Received: 30 April 2020 | Revised: 29 June 2020 | Accepted: 6 July 2020

DOI: 10.1002/pds.5083

ORIGINAL REPORT

WILEY

# Time-related biases in pharmacoepidemiology

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**Funding information**
Canada Foundation for Innovation; Canadian Institutes of Health Research

## Abstract

**Purpose:** Observational studies using computerized healthcare databases have become popular to investigate the potential effectiveness of old drugs for new indications. Many of these studies reporting remarkable effectiveness were shown to be affected by different time-related biases. We describe these biases and illustrate their effects using a cohort of patients treated for chronic obstructive pulmonary disease (COPD).

**Methods:** The Quebec healthcare databases were used to form a cohort of 124 030 patients with COPD, 50 years or older, treated between 2000 and 2015. Inhaled corticosteroids (ICS) and long-acting bronchodilators were used as exposures, with diverse outcomes, including lung cancer, acute myocardial infarction and death, to illustrate protopathic, latency time, immortal time, time-window, depletion of susceptibles, and immeasurable time biases.

**Results:** Protopathic bias affected bronchodilator-defined cohort entry with an incident rate of lung cancer of 23.9 per 1000 in the first year, compared with around 12.0 in the subsequent years. When latency and immortal times were misclassified, ICS were associated with decreased incidence of lung cancer (hazard ratio [HR] 0.32; 95% CI: 0.30-0.34), compared with 0.50 (95% CI: 0.48-0.53) after correcting for immortal time bias and 0.96 (95% CI: 0.91-1.02) after also correcting for latency time bias. Time-window, depletion of susceptibles and immeasurable time biases also affected the findings similarly.

**Conclusions:** Many observational studies of new indications for older drugs reporting unrealistic effectiveness were affected by avoidable time-related biases. The apparent effectiveness often disappears with proper design and analysis. Future studies should consider these time-related issues to avoid severely biased results.

KEYWORDS

case-control studies, cohort studies, databases, immortal time bias, observational research, pharmacoepidemiology

## 1 | INTRODUCTION

Observational studies have become an important element of the research armamentarium into the effects of medications, particularly as they relate to the real-world context of clinical practice.[1,2] These pharmacoepidemiology studies are typically conducted using existing healthcare computerized databases, an approach that is now recognized and that has led to an explosion in the availability of these databases worldwide. This greater accessibility to computerized data has resulted in a major upsurge in publications of drug effect studies in specialized medical journals. Indeed, the keyword "pharmacoepidemiology" in PubMed appeared in two publications in 1984, 102 in 2000 and increased considerably to 1427 publications in 2019.

  

With this surge came several methodological challenges, of which time-related issues may have had the largest impact on bias. A popular application, the investigation of the potential effectiveness of several old drugs for new indications, has resulted in inconsistent and, in many cases, unrealistic findings. One example is that of the association between metformin, a drug used to treat type 2 diabetes, and cancer after a case-control study reported a lower incidence of any cancer with metformin use.[3] This hypothesis was evaluated by dozens of observational studies conducted in different databases and summarized in several meta-analyses, concluding that an important reduction in cancer incidence and cancer mortality is observed with metformin.[4-8] Many of these observational studies, however, were shown to be subject to time-related biases that tend to underestimate the association and suggest a beneficial effect of metformin on cancer.[9] Nevertheless, randomized trials are currently underway to evaluate the effectiveness of metformin as a treatment for several cancers.[10] Another example is the tremendous effectiveness of statins in treating chronic obstructive pulmonary disease (COPD) proposed in several observational studies, refuted in a subsequent large randomized trial.[11-13]

In this article, we describe some time-related biases that have been identified in observational studies of drug effects over the years. We illustrate the impact of these biases and demonstrate their importance using data on a cohort of patients treated with drugs for COPD identified from the healthcare computerized databases of the Canadian Province of Quebec.

## 2 | DATA FOR ILLUSTRATION

The data source for the illustration is the *Régie de l'Assurance Maladie du Québec* databases resulting from the universal health insurance plan for the eight million residents of the province of Quebec. They include data on all outpatient and inpatients medical services rendered, along with ICD-9 and -10 diagnostic codes, as well as prescription drugs dispensed to all people aged 65 years or older, welfare recipients and other residents of all ages who opt to join the provincial drug plan, thus covering around half the population of Quebec.

The study cohort was formed from all subjects aged 50 years or older, new users of a long-acting bronchodilator inhalers dispensed between 2000 and 2014. These inhalers, namely, long-acting muscarinic antagonists (LAMA) and long-acting ß-agonists (LABA, not combined with an inhaled corticosteroid [ICS]), are specifically indicated for COPD. All subjects were followed from cohort entry (their first inhaler date) until death, the end of insurance drug coverage or data availability (December 31, 2015), or the outcome of interest, namely, lung cancer, acute myocardial infarction, and death. Lung cancer events were identified from diagnoses made by specialists or hospitalization with a primary diagnosis of lung cancer, while acute myocardial infarction was identified from hospitalization records. We used ICS and LABA or LAMA as the exposures of interest.

**KEY POINTS**

- Observational studies using computerized databases have become popular to investigate the potential effectiveness of old drugs for new indications.
- Many studies reporting remarkable effectiveness were shown to be affected by several different time-related biases.
- We describe several time-related biases and illustrate their impact on the effects of different drug treatments for COPD on the outcomes of lung cancer, acute myocardial infarction and death.
- Protopathic, latency, immortal time, time-window, depletion of susceptibles, and immeasurable time biases significantly impact the effects of the study drugs on the outcomes.
- The apparent remarkable effectiveness of new indications for older drugs often disappears with proper design and analysis that avoid these time-related biases.

## 3 | TIME-RELATED BIASES

We review several time-related aspects in the context of the effects of different drugs illustrated using the cohort of patients with COPD on these outcomes.

### 3.1 | Protopathic bias

Protopathic bias occurs when the initiation of a medication is in response to an early symptom of the outcome under study, for example, lung cancer, not yet diagnosed.[14,15] Thus, the exposure to the medication will appear to have occurred prior to the time point when the cancer is diagnosed clinically. However, the exposure actually occurred after the first manifestations of the cancer, causing misclassification that leads to protopathic bias, also referred to as "reverse causality." Protopathic bias is certainly plausible in this context since early respiratory symptoms of a yet undiagnosed lung cancer can be mistaken for another respiratory condition and treated with bronchodilators. Consequently, some new users of a LABA or LAMA that define the cohort may have in fact initiated their treatment for an undiagnosed lung cancer rather than for COPD (Figure 1). If these undetected cancers are more likely to occur during the study drug exposure (or the comparator), this bias will result in an increase (decrease) in the risk for the study drug, and thus an artificial increase in the relative risk. This bias can be minimized in the analysis by including a time-lag, ignoring or reclassifying cancer events occurring within a specified period of time after medication initiation.[16]

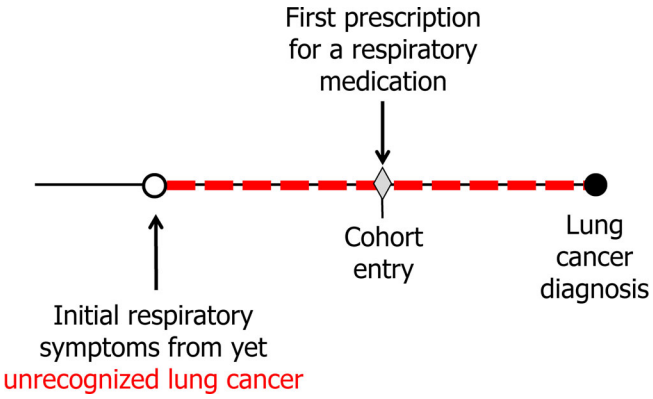


**FIGURE 1** Illustration of protopathic bias in a cohort study of respiratory drug use associated with and lung cancer incidence in COPD. It depicts a respiratory treatment initiated during the time span between the initial respiratory symptoms from a yet unrecognized lung cancer and the clinical diagnosis (red dashed line), which can lead to protopathic bias if this exposure is counted. COPD, chronic obstructive pulmonary disease [Colour figure can be viewed at wileyonlinelibrary.com]

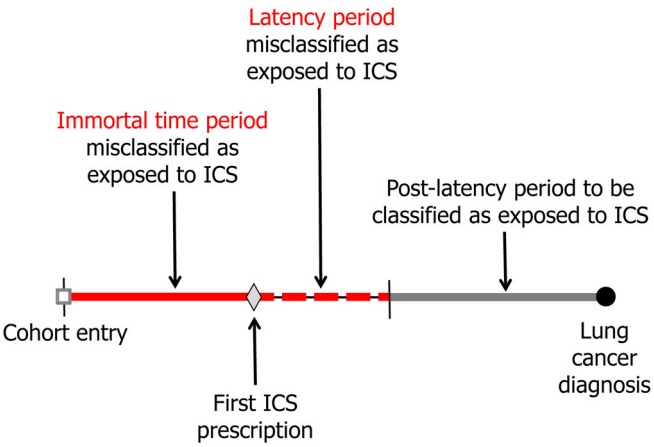


**FIGURE 2** Illustration of immortal time and latency time biases in a cohort study of ICS use and lung cancer incidence in COPD. It depicts the immortal time between cohort entry and the first ICS prescription (red solid line) misclassified as exposed to ICS when it should instead be classified as unexposed. The subsequent latency period after the first ICS prescription (red dashed line) should not be classified as exposed to ICS, only the postlatency period should. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids [Colour figure can be viewed at wileyonlinelibrary.com]

### 3.2 | Latency time bias

Latency is broadly defined as "the period between disease initiation and detection" or more specifically as "the time period between the initiation of the biologically relevant exposure and the development of cancer, or the ability to adequately recognize or detect the cancer in the context of database studies".[17-19]

While this issue can be relevant to any chronic condition, it is common with cancer outcomes. Nonetheless, while cancers are generally thought to develop a long time after initial exposure to a causal agent, drug-related cancer signals are often observed in trials of relatively short duration.[20] For example, the Salford randomized trial of COPD treatment reported eight lung cancer-related deaths in the treatment arm compared with 2 in the usual care arm, despite the short 1-year follow-up.[21] Nevertheless, a certain period of latency is necessary to avoid underestimating a difference in risk between two drugs by including a time period where no differences in risk are biologically plausible (Figure 2). Studies will typically use a 1 or 2-year latency period, so that cancer events occurring during this period could be classified as unexposed or simply not included in the analysis (Figure 2). To avoid making such assumptions, an alternative approach is to allow the analysis to include all cancers occurring after the first drug exposure and estimate the risk function over time to identify the time point where the risk changes, as was used to assess the association between long-acting insulin and breast cancer incidence, observing no risk increase in the first 5 years, with a subsequent increase in the risk.[22]

Some studies, however, inaccurately implemented the latency period.[23,24] For example, the study of antihypertensive drugs and cancer mortality introduced a 6-month latency period "because antihypertensive medications of interest might not immediately influence" the outcome, namely, mortality.[24] However, this latency criterion was implemented as "patients who used antihypertensive medications <6 months before study events or censoring were removed from the user group and treated as unexposed subjects in the analysis".[24] This latency definition properly classifies the exposure only for the patients who had their first antihypertensive prescription in the 6 months prior to death or end of follow-up. On the other hand, it misclassifies the first 6 months after the first antihypertensive prescription as "exposed" for all the patients who died or were censored more than 6 months after their first antihypertensive prescription (Figure 2). A similar approach was used in the study of ICS and lung cancer incidence.[23]

### 3.3 | Immortal time bias

In many cohort studies, the drug of interest is not prescribed at cohort entry but later during follow-up for a number of patients. Several studies, however, classify the patients as exposed to the drug for the entire follow-up, including the time before the first prescription for the drug of interest. This time prior to treatment initiation is in fact yet unexposed and is also called immortal since no outcome events can occur by definition (Figure 2). Such misclassification of this unexposed period as exposed results in so-called immortal time bias.[25,26] Immortal time bias from misclassifying unexposed time as exposed will systematically lead to a large apparent "protective" effect of the drug of interest, with the magnitude of the bias increasing with greater misclassification.[27]

For example, a cohort study of ICS and lung cancer incidence in women with COPD defined exposure as "patients who received an ICS prescription for > 28 days, and those who did not receive an ICS prescription were classified as nonusers of ICS".[28] Thus, a patient is

considered exposed to ICS throughout, even before their first prescription. The time between cohort entry and the first ICS prescription is unexposed to ICS and "immortal," thus misclassified.

Studies employing a new-user design can also introduce immortal time bias. For example, a recent study of the effectiveness of sodium-glucose cotransporter-2 inhibitors (SGLT2i) to treat type 2 diabetes identified all new users of SGLT2i in several databases and matched them to new users of other glucose lowering drugs (oGLD).[29] However, most initiators of SGLT2i had previously used oGLD, so that the time between the first oGLD prescription and the first SGLT2i prescription from the design and analysis introduces immortal time bias.[30] Indeed, the patient must be alive to have received their first SGLT2i prescription. Omitting this person-time will result in overestimating the mortality rate among the remaining oGLD users since the denominator of this rate will be curtailed by the excluded immortal person-time.

## 3.4 | Time-window bias

The nested case-control design is used in pharmacoepidemiology, particularly if the underlying cohort is very large and matching of cases is important.[31] However, while matching is done on several risk factors, duration of exposure opportunity time is sometimes overlooked, which can lead to time-window bias.[32] For example, a case-control study of statin use associated with lung cancer incidence that did not match on time of observation reported an odds ratio of 0.55 for this association. However, the study design resulted in the lung cancer cases having a shorter opportunity time period to measure exposure (around 3 years) while the controls had a longer period (around 6 years). This differential time window of exposure will result in an overrepresentation of exposed controls and a spurious appearance of benefit of the drug (Figure 3).

Even studies with similar observation periods between cases and controls can in some instances introduce this bias, such as a case-control study reporting a lower incidence of hepatocellular carcinoma (OR 0.3) in association with anti-diabetic drugs metformin and thiazolidinediones.[33] While the duration of diabetes was similar between cases and controls, the duration of treated diabetes was different. This differential drug-treated time-window likely led to the apparent lower incidence of hepatocellular carcinoma with these drugs.[9] Another situation is that of stratified analyses that can break the matching on observation periods between cases and controls, particularly when the stratification is based on time-related factors. Time-window bias can potentially be introduced depending on the distribution of observation period lengths in the cases and controls poststratification.

Unlike some of the other biases above, it is difficult with time-window bias to predict the direction of the bias, as it depends on the distribution of treatment observation periods in the cases and controls. Fortunately, this bias can be easily avoided at the design stage by equating the duration of treatment in the cases and controls (32).

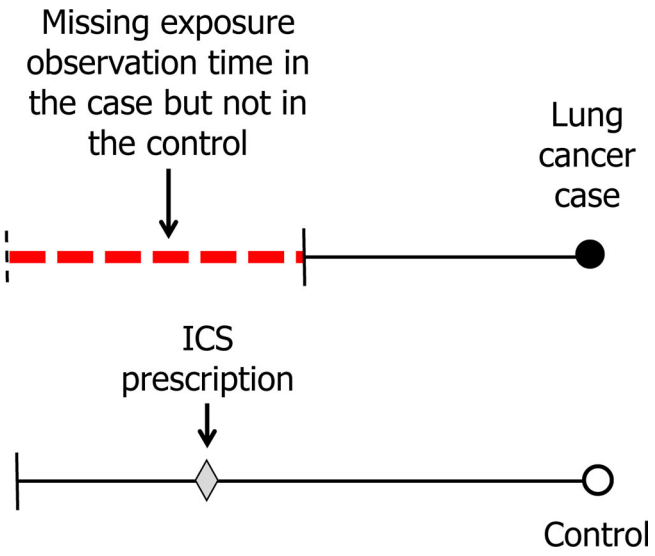


**FIGURE 3** Illustration of time window bias from a case-control study of ICS exposure and lung cancer incidence in COPD. Lung cancer cases have a shorter opportunity time period to measure exposure while controls have a longer period, which will result in an over-representation of "exposed" controls. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids [Colour figure can be viewed at wileyonlinelibrary.com]

## 3.5 | Depletion of susceptibles bias

The term "depletion of susceptibles", first coined by Miettinen, describes a phenomenon where the initiation of exposure to a drug is associated with an early increase in the incidence rate of an acute event, followed by a decrease in this incidence rate with longer duration of exposure to the drug.[34] In essence, a cohort of subjects exposed to the drugs is depleted of its susceptible subjects who had the event early on, with their follow-up necessarily stopped at the time of the event. This phenomenon will be reflected by an early peak in the hazard function, or by a rapid increase and subsequent stabilization of the cumulative incidence function.

It has been observed in the context of gastro-intestinal bleeding with NSAIDs, as well as venous thromboembolism with oral contraceptives and hormone therapy.[35-37] If overlooked, this pattern for the risk function can introduce bias in several ways. First, a case-control stidy comparing two drugs that entered the market at different times can generate imbalances in the durations of use for the two drugs with, for example, a greater number of short-term users with the newer drug and longer term users with the older drug.[37] Thus, the comparison of "current" users of the two drugs will necessarily be distorted by differing durations of use. Another way the bias can be introduced is in comparing a drug that induces depletion of susceptibles with a drug that does not. This situation where the hazards are not proportional can lead to a dilution of the risk difference with longer follow-up, as the hazard ratio is integrated across duration. Thus, in all instances where depletion of susceptibles is present or suspected, the rate ratio must be estimated as a function of duration of use to avoid this source of bias.

### 3.6 | Immeasurable time bias

Many studies in pharmacoepidemiology involve medications used to treat severe chronic diseases, such as heart failure or COPD, with a focus on death as the study outcome. Thus, a case-control study in this context would identify the patients with the chronic condition who die and match them to those who are alive at that time (index date). However, death in such chronic diseases is often preceded by hospitalizations and often occurs during a hospitalization. Exposure to the drugs under study is assessed from recent prescription records during a specified exposure time window prior to the index date. However, typical databases used for these studies only include data on medications obtained on an outpatient basis and no information on drugs received during a hospitalization. Thus, patients who will have been hospitalized sometime during the exposure time window will have missing exposure information during this time (Figure 4).

Immeasurable time thus refers to the period of time under study during which a subject cannot be recognized as being exposed.[38] This problem is rather unique to studies using claims databases, which generally do not cover in-hospital medication use. A result of such immeasurable time is that the cases and controls will not have the same time period available to define exposure, as cases will spend more time in hospital prior to death compared with controls. Thus, the probability of a prescription for the drug under study during the exposure time period will be affected by these varying periods. The resulting immeasurable time bias will generally tend to underestimate the rate ratio since greater hospitalized time in the cases will lead to an artificially lower probability of drug exposure.[38]

This issue is also relevant to any cohort designs that are based on as-treated analyses, where patients who are hospitalized during the exposure period soon after cohort entry will appear to be untreated and considered as unexposed, or treated for a short period. Indeed, hospitalizations occurring during follow-up will disrupt the continuity of exposure defined by consecutive prescriptions without interruption.

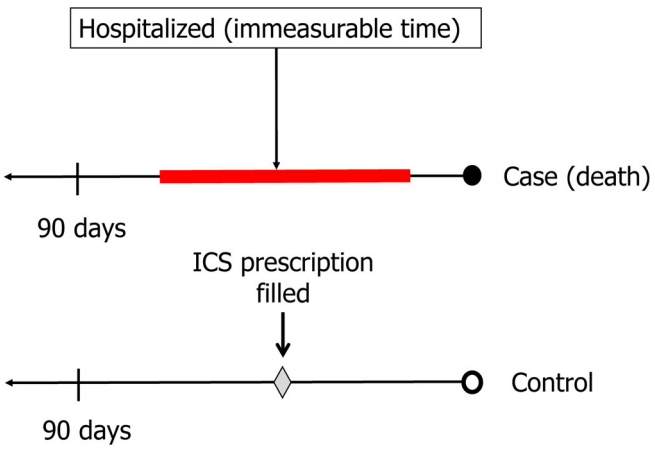


**FIGURE 4** Illustration of immeasurable time bias from a case-control study of current ICS exposure and death in COPD. Cases (deaths) are more likely to be hospitalized just before death while controls are less likely, resulting in shorter opportunity time period to measure exposure in cases compared with controls. COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids [Colour figure can be viewed at wileyonlinelibrary.com]

## 4 | DATA ANALYSIS FOR ILLUSTRATION

To illustrate the potential impact of protopathic bias, we identified the incident lung cancers occurring during the first year of follow-up after the first cohort entry defining LAMA or LABA (no ICS) bronchodilator prescription. The rate of lung cancer in this first year was compared with the rate in subsequent years.

For the effects of latency time bias in assessing the association between ICS and lung cancer incidence, we used a 2-year latency period after the first ICS exposure, which was classified as unexposed, with all subsequent person-time of ICS users classified as exposed. We also assessed the uncommon application used in some recent studies, namely, classifying as unexposed to ICS the person-time in the 2-year period prior to lung cancer, death or censoring, with all other person-time of ICS users classified as exposed to ICS. These analyses were repeated with no latency period.

For the effects of immortal time bias for the association between ICS and lung cancer incidence, we first considered a patient as exposed to ICS if they received an ICS prescription at any time during their follow-up. We then corrected the misclassification by classifying the person-time prior to the first ICS prescription as unexposed and as exposed afterwards. These analyses were repeated with and without the 2-year latency period.

Time-widow bias, also in assessing the association between ICS and lung cancer incidence, was illustrated using the distinctive case-control design where this bias is most evident. Thus, all lung cancer

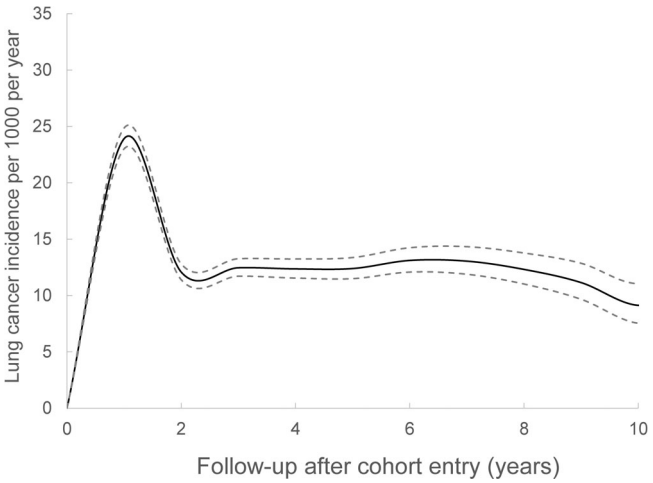


**FIGURE 5** Depiction of potential protopathic bias in the cohort study of patients treated for COPD, showing the peak incidence of lung cancer incidence just after cohort entry defined by the first LABA or LAMA bronchodilator, likely because the bronchodilator was the result of (yet undiagnosed) lung cancer rather than the reverse. COPD, chronic obstructive pulmonary disease; LABA, long-acting ß-agonists; LAMA, long-acting muscarinic antagonists

**TABLE 1** Immortal and latency time biases: Crude rates and rate ratios of lung cancer incidence comparing ICS use vs nonuse, comparing misclassified and correctly classified exposures according to immortal and latency times

| | ICS exposed | | | ICS nonexposed | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lung cancer cases | Person-years | Rate per 1000 person-years | Lung cancer cases | Person-years | Rate per 1000 person-years | Crude rate ratio (95% CI) | Adjusted[a] HR (95% CI) |
| Misclassified latency and immortal time | | | | | | | | |
| Immortal person-time | 0 | 43 121 | | 0 | | | | |
| Latency person-time | 0 | 71 330 | | 1305 | 11 792 | | | |
| At risk person-time | 2569 | 214 821 | | 1574 | 105 889 | | | |
| Total | 2569 | 329 272 | 7.8 | 2879 | 117 681 | 24.5 | 0.32 (0.30-0.34) | 0.30 (0.29-0.32) |
| Misclassified latency time only | | | | | | | | |
| Immortal person-time | 0 | 0 | | 0 | 43 121 | | | |
| Latency person-time | 0 | 71 330 | | 1305 | 11 792 | | | |
| At risk person-time | 2569 | 214 821 | | 1574 | 105 889 | | | |
| Total | 2569 | 286 151 | 9.0 | 2879 | 160 802 | 17.3 | 0.50 (0.48-0.53) | 0.47 (0.45-0.50) |
| Correctly classified latency and immortal time | | | | | | | | |
| Immortal person-time | 0 | | | 0 | 43 121 | | | |
| Latency person-time | 0 | | | 1305 | 83 122 | | | |
| At risk person-time | 2569 | 214 821 | | 1574 | 105 889 | | | |
| Total | 2569 | 214 821 | 12.0 | 2879 | 232 132 | 12.4 | 0.96 (0.91-1.02) | 0.97 (0.91-1.03) |

Abbreviation: ICS, inhaled corticosteroids.
[a]After adjusting for covariates from Table S1.

cases in the cohort were identified and an equally sized random sample of noncases, with exposure to ICS taken as a prescription for ICS prior to the event date for the cases and censoring date for the controls. This bias was corrected by incidence density sampling of an equal number of controls as cases, and exposure taken as a prescription for ICS prior to the event date for the cases and selected moment for the controls.

Depletion of susceptibles was assessed in the context of the effect of initiating a combined treatment with LABA and LAMA and the incidence of acute myocardial infarction. Thus, all new users of a LABA inhaler (combined or not with an ICS) after a LAMA, or vice versa, were identified and the incidence of AMI was computed monthly.

Immeasurable time bias was assessed on the association between ICS exposure and all-cause mortality using a case-control design. All deaths (cases) occurring during follow-up were identified and an equal number of controls was selected randomly using incidence density sampling. Exposure to ICS was defined as a prescription for ICS in the 90 days prior to the index date for each case and control. The bias was corrected by weighing the unexposed subjects by the proportion of the 90-day period spent out of hospital.[38]

## 5 | RESULTS

The study cohort included 124 030 COPD patients who were new users of LABA or LAMA or both between 2000 and 2014, with mean age 72 years at cohort entry and 48% female. The mean follow-up was 4.8 years (range 0-16), during which 82 086 patients received a first prescription for ICS at a mean time of 0.9 years (range 0-16) after cohort entry. The cohort was reduced to 114 715 COPD patients after the exclusion of 9315 patients with either lung or metastatic cancer documented in the year prior to cohort entry (Tables S1), with patient characteristics displayed in Tables S2-S4. There were 8030 incident lung cancers during the entire follow-up.

During the 1-year potential protopathic time period after the cohort entry defining LAMA or LABA prescription, there were 2582 incident lung cancer cases (rate 23.9 per 1000 patient-years). This rate was reduced to 12.1 in the second year and around 12.4 in the subsequent years (Figure 5). Thus, to account for this potential bias, all cases of lung cancer, patients who died or were censored during this first year of cohort follow-up were excluded, reducing the subsequent cohort size used to illustrate the other biases to 102 410 COPD patients.

Table 1, which illustrates the impact of latency and immortal time biases, displays the distribution of person-time and incident lung cancer events by ICS exposure. The exposure classification is based on the method used in the study of antihypertensive drugs and cancer mortality as described above.[24] The approach correctly classifies 11 792 person-years of latency time (1305 cases of lung cancer) as "unexposed," as their first ICS prescription was dispensed in the year

prior to the lung cancer or the end of follow-up. However, this approach misclassifies 43 121 person-years of immortal time and 71 330 person-years of latency time as "exposed." By definition, no lung cancers occurred during the 43 121 person-years of immortal time and 71 330 person-years of latency time. As a result, the rates of lung cancer are 7.8 and 24.5 per 1000 person-years for the ICS exposed and unexposed, respectively. The resulting crude rate ratio of 0.32 (95% CI: 0.30-0.34) suggests a strong protective effect of ICS. When immortal time is accounted for and only the latency time is misclassified, the rate ratio is 0.50 (95% CI: 0.48-0.53). With the proper reclassification of the 43 121 person-years of immortal time and 71 330 person-years of latency time as "unexposed," the corrected rates of lung cancer are 12.0 and 12.4 per 1000 person-years for the ICS exposed and unexposed, respectively. The corresponding crude rate ratio is 0.96 (95% CI: 0.91-1.02), after eliminating the effects of immortal and latency time biases. Statistical adjustment for confounders does not affect the estimates.

Table 2 illustrates the impact of time-widow bias. When the exposure time window is not considered in the design, the mean time window length is 4.3 year for the cases, compared with 5.5 years for the controls, leading to a rate ratio of 0.70 (0.65-0.76). Correcting this by a design that selects valid and representative control person-moments leads to equal-length time windows and a rate ratio of 1.00 (0.93-1.08).

Figure 6 depicts the phenomenon of depletion of susceptibles, based on the 41 375 patients from the cohort who initiated a combined treatment with LABA and LAMA on the same day, with no history of AMI. The figure shows that the incidence of acute myocardial infarction is increased in the first 3 months, decreasing subsequently, thus identifying the possible period of effect for this drug. The incidence rises early, peaking at 2.2 per 1000 person-months, and decreases to approximately 1 per 1000 over the subsequent months follow-up, which provides key information on the period of effect of this combination. Bias will be introduced in a hazard ratio if the comparator drug has, say, a constant hazard of AMI or if the duration of follow-up over which the hazard ratio is computed is much longer that the period of effect, for example, the 18 months shown in Figure 6.

Table 3 illustrates the impact of immeasurable time bias. The cases, 30 569 deaths during follow-up, spent a mean 66.3 days out of hospital within the 90-day exposure period prior to death, while the controls spent a mean 89.5 days. Thus, the measurable time for current exposure to ICS (in the 90-day window) was different between the cases and controls, resulting in a rate ratio of death associated with ICS use of 1.58 (1.53-1.64). Correcting this by weighting the unexposed subjects by the proportion of measurable days during the 90-day exposure period resulted in a rate ratio of 2.18 (2.10-2.26).

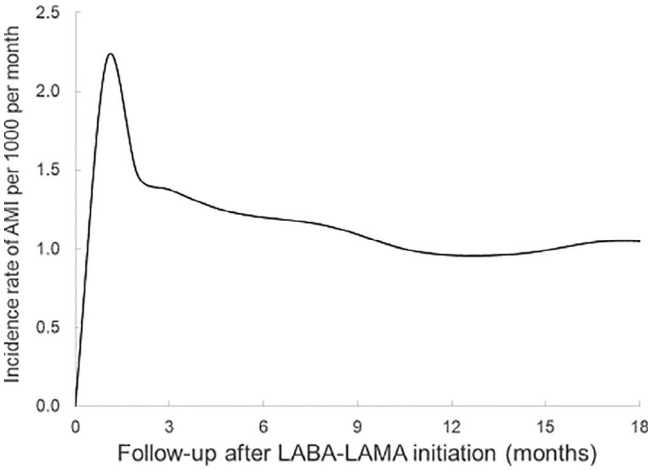


**FIGURE 6** Depiction of potential depletion of susceptibles bias in the cohort study of patients treated for COPD, showing the incidence of acute myocardial infarction just after combining a LABA or LAMA bronchodilator. COPD, chronic obstructive pulmonary disease; LABA, long-acting ß-agonists; LAMA, long-acting muscarinic antagonists

**TABLE 2** Time window bias: Crude and adjusted rate ratios of lung cancer incidence in a case-control study comparing any ICS use vs nonuse in patients with COPD

| | Lung cancer cases | Controls | Crude RR | Adjusted[a] RR (95% CI) |
|---|---|---|---|---|
| Number | 5448 | 5448 | | |
| Time window bias | | | | |
| Time window length (years), mean | 4.3 (2.6) | 5.5 (3.3) | | |
| No ICS use | 2878 (52.8) | 2480 (45.5) | 1.00 | 1.00 (reference) |
| ICS use | 2570 (47.2) | 2968 (54.5) | 0.75 | 0.70 (0.65-0.76) |
| Corrected[b] for time window bias | | | | |
| Time window length (years), mean | 4.3 (2.6) | 4.3 (2.7) | | |
| No ICS use | 2878 (52.8) | 2868 (52.6) | 1.00 | 1.00 (reference) |
| ICS use | 2570 (47.2) | 2580 (47.4) | 0.99 | 1.00 (0.93-1.08) |

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.
[a]After adjusting for covariates from Table S1.
[b]Corrected by using incidence density sampling to select control person-moments.

**TABLE 3** Immeasurable time bias: Crude and adjusted rate ratios of death in a case-control study comparing current (within 90 days) ICS use vs nonuse in patients with COPD

| | Deaths | Controls | Crude RR | Adjusted[a] RR (95% CI) |
|---|---|---|---|---|
| Number | 30 569 | 30 569 | | |
| Immeasurable time bias | | | | |
| Measurable time (days), mean | 66.3 | 89.5 | | |
| No ICS use | 17 964 (58.8) | 20 962 (68.6) | 1.00 | 1.00 (reference) |
| ICS use | 12 605 (41.2) | 9607 (31.4) | 1.53 | 1.58 (1.53-1.64) |
| Corrected[b] for immeasurable time bias | | | | |
| No ICS use | 12 779 (50.3) | 20 658 (68.3) | 1.00 | 1.00 (reference) |
| ICS use | 12 605 (49.7) | 9607 (31.7) | 2.12 | 2.18 (2.10-2.26) |

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids.
[a]After adjusting for covariates from Table S1.
[b]Corrected by weighting the unexposed by the proportion of measurable days during the 90-day period.[38]

## 6 | DISCUSSION

Several methodological challenges face observational studies conducted using existing databases when evaluating the effects of medications on outcomes. For example, the accurate identification of outcome events, the choice of comparators or the availability of confounder data are fundamental issues. Moreover, extensive research has been conducted on accurate design and analysis techniques to control for confounding bias, including methods for baseline and time-varying confounders that can affect subsequent exposure.[31,39,40] However, time-related issues in the design and analysis of these pharmacoepidemiology studies may have the largest impact on bias, impacting particularly on information and selection biases, as we described and illustrated with a study of the effect of ICS on lowering lung cancer incidence in patients with COPD.

We first showed how latency time and immortal time biases tend to result in an underestimation of the rate ratio of lung cancer incidence associated with ICS use, leading to an apparent protective effect. Our illustration introducing these two biases resulted in a significant 70% reduction in lung cancer incidence with ICS use, which disappeared when both sources of bias were removed. We also showed that protopathic bias is important to consider when the timing of the outcome event is in doubt. Indeed, the use of computerized claims databases or electronic medical records can make it difficult to identify the onset of an event, especially when it is insidious and takes time to diagnose, such as inflammatory bowel disease, making it vulnerable to time-related bias.[41] Similarly, early respiratory symptoms of a yet undiagnosed lung cancer can be treated with bronchodilators, so that some new users of such drugs may have initiated their treatment because of an undiagnosed lung cancer and be misclassified. Immeasurable time bias is quite unique to computerized database studies that include medication data on an outpatient basis, but no information on drugs received during hospitalization. This bias also tends to underestimate the rate ratio by misclassifying exposed person-time spent in hospital as unexposed, more so in cases than controls. On the other hand, time-related biases from time-widow and depletion of susceptibles are not as clear with respect to the direction of the bias. Nevertheless, they can lead to important bias that proper design and analysis can reduce.

Several study designs can help avoid many of these time-related biases. For example, the new-user designs, with active comparators or with prevalent users, can be used along with proper considerations for latency and protopathic biases to avoid such biases.[40,42,43] Moreover, the studies that used a new-user design, but introduced immortal time bias by excluding immortal person-time could avoid this bias by using a prevalent new-user design or similar approaches.[29,30,40] Finally, regarding the issue of depletion of susceptibles, we simply described the concept, useful to help identify the period of acute effect of a drug. It will introduce bias if the risk measure is based on the hazard ratio, with the hazard function assumed either constant or proportional, with the bias a function of the duration of follow-up over which the hazard ratio is computed. On the other hand, the ratio or difference in cumulative incidence functions will not be affected by this bias since it is inherently a function of follow-up time. Nevertheless, both measures over time can be affected by selection bias from the changing profile of patients at risk over time, an issue that entails particular attention.[44-46]

In all, observational studies are valuable to uncover unknown potential benefits of medications, which can be subsequently evaluated in randomized trials, but are susceptible to several time-related biases. Proper design and analysis strategies are available to avoid these biases, so that observational studies that are conducted accordingly are more likely to be trusted as a solid basis to investigate beneficial effects of new indications for old drugs in randomized trials.

### ETHICS STATEMENT

The authors state that no ethics approval was needed.

### ACKNOWLEDGEMENTS

This research was funded in part by grants from the Canadian Institutes of Health Research (CIHR) and the Canadian Foundation for

Innovation (CFI). Dr. Suissa is the recipient of the Distinguished James McGill Professorship award.

## CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Suissa S, Dell'Aniello S. Time-related biases in pharmacoepidemiology. *Pharmacoepidemiol Drug Saf*. 2020;29:1101–1110. https://doi.org/10.1002/pds.5083