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Case-crossover Studies of Therapeutics:

Design Approaches to Addressing Time-varying Prognosis in Elderly Populations

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Abstract

Background—Self-controlled analysis methods implicitly adjust for time-invariant confounding within individuals. A person's prognosis often varies over time and affects both therapy choice and subsequent health outcomes. Current approaches may not be able to fully address this within-person confounding. We evaluated the potential impact of time-varying prognosis in self-controlled studies of treatment effects and the extent to which alternative adjustment strategies could mitigate these biases.

Methods—We used Medicare data linked to prescription drug data from a pharmaceutical assistance program to conduct case-crossover studies of the relationship between intermittent use of five classes of preventive medications (statins, oral hypoglycemics, antihypertensives, osteoporosis, and glaucoma medications) and death—relationships that are strongly biased because of healthy-user and sick-stopper effects. We used the case-case time-control design to adjust for confounding from exposure trends related to prognosis. Each class of medications was evaluated separately, with the remaining four used as reference drugs to estimate prognosis-related exposure trends.

Results—The case-crossover odds ratios were 0.39, 0.38, 0.40, 0.39, and 0.45 for statin, antihypertensive, glaucoma, hypoglycemic, and osteoporosis drugs, respectively. After adjusting for the estimated noncausal prognosis-related trends in drug exposure among all eligible cases, odds ratios were clustered closer to null (0.99, 0.95, 1.02, 0.99, and 1.16, respectively).

Conclusions—Consideration of the sociology of medication use leading to health outcomes is essential in designing and analyzing self-controlled studies of treatment effects. Although the case-case time-control design was able to reduce bias from prognosis-related exposure trends in our examples, the difficulty in identifying appropriate reference exposures could be prohibitive.

Epidemiologic studies conducted among elderly populations can be particularly challenging because of the complex interplay of the aging process with accumulated comorbidities at the end of life. A growing body of literature on drug safety and effectiveness among the elderly has been conducted using secondary data from large administrative or clinical datasets.[1–3] When conducting longitudinal observational studies, measured confounders can be adjusted

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for; however, information on many important potential confounders are not routinely captured in large secondary datasets.[4]

Spurious protective associations between preventive therapies and death among the elderly have been found, because of what have been called “healthy-user” and “sick-stopper” effects.[5] These biases can occur when the use of drugs is related to unmeasured comorbidity, such that healthier patients are more likely to initiate and continue use of treatment and, conversely, frail patients approaching the end of life are more likely to discontinue preventive treatments for nonsymptomatic conditions.

The case-crossover design—a self-controlled, observational study design that requires information only from cases—was proposed by Maclure[6] in the mid-1990s. This design can be used to evaluate the relationship between transient exposures and abrupt-onset outcomes.[6] An attractive feature of the case-crossover design is the use of within-person comparisons; thus, any confounders that do not vary over time within individuals (time-invariant confounders) do not bias the analyses. An assumption of the design is that the within-person probability of exposure remains stable over the observation window preceding the case-defining event. Additional adjustment measures are necessary to deal with bias if this assumption is not met or if confounders that do vary over time within individual (time-varying confounders) are present.[6–8]

The case-case time-control design was recently proposed to ameliorate this issue.[8] This design can involve the use of crossover analyses of one or more reference treatments among cases (treatments not expected to be causally related to the outcome). This is in contrast to the case time control, which adjusts for population-level time trends through crossover estimates of the exposure of interest among a matched control population.[7]

For a case-case time-control study, the exposure trends from the reference treatments are used to estimate the magnitude of the association that would be observed because of relationships between exposure to treatments and prognosis, in the absence of a casual relationship between the reference treatments and outcome. The crossover in reference treatments among cases is meant to estimate changes in probability of exposure to treatment on an individual level; for example, changes in probability of exposure to medications associated with generally declining (or improving) health status. This includes adjustment for changes in the probability of capturing medication exposure in a given data source. For instance, many large claims data sources do not have inpatient pharmaceutical dispensations linked on an individual patient level to their outpatient claims. Thus, exposures that occur during the time that patients spend in hospitals or other institutions are not measurable in those data.[9]

One method of adjusting for the increasing probability of unmeasured exposure time, as patients become sicker and more likely to be hospitalized, is to estimate crossover exposure odds ratios for referent treatments among cases; these crossover odds ratios should represent the noncausal trend for exposure among cases that is because of structural limitations in capturing exposure during hospitalized time. Estimates derived from analyses using reference treatments can then be used to adjust case-crossover estimates of the exposure

under investigation. The aim of this study was to demonstrate the potential impact of healthy-user/sick-stopper biases in the self-controlled setting and to evaluate the extent to which adjustment strategies may mitigate these biases.

METHODS

We used data from the Pharmaceutical Assistance Contract for the Elderly, an outpatient state prescription benefits program for the elderly, linked with Pennsylvania Medicare Part A and Part B. The data include information on outpatient medication dispensations, physician encounters, diagnoses, and procedures; information on inpatient stays, diagnoses, and procedures within these stays were also captured, but inhospital medication dispensation was not captured. We used data from 1 January 1994 through 31 December 2003. Data on mortality were obtained from the Death Master File, which is verified and maintained by the Social Security Administration. The income ceiling for eligibility in Pharmaceutical Assistance Contract for the Elderly is low, resulting in a covered population of poor or near-poor elderly who are unlikely to be able to access medications by other means.[10]

We used these data to conduct case-crossover studies of the relationship between intermittent use of statins and death from any cause—a relationship known to be influenced by healthy-user and sick-stopper effects. We assumed that the true causal relationship between transient use of statins and short-term mortality was null because preventive therapeutics such as statins typically require lengthy induction periods to produce clinical benefits; in other words, these benefits are not likely to be present after only brief exposure (eg, <30 days). We then evaluated the ability of the case-case time-control design to adjust for exposure time trends induced by healthy-user and sick-stopper biases using four classes of preventive medications (oral hypoglycemics, antihypertensives, osteoporosis, and glaucoma medications) as reference treatments. Generic names and formulation of drugs included in each class of preventive medication are available in the eAppendix (http://links.lww.com/EDE/A661).

The case-crossover analyses compared exposure to statins during two time periods within identified cases—the “current” time was 30 days before death and the “reference” time was 90–120 days before death. Using the dispensation date and the days’ supply dispensed from claims data, we created binary exposure indicators for the current and referent windows, such that a person was considered exposed to a statin if there were at least 3 days’ supply within the window. Seven days were added to the days’ supply dispensed for every dispensation to allow for modest nonadherence.

We then conducted case-case time-control analyses using the other four classes of preventive medications as reference treatments. In these analyses, the estimate from the crossover analysis for statins was divided by the averaged crossover estimate from the reference treatments to adjust for trends in exposure to treatment related to prognosis or immeasurable time. We compared case-case time-control analyses that adjusted for trends estimated only among cases with crossover in the statin exposure (ie, cases who contributed to the case-crossover estimate) to analyses that estimated exposure time trends among all cases meeting

eligibility criteria. Standard errors and 95% confidence intervals were obtained through bootstrapping.

We also conducted case-crossover and case-case time-control analyses using oral hypoglycemics, antihypertensives, osteoporosis, and glaucoma medications as the exposure of interest and the remaining four classes of preventive medications as references.

RESULTS

The majority of the 175,067 persons who died and who met the eligibility criteria were white (94%), women (73%), and elderly (mean age = 83 years) (Table 1). Diagnoses for both chronic and acute conditions captured by claims data during the current and referent windows reflect greater contact with the healthcare system in the time more proximal to death, with 44% of cases hospitalized at some point during the current window and only 13% hospitalized during the referent window.

The case-crossover estimates of the relationship between intermittent use of statins and death are unadjusted for the strong confounding from healthy-user/sick-stopper biases and indicate a strong protective effect, where risk of death is 60% lower during time exposed to statin relative to time unexposed (Table 2). After adjusting for noncausal exposure time trends estimated among all cases who met eligibility criteria, the estimate for the relationship between intermittent use of statins and mortality was null (odds ratio = 0.99 [95% confidence interval = 0.94–1.06]). Analyses using the other drug classes as the exposure of interest produced similar results (Table 2).

DISCUSSION

A confounder that is often unaddressed in self-controlled studies of treatment effects is the potential for changing prognosis over time within individuals. In practice, changes in prognosis may affect both exposure to treatments and subsequent health outcomes; for example, healthy patients frequently initiate preventive medications, whereas moribund patients discontinue them.[5,11] In our example—looking at intermittent statin use, other preventive medication use, and mortality—one unmeasured factor biasing the case-crossover estimates could be that, when patients or their doctors know that death is imminent, they may choose to discontinue preventive medications that neither prolong nor improve the quality of life in the short-term (ie, sick-stopper).

Changes in prognosis may also be related to recording or capture of exposures in claims data. For many large claims data sources and practice-based research networks, information on medication exposure during inpatient or nursing home stays is not available for structural reasons, such as lack of data linkage. Another confounding influence in the case-crossover estimates for our example studies is that, as patients become sicker, they are more likely to be hospitalized and are therefore more likely to have nonmeasured exposure time.[9]

When prognosis is related to the probability of exposure to treatment, and prognosis is changing over time, the probability of exposure changes over time as well. Under these conditions, the estimate from the case-crossover analyses is a mix of the causal effect (if

present) and associations because of the relationships of both exposure and outcome to prognosis.[12]

Regardless of the reasons for noncausal changes in probability of exposure within persons, there are a few strategies available to estimate this exposure time trend using time sampled from cases. The article by Wang et al[8] used the strategy of matching cases to "future cases." That is, from the sample of identified cases, the authors used risk-set matching in calendar time to match each case to one or more future cases (cases that had not yet occurred at that point in calendar time and were at risk of the health outcome of interest). The crossover analysis among cases was adjusted for time trends in the exposure as measured among future cases.

Limitations of this approach include reduced sample size (cases occurring toward the end of the study period have no matches) and the potential for incomplete adjustment. If the change in probability of exposure leading up to the health outcome has, for example, an exponential shape, then exposure time trends measured further back in historical person-time would not be representative of the expected exposure time trends more proximal to the health outcome.

An alternative strategy that also uses cases as exposure time controls is the one used in this article. We adjusted the crossover estimate for the exposure of interest among the cohort of identified cases by the crossover estimate of reference exposures (negative controls) among the cohort of identified cases.

Although the magnitude of the noncausal association between exposure and outcome because of trends in exposure related to prognosis can be approximated by estimating the relationship between reference exposures and the outcome, the analysis is highly sensitive to the choice of reference exposures. Reference exposures should be known not to have a causal relationship with the outcome. Ideally, the forces that influence the probability of being exposed to reference medications should be as similar as possible to those for the exposure of interest. The ability to adjust for exposure time trends that confound the relationship between the exposure of interest and the outcome depends on the similarity of the trend for the exposure of interest and the reference exposures. Reference exposures should have similar indications (ie, preventive vs. symptomatic) and be of the same modality (ie, daily tablet vs. intravenous injection) as the exposure of interest. Using inappropriate reference exposures could incompletely adjust for bias or, worse, multiplicatively increase the magnitude of bias from the case-crossover estimate.

Either approach may be used to estimate and investigate exposure time trends because of protopathic bias or healthy-user/sick-stopper effects. The second strategy, using reference exposures, has the added benefit of counteracting the potential bias from immeasurable time that occurs when inpatient dispensing data are not available and patients spend time in the hospital before the health outcome. The lack of capture of inpatient data on the exposure of interest is mirrored by the lack of capture of inpatient data for the reference exposures (Wang, 2012, unpublished data).

As a cautionary note, adjusting case-crossover estimates using estimates of noncausal exposure time trends calculated only among cases that contributed to the case-crossover

analyses (ie, cases with crossover in the exposure under investigation) can result in overadjustment because of selection bias (example results in eTable, http://links.lww.com/EDE/A661). When selecting a population of cases by which to estimate exposure time trends, it is important to use all eligible cases. When the relationship between reference exposures and outcome is estimated only among patients who have crossover in the exposure of interest, this results in selection bias because the exposure time trend is estimated among a population that is selected on both exposure and outcome.

Our study has several limitations. The case-case time-control design inherently controls for time-invariant confounding within persons and adjusts for bias because of changes in within-person exposure probability by way of an active control comparison. However, this approach can be biased in the presence of trends in the study base of the exposure of interest, the reference exposure, or both. In addition, we assumed that the true causal relations between the study drug classes and short-term mortality were null.

When designing and analyzing self-controlled drug safety studies, it is essential to give careful consideration of the sociology of medication use—for instance, whether use in the time leading up to the case-defining event is associated with prognosis. In the presence of time-varying prognosis, the case-crossover can produce profoundly biased results. We have identified issues with conducting case-crossover studies among the elderly (or other populations with rapidly changing prognosis) and offer an approach to minimize their impact. Although the case-case time-control can mitigate this bias, the difficulty of selecting appropriate reference medications for estimation of noncausal drug exposure trends could be prohibitive.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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TABLE 1

Characteristics of Persons Who Died (n = 175,067)

Demographic Characteristics		
Age (years); mean (SD)	83.3 (7.6)	
Women; No. (%)	127,552 (73)	
Race; No. (%)		
White	164,524 (94)	
Black	9,242 (5)	
Other/unknown	1,301 (1)	
	Hazard window	**Referent window**
Diagnoses observed during observation windows; No. (%)		
Angina	3,101 (1.8)	1,251 (0.7)
Chronic kidney disease	9,957 (5.7)	2,332 (1.3)
Chronic obstructive pulmonary disease	21,665 (12.3)	5,833 (3.3)
Congestive heart failure	35,157 (20.1)	8,792 (5.0)
Coronary artery disease	27,783 (15.9)	7,617 (4.4)
Diabetes	17,260 (9.9)	5,464 (3.1)
End-stage renal disease	313 (0.2)	66 (<1)
Gastrointestinal bleeding	5,099 (2.9)	910 (0.5)
Hyperlipidemia	3,626 (2.1)	1,366 (0.8)
Hypertension	30,312 (17.3)	9,029 (5.2)
Osteoarthritis	5,820 (3.3)	2,314 (1.3)
Peptic ulcer disease	6,320 (3.6)	2,167 (1.2)
Peripheral vascular disease	3,286 (1.9)	1,167 (0.7)
Rheumatoid arthritis	938 (0.5)	309 (0.2)
Stroke	10,748 (6.1)	1,643 (0.9)
Transient ischemic attack	575 (0.3)	334 (0.2)
Myocardial infarction (current or previous)	10,873 (6.2)	1,227 (0.7)
Hospitalized during observation window	77,104 (44.0)	22,686 (13.0)

TABLE 2

Case-crossover, Time-crossover, and Case-case Time-control Estimates of the Relationship Between Five Classes of Preventive Medications and Death

Types of Prescriptions	Case-crossover OR (95% CI)	Time-control[a] OR (95% CI)	Case-case Time-control[a] OR (95% CI)
Lipid lowering	0.39 (0.37–0.41)	0.39 (0.38–0.41)	0.99 (0.94–1.06)
Blood pressure regulating	0.38 (0.37–0.39)	0.40 (0.39–0.41)	0.95 (0.92–0.98)
Glaucoma	0.40 (0.38–0.42)	0.39 (0.38–0.40)	1.02 (0.96–1.08)
Glucose regulating	0.39 (0.37–0.40)	0.39 (0.38–0.41)	0.99 (0.94–1.03)
Osteoporosis	0.45 (0.42–0.48)	0.39 (0.38–0.40)	1.16 (1.08–1.23)

OR, odds ratio; CI, confidence interval.

[a]Average crossover estimate for reference medication among all cases meeting eligibility criteria.