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The lag-time approach improved drug−outcome association estimates in presence of protopathic bias

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Abstract

Objectives: Protopathic bias is a systematic error which occurs when measured exposure status may be affected by the latent onset of the target outcome. In this article, we aimed to discuss the benefits and drawbacks of the lag-time approach to address this type of bias.

Study Design and Setting: The lag-time approach consists in excluding from exposure assessment the period immediately preceding the outcome detection date. With the help of simple causal diagrams, we illustrate the rationale and limitations of such strategy. The lag-time approach was illustrated in a case-crossover study, based on the health care utilization databases of the Italian Lombardy Region, on the real-world effectiveness of some respiratory drugs (exposure) in preventing asthma exacerbations (outcome).

Results: A total of 7,300 of patients who were admitted to an emergency department (ED) for asthma during 2010−2012 (cases) were included. Use (vs. nonuse) of short-acting beta-agonists (SABAs, an asthma reliever medication) during the 90 days before the ED admission date was associated with an increased risk of the outcome [odds ratio (OR): 1.95; 95% confidence interval (CI): 1.72, 2.22]. This paradoxical finding may be explained by protopathic bias, as SABA use prior the ED admission may be affected by preceding respiratory distress. Indeed, when a 120-day period preceding the ED admission was ignored from drug exposure assessment (lag time), SABAs were found to be associated with a reduced risk of the outcome (OR: 0.81; 95% CI: 0.84, 0.92), as expected.

Conclusions: The lag-time approach can be a useful strategy to circumvent protopathic bias in observational studies.

Keywords: Protophatic bias; Health care utilization database; Observational studies; Lag-time approach; Asthma exacerbations; Respiratory drugs

1. Introduction

Protopathic bias is a source of systematic uncertainty which occurs when exposure status may change in response to the latent onset of the target outcome. For instance, a drug could be prescribed in response to early signs or symptoms of some clinically undetected disease. In such case, when this disease is later discovered, the drug may fallaciously appear to be an etiologic factor for the same disease [1−4].

Because it was first defined by Horwitz and Feinstein [1] in the midst of the classical controversy on estrogen therapy and endometrial cancer of the 1970s−1980s, concerns about protopathic bias have affected a wide range of important health care issues. For example, other than being a general threat of studies investigating the effects of drugs for chronic respiratory diseases [5−8], protopathic bias has been recently evoked in studies of antimicrobials and antibiotic-resistant infections [9], alcohol use and systemic lupus [10], nonsteroidal anti-inflammatory drugs and cancer [11], and proton pump inhibitors and gastric cancer [12], among others.

Protopathic bias may be of general relevance in studies based on health care utilization (HCU) databases, a very important data source for studying the care effects in the real-world clinical practice [13]. These databases usually lack information on clinical end points that do not immediately require the use of health care services, such as emergency department (ED) care. If the use of such services is considered as a proxy of the true outcome of interest (e.g., ED admission for asthma as a proxy of asthma exacerbations), the delay between outcome onset and service use may open the door to potential protopathic bias.

Despite its relevance for epidemiologic research, protopathic bias has received little methodological attention in the literature. To address this issue, in this article, we first describe protopathic bias through simple causal diagrams

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What is new?

Key findings

- The lag-time approach can be a useful strategy to circumvent protopathic bias in observational studies.
- Our empirical analysis suggests that inhaled corticosteroids and beta-agonist bronchodilators are effective in preventing severe asthma exacerbations in the real-world clinical practice.

What this adds to what was known?

- Protopathic bias has received little methodological attention in the literature. We describe protopathic bias through simple causal diagrams and illustrate how the lag-time approach may help in circumventing protopathic bias.

What is the implication and what should change now?

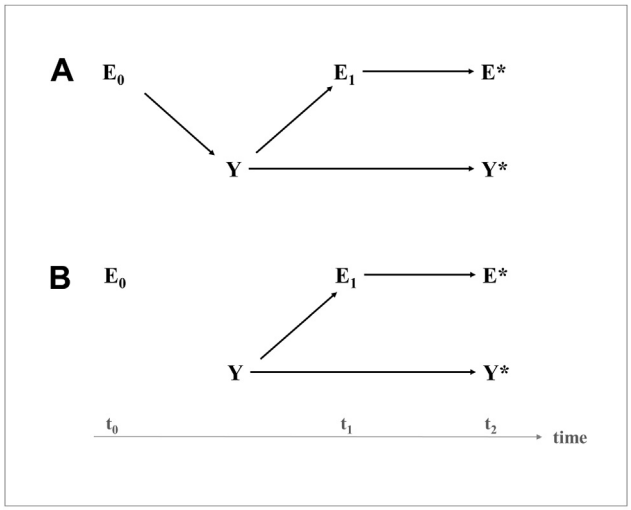
- When protopathic bias is suspected, the potential for exposure and outcome misclassification should also be considered.

[14,15]. These will provide a framework to illustrate how the lag-time approach [1,12] may help in circumventing protopathic bias. As a motivating application, the use of lag times was implemented in a case-crossover study on the association between use of drugs used for asthma control and severe asthma exacerbations based on the HCU databases of the Italian Lombardy Region.

2. Methods

2.1. Representing protopathic bias by causal diagrams

Causal diagrams, a graph-based representation of the assumed causal relations linking variables characterizing a specific population [14,15], may be helpful in describing protopathic bias. For example, Fig. 1A shows a simple causal diagram describing a hypothetical observational study in which protopathic bias is present (for simplicity, we will assume that no other systematic error affects the study). The study's objective is to assess the relationship between E (i.e., the exposure status taking values E = 1 or E = 0 according whether the exposure is or is not experienced, respectively) and Y (i.e., the outcome of interest taking values Y = 1 or Y = 0 according whether the outcome occur or do not occur, respectively). Individuals may experience exposure either at time t_0 or at time $t_1 > t_0$, and exposure status at these two instants is, respectively, represented



E_0 exposure at time t_0 (latent)
E_1 exposure at time $t_1 > t_0$ (latent)
E* observed exposure (assessed at t_0)
Y outcome onset between t_0 and t_1 (latent)
Y* observed outcome (assessed at t_2)

Fig. 1. Causal diagram representing protopathic bias. Arrows show that the undetected outcome Y directly influences both exposure E_1 and detected outcome Y*. Exposure E_0 directly influences Y and does not influence Y in (A) and (B), respectively.

by E_0 and E_1. Individuals are outcome free at t_0 and may experience the outcome at any time before t_1.

Suppose that investigators do not observe Y directly. Rather, they rely on some proxy Y* of outcome onset observed at time $t_2 > t_1$. Once they observe Y*, investigators assess exposure status by looking back from t_2 up to t_1, with the rationale that, from their perspective, exposure at t_1 precedes the "observed onset" of the outcome at t_2. Hence, denoting with E* the assessed exposure status, investigators observe E* = E_1 (so E* exactly captures exposure status at t_1). Clearly, however, because E* is temporally after Y, the E*−Y* association does not represent the effect of interest. For example, if the occurrence of Y increases the probability of subsequent exposure (e.g., because the outcome generates symptoms that lead to seek treatment), then the E*−Y* association is expected to be biased upward. This occurs even when the E has no real effect on Y (i.e., the situation represented in Fig. 1B).

Despite its artificial nature, this example highlights all the three base ingredients of protopathic bias. First, the time of outcome detection is delayed with respect to the time of outcome onset (as implicitly represented by the $Y \rightarrow Y^*$ arrow in Fig. 1A). Second, the outcome onset influences the subsequent exposure status (as represented by the $Y \rightarrow E_1$ arrow in Fig. 1A). Third, the measured exposure status concerns the period subsequent the outcome onset (as represented by the $E_1 \rightarrow E^*$ arrow in Fig. 1A).

2.2. The lag-time approach for addressing protopathic bias

Protopathic bias has been addressed in several studies [5−12,16] through the lag-time approach. A lag time