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Left truncation results in substantial bias of the relation between time-dependent exposures and adverse events

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ABSTRACT

Purpose: To assess the impact of random left truncation of data on the estimation of time-dependent exposure effects.
Methods: A simulation study was conducted in which the relation between exposure and outcome was based on an immediate exposure effect, a first-time exposure effect, or a cumulative exposure effect. The individual probability of truncation, the moment of truncation, the exposure rate, and the incidence rate of the outcome were varied in different simulations. All observations before the moment of left truncation were omitted from the analysis.
Results: Random left truncation did not bias estimates of immediate exposure effects, but resulted in an overestimation of a cumulative exposure effect and underestimation of a first-time exposure effect. The magnitude of bias in estimation of cumulative exposure effects depends on a combination of exposure rate, probability of truncation, and proportion of follow-up time left truncated.
Conclusions: In case of a cumulative or first-time exposure, left truncation can result in substantial bias in pharmacoepidemiologic studies. The potential for this bias likely differs between databases, which may lead to heterogeneity in estimated exposure effects between studies.

Introduction

The first-choice study design to assess the intended effects of medical treatments is the randomized controlled trial. However, in case of rare outcomes or adverse events a randomized trial may be unfeasible. Therefore, studies on adverse events are often based on observational data. An important potential limitation of observational studies is that the moment of initiation of treatment may not be known accurately. One of the reasons for this is that to study rare adverse events, researchers often use routinely collected health care data.

The period covered by health care registry databases is typically not the entire life span. For example, claims databases sometimes have substantive changes in membership over time, as for example employers may regularly change the insurer for their employees or as eligibility for the insurance changes over time. In databases containing delayed entry times left truncation may occur. Left truncation occurs when it cannot be accurately determined whether exposure and/or events have occurred before study entry [1].

Left truncation of data can bias the results of studies [2–4], particularly if the effect of exposure is not constant over time [5–7]. However, there are only few examples that quantify this problem [2,3,8,9]. We aimed to illustrate in which situations left truncation of data may bias exposure effects and to quantify this bias using simulations.

Bias of exposure effects due to left truncation

The term left truncation of data applies to situations in which subject information before cohort enrollment is unobserved. Obviously, because data are unobserved, they cannot be included for analysis, which may bias estimates of exposure effects, if the risk of the outcome is not constant and exposure changes over time [5,6]. We distinguish the following three temporal relations between exposure and the risk of an adverse event: (1) an immediate (i.e., on

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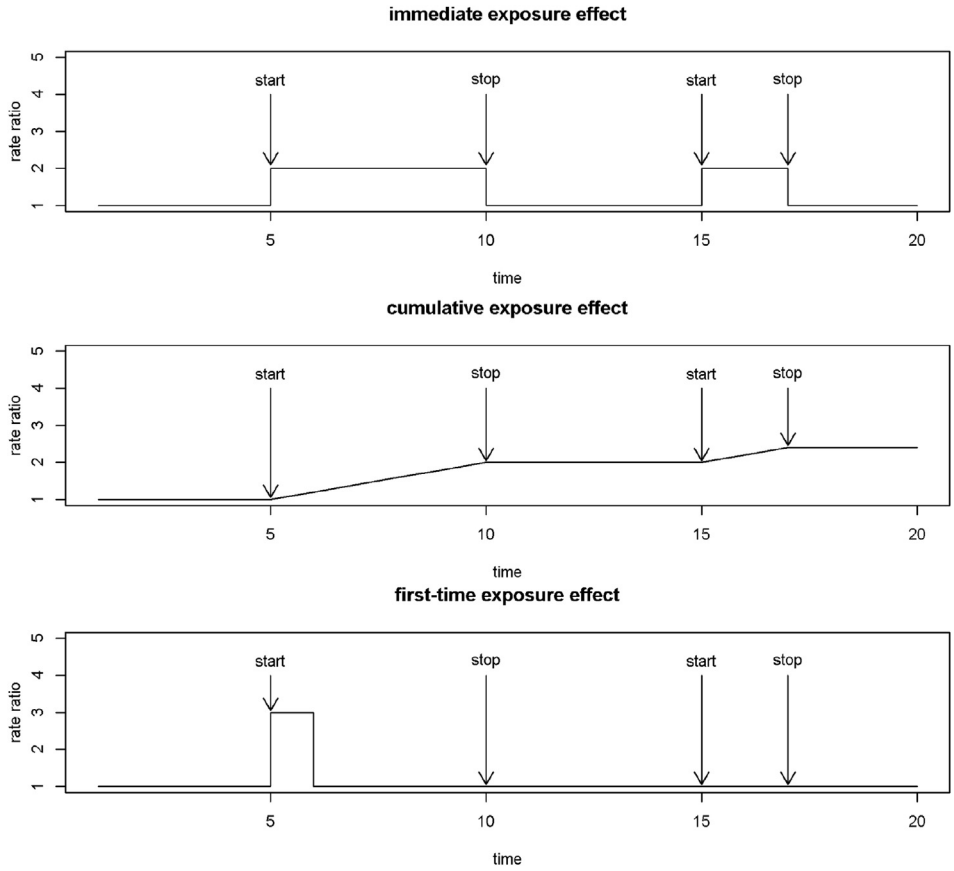

Fig. 1. Examples of an immediate exposure effect, a cumulative exposure effect, and a first-time exposure effect.

or off) exposure effect; (2) a cumulative exposure effect; and (3) a first-time exposure effect. These effects are illustrated in Figure 1.

An example of an exposure with an immediate effect is benzodiazepine use and the risk of a hip fracture (due to falling as a result of dizziness): the effect of exposure is acute and transient (on or off effect). In that case, the relation between exposure and outcome is constant over time and left truncation of data will likely not result in a bias of the exposure effect.

In case of a first-time exposure effect, the risk of an adverse event is increased already the first time a subject is exposed. If an adverse event occurs, it is unlikely that the drug is ever used thereafter. For example, an allergic reaction to antibiotic exposure typically develops within hours of the first or second use of the antibiotic, which is then probably not used anymore afterward. In case of left truncation of data, some of the first-time exposures may be unobserved. Hence, the first exposure that is observed during follow-up (but not necessarily the first exposure in life) may be incorrectly classified as being the first exposure. Because subjects who experienced an adverse event upon actual first exposure will likely refrain from subsequent use, subjects who tolerate the drug are overrepresented among those for whom a "first exposure" is observed during follow-up. Hence, the event rate among "first exposed" is underestimated and consequently the first-time exposure effect as well. This effect has also been coined as "depletion of susceptibles" and was evaluated previously in an example of nonsteroidal anti-inflammatory drug use and upper gastrointestinal bleeding [8].

A positive cumulative exposure effect means that the risk of an event increases with increasing cumulative exposure. For example, the risk of pancytopenia with methotrexate use increases with cumulative use. In case of left truncation of data, the observed cumulative exposure may be lower than the actual cumulative exposure, because part of the exposure is not observed. Such misclassification of cumulative exposure will then result in an overestimation of the relation between cumulative exposure and the risk of an adverse event.

The impact of left truncation in studies of cumulative or first-time exposure effects may be limited by restricting the study population to new users only [5–7]. However, often classification of new users is based on the available data that are possibly left truncated. To overcome this problem, researchers may define an inception cohort, which consists of a selection of patients at risk for developing a specific clinical outcome. Often a run-in period of nonuse is defined, after which users are considered new users [10,11].

The duration of the run-in period can have a large impact. For example, Gardarsdottir et al. [9] showed that the length of the drug-free interval before enrollment in an inception cohort can substantially influence the characteristics of the inception cohort, and thus the observed relation between exposure and adverse events. Thus, when conducting epidemiologic research using routinely collected health care data that is subject to left truncation, constructing a cohort of new users to overcome bias due to left truncation may not always be straightforward. It is therefore important to understand to what extent left truncation may bias estimates of exposure effects.

Methods

We used simulations to quantify the impact of left truncation of data on time-dependent exposures. In contrast to studies using empirical data, simulation studies allow investigators to change

parameters of interest (e.g., proportion truncation, proportion of subjects truncated, proportion of exposed subjects) in a systematic and controlled way, which allows them to evaluate their impact on bias of estimates of the exposure effect.

Simulation setup

Data sets with a sample size of 1000 subjects were simulated, containing information on exposure and outcome for 10-time intervals per subject. These intervals were independent of each other and of the same length (1 unit of time). Data generation started with sampling the individual probability of exposure for each subject from a uniform distribution. This exposure probability was considered to be constant over time within subjects (notably past exposure status did not affect future probability of exposure), except in scenario 2 (see in a later section). For each time interval, binary exposure status was sampled from a Bernoulli distribution, with the probability of success based on the individual exposure probability. Individual exposure probability was generated in such a way that approximately 20% of subjects were exposed in each time interval.

The binary outcome was simulated based on exposure status, using a log-linear outcome model:

$$\log(P(\mathrm{Y}|\mathrm{X})) = \alpha + \beta \mathrm{X},$$

where X indicates exposure status. The default setting for the parameter α was -2.30, corresponding to an incidence rate among the unexposed of 0.1 per unit time. The parameter β indicates the effect of exposure on the outcome. The relation between exposure and outcome was considered to be an immediate exposure effect, a cumulative exposure effect, or a first-time exposure effect. In simulations of cumulative exposure effects, the cumulative exposure within an individual was calculated at each time interval. In simulations of first-time exposure effects, only the first exposure was considered for the outcome model. In this scenario, subjects who experienced an adverse event the first time they used the drug, were considered not to use the drug after this first adverse event. The binary outcome was generated by sampling from a Bernoulli distribution with subject-specific probabilities of the outcome: $\pi = P(\mathrm{Y}|\mathrm{X})$.

To assess the impact of left truncation of the data, we adopted different scenarios and parameter settings (Table 1). When one of the parameters was varied, the other two were set to default values.

Table 1
Scenarios and parameters of the simulation study

Scenario	Characteristics		
Scenario 1	Standard scenario (random truncation)		
Scenario 2	Random truncation After first exposure, probability of exposure increases by 30%. No repeated events.		
Scenario 3	Truncation dependent on probability of exposure		
Scenario 4	Average probability of truncation is set to 0.75		
Parameters		**Default***	**Values**
Exposure effect			
- immediate exposure effect (RR)			1.5; 2.0
- cumulative exposure effect† (RR)			1.1; 1.2
- first-time exposure effect (RR)			3.0; 5.0
Moment of truncation (proportion of follow-up time)		0.5	0.1–0.9; steps of 0.1
Average probability of truncation		1	0–1; steps of 0.1
Exposure rate		0.2	0.05–0.45; steps of 0.05

RR = risk ratio.
* The default setting was applied in all simulations, unless indicated otherwise.
† Increase in risk per unit time exposure.

All observations before the moment of left truncation were omitted from the analysis (i.e., they were considered unobserved). No information is available for subjects before entry into the study (left-truncation time), these subjects are considered nonexistent in the outcome regression.

For each parameter we considered three scenarios. First, the standard scenario with random left truncation. Second, an extension of the standard scenario (again, with random left truncation), where the subjects probability to receive exposure increases by 30% once the subject is exposed for the first time and subjects are removed from the analysis after they experience their first event. In the third scenario, left truncation is proportional to the individual probability to receive treatment. The fourth scenario contains all of the previously mentioned scenarios, although the default value for average probability of truncation is set at 75%.

Analysis

Within each simulated data set, the effect of the exposure on the outcome was estimated using Poisson regression (a generalized linear model with a log link and a Poisson distribution). When the outcome is binary, the exponentiated coefficients from the Poisson regression model are risk ratios instead of incidence rate ratios [12–14]. Each unit of observation time contributed a record to the data. Clustering of observations within an individual was not accounted for in the analysis. Separate analyses in which clustering of observations was accounted for by means of a random effects Poisson model (with random exposure effects per individual) indeed yielded identical results as analyses in which clustering was ignored (data not shown).

For the different exposure effects, exposure was included differently in the analytical model. In case of a first-time exposure effect, only the first exposure during the observed time window was included in the analysis as “exposed”. All other exposure time intervals were included as “unexposed”. When estimating a cumulative exposure effect, the cumulative exposure during the observed time window (calculated as the sum of the number of exposures to this time window) was included in the model as a continuous variable.

Within each scenario, results from the simulations were pooled by averaging the estimated exposure effects, log(risk ratio), over 1000 simulation runs for every parameter. Bias was defined as the difference between the average of the estimates of the log(risk ratio) and the “true” log(risk ratio). Confidence intervals around the mean of the estimated log(risk ratio) were constructed based on the standard error of the mean (i.e., standard deviation of the distribution of exposure effect estimates, divided by the square root of the number of simulations). All simulations and analyses were performed in R for windows (R Foundation for Statistical Computing, Vienna, Austria), version 2.13.1 [15].

Results

In simulations of an immediate (on or off) exposure effect, random left truncation did not result in bias of the association between exposure and the risk of an adverse event, irrespective of the amount of time before cohort enrollment that was truncated (data not shown). Similarly, no bias was observed when the proportion of patients with left truncation was varied and when the exposure rate was varied.

Figure 2 shows the impact of left truncation in a study of first-time exposure effects. Random left truncation (scenario 1) resulted in an underestimation of the first-time exposure effect. The magnitude of the bias increases with the amount of data being left truncated for each subject (Fig. 2, top left), the proportion of

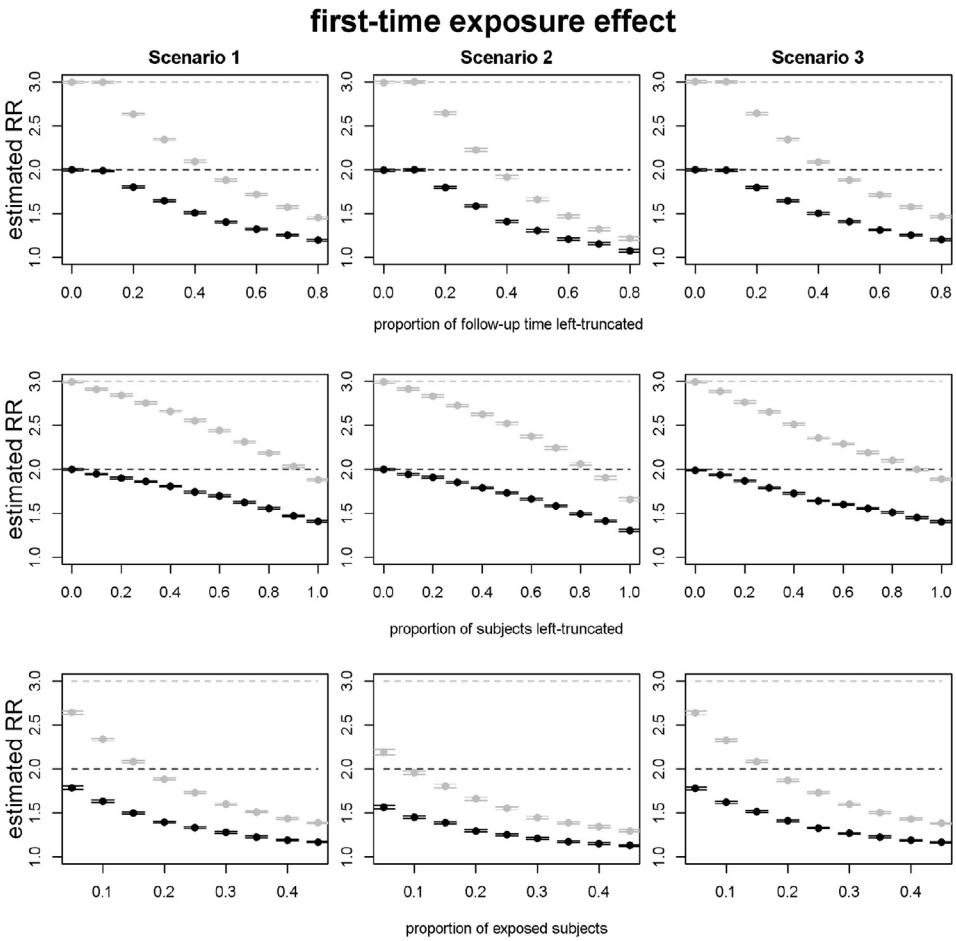

Fig. 2. The impact of left truncation on the estimated first-time exposure effect. Unless indicated otherwise, for all panels the proportion of truncated follow-up time was 50%, the individual probability of truncation was 100%, the exposure rate was 0.2 per unit time, and the incidence rate of the outcome was 0.1 per unit time, in scenarios with a true (unbiased) first-time exposure effect of risk ratio 2.0 (black) or risk ratio 3.0 (gray). The first row of plots shows the impact of different proportions of truncated follow-up time. The plots on the second row show the effect of a change in the proportion of subjects whose follow-up time is truncated. The bottom plots show the impact of different exposure rates. Dashed lines indicate the true (unbiased) exposure effect in case of no truncation. Scenario 1: standard scenario (random truncation). Scenario 2: extension of the standard scenario (random left truncation), where the subjects probability to receive exposure increases (by 30%) after the first time subject is exposed and subjects are removed from the analysis after they experience the outcome (no repeated events). Scenario 3: nonrandom left truncation, where truncation is dependent on the probability of exposure.

subjects who are truncated (Fig. 2, middle left), and the exposure rate (Fig. 2, bottom left). Bias increased in scenario 2 compared with scenario 1, particularly at higher proportions (0.8–1) of subjects truncated, and for lower proportions of exposed subjects. This can be explained by a higher probability of first-exposure misclassification in the second scenario. A similar pattern is observed for scenario 3.

Random left truncation (scenario 1) resulted in overestimation of the cumulative exposure effect (Fig. 3). The magnitude of bias in the cumulative exposure effect depends on the proportion of subjects for whom data were left truncated (Fig. 3, middle left). Compared with the first scenario, in the second scenario (Fig. 3, middle) the magnitude of bias is increased at low proportions of exposed subjects (0.05–0.25). The explanation for this difference is increased cumulative exposure underestimation when the probability to receive subsequent exposures increases after first exposure. The effect for cumulative exposure in the third scenario (nonrandom truncation; Fig. 3, right) is more biased at intermediate (0.5–0.9) proportions of subjects truncated compared with the first scenario. This is explained by increased probability of cumulative exposure underestimation because truncation is related to probability to receive exposure.

Figure 4 shows the impact of left truncation in a study of cumulative exposure effects, where the left truncation occurs in 75% of the subjects (scenario 4). Cumulative exposure is overestimated for intermediate (0.2–0.5) proportions of follow-up truncated, and cumulative exposure is underestimated for high (0.6–0.8) proportions of follow-up truncated (Fig. 4, top left). At high proportions of follow-up truncated individuals whose follow-up time is left truncated have lower observed values of cumulative exposure and higher a probability of experiencing the outcome relative to the nontruncated individuals. Because the risk of an event is high at low values of observed exposure, the intercept for the Poisson model is overestimated and consequently the effect of cumulative exposure is underestimated.

Discussion

Random left truncation can result in substantial bias in pharmacoepidemiologic studies of adverse events. According to theory, random left truncation may lead to an overestimation of a cumulative exposure effect and underestimation of a first-time exposure effect. In this simulation, both overestimation and underestimation of the cumulative exposure effect were observed. Our simulation

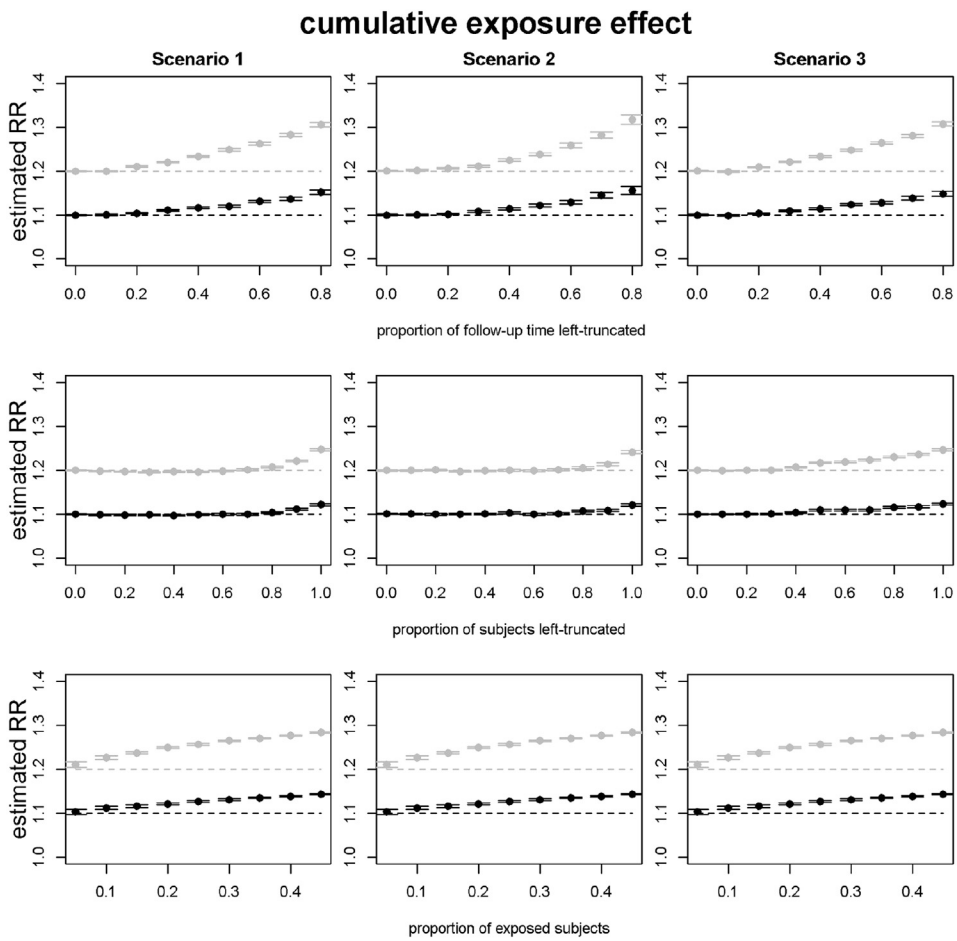

Fig. 3. The impact of left truncation on the estimated cumulative exposure effect. Unless indicated otherwise, for all panels the proportion of truncated follow-up time was 50%, the individual probability of truncation was 100%, the exposure rate was 0.2 per unit time, and the incidence rate of the outcome was 0.1 per unit time, in scenarios with a true (unbiased) cumulative exposure effect of risk ratio 1.1 (black) or risk ratio 1.2 (gray). The first row of plots shows the impact of different proportions of truncated follow-up time. The plots on the second row show the effect of a change in the proportion of subjects whose follow-up time is truncated. The bottom plots show the impact of different exposure rates. Dashed lines indicate the true (unbiased) exposure effect in case of no truncation. Scenario 1: standard scenario (random truncation). Scenario 2: extension of the standard scenario (random left truncation), where the subjects probability to receive exposure increases (by 30%) after the first time subject is exposed and subjects are removed from the analysis after they experience the outcome (no repeated events). Scenario 3: nonrandom left truncation, where truncation is dependent on the probability of exposure.

study indicates that the bias in the estimated exposure effect because of left truncation can be substantive. There were only minor differences in magnitude of bias between the different scenarios considered (repeated events vs. no repeated events; future exposure probability unrelated to prior exposure vs. future exposure probability dependent on prior exposure; and random truncation vs. truncation related to probability of exposure).

The bias of exposure effect estimates that was observed in our simulations is the result of misclassification of the exposure. This misclassification should not be confused with the misclassification that results in immortal time bias [16]. In case of immortal time bias prior unexposed time is misclassified as exposed time; however, true exposure status is known and should be treated correctly as time-dependent in the analysis [17]. In the current manuscript we discuss left truncation, in case of left truncation information on exposure and/or events study or database entry is unavailable.

In pharmacoepidemiologic studies, the effects of drug are often assessed by comparing periods of use with periods of no use. This is a valid analysis in case the drug effect is immediate (i.e., on or off, acute, and transient). In that case random left truncation will not bias exposure effect estimates, irrespective of whether the study includes incident or prevalent users and whether exposure is time-dependent or not. In studies of cumulative exposure effects, however, left truncation may result in a substantial bias of the exposure effect. The reason for this is that the observed cumulative exposure at the moment of an event underestimates the actual cumulative exposure and consequently the relation between cumulative exposure and the risk of an adverse event is overestimated. In studies of a first-time exposure effect, left truncation may result in a selective misclassification of first-time exposure (subsequent exposure may be incorrectly classified as being first-time exposure), which leads to underestimation of the exposure effect.

The impact of left truncation in studies of cumulative or first-time exposure effects may be limited by excluding prevalent users (i.e., analysis of an inception cohort). Inception cohorts are therefore frequently used in pharmacoepidemiologic research. The results of our simulation study underline the importance of this design in studies of cumulative or first-time exposure effects.

Left truncation time may be assumed as time since cohort start, or a proxy for left-truncation time such as age minus typical age of entry into the database may be used. When left truncation is nonrandom, the analysis could take this late entry bias into account by addition of left-truncation time as a covariate [18]. However, this does not remedy the misclassification of exposure. Inverse probability of censoring weighting, a method to account for informative

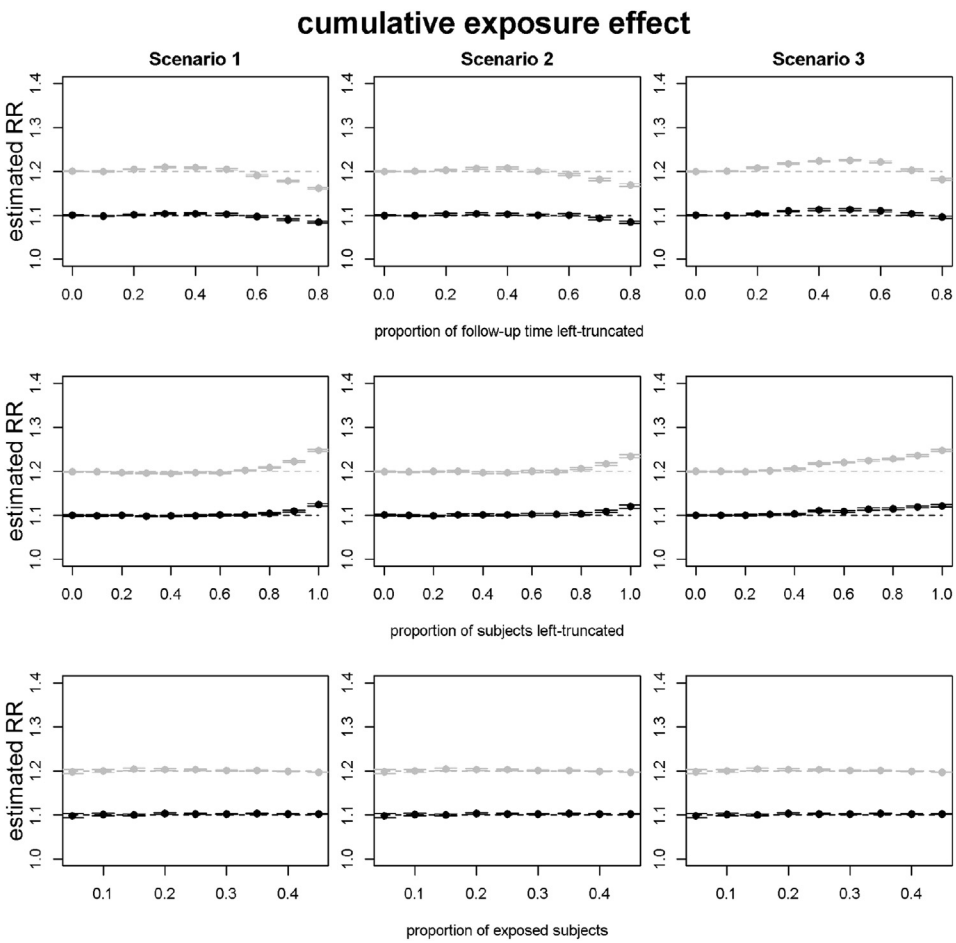

Fig. 4. The impact of left truncation on the estimated cumulative exposure effect. Unless indicated otherwise, for all panels the proportion of truncated follow-up time was 50%, the individual probability of truncation was 75%, the exposure rate was 0.2 per unit time, and the incidence rate of the outcome was 0.1 per unit time, in scenarios with a true (unbiased) cumulative exposure effect of risk ratio 1.1 (black) or risk ratio 1.2 (gray). The first row of plots shows the impact of different proportions of truncated follow-up time. The plots on the second row show the effect of a change in the proportion of subjects whose follow-up time is truncated. The bottom plots show the impact of different exposure rates. Dashed lines indicate the true (unbiased) exposure effect in case of no truncation. Scenario 1: standard scenario (random truncation). Scenario 2: extension of the standard scenario (random left truncation), where the subjects probability to receive exposure increases (by 30%) after the first time subject is exposed and subjects are removed from the analysis after they experience the outcome (no repeated events). Scenario 3: nonrandom left truncation, where truncation is dependent on the probability of exposure.

right censoring, could potentially be applied to left truncation [19]. However, this method is not fully studied in the context of informative left truncation. Additionally the left-truncation time may be considered a missing data problem on which imputation may be performed [20]. Future research concerning these methods would benefit by using an extended survival model [17].

Several possible limitations of our simulations require attention. In all simulations, the maximum number of time intervals per subjects was 10, and all time intervals were of the same duration (1 unit of time). Simulations in which the number of time intervals differs between subjects or the duration of those intervals differs, can be considered more realistic, yet yield the same patterns of bias. In addition, we did not consider right truncation (i.e., no information available after a certain moment in time), because this type of truncation is much better known and will probably have a similar impact on the exposure effects that we evaluated in this study. Additionally, misclassification of time-dependent exposure leads to nonconstant hazards [21]. This is a problem when Cox regression is used to analyze the time to an event. Here, we did not explore this alternative outcome model because when the hazard is constant (as in our simulation) Cox regression has no added value above estimating the risk ratio using a Poisson model (i.e., Cox regression takes into account the time at which a subject enters the database; however, this does not change the consequent misclassification of first-time exposure and underestimation of cumulative exposure). Furthermore, we did not include duration, dosage, and sensitivity time-window in the simulation of cumulative exposure. Finally, we did not consider confounding in our simulations. Whether confounding is likely to be present in observational pharmacoepidemiologic studies depends on the type of adverse event that is studied (i.e., unlikely to be present in studies of unexpected, type B, adverse events) [22]. Apart from that, inducing confounding would add to the complexity of our simulations and not necessarily provide more information on the impact of left truncation (with or without confounding being present). When baseline or time-dependent confounders have an immediate effect on the outcome, adjustment for these characteristics in the analysis will remove confounding bias. However, adjustment for confounders that exert a cumulative effect and are similarly misclassified as is the cumulative exposure in our simulation faces issues comparable to that of left-truncation bias. Adjustment for these confounders may not remove confounding bias. Note that typical adjustment for time-dependent confounders affected by prior exposure will not result in an unbiased effect estimate [23].

When comparing results from studies based on the information from different databases, differences in left truncation should be considered as one of the possible reasons for an observed heterogeneity in exposure effects between studies. For example, the population for whom information is available in a claims database may change quickly over time and is thus prone to left truncation. In contrast, databases containing electronic health records (e.g., electronic files of family physicians) typically have information over longer periods of time and are thus less sensitive to bias due to left truncation. Obviously, with periods of collection of data on exposure that cover a greater proportion of the life course, the misclassification in exposure status will become smaller [1], resulting in less impact of left truncation on the estimated exposure effects and hence less heterogeneity in results from studies conducted in different databases.

In conclusion, left truncation may result in substantial bias in pharmacoepidemiologic studies of adverse events. The potential for this bias likely differs between databases, which may lead to heterogeneity in estimated exposure effects between studies. Researchers should consider the potential for this bias, when evaluating and interpreting the results of pharmacoepidemiologic studies. Additionally, these results may be of interest to researchers in other areas of research, that is, reproduction and nutritional intake.

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