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The exposure-crossover design is a new method for studying sustained changes in recurrent events

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Abstract

Objectives: To introduce a new design that explores how an acute exposure might lead to a sustained change in the risk of a recurrent outcome.

Study Design and Setting: The exposure-crossover design uses self-matching to control within-person confounding due to genetics, personality, and all other stable patient characteristics. The design is demonstrated using population-based individual-level health data from Ontario, Canada, for three separate medical conditions ($n > 100{,}000$ for each) related to the risk of a motor vehicle crash (total outcomes, $>2{,}000$ for each).

Results: The exposure-crossover design yields numerical risk estimates during the baseline interval before an intervention, the induction interval immediately ahead of the intervention, and the subsequent interval after the intervention. Accompanying graphs summarize results, provide an intuitive display to readers, and show risk comparisons (absolute and relative). Self-matching increases statistical efficiency, reduces selection bias, and yields quantitative analyses. The design has potential limitations related to confounding, artifacts, pragmatics, survivor bias, statistical models, potential misunderstandings, and serendipity.

Conclusion: The exposure-crossover design may help in exploring selected questions in epidemiology science.

Keywords: Crossover studies; Epidemiologic research designs; Evaluation studies as topic; Self-matched analysis; Outcome and process assessment; Comparative effectiveness research; Statistics methods; Minimization of bias

1. Introduction

Clinical epidemiology is sometimes chastised as the science of unfair comparisons [1−3]. As a consequence, observational studies usually endeavor to identify cases and controls that are reasonably similar so that inferences are not unduly slanted by hidden confounding [4−6]. One method for ensuring equivalence is randomization, although doing so typically requires substantial sample size and individual cooperation [7]. Alternative methods include regression modeling, propensity score stratification, individual pair matching, subgroup stratification, or other analytical methods for making separate patient groups appear similar [8−10]. None of these methods is ideal, and methodological work developing new designs remains a priority for future progress.

One major advance in clinical epidemiology was the development of the case-crossover design in 1991 [11]. The main strength of this repeated-exposure approach is to define each patient as their own control and explore the transient effects of a brief exposure on the onset of an acute outcome [12]. An early contribution from this design examined heart attack patients ($n = 1{,}228$) and identified that 54 patients had exercised in the hour before the onset, whereas only nine patients had exercised in the same hour 1 day before the onset, equivalent to a sixfold temporary increase in heart attack risk associated with exercise [13]. Scientists

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What is new?

- A new self-matching approach named the exposure-crossover design can identify associations between exposures and outcomes while avoiding confounding due to genetics, personality, and other stable patient characteristics.
- The exposure-crossover design differs from the case-crossover analysis, case−time analysis, self-controlled case series analysis, and other case-only designs by including individuals who do and do not experience the outcome.
- The exposure-crossover design, unlike most self-matching designs, yields measure of both relative risk and absolute risk.
- The exposure-crossover design provides graphical and analytical methods for identifying and reducing confounding from transient temporal confounding.
- The exposure-crossover design requires a large sample size involving a recurrent outcome event with unambiguous time points of exposure and outcome.

in subsequent years expanded on the case-crossover design with further theory, modeling, and practical applications [14−17].

The purpose of this article is to introduce a new approach called the ''exposure-crossover'' design. Similar to other epidemiology methods, the intent of the design is to test for a potential link between exposure and outcome [18,19]. The name is selected to convey a notion that each patient serves as their own control and undergoes observation during a time with an exposure and a time without an exposure. The name is also intended to be reminiscent of the case-crossover design, the epidemiologic approach that the exposure-crossover design most closely resembles. Some additional names that were considered but rejected include the exposed crossover design, sustained impact design, interventional analysis design, and individual-level interrupted time-series design.

2. Methods

2.1. Background

The exposure-crossover design was first inspired by the methods for examining large economic changes [20,21]. For example, the 23% decrease on Monday October 19, 1987, in the US stock market is apparent when evaluated as a time-series graph (Fig. 1). Such time-series analytical studies are not limited to financial markets and have extended to several other nonmedical fields, for example, a study on the effect of contaminated milk leading to a sustained decrease in dairy product consumption [22]. The main limitation of these methods is that the unit of analysis is a large region or population rather than an individual patient [23]. As such, the adjustment for individual variation is difficult, and ecological biases can be problematic [24,25].

2.2. Perspective

The exposure-crossover design adopts the individual perspective to examine whether a specific exposure changed a person's risks of a recurrent outcome. The exposure can be a medication, procedure, or other intervention with a documented start date and somewhat ongoing effects. The outcome can be any event, that is, recurrent, relapsing, or otherwise repeated with a documented time for each occurrence. Specific examples might include studies of monoclonal antibody treatments for lessening exacerbations of Crohn's disease, coronary surgery to prevent repetitive episodes of angina, or behavioral therapy to stop recurrent falls in the elderly. In each study, the analysis would evaluate whether patient outcome rates are different before and after the exposure.

2.3. Time-zero

The exposure-crossover design designates the individual as the unit of analysis. The first requirement, therefore, is to align each individual on a consistent time scale because calendar date is not suitable for gauging time-zero (unlike a large economic time-series analysis in which an entire region experiences the same calendar date simultaneously) [26]. A randomized trial typically defines time-zero as the date of randomization for each patient (although recruitment might extend over several years) [27−29]. A case-crossover analysis typically defines time-zero as the date of the outcome for each patient (and usually directs attention to intervals before the onset of time-zero) [30−32]. The exposure-crossover design establishes time-zero as the date of the exposure for each patient.

2.4. Follow-up

The next requirement for the exposure-crossover design is to track the individual forward and backward from time-zero. In theory, such observations could be obtained by prospective or retrospective data collection, although a retrospective approach is generally more expedient when feasible. The dual direction in time sampling is distinct from cohort analytical designs that tend to track patients forward from the time of an exposure and also distinct from case−control designs that tend to track patients backward from the time of an outcome [33−38]. The exposure-crossover design, therefore, is not appropriate for examining terminal events such as death but can be appropriate for examining