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Metformin use and risk of total joint replacement in patients with diabetes: a longitudinal cohort study of Alberta's Tomorrow Project

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Abstract

Purpose To characterize the association between metformin use and risk of total joint replacement in patients with diabetes using data from Alberta's Tomorrow Project (ATP), a population-based cohort study of chronic diseases in Alberta, Canada.

Methods The ATP participants with incidence of diabetes after enrollment were included and followed up to March 31, 2021. Metformin use, including daily doses, was measured by a time-varying approach during the follow-up. A multivariable Cox regression model was used to characterize the association between metformin use and risk of total joint replacement, after controlling for time-related variation in drug use, clinical status, BMI, lifestyles and concurrent medications.

Results Among 3,001 incident cases of diabetes (52% females, age at diagnosis 61.3 ± 9.5 years, average follow-up of 7.3 ± 4.7 years), the rate of total joint replacement was 7.57 per 1,000 person-year (PY) for metformin users and 9.31 per 1,000 PY for non-metformin users, with rate ratio = 0.81 (95% CI = 0.59–1.11, *p*-value = 0.09). In multivariable Cox regression analysis, metformin use was not significantly associated with risk of total joint replacement, with hazard ratio of 0.74 (95% CI = 0.52–1.03, *p*-value = 0.07) for patients with metformin medication, HR = 0.75 (95% CI = 0.46–1.22) for 0–1.0 g/day metformin use, and HR = 0.73 (95% CI = 0.49–1.08) for 1.0 + g/day use ('no metformin use' as the reference group).

Conclusions Although our findings are not statistically significant, our study suggests clinically a potential benefit of metformin use in reducing risk of total joint replacement in patients with diabetes.

Keywords Diabetes, Metformin, Total joint replacement, Time-varying, Cohort study

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Introduction

Patients with diabetes often have higher risk of developing osteoarthritis (OA) due to obesity and insulin resistance induced inflammation [1–3]. Metformin, the most commonly prescribed anti-diabetic drug [4], has been reported to have anti-inflammatory and chondro-protective effects [5], and therefore often recommend as treatment of cardiovascular conditions [6–8] and certain inflammatory diseases [9–12], including OA [13].

Patients with severe OA often progress to joint replacement [14] and inflammation is a key factor leading to this progression [15]. While preclinical and human studies have provided evidence supporting use of metformin in reducing risk of OA [13], mixed results have been reported on the impact of metformin on total joint replacement in patients with diabetes. Two population-based cohort studies in Hong Kong and Taiwan showed that metformin use was associated with reduced risk of total joint replacement in patients with diabetes [16, 17]. Another cohort study in Taiwan showed that when combined with COX-2 inhibitor, a nonsteroidal anti-inflammatory drug for pain treatment, metformin use had more significant effect in reducing risk of joint replacement than treating with either metformin or COX-2 inhibitor alone in patients with diabetes and OA [18]. On the other hand, a prospective cohort study in Australia showed no significant difference in risk of total knee replacement (odds ratio = 0.30, 95% CI = 0.07–1.30) between metformin users vs. non-users, although metformin use was associated with reduced loss of medial cartilage volume in patients with obesity and knee osteoarthritis [19]. A recent cohort study in the U.S. also found no significant difference in risk of total joint replacement (HR = 0.80; 95% CI, 0.50–1.27) between metformin users and non-metformin users, even though metformin use was significantly associated with reduced risk of OA in patients with diabetes [20]. Nevertheless, very few studies on this topic have considered the potential time-related measurement bias in metformin use [17, 20] and the impact of key confounders [19, 21], including age, body weight, comorbidities and concurrent medications, on joint replacement.

To fill this knowledge gap, in this study, we used data from Alberta's Tomorrow Project (ATP), a population-based cohort study of chronic diseases in Alberta, Canada, linked to administrative healthcare data, with consideration of the time-varying metformin use and a wide range of confounders, especially difficult-to-capture lifestyle factors (e.g., diet and physical activity) and concurrent medications, to characterize the impact of metformin on total joint replacement in patients with diabetes.

Methods

Study design

We conducted a longitudinal cohort study to characterize the association between patient's time-varying metformin use (exposure) and incidence rate of total joint replacement, using data from ATP with linkage of Alberta Health (AH) administrative healthcare data.

Study participants

As described previously [21], from 2000 to 2008, ATP randomly recruited a total of 29,876 participants (aged 35–69 years) from the general adult population in Alberta, Canada, with no history of cancer other than non-melanoma skin cancer at the time of enrollment, to study how lifestyle, genetics and environment influence health and wellbeing. All ATP participants had provided consent to data linkage to healthcare data for research.

In the ATP cohort, 3,050 incident cases of diabetes (i.e. diabetes diagnosed after enrollment in ATP) were identified, among which 3,001 cases with healthcare records documented only in Alberta (i.e., no health records from other provinces/territories), were included in the final analysis. Detailed inclusion and exclusion criteria for the study cohort are shown in Supplementary Figure S1.

Data sources

A wide range of chronic disease risk factors, including sociodemographic and socio-economic factors, anthropometrics (e.g. BMI) and lifestyle factors (e.g. dietary intake and physical activity), were provided by participants at time of enrollment with the ATP self-administered questionnaire. Detailed information on these questionnaires can be found at www.myATP.ca.

Individual-level Alberta Health (AH) administrative healthcare data were linked to the ATP cohort using the unique identifier Personal Health Number (PHN). The AH datasets utilized in this study included hospital discharge abstract data (DAD), ambulatory care data, practitioner/physician claims data and drug dispense records from Alberta Blue Cross (ABC) and Pharmaceutical Information Network (PIN). Detailed descriptions of AH administrative datasets for research can be obtained from Alberta Health (http://www.health.alberta.ca/initiatives/health-research.html).

Cases of diabetes

Patients with diabetes were identified using a modified version of the validated Canadian National Diabetes Surveillance System (NDSS) algorithm [22, 23]:

> *one hospitalization record with an ICD code of diabetes (ICD-9: 250, ICD-10: E10-E14) OR two physician claims within two years with an ICD code of diabetes OR self-report by participants, plus any of*

the following conditions: (i) one hospitalization with ICD code for diabetes, (ii) one physician claim with ICD code for diabetes, or (iii) one diabetes medication with Anatomical Therapeutic Chemical Classification (ATC) code for insulin (A10A) or glucose-lowering drugs (A10B).

The index date of diabetes was determined by the earliest date of medical records that contributed to the case definition. Cases were considered as "incident cases" (new cases) only if the index date was more than 6 months after ATP enrollment to ensure true incident cases were identified for the study.

Outcome of interest

The incident cases of total joint replacement, including knee and hip replacement, were identified using the Canadian Joint Replacement Registry (CJRR) algorithm, with clinical procedure codes (CCI: 1VA53LAPN/1VA53LLPN, 1VG53LAPN/1VG53LAPP; CCP: 934, 935) in the DAD and/or ambulatory care data [24]. The index date of total joint replacement was determined by the earliest date of medical records that contributed to the case definition.

Metformin exposure

We measured metformin use by drug dispense records with ATC code of A10BA02 in PIN and ABC datasets. As previously described, we considered the time-related variation in metformin use, including daily doses, for patients with diabetes [25]. First, we defined a continuous course of metformin use as a period when patients filled a prescription for metformin within 60 days or less of the last day of the previous metformin dispense (with days-of-supply taken into account) [25]. Metformin exposure was thereafter modeled as a time-varying variable, with patients considered as being exposed when they were in a course of metformin use; otherwise they were deemed unexposed, until the end of study or incidence of total joint replacement or death [25]. To reduce the potential prevalent drug user bias [26], historical metformin use with an end date in 6 months or more before diabetes index (diagnosis) date were considered diabetes-unrelated use and excluded from the analysis. To reduce the potential protopathic bias [27], metformin use with a start date in 6 months or less before incidence of total joint replacement were excluded from the analysis. We also calculated the daily dosages per course and based on daily doses, patients were categorized into three groups (no use, 0–1.0 g/day and > 1.0 g/day).

Statistical analysis

The characteristics of the study participants and incidence rate of total joint replacement were summarized using standard exploratory data analysis method [28]: means and standard deviations were calculated for continuous variables; proportions were calculated for categorical variables; incidence rates (density) were calculated for person-year data. Comparisons between groups were made using Student *t*-test for continuous variables and $\chi 2$ test for categorical variables and rates.

The impact of metformin on risk of total joint replacement was examined by a multivariable Cox proportional hazard model with metformin use as a time-varying exposure variable [29] and incidence of total joint replacement as the outcome variable [30]. Survival time in the Cox regression models was defined as the time (the number of year) to the incidence of total joint replacement or death or the end of study (March 31, 2021). Time-varying exposures were handled by splitting time-to-event data into multiple observations based on the dates when metformin use status were changed (i.e., switching between on/off metformin use) and non-time-varying covariates (e.g. sex) remained the same after splitting [31].

In the Cox regression model, hazard ratio (HR), including its 95% CI, for total joint replacement, was computed after adjusting for the following covariates: age at diabetes diagnosis, sex (male/female), ethnicity (European ancestry vs. other), living in rural vs. urban areas, education attainment (secondary or less, some post-secondary, post-secondary), BMI categories (≤ 24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30.0 kg/m^2), ever smoker (yes/no), physically active (yes/no, based on accumulating at least 210 min of moderate- to vigorous-intensity recreational physical activity per week in the past 12 months) [32], tertiles of the Canadian Healthy Eating Index for diet quality assessment [33, 34], the number of Elixhauser comorbidities (0, 1–2, 2 + comorbidities) at diagnosis [35], diabetes complication severity index (DCSI) [36], concurrent medications, including insulin, other oral anti-hyperglycemic agents as a group of drugs with similar major effect on diabetes patients (sulfonylureas, α-glucosidase inhibitors, thiazolidinediones and inhibitors of dipeptidyl peptidase-4), pain management drugs (systemic corticosteroids, nonsteroidal anti-inflammatory drugs, glucosamine and opioids), anti-obesity drugs, anti-depressants, drugs for bone health & mineralization and drugs for cardiovascular diseases (lipid-lowering agents, diuretics, beta blocker, calcium channel blocker, agents on renin-angiotensin system and anti-hypertensive drugs). Detailed classification of these drugs is described in Supplementary Table S1. For participants who had missing values in the ATP self-report covariates (e.g., education attainment), a 'missing indicator' category was created to ensure all participants were included and results were minimally affected by missing values. Potential effect modifications from BMI and concurrent

use of drugs for treatment of pain, CVD and depression were examined by adding an interaction term of these covariates with metformin exposure in the Cox regression model.

We conducted four sensitivity analyses: (i) to assess the over-adjustment bias by building a parsimonious model with statistically significant (i.e., p-value < 0.05) as well as covariates that may not be statistically significant but with clinically or epidemiologically meaningful prediction power (i.e., hazard ratio > = 1.5 or < = 0.7); (ii) to assess the potential attenuating effect from low-risk patients (i.e., patients without OA) by including only patients with OA (high-risk population) in the analysis. Patients with OA were identified as individuals with at least one hospitalization OR two physician claims OR two ambulatory care encounters within two years, with ICD-9/10 codes of osteoarthritis (ICD-9 = 715; ICD-10 = M15-M19) in hospital DAD, physician claims and ambulatory care datasets [37]; (iii) omitting patients with missing data to assess the impact of missing data on the associations; (iv) separate analyses for total knee replacement and hip replacement to assess the potential site-specific difference. All statistical analyses, with significant level at alpha = 0.05, were conducted using STATA®14 software.

Results

Characteristics of study participants

This cohort study included 3,001 incident cases of diabetes with an average (SD) follow-up of 7.3 (4.7) years (range 0.05–19.4 years) from diabetes diagnosis to incidence of total joint replacement or March 31, 2021 or death. The average age at diabetes diagnosis was 61.3 ± 9.5 years and 51.5% of the participants were women. The majority (87.9%) of participants self-reported as being of European ancestry and 26.7% of participants lived in rural areas. Overall, 67.5% of participants had ever used metformin at some point since diabetes diagnosis. These metformin users were at a younger age when diagnosed with diabetes, more likely to have BMI > 30 kg/m^2 and less likely to be physically active (Table 1). In addition, compared to non-metformin users, on average, metformin users had a lower number of Elixhauser comorbidities at baseline, higher severity of diabetes (i.e., higher DCSI score) and more likely to be taking insulin and other anti-hyperglycemic agents, anti-obesity drugs and drugs for bone health, cardiovascular diseases and pain management (Table 1).

Among metformin users (n = 2,026), the average time on metformin medication was 4.1 ± 3.2 years (8326.7 person-year) during a total of 8.0 ± 4.6 years of follow-up (16220.7 person-year). When these patients were taking metformin medication, the average daily dose was 1.24 ± 8.97 g/day (median = 1.06 g/day, IQR = 1.00–1.88 g/day).

Incidence rates of total joint replacement

During the follow-up period (21972.6 person-year in total), 190 patients had total joint replacement, with an overall incidence rate of 8.65 per 1,000 person-year (PY). Compared to non metformin users (12.2 per 1,000 PY), metformin users had a significantly lower incidence rate of total joint replacement (7.40 per 1,000 PY), with an incidence rate ratio of 0.61 (95% CI = 0.45–0.83, p = 0.002). Nevertheless, when considering time-related variation, metformin use was not sigificantly associated with the incidence rate of total joint replacement, with an incidence rate ratio = 0.81 (95% CI = 0.59–1.11, p = 0.09) (Table 2). In addition, no significant difference was observed in incidence rate for different daily doses (7.43 per 1,000 PY for daily dose of 0–1.0 g vs. 7.63 per 1,000 PY for daily dose of 1.0 + g, p = 0.89) (Table 2).

Association between Metformin use and risk of total joint replacement

In multivariable time-varying Cox regression analysis, after controlling for patient's socio-demographic and socio-economic factors, BMI, lifestyle behaviors, diabetes severity, comorbidities and time-related variation in medications, metformin use was not significantly associated with the incidence rate of total joint replacement, with HR = 0.74 (95% CI = 0.52–1.03, p-value = 0.07) (Table 3). For every increment of daily dose of 1.0 g/day in metformin use, HR for total joint replacement was 0.85 (95% CI = 0.68–1.06, p-value = 0.15), and no dose-responsive relationship was observed (HR = 0.74, 95% CI = 0.46–1.20 for daily dose of 0–1.0 g and HR = 0.73, 95% CI = 0.49–1.08 for daily dose of 1.0 + g, with no metformin use as reference) (Table 3).

No significant interactions were observed for BMI and concurrent use of drugs for CVD and depression (data not shown). Nevertheless, a borderline significant difference (p-value = 0.053 for testing interaction) was observed in the association between metformin use and total joint replacement for patients with concurrent use of pain drugs (HR = 1.24, 95% CI = 0.63–2.45) vs. without (HR = 0.56, 95% CI = 0.36–0.89) (Supplementary Table S2). Similar results were observed in our sensitivity analyses when (i) parsimonious models were built (Supplementary Table S3) and (ii) only patients with OA (41.1% of total participants) were included in the analysis (Supplementary Table S4); (iii) omitting patients with missing values in covariates (Supplementary Table S5); (iv) conducting analyses for patients with total knee replacement and hip replacement separately (Supplementary Table S6).

Table 1 Characteristics of study participants by ever use Metformin during the study period [a]

	Non metformin users (*n* = 975, 32,5%)	**Metformin users (*n* = 2,026, 67.5%)**	**Total (*n* = 3,001, 100%)**
	Mean (SD), %	**Mean (SD), %**	**Mean (SD), %**
Age at diagnosis *			
years	63.9 (9.6)	60.0 (9.2)	61.3 (9.5)
Sex *			
Female	55.4	49.6	51.5
Male	44.6	50.4	48.5
Ethnicity			
European ancestry	88.2	87.7	87.9
Other	11.8	12.1	12.0
missing	0	0.2	0.1
Rural/urban			
Rural	27.3	26.4	26.7
Urban	72.7	73.6	73.3
Education level			
High school or less	34.9	36.4	35.9
Some post-secondary	46.0	47.4	47.0
Post-secondary	19.1	16.2	17.1
Body mass index *			
≤ 24.9 kg/m^2	12.3	5.1	7.5
25.0–29.9 kg/m^2	31.3	27.5	28.7
≥30.0 kg/m^2	55.9	66.5	63.0
missing	0.5	0.9	0.8
Ever smoking			
No	36.3	37.9	37.4
Yes	63.7	62.1	62.6
Physically active [b]*			
No	51.6	52.5	52.2
Yes	36.5	31.9	33.4
missing	11.9	15.6	14.4
Diet quality (Healthy Eating Index) [c]			
average	52.1 (10.3)	52.2 (9.5)	52.2 (9.8)
lowest tertile	35.2	33.3	33.9
medium tertile	28.5	27.9	28.1
highest tertile	24.7	23.6	24.0
missing	11.6	15.2	14.0
Number of Elixhauser comorbidities *			
average	2.3 (2.3)	1.7 (1.6)	1.9 (1.9)
0	16.0	18.8	17.9
1–2	49.2	60.7	56.9
2+	34.8	20.5	25.2
Diabetes complication severity index *			
average	0.02 (0.17)	0.65 (0.95)	0.44 (0.84)
Osteoarthritis *			
no	54.4	61.1	58.9
yes	45.6	38.9	41.1
Insulin medication*			
no	100	90.8	93.8
yes	0	9.2	6.2
anti-obesity medication *			
no	100	95.6	97.0
yes	0	4.4	3.0
Bone health & mineralization medication *			

Table 1 (continued)

	Non metformin users (*n* = 975, 32,5%)	Metformin users (*n* = 2,026, 67.5%)	Total (*n* = 3,001, 100%)
	Mean (SD), %	**Mean (SD), %**	**Mean (SD), %**
no	100	95.0	96.6
yes	0	5.0	3.4
CVD medication *			
no	96.8	40.4	58.7
yes	3.2	59.6	41.3
Anti-depression medication *			
no	98.8	77.9	84.7
yes	1.2	22.1	15.3
Pain management medication *			
no	98.9	56.4	70.2
yes	1.1	43.6	29.8

a. the number of Elixhauser comorbidities (diabetes excluded) within first years of diagnosis;

b. Categories (Yes/No) were created according to accumulating at least 210 min of moderate- to vigorous- intensity recreational physical activities per week in the past 12 months;

c. Scores determined from the Canadian Diet History Questionnaire and using the 2005 Canadian Healthy Eating Index

* Statistically significant different ($p < 0.05$) across groups

Abbreviations: SD = standard deviation

Table 2 Metformin use and incidence (unadjusted) rates of total joint replacement

I. Non time-varying measures					
	Non-metformin users	**Metformin users**			**Total**
# patient	975	2,026			3,001
# cases	70	120			190
Person-year	5,751.8	16220.8			21972.6
Rate (per 1,000 PY)	12.17	7.40			8.65
Rate ratio *	Ref.	0.61 (0.45–0.83)			-
II. Time-varying measures					
	Metformin use = no		**Metformin use = yes**		
# cases	127		63		190
Person-Year	13645.8		8326.7		21972.6
Rate (per 1,000 PY)	9.31		7.57		8.65
Rate ratio**	Ref.		0.81 (0.59–1.11)		-
	From non-metformin users	From metformin ever users	**0–1.0 g/day**	**1.0 + g/day**	
# cases	70	57	20	43	190
Person-Year	5,751.8	7,894.0	2693.6	5633.1	21972.6
Rate (per 1,000 PY)	12.17	7.22	7.43	7.63	8.65
Rate ratio**	-	-	0.80 (0.47–1.28)	0.82 (0.57–1.17)	-

***non metformin users as reference**

**** no metformin use (from both metformin user and non users) as reference**

Discussion

This longitudinal cohort study shows that the impact of metformin on risk of total joint replacement was not significant in patients with diabetes, after controlling time-related variation in metformin use and key confounding factors, including age, sex, BMI, lifestyle factors, diabetes severity, comorbidities and concurrent medications. Similar results were observed when stratifying patients by different daily doses of metformin, using parsimonious models, and including only patients with OA in the analysis. These findings are consistent with previous population-based cohort studies in Australia [19] and the U.S [20] showing no significant difference in risk of total joint replacement between metformin users and non-users.

In addition to its glucose-lowering effect, metformin has been reported to have chondro-protective, immunomodulatory and anti-inflammatory effects [5]. Results from preclinical trials and epidemiology studies have suggested metformin use was associated with reduced risk of developing OA in patients with diabetes [13]. Nevertheless, the relationship between metformin use

Table 3 Metformin use and risk of total joint replacement in patients with diabetes: results from time-varying multivariable Cox regression analysis

n = 3,001	HR *	95% CI	*p*-value
Metformin medication			
no	ref.	-	-
yes	0.74	0.52–1.03	0.07
Metformin daily dose			
per 1.0 g /day	0.85	0.68–1.06	0.14
Category			
0 g	ref.	-	-
0–1.0 g	0.75	0.46–1.22	0.25
1.0 + g	0.73	0.49–1.08	0.11

* Hazard ratio (HR) was estimated using multivariable Cox regression models, with time-varying metformin use as the exposure variable, after adjusting for age at diagnosis, sex (male/female), ethnicity (European ancestry vs. other), living in rural vs. urban areas, education attainment (secondary or less, some post-secondary, post-secondary), BMI categories (< 24.9 kg/m^2, 25.0–29.9 kg/m^2, ≥30.0 kg/m^2), ever smoker (yes/no), physically active (yes/no, based on accumulating at least 210 min of moderate- to vigorous-intensity recreational physical activities per week in the past 12 months), tertiles of Healthy Eating Index Canada score for diet quality assessment, the number of Elixhauser comorbidities (0, 1–2, 2 + comorbidities) at diagnosis, diabetes complication severity index (DCSI), time-varying measures of use of insulin, other oral anti-hyperglycemic agents for diabetes (sulfonylureas, α-glucosidase inhibitors, thiazolidinediones and inhibitors of dipeptidyl peptidase-4), pain management drugs (systemic corticosteroids, nonsteroidal anti-inflammatory drugs, glucosamine and opioids), anti-obesity drugs, drugs for bone health & mineralization, drugs for cardiovascular diseases (lipid-lowering agents, diuretics, beta blocker, calcium channel blocker, agents on renin-angiotensin system and anti-hypertensive drugs) and drugs for depression

and risk of total joint replacement is unclear in patients with diabetes [16–20]. Discrepancies between studies were most likely due to lack of controlling of the time-related variation in drug use and other confounders, such as BMI. Our study using the time-varying approach to reduce person-time related bias in metformin use [29] and controlling a wide range of confounders, especially BMI [17, 19], diabetes severity and comorbidities [16, 17] and concomitant medications [17, 19], provide a new piece of evidence on the association between metformin use and risk of total joint replacement.

Our study also suggests that metformin use only does not have a determinative impact on the progression of OA if we consider total joint replacement as an outcome indicator of severe or end-stage OA [38]. Therefore, a single significant influencer does not seem to exist to prevent the progression of OA. Given that body weight control and lifestyle interventions have been approved as effective tools in controlling diabetes and related complications [39, 40], a holistic approach, including anti-hyperglycemic medication (e.g., metformin), lifestyle intervention and body weight control [41], drugs for complications (e.g. statin) and supplements for bone health, would likely be more effective in reducing risk of total joint replacement in patients with diabetes.

When examining the interaction between metformin and concurrent use of pain drugs, we found that there was a potentially protective effect of metformin on total joint replacement if patients were not on pain medication, and this protective effect was substantially diminished if patients were using pain drugs. We speculate that using medication for severe pain can be an important clinical indicator for progression and/or outcome of patients with OA [14]. Once the disease progresses passes a certain point, e.g., a patient is starting to take pain drugs regularly, the chance of having total joint replacement will become very high and the progression to the end-stage OA could be irreversible [42, 43]. Further investigation on OA progression, clinical stage and influence of relevant medications (e.g., pain drugs) is warranted.

Several limitations exist in our study. First, the ATP participants may not be representative of the general population in Canada [21]. However, given the high internal validity, including a large sample size, nearly 20 years of follow-up and adjusting time-related variation in drug use and a wide range of confounders, our study provides robust evidence on the relationship between metformin use and risk of total joint replacement in patients with diabetes. Second, in our study, metformin use was measured using pharmacy-based drug dispense records. Although these dispense records are reliable data currently available for post-market research on drug effect, no direct data were collected on patient's compliance to drug prescriptions (i.e. the actual dose a patient took). This may have resulted in misclassification of metformin use, especially when examining the potential dose-response effect, and the beneficial effect of metformin, if any, might have been overestimated due to non-adherence in those metformin users. In addition, indication bias related to prescription of metformin may exist [27]. However, by adjusting for those key confounders, especially age, BMI, diabetes severity, comorbidities, the potential impact from indication bias may have been significantly minimized.

By linking the ATP cohort data to administrative healthcare data, our study found the impact of metformin on total joint replacement was not statistically significant, but the estimates of our data suggests with some variations, on average, metformin may be associated with a protective effect on progression of osteoarthritis in clinical settings in patients with diabetes. Although metformin has been suggested to have chondro-protective and anti-inflammatory effect [5], use of metformin is not a single determinative factor in reducing risk of total joint replacement in patients with diabetes. Future clinical trials to investigate the effectiveness of comprehensive approach (e.g. anti-diabetic medication along with lifestyle invention and weight control) in reducing total joint replacement in patients with diabetes are warranted.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12891-025-08562-7.

Supplementary Material 1

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Author contributions

MY, JAJ and DTE conceived the idea and originated the study. Together with JEV and GST, MY, JAJ and DTE designed the study, defined variables and acquired the healthcare data. MY conducted all data analyses. MY, DTE, JAJ, JEV and GST jointly wrote the manuscript. All authors revised and reviewed the manuscript, agreed to be accountable for the intellectual content of the article, and approved the final submission.

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Data availability

To comply with the Alberta Health (AH) Health Information Policy and Alberta's Tomorrow Project data disclosure guidelines, individual-level data used in this study are not directly available for readers. Access to individual-level data is only available with approval and agreement with the Health Information Act of Alberta and the Alberta's Tomorrow Project (ATP) Access Guidelines and Procedures. More information can be obtained via https://www.alberta.ca/health-research and https://myatpresearch.ca (both links are accessible by using Chrome, Edge, Firefox, dated December 4, 2024).

Declarations

Ethics approval and consent to participate

This study was approved by the Health Research Ethics Board (HREB) of the University of Alberta (study ID Pro00058561). This study is in compliance with the Declaration of Helsinki to protect human participants in our research. All participants of this study provided valid written consent for data linkage with administrative healthcare and other health-related data. The storage, use and disposition of participants' data in this study complies with the Personal Information Protection and Electronic Documents Act (PIPEDA) in Canada.

Competing interests

The authors declare no competing interests.

Clinical trial number

not applicable.

Consent to participate

All participants of this study had provided valid written consent for data linkage with administrative healthcare and other health-related data for research purposes, and informed consent to participate was obtained from all of the participants in this study.

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