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Quantifying the Impact of Drug Exposure Misclassification due to Restrictive Drug Coverage in Administrative Databases: A Simulation Cohort Study

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A B S T R A C T

Objective: Drug exposure misclassification may occur in administrative databases when individuals obtain nonreimbursed drugs by paying "out-of-pocket" or via alternative drug coverage plans. We examined the apparent association between oral antidiabetic therapy and mortality by simulating the effects of restrictive drug coverage policies. **Methods:** Population-based cohort study of 12,272 new patients using oral antidiabetic agents were identified using the administrative databases of Saskatchewan Health, 1991 to 1996. We randomly misclassified 0% [base case], 10%, 25%, and 50% of known patients taking metformin according to either overt drug exposure (e.g., metformin users switched to nonusers) or time of metformin initiation (e.g., delayed capture of exposure); thereby simulating the use of a "non-formulary" or "special authorization" policy, respectively. We also simulated an age-dependent coverage policy, mimicking a policy restricted to seniors. **Results:** Metformin use was associated with lower mortality compared with sulfonylurea use in the base case (adjusted hazard ratio [aHR] 0.88, 95% confidence interval [CI] 0.78–0.99) and the nonformulary simulations. The special authorization simulations demonstrated, however, an increasing relative mortality hazard of metformin versus sulfonylurea exposure: aHR 0.96, 95% CI 0.96–0.97 and aHR 1.34, 95% CI 1.31–1.37, for 10% and 50% delays in coverage capture respectively when 50% of metformin users were misclassified. Age-dependent drug coverage had a variable impact on mortality risk compared with the base-case cohort; however, a new-user simulation with a 1-year washout revealed consistent results to the base-case analysis. **Conclusion:** Restrictive drug coverage policies may result in substantial drug exposure misclassification, potentially severely biasing the results of drug-outcome relationships using administrative databases.

Keywords: bias, formularies, mortality, pharmaceutical policy, pharmacoepidemiology simulation.

Introduction

Administrative claims databases are commonly used for pharmacoepidemiologic studies assessing the relationship between drug exposures and health outcomes [1,2]. Like any epidemiologic study, valid results from studies based on administrative claims rely on accurate classification of disease state [3] and drug exposure [4]. Misclassification bias may result in spurious conclusions of benefit or harm. Potential sources of drug exposure misclassification that are well known include nonadherence [5], over-the-counter drug exposure [6], and free samples [7].

Although often overlooked, another potential source of drug exposure misclassification is restrictive drug coverage policies [8]. Administrative drug databases commonly capture drug dispensation data through an electronic claims system, whereby the only drugs captured are those that are either widely available on formulary or only covered for those patients who meet special authorization criteria (i.e., pre-specified clinical criteria) [9]. In other words, each time a pharmacist processes and dispenses a prescription specific details (e.g., drug name, dosage, quantity, price) are sent to the payer via an electronic system; however, information is only collected by the payer if the product is included in the payer's formulary. Although some administrative databases capture all drugs irrespective of drug coverage, this is the exception rather than the norm. Drug policies that limit coverage through nonformulary status or "special authorization" criteria for coverage are common cost-containment mechanisms employed by single party payers to guide prescribing [10,11]. However, to the extent that drugs with restrictive coverage policies are still used in the population, but not captured in administrative databases, these policies have the potential to result in drug exposure misclassification in pharmacoepidemiologic studies [8]. For example, an individual's drug exposure may not be captured if they choose to pay for the medication "out-of-pocket" or have a private (nongovernment) drug coverage plan [12]. This may occur over the entire drug exposure period (i.e., never captured in the adminis-

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trative data) or may change over time, depending on the nature of the policy (e.g., policy changed from restrictive coverage to full coverage, or a patient passes a certain age threshold and becomes eligible for coverage).

Thus, we designed this study to quantify the potential degree of bias resulting from exposure misclassification due to a policy restricting drug coverage. Specifically, we provide three simulations that represent the potential consequences of restrictive drug policies for pharmacoepidemiologic studies and measure the impact of varying degrees of both drug category misclassification and person-time exposure misclassification on estimates obtained using administrative data.

Methods

Population and setting

The data sources and population studied were previously discussed in detail [13]. Briefly, 12,272 new-users of metformin or a sulfonylurea were identified between January 1, 1991 and December 31, 1996 using the administrative databases of Saskatchewan Health. Individuals were prospectively followed to the first occurrence of death, termination of Saskatchewan Health coverage, or December 31, 1999, providing a maximum follow-up of 9 years [13]. Saskatchewan Health provides universal health coverage to its approximately one million residents with the exception of federal inmates, Royal Canadian Mounted Police, and members of the armed forces (~1% of the population). All health beneficiaries regardless of age are eligible for prescription drug coverage except those who receive these benefits through the federal government (primarily First Nations, ~9% of the population). Both metformin and glyburide were listed in the provincial formulary with unrestricted coverage for the entire study period [14].

Patients who are new users of these antidiabetic agents were categorized into mutually exclusive groups and followed from their first dispensation date (index date) of an oral antidiabetic therapy: 1626 (13%) were treated with metformin monotherapy, 4730 (39%) with sulfonylurea monotherapy, and 5916 (48%) were treated with combination of sulfonylurea and metformin therapy. As previously reported, metformin monotherapy was associated with lower all-cause mortality compared with sulfonylurea therapy [13]. Ethical approval was obtained from the Health Ethics Research Board of the University of Alberta.

Exposure misclassification simulations

For the purposes of this article, we reanalyzed the association between metformin use and all-cause mortality under varying amounts of exposure misclassification. Specifically, we conducted simulations to mimic potential consequences of three common restrictive drug policies, which are non-formulary status, special authorization, and age-based restrictions. We chose metformin as our "policy drug" because there was little or no exposure misclassification of metformin in our original cohort study because it was listed as a full benefit on the formulary in Saskatchewan throughout the years of our study. Likewise, sulfonylurea use consisted almost exclusively of glyburide and was also listed as a full benefit during this period in Saskatchewan.

In our nonformulary and special authorization simulations, we randomly selected 0% (i.e., base case), 10%, 25%, and 50% of all patients taking metformin to be subject to the hypothetical drug policy and therefore have their drug exposure misclassified. Random selection was conducted using a uniform random variable generator in Stata SE version 11.2 (StataCorp LP, College Station, TX) statistical software. Indeed, these simulations represent a realistic approximation of the degree of potential drug exposure misclassification. For example, a recent study reported that ~70% of thiazolidinedione users were receiving therapy and were not captured in a dataset limited to provincial claims only, due to a special authorization policy resulting in the use of third party insurance or out of pocket payment for the medications [15].

Our first policy simulation is perhaps the simplest case of a restrictive drug policy – a nonformulary drug, where exposure occurred but the administrative claims database failed to capture this via claimed dispensations. Thus, randomly selected individuals who were originally receiving metformin as monotherapy were reclassified as nonexposed and therefore removed from analyses (i.e., analysis comparing metformin vs. sulfonylurea but would be included in a "no use" comparison) for their entire follow-up. For metformin use in combination with sulfonylureas, individuals were reclassified as sulfonylurea monotherapy users.

Our second simulation is an example of a "special authorization" drug use policy, whereby an initial period of exposure may occur (e.g., through private insurance or out-or-pocket), but is not captured within the claims databases until specific coverage criteria have been met. As a result, a patient's actual or true number of person-years exposed to the policy drug would be underestimated due to the delayed capture of exposure. To simulate this "blind period" while individuals fulfilled coverage criteria, we delayed the metformin index date for randomly selected individuals by 10%, 25%, and 50% of the total exposure time between an individual's first metformin dispensation and exit from the cohort. As in the previous simulation, we randomly selected 10%, 25%, and 50% of individuals to be subject to the hypothetical policy.

We intentionally introduced drug exposure misclassification in a random fashion for the above simulations because there may be several reasons why specific drugs will not be fully reimbursed. Age-based criteria, however, are often used to define eligibility criteria for drug insurance plans, of which seniors are the most common beneficiary group. We therefore, ran a third simulation whereby we considered any drug exposure prior to age 66 not available within the administrative database (even though the Saskatchewan Health datasets we used do capture prescriptions in younger patients). Drug exposure prior to age 66 was reclassified as nonexposed. Individuals who died or were censored prior to age 66 were therefore excluded from the analysis. For individuals with an oral antidiabetic index date prior to their 66th birthday, we shifted the index date to the date they turned 66 years of age to represent the first captured dispensation within the age based restrictive drug policy.

In summary, we varied the number of people exposed to metformin (simulation one) and the time of metformin initiation due to specific coverage (simulation two) or age based criteria (simulation three).

Statistical analysis

Cox proportional hazards regression models were used to assess the relationship between drug exposure and mortality. Individuals were considered exposed to metformin or sulfonylurea therapy from the date of their first dispensation until the date they died, left the province, or December 31, 1999, whichever occurred earliest. We adjusted the analyses for baseline age, sex, chronic disease score [16], and insulin use, as previously published [13]. To estimate the adjusted hazard ratios (aHR) and confidence intervals (CI), we used 1000 bootstrap samples for the nonformulary and special authorization simulations. For these simulations, we report the mean HR and the 2.5th and 97.5th percentiles of the 1000 repetitions. For the age-dependent coverage policy simulation, we report HR and 95% CI based on the eligible cohort 66 years and older. We used the HR point estimate from the base-case cohort as our reference standard to assess the degree of potential bias.