Can J Diabetes 43 (2019) 322–328

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Evaluation of Healthy User Effects With Metformin and Other Oral Antihyperglycemia Medication Users in Adult Patients With Type 2 Diabetes

Maxim Eskin BPharm, MSc [a,b]; Scot H. Simpson BSP, PharmD, MSc [b,c]; Dean Trevor Eurich BSP, PhD [a,b,*]

[a] School of Public Health, University of Alberta, Edmonton, Alberta, Canada
[b] Alliance for Canadian Health Outcomes Research in Diabetes, University of Alberta, Edmonton, Alberta, Canada
[c] Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada

Key Messages

- The healthy user effect has gained increasing attention as a potential source of bias in observational studies of preventive therapies.
- The healthy user effect may be a key source of bias in studies that suggest great benefits with the use of metformin therapy in patients with type 2 diabetes.
- This study suggests that metformin users are healthy users (engaged in more healthy behaviours), and that needs to be accounted for in studies of metformin therapy.

ARTICLE INFO

Article history:
Received 13 February 2018
Received in revised form
4 December 2018
Accepted 7 December 2018

Keywords:
bias
healthy user effect
metformin

ABSTRACT

Objectives: Healthy user bias, whereby health-seeking patients are more likely to initiate preventive therapies and engage in healthy lifestyle behaviours, is well known in observational studies, particularly with statins. However, its influence in studies of oral antihyperglycemic therapies is unknown. We sought to explore the healthy user effects in metformin users vs. nonusers on various health outcomes that should not be associated with metformin use.
Methods: We conducted a retrospective cohort study using data from Alberta, between 2008 and 2015, to examine the association between metformin use and various health outcomes.
Results: We identified 135,301 new users of oral antihyperglycemic agents. The mean age was 55 years, 75,949 (56%) were men and 130,725 (97%) had had at least 1 metformin prescription during a mean follow-up period of 3.4 years. Metformin users were less likely to be involved in accident-related events (adjusted hazard ratio [aHR] 0.90; 95% CI 0.85 to 0.96), were more likely to have preventive screening services (aHR 1.16; 95% CI 1.11 to 1.21), were less likely to experience other clinical events, such as asthma and gout attacks (aHR 0.90; 95% CI 0.84 to 0.97), and had lower risks for all-cause mortality (aHR 0.57; 95% CI 0.51 to 0.63) compared to nonusers.
Conclusions: Our results suggest that metformin users are more likely to initiate preventive therapies and engage in other healthy behaviours. Failure to account for these behaviours may introduce healthy user bias into studies evaluating the effects of oral antihyperglycemic therapies.

Mots clés:
biais
effets liés aux utilisateurs sains
metformine

RÉSUMÉ

Objectifs : Le biais lié aux utilisateurs sains selon lequel les patients ayant recours aux soins de santé sont plus susceptibles d'entreprendre des traitements préventifs et d'adopter des comportements sains liés au mode de vie est bien connu dans les études observationnelles, particulièrement en ce qui concerne les statines. Dans les études portant sur les traitements antihyperglycémiants par voie orale, son influence

* Address for correspondence: Dean Trevor Eurich, BSP, PhD, School of Public Health, University of Alberta, Edmonton, Alberta T6G 2G3, Canada.
E-mail address: deurich@ualberta.ca

1499-2671/
https://doi.org/10.1016/j.jcjd.2018.12.001

demeure toutefois inconnue. Nous avons cherché à explorer les effets liés aux utilisateurs sains entre les utilisateurs et les non-utilisateurs de metformine sur les divers résultats cliniques qui devraient être associés à l'utilisation de la metformine.
Méthodes : Nous avons mené une étude de cohorte rétrospective à partir des données de l'Alberta, entre 2008 et 2015, pour examiner l'association entre l'utilisation de la metformine et les divers résultats cliniques.
Résultats : Parmi les 135 301 nouveaux utilisateurs d'antihyperglycémiants par voie orale, 75 949 (56%) étaient des hommes et 130 725 (97%) avaient reçu au moins 1 ordonnance de metformine au cours d'un suivi moyen de 3,4 ans. L'âge moyen de ces utilisateurs était de 55 ans. Les utilisateurs de metformine étaient moins susceptibles d'être touchés par des événements liés à un accident (ratio d'incidence approché ajusté [RIAa] 0,90; IC à 95% 0,85 à 0,96), étaient plus susceptibles de recevoir des services de dépistage préventif (RIAa 1,16; IC à 95% 1,11 à 1,21), étaient moins susceptibles de subir d'autres événements cliniques, comme l'asthme et les crises de goutte (RIAa 0,90; IC à 95% 0,84 à 0,97) et avaient des risques plus faibles de mortalité toutes causes confondues (RIAa 0,57; IC à 95% 0,51 à 0,63) que les non-utilisateurs.
Conclusions : Nos résultats montrent que les utilisateurs de metformine sont plus susceptibles d'entreprendre des traitements préventifs et d'adopter d'autres comportements liés à la santé. Le fait de ne pas tenir compte de ces comportements peut introduire un biais lié aux utilisateurs sains dans les études portant sur l'évaluation des effets des traitements antihyperglycémiants par voie orale.

Introduction

Observational studies are commonly used in modern pharmacoepidemiology to evaluate drug safety and effectiveness. They have become increasingly popular and make important contributions to medical knowledge, especially when gold-standard randomized controlled trials (RCTs) are not always feasible. However, a major limitation of observational studies is their subjectivity to a number of potential biases that may cause erroneous results (1).

One source of bias has been termed the *healthy user effect* or the *healthy user bias.* It is a tendency of health-seeking patients to initiate preventive therapies and engage in behaviours that are consistent with healthy lifestyles which, in turn, can affect their outcomes (1–3). Aspects of a healthy lifestyle include balanced diet, regular exercise, moderation of alcohol consumption and tobacco use, avoidance of risky behaviours (e.g. excessive sunlight exposure, reckless driving, etc.), participation in vaccination programs and using preventive therapies and health services (2,4–6). Many of these healthy lifestyle behaviours are not recorded in typical administrative databases, and failure to account for these factors in observational studies of preventive therapies could introduce bias and produce spurious associations (1,5).

The healthy user effect has gained increasing attention as a potential source of bias in observational studies of preventive therapies and treatment of asymptomatic conditions (1,7,8). Numerous studies have demonstrated that the healthy user effect can be a plausible explanation for the discrepancies between RCTs and observational studies (1,5,9)—for example, hormone-replacement therapies (9–11) and vitamin E studies, among others (12). Indeed, after publication of RCTs showing significant harms resulting from hormone-replacement therapy, healthy user bias was deemed responsible for the large benefits observed in observational studies of hormone-replacement therapy (9–11). Healthy user bias has also been explored in users of statin therapies (5,7,13). Indeed, statin therapy is associated with increased use of a number of other preventive therapies and health services and a reduction in clinical events that are not intuitively associated with statin use, including reduced risk for cancer, sepsis, Alzheimer disease and hip fractures (1,4,5). It has also been extensively discussed as a potential source of bias in observational studies showing large reductions in all-cause mortality associated with influenza vaccination in elderly persons (6,8).

Although less studied, healthy user bias may explain the discrepancies in results between observational studies and RCTs of metformin use in patients with type 2 diabetes. Meta-analyses of RCTs have failed to replicate the strong association between metformin use and all-cause or cardiovascular (CV) mortality reported in observational studies (13,14); however, it should be noted that the vast majority of these RCTs did not look at mortality associated with metformin per se as the main outcome. As a result, a large body of observational studies have further explored the issue and have consistently shown clinically important benefits, including substantial reductions in all-cause and CV-related mortality, as well as beneficial effects in patients with diabetes and heart failure (15–18). The underlying reasons for the substantial discrepancy between experimental and observational studies in diabetes are unknown, but we surmise that unaccounted-for healthy user bias may explain partially or fully the difference between the study designs.

Therefore, our primary objective in this study was to gather evidence of healthy user bias in metformin users as compared to nonusers (i.e. users of other oral antihyperglycemic medications) in a large, unselected population of patients with type 2 diabetes. We hypothesized that patients with type 2 diabetes who use metformin, as compared to those not using metformin, would be at lower risk for events that should not be associated with metformin (e.g. accident events, asthma exacerbations, gout attacks, etc.) and, conversely, would be more likely to participate in more healthy behaviours (e.g. using preventive services, vaccines and diagnostic tests).

Methods

We conducted our analysis in a large population-based cohort of new users of oral antihyperglycemic medications in Alberta, based on administrative data augmented by clinical laboratory data from 2008 to 2015 that were provided by Alberta Health and Alberta Health Services. These databases capture health-care utilization from the provincially funded programs that provide coverage to all Alberta residents for prescription medications, physician visits, emergency department visits and hospitalizations. The databases included laboratory test results, the Pharmaceutical Information Network, Practitioner Payments (coded with the International Classification of Diseases [ICD-9] for medical conditions and with Alberta Medical Association services billing codes for medical services) and Ambulatory Care and Inpatient information (coded with the ICD-10 for medical conditions). Demographics and mortality data were collected from Population Registry and Vital Statistic databases. The University of Alberta Health Research Ethics Board approved our study's protocol.

Cohort selection

Patients were eligible for inclusion if they were at least 30 years of age on the index date (date of first dispensing record for an oral antihyperglycemia medication) (17). We identified new oral antihyperglycemic medication users between April 1, 2009, and March 31, 2015. A 1-year washout period defined new users by ensuring that there were no prior dispensing records for antihyperglycemia medications, including insulin, before the index date. Women using metformin as a single oral antihyperglycemic medication for polycystic ovary syndrome were excluded from the analysis.

Exposure

Patients were considered to be metformin users if they had at least 1 dispensation record for metformin during the follow-up period. Metformin exposure was modeled as a time-dependent variable by considering the patient unexposed until the date of the first metformin dispensation; after this date, the patient was coded as a metformin user until the end of the follow-up period (Fig. 1) (19). Metformin exposure was modeled in this manner because we were not necessarily interested in the true underlying effects of metformin on the outcomes per se but were interested in metformin as a marker of healthy user bias.

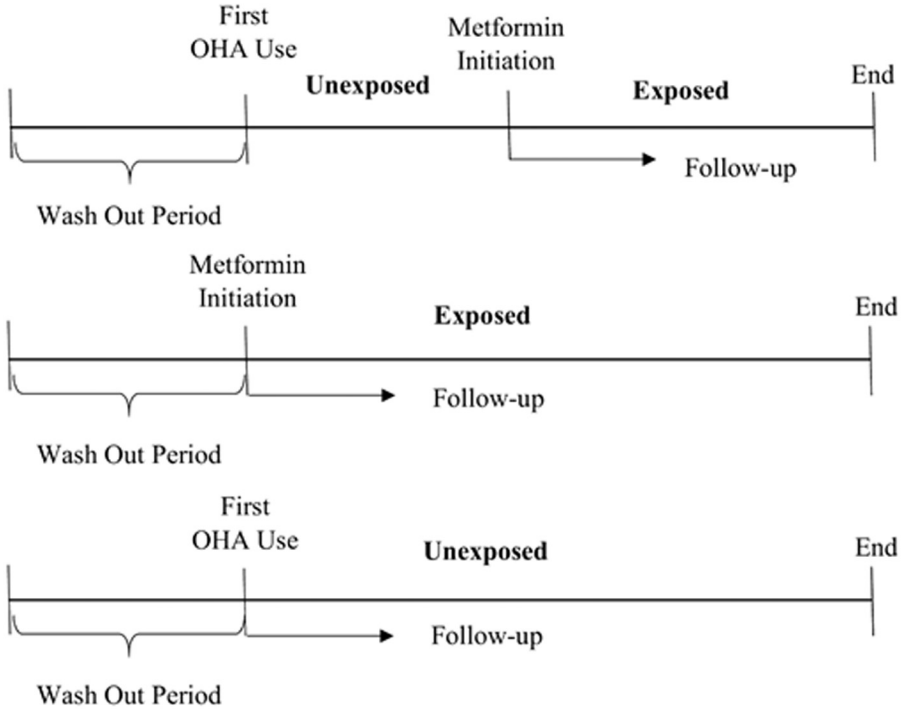
Outcomes

We evaluated a variety of clinical events and health behaviours that have been postulated in the literature to be associated with healthy user bias and that were identifiable in the administrative databases (1,5,7,13). Clinical events were identified using ICD-9 and ICD-10 codes in hospitalization records, emergency department visit records and physician visit records. Receipt of screening tests and vaccines were extracted from provincial laboratory records and procedure codes in physician visit records.

Clinical events and preventive services were selected a priori using information from previous studies and Diabetes Canada recommendations (20) and were grouped into 5 broad categories: accident events (e.g. burns and fractures); screening events (e.g. eye examinations, mammography); vaccinations (e.g. flu and pneumonia); clinical events without possible expected association (e.g. asthma and gout); and clinical events with possible expected association (e.g. all-cause mortality and myocardial infarction) (1,5,7). Additionally, the occurrence of annual laboratory screening for glycated hemoglobin (A1C) levels, lipids, kidney function as well as preventive pharmacotherapy (i.e. statins and angiotensin-converting-enzyme inhibitors) use were evaluated (21,22).

Covariates

We obtained baseline demographics, health services utilization and medication management during the year prior to the initiation of first oral antihyperglycemic medication use. The covariates were defined at the index date and included age, sex and other antihyperglycemic medication use. Most observational studies include comorbidity scores to control for confounding, so we also included the Elixhauser comorbidity score based on chronic conditions identified in the year prior to the first oral antihyperglycemic medication use (23). We included adjustments for use of other antihyperglycemic medications in our models to protect against



Schema depicting the methods used to define time-dependent metformin exposure: The index date assigned to the date of first metformin or oral anti hyperglycemic prescription dispensation after a 1 year wash out period. The patient considered exposed only after a receipt of first metformin prescription and remains exposed until the follow-up end (i.e., diagnostic test date, hospital admission with desired outcome diagnosis, death date, censoring from the study or reaching the study end March 31, 2015). Abbreviation: OHA – oral anti hyperglycemic agent

Figure 1. Time-dependent metformin exposure definition.

possible negative effects on the the health outcomes of interest (e.g. thiazolidinedione is associated with negative CV health outcomes) (24).

Statistical analyses

A separate Cox proportional hazard model, which adjusted for the same covariates, was used to assess the association between metformin exposure and each outcome of interest. For these analyses, the time to the first occurrence of each outcome was determined, with subjects censored by death (for nonmortality endpoints) or departure from the provincial benefits program (moved out of the province) or reaching the end of our observation period, March 31, 2015. Crude and adjusted hazard ratios (HRs), along with the 95% confidence interval (95% CI) were calculated for each outcome as was a composite measure for each of the 5 broad categories of outcomes. In addition, we completed Poisson regression, evaluating A1C, lipid and kidney function blood tests, which may be repeated several times a year. In these analyses, the adjusted incidence rate ratio (aIRR), which is the number of events observed divided by the time at risk for an event during the observation period for metformin compared to nonusers of metformin, was evaluated using Poisson regression. Finally, to observe whether control for health user bias would attenuate the effect of metformin's association with all-cause mortality we completed sequential Cox models where we: 1) adjusted only for age, sex and Elixhauser comorbidities; 2) added in commonly used medications by patients with diabetes as well as hospitalizations in the year prior to initial use of antihyperglycemic medications; and 3) added additional markers of healthy user bias (e.g. use of angiotensin-converting-enzyme inhibitors and statin use, vaccinations, screening tests, accident events, motor vehicle accidents, etc.). All analyses were conducted using STATA, v. 13.1 statistical software (StataCorp, College Station, Texas, United States).

Results

Our cohort consisted of 135,301 new users of oral antihyperglycemic medications. The average age was 55 years, 75,949 (56%) were male, the average follow-up time was 3.4 (SD±2) years, and 4.9% (6,677) of cohort patients died during the study period. Metformin was used by 97% of the cohort patients (130,725) (i.e. filled at least 1 metformin prescription during the follow-up period), among whom 6,661 started metformin therapy with the average delay of 1.1 years after initial diabetes management with another oral antihyperglycemic agent. Compared to nonusers, metformin users tended to be younger (55 vs. 60 years) and had lower comorbidity indexes (0.6 vs. 1.4) (Table 1). During the year prior to the index date, metformin users had fewer physician visits than nonusers (16 vs. 24) and had fewer ambulatory care service visits (5 vs. 11) but had a similar number of hospitalizations (1.5 and 1.7).

In time-dependent Cox proportional multivariable models, we found statistically significant lower risks for accident events (adjusted hazard ratio [aHR] 0.90; 95% CI 0.85 to 0.96), and other clinical outcomes without an expected association with metformin (aHR 0.90; 95% CI 0.83 to 0.97), including all-cause mortality (aHR 0.57; 95% CI 0.51 to 0.63) for metformin users compared to nonusers (Table 2). Furthermore, metformin users were more likely to have diagnostic screening tests and procedures applicable to both sexes (aHR 1.16; 95% CI 1.11 to 1.21) as well as those specific to women (aHR 1.12; 95% CI 1.07 to 1.18) and to men (aHR 1.48; 95% CI 1.41 to 1.55). However, clinical events possibly associated with metformin use showed no association (aHR 1.01; 95% CI 0.96 to 1.06), and the association between metformin use and vaccination rates was not statistically significant (aHR 1.11; 95% CI 0.99 to 1.23).

Table 1
Incident user cohort characteristics

	≥1 metformin dispensation	No metformin dispensation	p value[a]
No.	130,725	4,576	
Age, years, mean (SD)	55 (±13)	60 (±16)	<0.001
Men (%)	73,680 (56)	2,269 (50)	<0.001
Elixhauser Comorbidity Score, mean (SD)	0.6 (±2.5)	1.4 (±5)	<0.001
Death, no. (%)	6,025 (4.6)	652 (14.3)	<0.001
Follow-up[b], year, mean (SD)	3.4 (±2)	3.1 (±2.1)	<0.022
Physician visits[c], mean (SD)	16 (±24)	24 (±40)	<0.001
Hospitalizations[c], mean (SD)	1.4 (±0.9)	1.7 (±1.2)	<0.001
Ambulatory care[c], mean (SD)	5 (±11)	12 (±31)	<0.001
Anticoagulants, no. (%)	40,858 (31)	1,619 (35)	<0.001
Beta blockers, no. (%)	33,535 (26)	1,536 (34)	<0.001
Diuretics, no. (%)	40,609 (31)	1,932 (42)	<0.001
Dihydropyridine calcium channel blockers, no. (%)	30,209 (23)	1,267 (28)	<0.001
Nondihydropyridine calcium channel blockers, no. (%)	4,235 (3)	341 (7)	<0.001
Nitrates, no. (%)	14,233 (11)	675 (15)	<0.001
Inpatient hospital admissions during the year before index date, no. (%)			
0	115,927 (87)	3,747 (82)	
1	10,714 (8)	496 (11)	<0.001
≥2	4,084 (3)	333 (7)	

no., number; *SD*, standard deviation.
[a] The p value indicates the differences in characteristics between groups when metformin users and nonusers within a treatment cohort are compared by analysis of variance or by the chi-square test.
[b] Follow-up time from first oral antihyperglycemia use until death, censoring or study's end.
[c] The number of services in the year prior to cohort entry.

The overall likelihood of initiating preventive therapies recommended for patients with diabetes by Diabetes Canada (ACE inhibitors and statins) (21) did not differ between the groups (aHR 0.96; 95% CI 0.92 to 1.00).

Cohort patients had an average of 1.75 A1C blood tests during the follow-up period, which translated to an incidence rate of 39.6 tests per 100 patient-years (Table 2). Metformin users had their A1C levels measured more frequently than nonusers (aIRR 1.10; 95% CI 1.09 to 1.12). In contrast, measurement of serum creatinine was less frequent for metformin users compared to nonusers (aIRR 0.96; 95% CI 0.95 to 0.97). The frequency of blood tests for lipids was similar in metformin users and nonusers (aIRR 1.05; 95% CI 1.02 to 1.09). Overall, the frequency of recommended blood tests was not different between groups (aIRR 1.00; 95% CI 0.99 to 1.01).

Finally, in our sequential models, after adjusting only for age, sex and Elixhauser comorbidities, metformin was associated with a 46% reduction in time to all-cause mortality (aHR 0.54; 95% CI 0.50 to 0.59); a 43% reduction when medications and prior hospitalizations were added to the model (aHR 0.57; 95% CI 0.53 to 0.63); and a 39% reduction when markers of healthy use were added to the model (aHR 0.61; 95% CI 0.56 to 0.67) (Table 3).

Discussion

In our cohort of new users of oral antihyperglycemic medications, metformin users were less likely to experience accident events and were more likely to use preventive services and screening and to take diagnostic tests. Collectively, these data suggest that metformin may be a marker of healthy users. These findings have important implications for observational studies involving exposure to oral antihyperglycemic medication, studies in which metformin often constitutes a high proportion of use, and its users are commonly a group of interest in the study.

Table 2
Associations between metformin therapy and risk for health-related events

Outcome	Event rate/100 person-years	Time-dependent exposure definition model		
		Adjusted hazard ratio[a] (8 covariates)	Adjusted hazard ratio[b] (15 covariates)	Adjusted hazard ratio[a] (15 covariates excluding switchers[c])
Accident events				
Burns	0.37	1.10 (0.89–1.37)	1.10 (0.89–1.37)	0.98 (0.76–1.26)
Falls	0.04	1.25 (0.69–2.24)	1.23 (0.68–2.21)	1.03 (0.52–2.05)
Fractures	0.73	0.98 (0.86–1.11)	0.99 (0.88–1.13)	0.87 (0.75–1.00)
Motor vehicle accidents	0.18	0.77 (0.58–1.03)	0.77 (0.57–1.02)	0.92 (0.61–1.39)
Open wound	2.26	1.05 (0.96–1.14)	1.05 (0.96–1.14)	0.94 (0.85–1.05)
Poisoning	0.73	1.02 (0.88–1.18)	1.00 (0.86–1.16)	0.76 (0.63–0.91)
All (first occurrence)	5.82	0.84 (0.79–0.89)	0.90 (0.85–0.96)	0.72 (0.67–0.76)
Screening events				
Both sexes (n=135,301)				
Eye examinations	10.95	1.14 (1.09–1.19)	1.02 (0.97–1.06)	0.82 (0.78–0.87)
Fecal occult blood test	0.80	1.60 (1.65–1.91)	1.62 (1.36–1.94)	1.10 (0.92–1.31)
Sigmoidoscopy	0.55	0.87 (0.73–1.03)	0.87 (0.73–1.04)	0.84 (0.68–1.03)
All (first occurrence)	12.4	1.17 (1.12–1.22)	1.16 (1.11–1.21)	1.11 (1.05–1.18)
Women (n=59,352)				
Papanicolaou test	13.14	1.11 (1.03–1.19)	1.10 (1.03–1.18)	1.17 (1.08–1.28)
Mammography	74.46	1.21 (1.14–1.29)	1.20 (1.14–1.28)	1.28 (1.18–1.38)
Bone mineral density test	9.49	1.17 (1.09–1.26)	1.16 (1.08–1.25)	1.25 (1.15–1.38)
All (first occurrence)	33.22	1.13 (1.08–1.19)	1.12 (1.07–1.18)	1.17 (1.10–1.25)
Men (n=75,949)				
Prostate-specific antigen test	17.48	1.64 (1.53–1.75)	1.48 (1.41–1.55)	0.93 (0.88–0.97)
Laboratory tests[d]				
A1C	39.63	1.10 (1.09–1.12)	1.10 (1.09–1.12)	1.23 (1.20–1.26)
Creatinine	39.83	0.95 (0.94–0.96)	0.96 (0.95–0.97)	0.93 (0.91–0.94)
Lipids	43.76	1.02 (0.97–1.06)	1.05 (1.02–1.09)	1.06 (1.02–1.11)
All	33.89	0.97 (0.96–0.98)	1.00 (0.99–1.01)	1.09 (1.04–1.14)
Preventive therapies				
Vaccination				
Pneumonia	0.11	1.22 (0.79–1.88)	1.22 (0.80–1.89)	0.86 (0.53–1.38)
Influenza	2.04	1.10 (0.98–1.24)	1.11 (0.99–1.25)	0.88 (.077–0.99)
All (first occurrence)	2.14	1.10 (0.98–1.23)	1.11 (0.99–1.23)	0.87 (0.77–0.98)
Preventive pharmacotherapies				
Statin use	9.76	0.99 (0.94–1.03)	0.98 (0.94–1.03)	1.70 (1.57–1.84)
ACE inhibitors use	6.07	0.88 (0.83–0.93)	0.87 (0.83–0.92)	1.50 (1.36–1.64)
All (first occurrence)	13.85	0.97 (0.93–1.00)	0.96 (0.92–1.00)	1.59 (1.48–1.70)
Clinical events, possible association expected				
Ambulatory services use	42.41	1.01 (0.96–1.06)	1.01 (0.97–1.06)	1.00 (0.94–1.07)
Emergency department admissions	14.38	0.92 (0.87–0.97)	0.92 (0.87–0.97)	1.08 (0.99–1.06)
Lung cancer	0.33	0.90 (0.73–1.10)	0.99 (0.80–1.21)	0.82 (0.65–1.03)
Mortality (all-cause)	1.49	0.54 (0.50–0.59)	0.57 (0.51–0.63)	0.55 (0.50–0.60)
Myocardial infarction	0.44	1.11 (0.93–1.34)	1.12 (0.94–1.35)	0.88 (0.71–1.10)
All (first occurrence)	42.56	1.01 (0.96–1.06)	1.71 (1.66–1.77)	1.25 (1.22–1.30)
Clinical events, no association expected				
Asthma/COPD	5.38	0.91 (0.86–0.97)	0.92 (0.87–0.97)	0.90 (0.84–0.96)
Bacterial Infection	0.62	0.85 (0.74–0.98)	0.88 (0.77–1.01)	0.69 (0.59–0.81)
DVT and PE	0.84	0.96 (0.84–1.10)	0.99 (0.86–1.13)	0.83 (0.71–0.97)
Dental problems	2.1	0.95 (0.86–1.04)	0.97 (0.88–1.06)	0.89 (0.79–1.00)
Diverticulitis	0.48	1.15 (0.95–1.38)	1.16 (0.97–1.40)	1.04 (0.83–1.30)
Drug dependency	2.56	1.10 (1.00–1.21)	1.09 (0.99–1.21)	0.92 (0.80–1.04)
Food-borne bacterial infection	1.68	0.98 (0.88–1.08)	0.99 (0.80–1.10)	0.82 (0.72–0.93)
Gallstones	0.88	1.05 (0.91–1.20)	1.05 (0.91–1.20)	0.97 (0.82–1.13)
Gastrointestinal bleeding	0.40	1.00 (0.85–1.18)	1.01 (0.86–1.20)	0.86 (0.71–1.04)
Gout	0.18	0.88 (0.80–0.96)	0.89 (0.80–0.96)	0.83 (0.74–0.92)
Kidney stones	0.73	1.05 (0.90–1.23)	1.04 (0.89–1.22)	0.81 (0.67–0.97)
Migraine	0.91	0.87 (0.76–1.00)	0.89 (0.77–1.02)	0.75 (0.63–0.88)
Skin infection	5.11	1.00 (0.94–1.06)	1.00 (0.94–1.06)	0.87 (0.81–0.94)
Sexually transmitted diseases	351	0.99 (0.90–1.09)	0.99 (0.90–1.09)	0.94 (0.78–1.12)
All (first occurrence)	25.14	0.90 (0.84–0.97)	0.90 (0.83–0.97)	0.82 (0.75–0.90)

A1C, glycated hemoglobin; *COPD*, chronic obstructive pulmonary disease; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism.
[a] Adjusted for age, sex, Elixhauser comorbidity index and other antidiabetes medication use.
[b] Adjusted for age, sex, Elixhauser comorbidity index, other antidiabetes medication use, other antihypertension medications: calcium channel blockers (dehydro- and nondehydropyridines), beta blockers, diuretics, nitrates; anticoagulants and number of hospital admissions 1 year prior. to cohort entry.
[c] Patients who initiated other antidiabetes medication first and during the therapy, switched or added metformin.
[d] Incidence rate ratios were evaluated using Poisson regression to evaluate tests, which may be repeated several times a year during the follow-up time.

Numerous observational studies of diabetes have consistently shown metformin to be associated with an approximate 30% reduction in all-cause or CV-specific mortality compared to other oral antihyperglycemia agents (14,17). Yet only 1 small substudy within the United Kingdom Prospective Diabetes Study randomized controlled trial has suggested a similar benefit in obese patients with type 2 diabetes (16). Indeed, a recent meta-analysis of 13 RCTs failed to show similar CV- and all-cause mortality reductions in the metformin benefits reported by observational studies relative to other oral antihyperglycemia treatments (13).

Table 3
Metformin use and mortality models adjusted for differing covariates of interest

Metformin use Crude/unadjusted estimate	0.30 (0.28–0.33)
Metformin use Adjusted to 8 covariates: age sex, Elixhauser comorbidity score and other antidiabetes medications use	0.54 (0.50–0.59)
Metformin use Adjusted to 8 covariates used in previous model and additional 7: anticoagulants, beta blockers, calcium chanel blockers (dihydropyridine), calcium chanel blockers (nondihydropyridine), diuretics, nitrates use and the number of hospitalization per year prior to cohort entry	0.57 (0.53–0.63)
Metformin use Adjusted to 15 covariates used in previous model and additional healthy user markers (ACE inhibitors and statins use, flu and pneumonia vaccinations, screening tests, accident events, motor vehicle accidents).	0.61 (0.56–0.67)

In our study, although metformin use was associated with substantially lower risks for all-cause mortality compared to the risks in nonusers and consistent with previous observational studies (14), the collective data strongly suggest that this estimate is influenced by the healthy user bias associated with metformin use. Usually, patients who are being prescribed preventive therapies have better functional status and cognition and are often more likely to engage in other health-promoting behaviours (e.g. better diets, more exercise, smoking cessation, alcohol in moderation). Moreover, they are more likely to seek preventive services (e.g. cancer screenings, immunizations); are more likely to be subject to physician-selection bias (i.e. healthy users initially interact more often with physicians due to health-seeking behaviours); and are more likely to seek and adhere to other preventive drug therapies (e.g. multivitamins and aspirin). This interplay among healthy user bias, patients, physicians and improved outcomes has been described previously (1,2). Although we were able to account for some healthy user attributes, other, more difficult to capture effects (e.g. physicians' attitudes and perspectives of preventive services) are not fully accounted for. Thus, although inclusion of healthy user markers in our models did attenuate the results, a large unexpected benefit was still observed.

Although the observed association between metformin and clinical events is likely to be attributed to unmeasured confounding, due at least in part to health-seeking behaviours, other explanations for these findings are also possible. First, the association between metformin and reduced risk for fracture could be due to differences in actual health status and, particularly, due to body mass index. Second, falls, an outcome that was previously used in healthy user bias studies with statins (5), can be associated with other medications' side effects (syncope due to blood pressure medications) or hypoglycemic events when taking nonmetformin therapies. Therefore, although the studied outcome events might be less appropriate markers for healthy behaviours and not attributable to healthy user bias per se, they are nevertheless major potential sources of bias, which may be different in metformin and nonmetformin users.

Future observational studies of oral antihyperglycemic medications should include better control for healthy user bias, particularly where metformin is concerned. Beyond traditional methods, such as new user design (4,25), active comparator implementation (26–28) and time-dependent exposure definition (27), researchers should consider controlling for prior use of preventive tests and health services and for propensity scores that include healthy user markers in the prediction of drug exposure (29). Additional methods such as instrumental variables (7,25) have also been put forth; however, the identification of an appropriate instrumental variable for many observational studies is difficult.

Despite several strengths of our study, including the large population-based sample and rich clinical data, several limitations are inherent in our work. First, and most important, we fully acknowledge that additional unmeasured confounding could be present in our study; for example, body mass index, tobacco use, alcohol consumption and socioeconomic status were not available in our database. Second, our data did not allow us to evaluate the patients who were diagnosed with diabetes but were prescribed lifestyle modifications by the family physician or the patients who were prescribed oral antihyperglycemia medications but were noncompliant and never filled the prescription at the pharmacy. Third, a 1-year washout may be insufficient to identify first use of diabetes medications. Last, we acknowledge that ICD coding may not be sensitive or specific for all outcomes evaluated by the administrative data; however, there is no reason to believe the coding would be different based on metformin-exposure status.

This study suggests that metformin users take better care of themselves by engaging in various healthy behaviors and initiating preventive therapies. Therefore, a failure to account for these behaviours can introduce bias to observational studies evaluating the effect of oral antihyperglycemic therapies on health outcomes. Moreover, observational studies that attribute surprisingly protective effects to antihyperglycemia therapies should be interpreted cautiously. Further work is required to gain a better understanding of the healthy user effect in patients with diabetes and to develop methods for guarding against this effect in observational studies.

Funding

This study was funded by an operating grant provided by Diabetes Canada (#OG-2-09-2693-SS). ME was supported by an Alberta Diabetes Institute Studentship for Diabetes Research. DTE is a Canada Research Chair funded by the Government of Canada. This study was based, in part, on data provided by Alberta Health. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta. Neither the Government of Alberta nor Alberta Health express any opinion in relation to this study.

Author Disclosures

None. The patients were not involved in the development of the study, and ethics approval was obtained from the University of Alberta Research Ethics Committee.

Author Contributions

ME was responsible for the study design, statistical analysis and interpretation of data and for drafting the manuscript; DTE and SHS were responsible for the study design, interpretation of data and critical revision of manuscript; all authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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