JAMA Guide to Statistics and Methods

Immortal Time Bias in Observational Studies

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Observational studies are commonly used to evaluate the association between a risk factor or "exposure" and the time that elapses until an outcome of interest occurs (eg, smoking decreasing the time to cardiovascular death). This relationship may be assessed by analyzing natural variation in the exposure and patient outcomes. Such studies may be subject to immortal time bias, meaning that, during the period of observation, there is some interval during which the outcome event cannot occur. The research participants are "immortal" in that they must survive long enough to receive the intervention being studied. An example of immortal time bias can be found in a study by Honigberg et al[1] that evaluated the hypothesis that menopause occurring before age 40 years is associated with the development of cardiovascular disease (CVD). In that study, the authors examined CVD outcomes for postmenopausal women aged 40 to 69 years using the UK BioBank and found an increased risk of CVD associated with both natural premature menopause (hazard ratio, 1.36 [95% CI, 1.19-1.56]) and surgical premature menopause (hazard ratio, 1.87 [1.36-2.58]), relative to women who had experienced normally timed menopause.

What Is Immortal Time Bias?

Bias from immortal time periods is the error in estimating the association between the exposure and the outcome that results from misclassification or exclusion of time intervals.[2] Depending on how the exposed and unexposed groups are defined in an observational study, periods may be misclassified as time spent as exposed to an intervention when, in fact, an individual was not yet exposed (**Figure**). Similarly, the study enrollment process may have led to potential participants being excluded from the accounting of the time spent while either exposed or not exposed to the intervention.[2]

A key feature of the study by Honigberg et al[1] was that the analysis was restricted to postmenopausal women. Eligible women in the study age range (40-69 years) who had already experienced the outcome of interest, or who had not undergone menopause at the time of enrollment, were excluded. Exclusion of these women may result in "excluded immortal time bias." A study participant who was enrolled at age 55 years and underwent menopause at, for example, age 54 must necessarily have survived to age 54. In contrast, there is no guarantee that a woman who underwent menopause at age 35 years would live to age 54. Excluded immortal time refers to time intervals between exposure and the outcome of interest that are excluded from the study; thus, enrolled patients are effectively "immortal" during those time intervals.

Why Is Immortal Time Bias Important?

Immortal time bias can lead to overestimation of the outcome event rate in the unexposed group, underestimation of the event rate in the exposed group, or both.[2] Misclassifying participants to the unexposed group if they are enrolled for drug treatment but experience the outcome prior to filling the prescription for the study drug would overestimate the outcome event rate in the unexposed group. Attributing the immortal time between enrollment and receipt of the study drug as conferred survival time for the exposed group would underestimate the event rate in the exposed group. In pharmacoepidemiology studies, these biases would all lead to a substantial overestimation of the benefit associated with a drug during postmarketing surveillance.[3]

Avoiding Immortal Time Bias

In the study by Honigberg et al,[1] the patient population was restricted to women enrolled into the UK BioBank who were postmenopausal and had not yet experienced a CVD event at the time of BioBank enrollment. This creates at least 1 immortal time interval during which women could potentially experience CVD events, namely the interval from menopause to BioBank enrollment, because women experiencing a CVD event in that interval would be excluded (Figure). The study by Honigberg et al[1] also excluded 2 other groups, namely women with CVD events that occurred in the time interval from menopause to BioBank enrollment and those who experienced menopause after study enrollment (Figure).

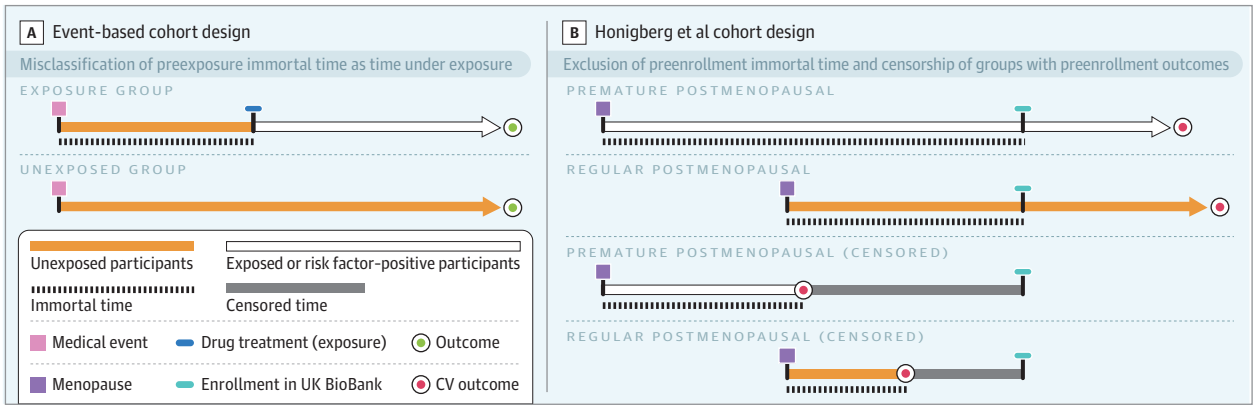
Immortal time bias can be avoided by ensuring that all time intervals during which study participants may experience the outcome of interest are captured and included in the analysis, including time before the exposure first occurred.[2] For example, in a hypothetical observational study in which premenopausal women are enrolled at age 30 years and followed up prospectively using National Health Service medical records to determine if they experience premature menopause and incident CVD events, women would be enrolled into the UK BioBank while they were middle-aged. Except for the small number of women who died before menopause, all women would be followed up from enrollment at age 30 years and would be classified as exposed (premature menopause) or unexposed (normally timed menopause) based on onset of menopause during the study period. The women would then be followed up to determine the time to incident CVD events. This study design would avoid immortal time bias.

To minimize or avoid immortal time bias, patient groups and time intervals should generally be defined similarly to how they would be defined in a prospective cohort study.[4] The available observational data, whether from administrative data, electronic medical records, or other data sources like the BioBank may not always be sufficient to accomplish this. When close emulation of a clinical trial is not possible, then the potential for immortal time bias should be addressed to the extent possible, eg, through sensitivity analyses or other statistical adjustments.

How Was Immortal Time Bias Addressed in This Study?

The sources of immortal time bias in the study by Honigberg et al[1] are challenging to address because of limitations of the UK BioBank data set. Two key limitations of the UK BioBank data are (1) the menopausal status of participating women was ascertained only once, at the time of BioBank enrollment; and (2) no information was available on menopause timing relative to incident CVD events prior to enrollment of the study population. However, because the study was restricted to postmenopausal women, the analysis relied on backward extrapolation from the experience of older postmenopausal women to earlier ages, at which many of them were premenopausal (Figure 3 in their study).[1]

Figure. Examples of Immortal Time Intervals



A, Participants are included based on a qualifying medical event that starts the time interval. Those ultimately included in a drug treatment group may have a period of unexposed immortal time before starting the drug. Events in this period would be erroneously assigned to the drug that had not yet been received, and benefit associated with a drug would be overestimated. B, Participants are included based on UK BioBank enrollment, which sets the time interval, but all included participants may have varying periods of excluded immortal time before enrollment, beginning with the medical event of menopause. Two censored groups represent excluded immortal time bias: anyone undergoing a cardiovascular (CV) outcome prior to enrollment and participants undergoing menopause after enrollment (latter not shown).

For example, consider the CVD risk at age 41 years for a study woman who experienced premature menopause at age 35 and entered the study at age 40. To whom is her CVD risk compared? In estimating the hazard ratio for premature menopause, that woman's risk was compared with the estimated CVD risk at age 41 of women who experienced menopause at an average age of 50 and were enrolled at an average age of 60 (Table 1 in their study).[1] No direct data were collected on CVD risk at age 41 among women who underwent normally timed menopause because women became eligible for study only when they were postmenopausal. The comparison can be made only by back-extrapolation, and it likely involves magnifying prediction error as earlier age periods are included.

Acknowledging the risks of this approach, Honigberg et al[1] conducted several sensitivity analyses, one of which was to address immortal time bias. In eTable 9 in the study Supplement, only women older than 55 years at enrollment were followed up for subsequent cardiovascular events in relation to age at menopause, effectively controlling for age at study entry. That approach sacrifices sample size to avoid immortal time bias but revealed that premature menopause was associated with a higher risk for cardiovascular events.

These analyses, while important and supportive, cannot definitively address potential bias arising from the exclusion of events that occurred after menopause and prior to BioBank enrollment. However, the number of women excluded from the trial based on preexisting cardiovascular events sheds light on magnitude of the potential bias. Figure 1 in the study by Honigberg et al[1] reveals that 102 of 746 women (13.7%) with surgical premature menopause, 576 of 5480 (10.5%) with natural premature menopause, and 8397 of 147 109 (5.7%) with normally timed menopause were excluded from the primary analysis. It is unknown which of these events occurred after menopause in the 3 groups and therefore impossible to know how much immortal time was excluded and the direction of any bias that exists (Figure). However, the larger percentage of events in the women with either form of premature menopause would suggest the bias from exclusion of these events is likely small.

How Should the Results of the Study Be Interpreted?

The primary finding from the study, that middle-aged women who experienced natural premature or surgical premature menopause have an increased risk of incident cardiovascular disease compared with women who experienced normally timed menopause, was consistent across a variety of sensitivity analyses. The possibility that immortal time bias may have influenced the quantitative results remains, and caution should be exercised in extrapolating these findings to younger women; however, the sensitivity analyses and a comparison of cardiovascular events prior to enrollment across the 3 groups suggest that immortal time bias is unlikely to explain away the main association among middle-aged women.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: None reported.

Additional Contributions: We thank Thomas D. Koepsell, MD, MPH, for reviewing the manuscript. Dr Koepsell received no compensation for his contributions.

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