. For the time-based and event-based cohorts, Suissa¹ showed the approach for quantifying immortal time bias with the assumption that the outcome occurs with an exponential distribution. The bias is quantified as the ratio of the biased to the unbiased rate ratios and is a function of the proportion of misclassified immortal time p and the ratio of unexposed to exposed person-time k , $k(1-p)/(k+p)$. In the exposure-based cohorts, the magnitude of the bias is $k/(k+p)$. The magnitude of the bias for Weibull distribution is more pronounced than that for exponential distribution.¹

Quantification of immortal time bias when outcomes are not fatal

Suissa’s approach to quantification of immortal-time bias can be modified to quantify the magnitude of immortal time bias when the study outcome is nonfatal. We extended Suissa’s formula for quantifying this bias from misclassified or excluded immortal time in the setting of nonfatal outcomes, assuming a constant rate of outcome (exponential distribution).

Figure 1 is a schema of the person-time categories of interest in the design of time-based or event-based cohorts. In this scenario, the immortal person-time is misclassified as exposed while it should be included in the unexposed group. To calculate the unbiased incidence rate, the immortal time and its corresponding events are included in the comparison group. Note that Suissa assumed there were no deaths because he dealt with the outcome of death. The formulas to quantify bias from mishandling the immortal time in time-based or event-based cohorts when outcome is nonfatal are as follows:

$$RR_b = ((C_1 + C_m)/(T_1 + T_m))/(C_0/T_0)$$

$$RR_u = (C_1/T_1)/((C_0 + C_m)/(T_0 + T_m))$$

where T_1 , person-time in the exposed group; T_0 , person-time in the comparison group; T_m , person-time in the immortal time; C_1 , number of events in the exposed group; C_0 , number of events in the comparison group; C_m , number of events in the immortal time; RR_u , unbiased relative rate; RR_b , biased relative rate.

The magnitude of relative bias is

$$\begin{aligned} \text{Relative bias} &= RR_b/RR_u = \frac{(C_1 + C_m)(C_0 + C_m)}{(C_1/T_1)(T_1 + T_m)(C_0/T_0)(T_0 + T_m)} \\ &= \frac{((T_1/T_m) + (IR_m/IR_1))((T_0/T_m) + (IR_m/IR_0))}{((T_1/T_m) + 1)((T_0/T_m) + 1)}, \end{aligned}$$

which is a function of T_0/T_m , T_1/T_m , IR_m/IR_0 , and IR_m/IR_1 , where IR_m , IR_1 , and IR_0 are the incidence rates within the immortal time, during the exposed time, and in the comparison group, respectively. Compared to Suissa’s approach, the quantification of immortal time bias with nonfatal events involves additional parameters, including the ratios of person-time between unexposed time (and exposed) and the immortal time and the incidence rate ratios comparing immortal time and unexposed (and exposed) time. When the two incidence rate ratios are equal to zero (i.e., there are no outcome events in the immortal time), the formula for the magnitude of relative bias can be simplified to Suissa’s formula for the time- and event-based cohorts.¹

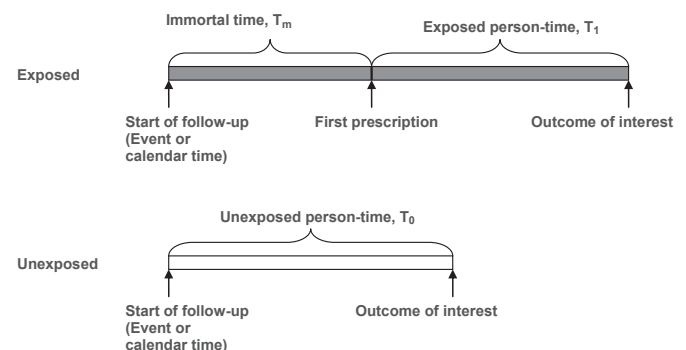


Fig. 1. A schema of the person-time categories in the design of time-based or event-based cohorts. Adapted from Figure 1 in the study by Levesque et al.⁵

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