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Time-dependent study entries and exposures in cohort studies can easily be sources of different and avoidable types of bias

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Abstract

Objectives: To display and discuss the reasons and consequences of length and time-dependent bias. They might occur in presence of a time-dependent study entry or a time-dependent exposure which might change from unexposed to exposed.

Study Design and Setting: Recalling the popular study of Oscar nominees and using a real-data example from hospital epidemiology, we give innovative and easy-to-understand graphical presentations of how these biases corrupt the analyses via distorted time-at-risk. Cumulative hazard plots and Cox proportional hazards models were used. We are building bridges to medical disciplines such as critical care medicine, hepatology, pharmaco-epidemiology, transplantation medicine, neurology, gynecology and cardiology.

Results: In presence of time-dependent bias, the hazard ratio (comparing exposed with unexposed) is artificially underestimated. The length bias leads to an artificial underestimation of the overall hazard. When both biases coexist it can lead to different directions of biased hazard ratios.

Conclusion: Since length and time-dependent bias might occur in several medical disciplines, we conclude that understanding and awareness are the best prevention of survival bias.

Keywords: Length bias; Time-dependent bias; Time scale; Immortal time bias; Survival bias; Selection bias

1. Introduction

This article is motivated by a recent debate in the *Annals of Internal Medicine* about the correct statistical approach to analyze a cohort of Oscar nominees [1,2]. The editors pointed out that the central issue was how best to analyze a sudden change in risk because of some life event (becoming ill, starting a high-risk behavior, or starting a treatment) [3]. This debate stimulated statistical research [4,5] because it is a phenomenon in many fields in biomedicine. We illustrate the basic essentials in a technically less sophisticated way by using one real-data example and show direct analogies to several medical disciplines.

Our understanding of diseases and medical decisions relies on unbiased study results. Incorrect results may directly impact patient care, especially if there is no awareness of potential bias. Therefore, much effort is needed to understand and avoid any type of bias [6,7]. Often, as demonstrated in this article, the bias can simply be avoided by applying adequate statistical methods.

Survival models have been established as one of the major statistical methods in medical research [8]. In the analysis, one models the interval between the time of origin (often called as ‘‘time zero’’) and the occurrence of the event [9]. Cnaan and Ryan [10] used the term ‘‘onset’’ as time origin of relevance from a natural history perspective. In the presence of a time-dependent study entry, the entry time (the time when an individual starts contributing to the study) is later than the time of origin; in this case, we say the data are left truncated [9−12]. Sometimes, the impact of a time-dependent exposure that may occur during that interval is being studied.

In this article, we discuss the nature and medical consequences of two types of survival bias. The first is the *length bias* that occurs if one ignores left truncation, that is, the gap between time zero and the entry time of cohort individuals [4,10], and the second is the *time-dependent bias* that occurs if one ignores that a time-dependent exposure is not

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What is new?

Key findings

- Length and time-dependent biases might occur in several medical disciplines. They are best understood with a simple graphical exploration.

What this adds to what was known?

- They can lead to different directions of biased hazard ratios when both biases coexist.

What is the implication and what should change now?

- Already in the design phase of a study, one should discuss and specify the time scale of interest. The timing of all events should be recorded. Careful analysis and reporting of important details of the statistical analysis (including time origin and entry time) are required in the presence of time-dependent study entries and exposures.

happening at time zero, that is, treating a time-dependent exposure as time fixed [4,9,13]. Time-dependent bias has been shown to be very common in medical research and has been studied in several methodological articles [13−25]. Synonymous terms for time-dependent bias are *immortal time bias* [15,26] or *survivor treatment selection bias* [19] in observational treatment studies. This bias can be substantial. Recently, Lévesque et al. [26] demonstrated in an impressive example on using statins for preventing progression of diabetes that it even can lead to an opposite interpretation of the results if data are analyzed incorrectly. Chavalarias and Ioannidis [27] showed that both types often occur together.

The aims of this article were fourfold. First, we attempt to raise awareness of typical and avoidable survival bias by visualizing the bias with a focus on the risk sets (the set of individuals in the study at a specified time). In the presence of a time-dependent exposure, the risk sets are dynamically distinguished between exposed and nonexposed. Second, we generalize the examples and demonstrate analogies to other medical disciplines. Third, we refer to techniques of how these types of bias can be avoided in the statistical analysis (see R computer code in the supplementary material of this article). Finally, we intend to enable interested readers to assess and judge the direction and magnitude of biased results from already published studies.

2. The cohort of Oscar nominees

In 2001, Redelmeier and Singh [1] analyzed a cohort of Oscar nominees and attempted to study the impact of an Oscar award on survival, that is, on age at time of death. The measure of interest is age-specific mortality and the time origin is birth, meaning the time scale is age. The best way to explore a sudden change in risk because of winning an Oscar is to study the time-dependent death *hazard*, that is, the instantaneous risk of dying depending on age. The death hazard is, loosely speaking, the number of death events at age t divided by the number of people at risk just before age t.

In this type of analysis, one is confronted with two challenges. First, actors entered the study at the time of nomination (time-dependent study entry) and were thus not nominated at the time of birth. The time scale is age; hence, beginning of the scale (time origin) is age 0, that is, birth. Second, once nominated for the first time, it may occasionally take some years to win the first Oscar; some nominees may never win the award. Winning the prize is, in statistical terms, a time-dependent exposure. Both facts are displayed in Fig. 1 for some selected actors. In this figure, one can see at which age an individual actor contributes to which risk set (the risk set of either the Oscar nominees or winners). Before nomination, the individual actor does not contribute to any risk set. The corresponding risk sets are illustrated in Wolkewitz et al. [4].

Ignoring the fact that actors were nominated later than birth leads to length bias. Because one incorrectly models a longer period of time, the risk sets are artificially inflated. This leads to an underestimation of the death hazard but only for actors without the Oscar because winning is later than nomination. To account for length bias, data should be analyzed as left-truncated data. Thus, before nomination, the individual actor does not contribute to any risk set.

Ignoring the second fact that winning an Oscar is a time-dependent exposure leads to time-dependent bias. This happens if it is implicitly assumed in the statistical analysis that all Oscar winners have won the Oscar at the time of the first nomination (Oscar win is treated as a time-independent variable). This leads not only to an artificial reduction of the risk set of nominees without an Oscar but also to an artificial inflation of the risk set of Oscar winners (see Fig. 1 and further details in the study by Wolkewitz et al. [4]). To account for time-dependent bias, Oscar win has to be treated as a time-dependent covariate in the statistical model.

Finally, if both facts are ignored, one incorrectly assumes that the group membership Oscar winner−nonwinner is fixed already at the time of birth. In this example, this incorrect assumption leads to an inflation of both risk sets. The risk sets play an important role in the statistical analysis: they appear in the denominator of the estimated death hazard [4]. The number of deaths that appears in the numerator, however, is not affected. To explore the sudden change in risk because of winning an Oscar, the hazard of Oscar winners is compared with that of Oscar nominees, usually in a multiplicative way in terms of hazard ratios.

In this data example, the impact of both biases on the results is not very remarkable even though significance differs [4]. The main reasons are that many actors reach