Immeasurable Time Bias in Observational Studies of Drug Effects on Mortality

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Observational studies suggesting that some drugs are effective at reducing mortality may have been subject to “immeasurable time bias” arising from the unidentified presence of hospitalizations when defining drug exposure with computerized health databases. The author illustrates the bias using a case-control study of 1,313 deaths and 1,313 controls selected from a cohort of 2,049 patients with chronic obstructive pulmonary disease from Saskatchewan, Canada, identified from 1990 and followed up through 1999. Different approaches were used to estimate the rate ratio of death associated with inhaled corticosteroid exposure, defined by a prescription dispensed in the 30-day period prior to the index date. More cases had been hospitalized during the 30-day exposure period (72%) than controls (26%), with lower durations of stay for cases who received an inhaled corticosteroid prescription (9.9 vs. 16.2 days), thus introducing variations in measurable exposure times. The raw analysis that did not consider hospitalization found a rate ratio of 0.60 (95% confidence interval (CI): 0.50, 0.73). Alternatively, analyses accounting for variations in measurable times resulted in a rate ratio of 0.93 (95% CI: 0.76, 1.14) when weighted by measurable time, while use of the Kaplan-Meier estimator of the 30-day cumulative incidence of exposure found a rate ratio of 1.35 (95% CI: 1.14, 1.60). In conclusion, immeasurable time bias may be present in several observational database studies suggesting that certain drugs are effective at reducing mortality.

Abbreviations: CI, confidence interval; HR, hazard ratio.
a case-control approach to assess the effectiveness of inhaled corticosteroids in preventing mortality.

DESCRIPTION OF THE BIAS

Typically, in these database studies, a population of subjects with a given chronic disease is identified by use of physician or hospital discharge diagnoses, and a cohort or case-control analysis is performed. Exposure to the drugs under study is assessed on the basis of prescription records, based on prescriptions either written by the physician or dispensed by the pharmacy, on an outpatient basis. Two designs are usually found in these studies.

Study designs

In the case-control approach, the deaths are compared with controls from the same diseased population on the use of the drug, usually around the index date. This index date is defined as the date of death for the case and the corresponding date for the controls, often selected from the case’s risk set. Most studies are particularly interested in the proximate effect of the drug on mortality. Thus, cases and controls will be considered exposed to the drug if they received a prescription for the drug during an exposure time period taken as a short period, such as 30 or 60 days, prior to the index date. In the cohort approach, exposure to the drug is assessed by a prescription around the time of cohort entry or by continuous exposure defined by identifying successive prescriptions over follow-up time. Cohort follow-up ends with the outcome of death, the end of the observation period, possibly the end of continuous exposure, or even perhaps the time that a switch to another drug occurs.

Immeasurable time bias

Immeasurable time refers to a period of time during follow-up, for a cohort study, or prior to the index date, for a case-control study, during which a subject cannot be recognized as being exposed, albeit unknowingly to the investigator. This problem can arise in several ways. First, several deaths occur in the hospital. Such patients will have been hospitalized during a certain period prior to death (index date), so that no outpatient prescriptions could have been received during this time. Exposure during this time period is thus immeasurable. Second, in the study of serious chronic diseases that lead to frequent and lengthy hospitalizations, deaths that do not occur in the hospital can be preceded by hospitalizations that span a portion of the exposure period of interest. Here, again, no outpatient prescriptions could have been written or dispensed during this time period. For cohort designs, patients who are hospitalized during the exposure period soon after cohort entry will appear to have few or no prescriptions dispensed and thus may be more likely to be considered as unexposed. Moreover, hospitalizations occurring during follow-up will affect the continuity of exposure defined by consecutive prescriptions without interruption. Figure 1 illustrates the phenomenon for two subjects from a case-control study using as the exposure definition an outpatient prescription in the 30-day period prior to the index date, while figure 2 describes it for two subjects in a cohort study with exposure and hospitalizations occurring throughout follow-up.

A result of such immeasurable time is that the study subjects will not all have the same time period available to define exposure. Thus, the probability of having a prescription for the drug under study being dispensed during the exposure time period, which forms the basis for the estimation of the rate or odds ratios, will be affected by these varying periods. This immeasurable time will be particularly pronounced in serious chronic diseases where hospitalizations preceding death are numerous and prolonged. The key concern with this phenomenon is that multiple hospitalizations will lead to an artificially lower probability of drug exposure, while being likely associated with an increased risk of death, thus resulting in an underestimation of the rate or odds ratios. We call this the immeasurable time bias.

We discuss below two exemplary studies, case-control and cohort, where immeasurable time periods were doubtless present and likely led to immeasurable time bias.

FIGURE 1. Description of typical case and control subjects with a 30-day exposure time period prior to the index date, with the time in hospital being immeasurable as outpatient prescriptions that define exposure cannot occur.

FIGURE 2. Description of two subjects from a typical cohort study, one being hospitalized more frequently during follow-up, creating immeasurable time periods for outpatient prescriptions that define exposure.
PUBLISHED EXAMPLES

Case-control study: drug combinations in ischemic heart disease

This case-control study used the United Kingdom’s QRESEARCH database to identify the study population of all 13,029 patients with a diagnosis of ischemic heart disease between 1996 and 2003 (4). All 2,266 deaths that occurred after diagnosis were matched to 9,064 controls from this study population who were at risk on the date of death of the case (index date). Prescriptions for statins, angiotensin-converting enzyme (ACE) inhibitors, beta blockers, and aspirin received during the 90-day period prior to the index date were identified and were used to define current exposure. Current use of the combination of statins, aspirin, and beta blocker was associated with the largest reduction in all-cause mortality (odds ratio = 0.17, 95 percent confidence interval (CI): 0.12, 0.23). Other combinations were also associated with important reductions in mortality, including the combination of all four drugs (odds ratio = 0.25, 95 percent CI: 0.18, 0.35).

Although patients with ischemic heart disease often die in the hospital after a possibly lengthy hospitalization or are hospitalized often just prior to death, no data on hospitalization were provided. During these hospitalization episodes, it is clear that the patient could not receive any prescriptions for these drugs from their general practitioner. The time period spent in the hospital during the 90-day exposure period is thus immeasurable by the nature of the database. If the cases are more immeasurable than the controls and differentially so among the exposed and unexposed, immeasurable time bias will occur and result in an underestimation of the true odds ratio.

Moreover, the magnitude of this bias may also be influenced by the evaluation of drug combinations. The combination of all four drugs requires four different prescriptions to be written during the 90-day exposure defining period. If the probability of a prescription for one of the drugs is already lower in the cases than the controls, because of hospitalizations, the resulting immeasurable time bias will tend to be greater.

Cohort study: statins in congestive heart failure

This cohort study used the Ontario, Canada, health databases to identify all residents aged 66 years or more who had been hospitalized for congestive heart failure in 1995–2001 and who survived the first 90 days postdischarge (6). The cohort included 28,828 subjects who were observed from day 91 postdischarge until March 2002. Exposure was defined as a prescription for a statin during the 90-day exposure period, and follow-up continued until more than 180 days elapsed between successive statin prescriptions, death, or March 2002. Subjects with no statin prescription during the 90 days postdischarge were considered unexposed, and follow-up stopped when they received a statin, died, or lived until March 2002. By use of a Cox proportional hazards analysis, statin use thus defined was found to be associated with a 33 percent reduction in all-cause mortality (hazard ratio (HR) = 0.67, 95 percent CI: 0.57, 0.78).

Here again, patients with congestive heart failure are hospitalized frequently, leading to two key immeasurable time periods. First, the rate of readmission within 90 days after the first admission is elevated, so that the hospitalized patients will have less likelihood to be dispensed outpatient prescriptions during this key 90-day exposure-defining period. In this case, the more severe patients, who are prone to be hospitalized more frequently during this key period, will be both more likely to be found unexposed and more likely to die subsequently, thus resulting in an underestimate of the true hazard ratio. Second, the end of exposure defined by no subsequent statin prescription within 180 days of the last one could in fact have simply been an upshot of the patient’s being hospitalized at that time. Such informative censoring, particularly if that hospitalization ended in death, will result here again in an underestimate of the true hazard ratio. In both instances, immeasurable time bias can make the statin exposure appear to reduce mortality.

ILLUSTRATION OF THE BIAS

Methods

To illustrate immeasurable time bias, we use a cohort of patients with chronic obstructive pulmonary disease formed from the health databases of the Canadian Province of Saskatchewan and described previously (10). For the purposes of this example, we identified the subcohort of patients hospitalized for chronic obstructive pulmonary disease, a serious condition, who were discharged alive on or after January 1, 1990, and followed up until December 31, 1999.

A case-control analysis was performed whereby for each death (cases) occurring during cohort follow-up, one control person-moment was selected randomly from the subjects who entered the cohort in the same calendar year and who were in the risk set defined by the case. The date of death was used as the index date for the case and control from the risk set. All (outpatient) prescriptions for inhaled corticosteroids and hospitalizations occurring during the 30-day period prior to the index date were identified for all cases and controls.

Data analysis

We estimated the rate ratio of death associated with the use of inhaled corticosteroids from the corresponding case-control odds ratio, because of the person-moment sampling of controls. The estimation of this odds ratio is based on the probability of a prescription for inhaled corticosteroids dispensed while an outpatient during the 30-day period prior to the index date. When this 30-day period is complete for all subjects, the exposure probability is simply estimated by the proportion of subjects who receive a prescription, and the corresponding odds ratio follows directly. However, since in the situation under consideration this 30-day period is censored for some subjects because of a hospital stay, several possible estimation approaches could be considered. We thus computed the odds ratio in seven different ways. 1) All subjects were simply analyzed according to the inhaled corticosteroid exposure without any consideration for hospitalization or variations in the measurable duration within
the 30-day exposure period; The next two approaches considered the presence of hospitalization by either restriction or adjustment: 2) The analysis was first restricted to subjects who were not hospitalized in the 30-day exposure period prior to the index date and thus had a complete 30-day period to assess exposure for these subjects; and 3) the analysis included all subjects according to their exposure, irrespective of the varying exposable period, adjusting for the presence of a hospitalization in the 30-day period prior to the index date.

The subsequent two approaches involved weighting of each observation according to the number of measurable days: 4) All subjects were analyzed according to the exposure during the 30-day exposure period, weighting each subject according to the number of measurable (nonhospitalized) days in the 30-day exposure period prior to the index date (weight = 1 for full measurable period and proportion thereof if incomplete); and 5) all subjects were analyzed according to the exposure during the 30-day exposure period, considering all subjects with a prescription in the 30-day period as exposed and therefore with a weight of 1, irrespective of the length of their measurable period, and weighting the unexposed subjects proportionately to the number of measurable days in the 30-day exposure period prior to the index date. The final two approaches use the measurable time during the 30-day exposure period to compute either the 30-day rate of exposure or the 30-day cumulative incidence of exposure: 6) The rate of exposure was computed from the number of exposed subjects divided by the number of measurable person-days, standardized to 30 days; and 7) the 30-day cumulative incidence of exposure was computed using the Kaplan-Meier product-limit estimator to account for varying exposable time periods and used this 30-day exposure probability to estimate the odds ratio. The cumulative incidence was computed from the index date backwards in time, using the accumulation of measurable times, thus skipping hospitalized times, until a prescription was found during the 30-day period.

The first five analyses were performed by use of logistic regression with the subject as the unit of analysis to estimate the rate ratios crude and adjusted for age and sex. For the sixth analysis, logistic regression was used with the person-day of measurable time as the unit of analysis to estimate the rate ratios crude and adjusted for age and sex. For the seventh approach, the odds ratio was computed by use of the product-limit estimator of the 30-day cumulative incidence of exposure, and its variance was computed with the delta method applied to Greenwood’s formula for the standard error of the product-limit estimator (11). The adjusted odds ratio was computed by stratifying the cases and controls by age and sex and using a weighted average of the stratum-specific odds ratios, after a logarithmic transformation.

RESULTS

The cohort included 2,049 patients, of whom 1,313 died (cases) during follow-up. A sample of 1,313 controls was selected from the cases’ risk sets. Table 1 shows that the cases spent 11 days, on average, in the hospital during the 30 days prior to death, with 72 percent spending at least 1 day. In contrast, the controls spent 2.3 days in the hospital, with 26 percent spending at least 1 day. Among the controls that had been in the hospital during this 30-day period, the duration of stay was similar at 8.1 and 8.8 days, respectively, for those who received and who did not receive an inhaled corticosteroid prescription in that same period. On the other hand, for the cases, the duration of stay was 9.9 days for those who received an inhaled corticosteroid prescription compared with 16.2 days for those who did not.

Table 2 presents the results of the seven different data analyses. The straightforward naïve analysis that does not take hospitalization into account finds an adjusted rate ratio of 0.60 (95 percent CI: 0.50, 0.73). Restricting or adjusting for the presence of a hospitalization in the 30-day period prior to the index date produces rate ratios of 0.81 and 0.63, respectively. The first weighted analysis, which considered
the measurable time outside the hospital during the 30-day period as a weight for all subjects, found a rate ratio of 0.79 (95 percent CI: 0.64, 0.98). However, considering that the exposed subjects are already exposed, the second weighted analysis that considered the measurable time outside the hospital as a weight only for unexposed subjects found a rate ratio of 0.93 (95 percent CI: 0.76, 1.14). Finally, by using the measurable time during the 30-day exposure period to compute the 30-day rate of exposure, the odds ratio of death becomes 0.93 and 0.98 (95 percent CI: 0.83, 1.17) after adjustment. With the use of the product-limit estimator of the 30-day cumulative incidence of exposure to estimate the probability of inhaled corticosteroid exposure, the odds ratio of death becomes 1.21 and, after age and sex adjustment, 1.35 (95 percent CI: 1.14, 1.60).

**DISCUSSION**

We described immeasurable time bias that can result from the casual use of computerized health databases in conducting observational studies of the effects of medications on mortality. This bias is caused by the impossibility of exposure identification, measured by a prescription given as an outpatient in these studies, when the patient is hospitalized. Because this phenomenon is more likely and persists for longer periods of time for cases than for controls, the result will be an underestimate of the rate ratio, producing the illusion that the drug is effective at preventing mortality. Its importance lies in the rapidly increasing use of computerized health-care databases in the study of serious chronic diseases that can involve frequent and lengthy hospitalizations.

The recently published studies we used to describe the bias showed surprisingly major reductions in mortality, such as the 83 percent (95 percent CI: 77, 88) reduction associated with the combination of statins, aspirin, and beta blockers in the case-control study of patients with ischemic heart disease (4). Although this study could have other sources of bias, such as the choice of the unexposed reference group which may include more severe patients for whom these drugs are contraindicated, it can also in fact reveal two important aspects of immeasurable time bias. First, patients with serious life-threatening chronic diseases are likely to spend an important part of the time prior to death in the hospital. Thus, outpatient prescriptions, used as the measure of exposure in these studies, will necessarily be more likely

**TABLE 2. Crude and adjusted rate ratios of death associated with current use of inhaled corticosteroids by different methods of data analysis with the cases (deaths) and controls selected from a cohort of 2,049 chronic obstructive pulmonary disease patients from Saskatchewan, Canada, 1990–1999**

<table>
<thead>
<tr>
<th>Inhaled corticosteroid use by method of data analysis</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude rate ratio</th>
<th>Adjusted* Rate ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>1,313</td>
<td>1,313</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method 1—all subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in the last 30 days</td>
<td>217</td>
<td>341</td>
<td>0.56</td>
<td>0.60</td>
<td>0.50, 0.73</td>
</tr>
<tr>
<td>No use in the last 30 days</td>
<td>1,096</td>
<td>972</td>
<td>1.00</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Method 2—nonhospitalized subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in the last 30 days</td>
<td>73</td>
<td>247</td>
<td>0.73</td>
<td>0.81</td>
<td>0.60, 1.10</td>
</tr>
<tr>
<td>No use in the last 30 days</td>
<td>290</td>
<td>719</td>
<td>1.00</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Method 3—all subjects adjusted for hospitalization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in the last 30 days</td>
<td>217</td>
<td>341</td>
<td>0.59</td>
<td>0.63</td>
<td>0.51, 0.79</td>
</tr>
<tr>
<td>No use in the last 30 days</td>
<td>1,096</td>
<td>972</td>
<td>1.00</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Method 4—weighted by exposable time†</td>
<td></td>
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<tr>
<td>Use in the last 30 days</td>
<td>169.6</td>
<td>315.5</td>
<td>0.73</td>
<td>0.79</td>
<td>0.64, 0.98</td>
</tr>
<tr>
<td>No use in the last 30 days</td>
<td>661.8</td>
<td>897.8</td>
<td>1.00</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Method 5—weighted by exposable time in the unexposed†</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Use in the last 30 days</td>
<td>217</td>
<td>341</td>
<td>0.86</td>
<td>0.93</td>
<td>0.76, 1.14</td>
</tr>
<tr>
<td>No use in the last 30 days</td>
<td>661.9</td>
<td>897.9</td>
<td>1.00</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>Method 6—rate of exposure per 30 person-days</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Use in the last 30 days</td>
<td>0.26</td>
<td>0.28</td>
<td>0.93</td>
<td>0.98</td>
<td>0.83, 1.17</td>
</tr>
<tr>
<td>No use in the last 30 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Method 7—probability of exposure within 30 days</td>
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<td></td>
</tr>
<tr>
<td>obtained by the Kaplan-Meier product-limit estimator</td>
<td>0.36</td>
<td>0.32</td>
<td>1.21</td>
<td>1.35</td>
<td>1.14, 1.60</td>
</tr>
</tbody>
</table>

* Adjusted for age and sex.
† Frequencies weighted by exposable time correspond to the number of 30-day person-days.
to be underestimated in the presence of lengthy hospitalizations common with these chronic diseases. Second, the use of multiple medications requiring different prescriptions given within the same time span will be more likely to be affected by the time spent in the hospital. Thus, one could suspect that the magnitude of immeasurable time bias could be compounded by the study of multiple medications in these studies. Nonetheless, the magnitude of the bias depends on the prescription interrefill times and the duration of hospitalizations before death. The former depend on not only compliance but also the refill schedule, which is often 30 days for most conditions, but which could be longer such as 90 days for preventive medications such as hormone replacement therapy or statins, while the latter depends on the disease or diseases leading to death as well as the healthcare system of that country. For the cohort study of statins in disease or diseases leading to death as well as the health-care system of that country, for the cohort study of statins in congestive heart failure, the presence of this bias in this study is reinforced by the findings for nonfatal outcomes (6). In contrast with all-cause mortality (hazard ratio (HR) = 0.67, 95 percent CI: 0.57, 0.78), lower and nonsignificant reductions were found for hospitalization for myocardial infarction (HR = 0.81, 95 percent CI: 0.63, 1.03) and stroke (HR = 0.81, 95 percent CI: 0.53, 1.25). Since, unlike death, the first hospitalization for myocardial infarction or stroke is less likely to be preceded by multiple hospitalizations, the immeasurable time will be less important, thus resulting in smaller bias.

The bias will affect case-control and cohort studies differently. For case-control studies with an interest in the effect of current use on mortality, irrespective of how long or irregularly it was used, the bias will be affected by hospitalizations just prior to death. For cohort studies, with an interest in the effect of a drug used continuously and regularly from the start of cohort follow-up until the event time, the bias will be affected by hospitalizations just after cohort entry. In both instances, however, exposure will systematically be underevaluated, because the times of hospitalization will be considered as times of nonexposure.

Of course, other sources of bias could also be playing a role here. For instance, the unexposed reference group used in several of these studies may include more severe patients for whom the study drugs are contraindicated. Moreover, approaching death may lead to reduced prescribing of some drugs, especially preventive agents, and lower adherence by the patient, leading to healthy user effects. Finally, immeasurable time is conceptually simpler than the notion of exposure opportunity (12, 13). Although the latter concept involves questions such as whether the inclusion of men in a study of the effects of female hormone replacement therapy on the risk of stroke will bias the rate ratio, immeasurable time simply involves a mechanism (hospitalization occurrence over time) that causes exposure misclassification. Whether patients may actually have been taken off the drug during the hospitalization and were thus indeed unexposed, or whether they were not prescribed the drug before hospitalization but were actually administered the drug during the hospitalization, which are both concerns for all database studies, the basic feature of immeasurable time bias is that the patients will systematically be considered unexposed by the definition of exposure assessment. This bias will thus lead to a differential misclassification of exposure between cases and controls and, thus, result in significant bias.

In our illustration, the naive approach that does not account for the immeasurable hospitalized time during the 30-day period prior to the index date estimated a significant 40 percent reduction in mortality associated with a prescription of inhaled corticosteroids during this period. However, there were 806 cases (deaths) that had been hospitalized during this same 30-day period and that were considered unexposed by this analysis since they did not receive a prescription. These cases had spent 16.2 out of the 30 days in the hospital, time during which they could not receive outpatient prescriptions, compared with 8.8 days for the corresponding 253 such controls. In fact, 190 of these 806 cases (24 percent) had spent the entire 30-day period in the hospital, compared with seven of the 253 controls (3 percent), and could not possibly have received any prescription at all. Such discrepancies are never noted in studies nor are they taken into account. One recent study that recognized the problem repeated the analysis with cases whose death was not in the hospital (similar in part to the second approach to data analysis) and found similar results (9).

There is no clearly valid approach to data analysis that can circumvent this bias. We showed six different approaches to data analysis that could nevertheless conceivably be undertaken in case-control studies under this situation, from the most naive one to ones that account somehow for the time-varying exposable period. Although such data should perhaps not even be analyzed in the presence of such differential exposure misclassification, at the very least the approach describes the variability in exposable time during the exposure time period. We showed that if these truncated times are considered as censored, the Kaplan-Meier product-limit estimator can be used to compute the 30-day cumulative incidence of exposure, so that the resulting odds ratio will be based on an unbiased estimate of the 30-day exposure probability for both the cases and controls. In our illustration, this analysis changed the rate ratio of 0.60 from the naive approach that did not account for variable immeasurable time to 1.31. Although better than a naive approach, as it accounts for the variable exposable times, this approach is not necessarily valid because it assumes that censoring is random and that gaps in exposable time can be combined. A further challenge with this approach is in its application within a regression model, because the cumulative incidence of exposure is estimated at the group level, so that only a stratified approach to adjustment is possible. Some recent approaches to dealing with differential exposure misclassification could be explored (14–16).

Observational studies of drug effects are an important complement to randomized trials, and their use of computerized databases results in timely results. Although the outcomes movement promoted the use of such studies in evaluating the benefit of health technologies, caution was also given as to their methodological complexity (17). These observational database studies, in addition to the special care usually given in defining outcomes, must, however, also take equal care in their consideration of medication exposure. Immeasurable time bias can, if not recognized,
produce an illusion that a drug is effective, and reporting such findings can have a major impact on the use of the medication, albeit inappropriate.

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