Annals of Epidemiology 25 (2015) 590–596

Contents lists available at ScienceDirect

Annals of Epidemiology

journal homepage: www.annalsofepidemiology.org

Original article

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

Christijan M. Hazelbag Msc [a,*], Olaf H. Klungel PharmD, PhD [a,b], Tjeerd P. van Staa MD, PhD [b,c], Anthonius de Boer MD, PhD [b], Rolf H.H. Groenwold MD, PhD [a,b]

[a] Department of Epidemiology, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands
[b] Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, Utrecht, The Netherlands
[c] Health eResearch Centre, The Farr Institute of Health Informatics Research, University of Manchester, Manchester, UK

ARTICLE INFO

Article history:
Received 4 November 2014
Accepted 15 March 2015
Available online 1 April 2015

Keywords:
Time-dependent exposure
Simulation study
Bias
Truncation
Inception cohort

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

* Corresponding author. Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands. Tel.: +31-88-755-0461; fax: +31-88-756-8099.
E-mail address: c.m.hazelbag@umcutrecht.nl (C.M. Hazelbag).

http://dx.doi.org/10.1016/j.annepidem.2015.03.019
1047-2797/

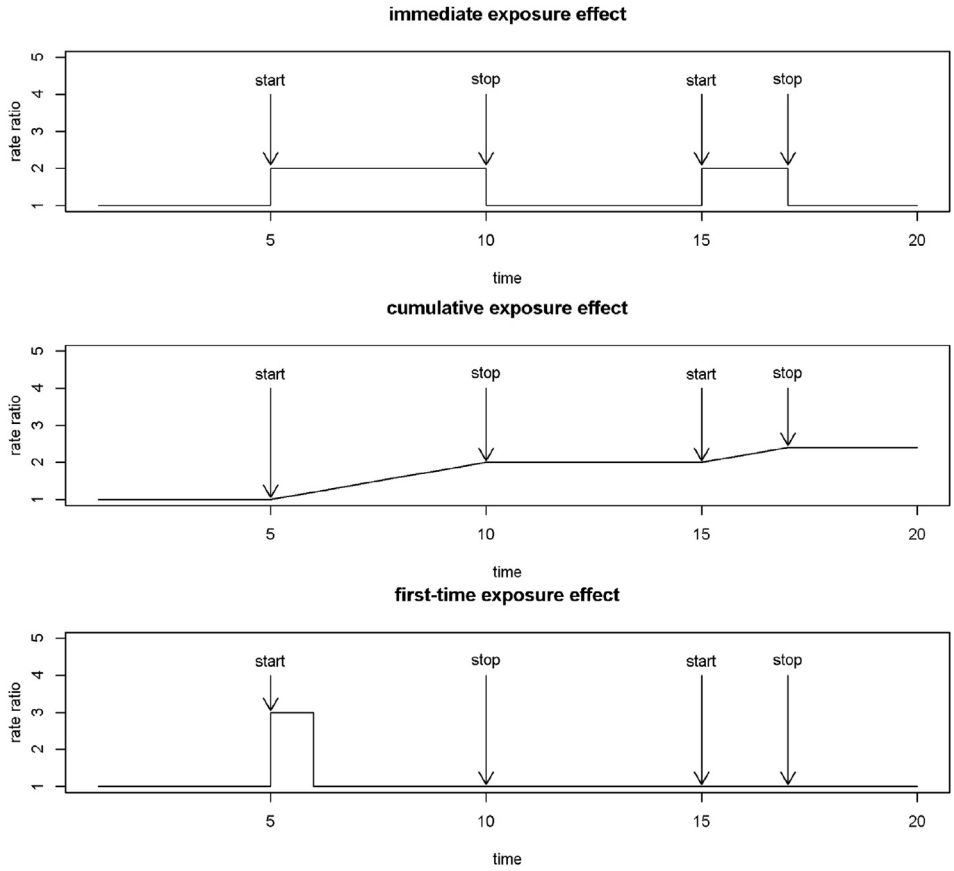

Fig. 1. Examples of an immediate exposure effect, a cumulative exposure effect, and a first-time exposure effect.

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