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EPIDEMIOLOGIC METHODS (R MACLEHOSE, SECTION EDITOR)

Immortal Time Bias in Epidemiology

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Abstract

Purpose of Review Immortal time occurs when study subjects' person-time is misclassified. For example, if exposure is assigned over time, but treated as a binary "ever-exposed" variable, subjects in the exposed group are "immortal" prior to their exposure. We describe immortal time and the context in which it introduces bias and describe several approaches to avoid immortal time bias via design or mitigate it through analysis.

Recent Findings Several authors have described examples of immortal time bias in clinical epidemiology, pharmacoepidemiology, and perinatal epidemiology. Solutions to immortal time bias include analyses that appropriately account for time-varying exposure, and design solutions that align exposure with the start of follow-up.

Summary Immortal time bias is pervasive in epidemiology. It can cause substantial bias. It is, however, easily avoided and can be controlled using appropriate analytic and design strategies.

Keywords Immortal time · Time-varying exposure · Target trial

Introduction

The concept of immortal time has been recognized for at least two centuries [1]. In the 1840s, William Farr noted that "Certain professions, stations, and ranks are only attained by persons advanced in years," and that if one were to compare the longevity of different professions based on death certificates, bias was inevitable because the time spent qualifying for jobs that required longer training became "immortal" [2]. Early deaths could only be attributed to professions where it is possible to start early in life.

One of the first descriptions of immortal time in the modern medical literature was by Gail [3], who critiqued two cohort studies of heart transplantation. Both cohort studies showed an apparent benefit of transplant. Gail, however, noted that in both studies, subjects must have survived long enough to receive a transplant, and that allocating these individuals' pre-transplant time to their total follow-up time introduced artificially longer survival times. Suissa [4, 5•] popularized the term "immortal time," and showed that this phenomenon is fairly common in studies of drug safety using administrative data. For example, when exposure to a drug is defined using repeated prescriptions filled during the follow-up period (e.g., "exposure" to a drug requires two or more prescriptions filled) but treated as time-fixed (ever- vs. never-exposed), there is a period of time between cohort entry and the time when the exposure definition is satisfied in which an exposed event cannot occur (otherwise, the subject would be considered unexposed when the event occurs). If this immortal time is differential between exposure groups (as would be typically the case in comparing a prescribed treatment with no exposure), then comparisons would be biased. Suissa [5•] computed the potential bias under a variety of distributions and scenarios.

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In this paper, we review recent developments in the description of, and solutions to the problem of, immortal time bias.

Illustration of Immortal Time Bias

In general, immortal time bias occurs when person-time is misclassified. In studies where person-time is the denominator, this can occur when a time-varying exposure is treated as time-fixed. In studies where counts of individuals are the denominator (as in the case of pregnancy described in a later section), a time-to-event outcome is treated as a binary event, which automatically produces an ever-/never-exposure classification.

Figure 1 describes a typical example of immortal time. This example describes the setting initially proposed by Suissa et al. in pharmacoepidemiology settings, but generalizes to other settings as well. Subjects A, B, and C enter the cohort at time 0. The exposure changes over time (i.e., time-varying). Subject A becomes exposed at time *t*. Subject B is unexposed throughout the time window. Subject C is unexposed, but has the event at time *t**, prior to *t*. Immortal time bias arises when such a time-varying exposure is treated as time-fixed, i.e., when exposed vs. unexposed person-time is ignored and subjects are treated as ever-exposed or never-exposed. A simple comparison of adverse outcome rates in ever-exposed vs. never-exposed subjects will be biased, because subject A's immortal (unexposed) time is credited to the exposed group. This inflation of the denominator for the exposed group will result in an artificially lower adverse outcome rate among the exposed. Subject C illustrates the problem; if she were identical to A and *would have become* exposed at time *t* had she survived, any subsequent event would be assigned to the exposed group. However, since she did not survive long enough to become exposed at time *t**, her event was assigned to the unexposed group. These early events can only be assigned to the unexposed group. This leads to an overestimate of the rate of the outcome in the unexposed group, an underestimate in the exposed group, and biased estimates comparing the two groups.

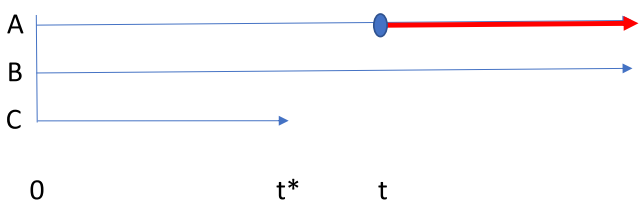

Fig. 1 Example of immortal time. Subject A is exposed to an active treatment at time *t*; subject B is unexposed throughout; subject C has an event at time *t** prior to time *t*

Examples of Immortal Time Bias

Immortal time bias is prevalent in the medical literature. The recurring theme is that described by Farr and Suissa: when subjects must remain at risk long enough to be assigned a specific exposure, and that survival prior to exposure is counted as exposed person-time, bias occurs. Several authors have described examples of immortal time bias in pharmacoepidemiology.

Suissa et al. [4] reviewed 20 studies in which drugs presumed to be unrelated to cardiovascular disease (CVD) had apparent protective effects on the disease. In a cohort of patients with chronic obstructive pulmonary disease, they demonstrated that an inappropriate analysis that failed to account for immortal time bias showed apparent protective effects of gastrointestinal drugs and inhaled beta-agonists on CVD. A second analysis that properly accounted for immortal person-time showed null effects for both drugs.

Hanley and Foster [1] discussed an example in organ transplantation. They reviewed a study of transplant removal in which patients were followed from transplant until death, with the objective of comparing patients whose transplant was removed with those who retained their transplant. They demonstrated that time prior to transplant removal was immortal if removal status was treated as a time-fixed (ever/never) exposure and that substantial bias could arise in comparisons of removal vs. non-removal. They also provided several graphical displays to illustrate how immortal time bias occurs in this setting.

Weberpals and colleagues [6] demonstrated that immortal time bias could substantially affect studies of cancer. Using beta-blocker drugs as an example, they showed that if drug exposure was defined ignoring time, bias arose (suggesting a strong protective effect of beta-blockers on cancer prognosis). A correct analysis using time-varying exposures demonstrated a null effect.

Hernán and colleagues [7] describe another setting in which a form of immortal time can occur. Occasionally, for example when studying an outcome that could not reasonably occur and be ascribed to the treatment, eligibility time may be delayed relative to treatment assignment. Only subjects who are event-free through this time window are counted as part of the study. For example, in the Womens Health Initiative trial, cases of breast cancer recorded in the first year of follow-up were disregarded, because these events were assumed unrelated to treatment. In an observational study, this could occur when eligibility is measured over time and only finalized after a certain event occurs. The time between treatment initiation and eligibility is immortal because events cannot occur in this window. If the window is defined equivalently in both treatment arms, and events are excluded from both arms in an identical manner, then unbiased estimation of a different parameter is possible. On the other hand, if this time window

between treatment initiation is defined differently in the two treatment arms, then a form of immortal time bias occurs.

Immortal Time Bias in Pregnancy

Several recent papers have addressed immortal time bias in pregnancy. Matok et al. described the role of immortal time in the study of exposures to medication in pregnancy [8]. In studies of medication in pregnancy as risk factors for preterm birth, immortal time–related bias can arise if the outcome (preterm birth) is treated as a yes/no outcome rather than a time-to-event variable, or when exposure can occur at any point during the pregnancy but is treated as a time-fixed variable (ever-exposed vs. never-exposed [yes/no]). Women who remain pregnant until full term have a greater opportunity to become exposed by virtue of their longer gestational duration, so that a preterm birth may prevent a woman from having the opportunity to be exposed, rather than being the result of lack of exposure. Bias is again inevitable in comparisons of exposed vs. unexposed. Matok et al. also studied exposure to decongestants during the second or third trimester and demonstrated that if exposure is treated as time-fixed, bias occurs. A similar phenomenon was noted when the exposure was influenza vaccination during pregnancy [9].

Daniel et al. [10] described immortal time bias in the study of non-steroidal anti-inflammatory drugs (NSAIDs) and spontaneous abortion. The structure of this problem is quite similar to that described by Matok et al. Spontaneous abortion occurs early in pregnancy, while NSAID exposure can occur at any time during pregnancy; thus, exposure to NSAID can often be the *result* of not experiencing a spontaneous abortion, rather than the *cause* of it.

Hutcheon et al. [11•] illustrated that immortal time can be present in other studies of pregnancy exposures. Gestational diabetes mellitus (GDM) is typically diagnosed at 24–28 weeks gestation. Pregnancy cohorts, whether using publicly available data or using administrative claims data, typically start following subjects at 20 weeks gestation (which is the gestational age required for legal registration of births in many jurisdictions). If GDM is treated as an ever-/never-exposure, then time between cohort entry and diagnosis of GDM is immortal in GDM-exposed pregnancies. Those events (such as stillbirth) that occur between cohort entry and 24–28 weeks, when GDM is diagnosed, can only be assigned to the unexposed group. Again, bias is inevitable when comparing exposed pregnancies with unexposed.

In each of these problems, the outcome is either gestational age itself (in the case of preterm birth) or strongly associated with gestational age (stillbirth, spontaneous abortion). If the exposure is treated as time-fixed, and thus pregnancies are either exposed or unexposed, immortal time bias will always occur, because shorter pregnancies that do not have the same opportunity to be exposed will be assigned to the unexposed group as those continuing to full term.

Mumford et al. [12] described a problem related to immortal time in the study of time-to-pregnancy similar to the issue described by Hernan et al. When events cannot occur in either arm of a study over a certain time window, it may make sense to ignore person-time in that window for all study arms. Mumford et al. noted that these exclusions do change the target parameter; for example, in the time-to-pregnancy setting, the intent-to-treat parameter based on time that includes the person-time in which no event can occur, and the parameter based on excluding that time period, may be different. However, in the presence of a treatment effect, these parameters should both be in the same direction, and both can be estimated unbiasedly.

Time Axes and Prevention

Several authors have written on how to avoid immortal time bias at both the design and analysis stages [4, 13–15, 17]. In the following, we review analytic and design solutions for immortal time bias.

Analytic Solutions

Suissa et al. [4] showed that accounting for exposure as a time-varying variable (that is, using person-time as the unit of analysis and classifying the person-time before exposure as unexposed) would lead to unbiased treatment effect hazard ratios. Briefly, a Cox proportional hazard model with time-varying covariates (or the equivalent nested case-control design with risk set sampling [13], or an appropriately parameterized Poisson model for rate ratios) will all provide unbiased estimates of the effect of exposure. However, these methods do not allow estimation of cumulative risks, or of survival curves.

Mi et al. [14] compared analytic methods for data in which exposure measurement is time-varying and there is the potential for immortal time bias. They demonstrated via simulation that naïve methods, which either ignore or exclude immortal time, will generally be biased, and that treating exposure as time-varying, which they refer to as the Mantel-Byar method, led to unbiased point estimates. This method assigns person-time to the subject's exposure at that time. If a patient starts follow-up on no treatment and then starts treatment, his or her exposure status will be unexposed, switching to exposed at the time of treatment initiation. Finally, they discussed the landmark method, in which a standard, or landmark, time is determined and exposure is only measured in the period prior to the landmark. Subjects who have the event prior to the landmark time are censored. For example, in a study of pregnancy, one might define exposure prior to 20 weeks gestation, censor events prior to 20 weeks, and only count events after 20 weeks.

This method is shown to have relatively less bias than the naïve methods, but bias does occur when the landmark time is relatively short compared with the overall time axis.

There is one situation in which the Mantel-Byar (time-varying exposure) method will lead to bias. When treatment is determined as a function of a time-varying covariate that is potentially itself a consequence of prior treatment, the Cox model with time-varying exposure cannot reliably estimate treatment effects. This can occur in studies of HIV infection, where CD4 counts or other biomarker measures are predictive of mortality and are both consequences of and causes of changes in treatment [15]. Only methods that appropriately account for this intermediate variable, i.e., the g-methods, provide unbiased estimates of the treatment effect in this setting.

Design Solutions

Hernán and colleagues [16•] framed the problem of immortal time in the context of a target trial, and proposed several design solutions that avoid immortal time bias. They advise researchers to map their observational study to the design of a hypothetical randomized trial. To do this, researchers should identify three important time points: time at which eligibility criteria are assessed and met, time of treatment initiation, and time of start of follow-up. In a typical randomized trial, these three time points are identical; eligibility is measured at the time of randomization, and follow-up typically starts immediately. In an observational study, however, time of eligibility, start of follow-up, and treatment assignment are selected by the investigator, and will not necessarily be identical. This phenomenon is prevalent in pharmacoepidemiologic research. In the examples described above of the classical immortal time problem, start of follow-up is set at the time of initial diagnosis, whereas treatment assignment (i.e., exposure status) is not known until after follow-up has occurred. This is because only those who complete the course of the study follow-up without exposed to active treatment can be assigned to the "no treatment" group. Time of initiation of treatment will be different in the two treatment groups, because the unexposed will be retroactively (at end of study) assigned to "no treatment" and assumed to initiate at time zero while the active arm will start treatment at the time of initiation. If unexposed time prior to treatment initiation is assigned to active treatment (as would occur in an ever/never classification of exposure), this time is immortal.

An important consideration of using a target trial is that one should not focus on the "trial" per se. It is not necessary to think of whether the target trial is feasible and/or ethical. What is important is that the three time points referred to by Hernán should be clearly identified, and that these are as close to identical as possible, or set up in a way that is compatible with the absence of bias. Further, following Mumford [10], a typical trial in practice may not estimate a relevant parameter; when considering a target trial, one does not need to make such a restriction.

General approaches to avoiding immortal time revolve around this target trial principle. Consider exposure to medication during pregnancy. If exposure can occur at any time during pregnancy, treating exposure as a time-fixed yes/no variable leads, as discussed, to bias. How can such bias be prevented? The simplest way to do so is to consider exposure at the time that it occurs; that is, if a pregnant woman is exposed to a medication at 27 weeks, she should be compared with other women who were unexposed up to week 27 and at risk for the event going forward in time. This approach follows the logic in Hernan et al. [7].

The active comparator new-user design [17] is a general design used in pharmacoepidemiology that avoids immortal time bias by design. This design compares newly exposed subjects with others newly exposed to an active comparator drug at an equivalent time. This ensures that the three key time points (exposure, eligibility, and start of follow-up) coincide. There is a natural link to the target trial principle, as this design compares new users of both treatments at the time that the treatment decision is made. Brookhart et al. [18] broadened the active comparator new-user design to in describing the treatment decision design. Suissa et al. recently proposed an extension, the prevalent new-user design [19], which further generalizes the new-user design to include a less-restrictive range of control groups provided certain assumptions hold. These designs can be thought of as the design analogue to the landmark method referred above [14].

Discussion and Conclusions

Immortal time has long been recognized as an important, yet generally easily addressed, phenomenon that can lead to significant bias in estimation of treatment effects. Immortal time has been shown to substantially affect results, particularly in pharmacoepidemiology, and has led to strongly inflated estimates of effectiveness for treatments that have later been shown to be ineffective using correct analyses. Yet, it remains prevalent in the published literature, particularly in studies of medication effectiveness. Recent studies of metformin, which are likely to suffer from immortal time bias [20], have been used as the basis for significant investment in randomized trials.

Design and analytic approaches are readily available that address immortal time and other time-related biases. Consideration of the "target trial" principle, and the synchronization of eligibility, treatment assignment, and time zero of follow-up help eliminate the bias, while appropriate analyses using methods that account for time-varying exposures can prevent immortal time. While these methods do not guarantee unbiased results, as unmeasured confounding is always a

concern, they do at least ensure that immortal time bias is not an issue.

What else can be done to eliminate immortal time bias? First, investigators and individuals setting up population or clinical databases should ensure that information on the *timing* of treatments or exposures is collected in addition to the occurrence of the treatment or exposure itself. For example, maternal and infant health public health surveillance efforts during the H1N1 influenza pandemic in several jurisdictions only collected information on receipt of influenza immunization among pregnant women (as a yes/no treatment), but did not collect information on the gestational age of immunization. As a result, it was subsequently not possible to examine the association between immunization status and adverse outcomes such as preterm birth or stillbirth using a time-varying treatment status. Second, most vital statistics data, and many research cohorts, are restricted to pregnancies that survive past a fixed gestational age. In this setting, immortal time bias cannot be ruled out, should the exposure have effect on early pregnancy losses. For such studies, strategies to extend the gestational age window (for example, by using outpatient care information to identify early losses) would be valuable. Finally, inclusion of immortal time bias in checklists such as STROBE [21] would help increase awareness and help prevent occurrence of this bias.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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