

Anti-Hyperglycemic Medication Adherence and Health Services Utilization in People with Diabetes: A Longitudinal Study of Alberta's Tomorrow Project

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Background: Little is known about the long-term (>2 years) relationship between the time-varying drug adherence and healthcare utilization for patients with diabetes.

Objective: To characterize the relationship between time-varying anti-hyperglycemic medication adherence and healthcare utilization in patients with diabetes, using data from Alberta's Tomorrow Project, a population-based cohort study in Alberta, Canada.

Methods: Incident cases of diabetes with at least 24 months of follow-up were included in the study. Anti-hyperglycemic drug adherence was measured by proportion of days covered (PDC) in the past 12 months for each year after diagnosis. The rate of healthcare utilization was assessed for the subsequent 12 months, 36 months and 60 months. A time-varying, negative binomial generalized estimating equation model was used to examine the association between medication adherence and healthcare utilization.

Results: Among 2155 incident cases of diabetes, average age at diagnosis was 59.6±9.3, 51.0% were female and average duration of follow-up was 7.3±3.7 (range, 2.0–16.2) years. The proportion of patients taking anti-hyperglycemic medications was 47.6% during the first year of diagnosis, which increased to 77.3% by the end of follow-up. Compared to adherent patients (PDC≥0.8), non-adherent patients (PDC<0.8) had substantially higher rate of all-cause hospitalization [incident rate ratio, IRR=1.48 (1.22–1.79), ED visits [1.30 (1.15–1.47)] and GP visits [1.17 (1.08–1.27)] in the subsequent 12 months. However, these associations became weaker with longer follow-up [eg, IRR=1.18 (0.98–1.39) and 1.05 (0.94–1.18) for all-cause hospitalization in the subsequent 36 and 60 months, respectively].

Conclusion: Poor adherence among diabetic patients was associated with substantially higher rate of healthcare utilization in the short term (eg, 12 months); however, this association weakened over a longer period (eg, 36–60 months).

Keywords: diabetes, anti-hyperglycemia, adherence, time-varying, healthcare, longitudinal

Background

Anti-hyperglycemic medication is critical for diabetes control and management. Failure to maintain adherence to anti-hyperglycemic medication often leads to worse health outcomes, such as poor glycemic control,¹ higher level of LDL cholesterol,² higher systolic and diastolic blood pressure³ and increased risk of cardiovascular diseases.⁴ The risk of all-cause mortality in non-adherent patients has been reported to be approximately 50% higher than in adherent patients.⁵

Non-adherent patients also require higher amount of healthcare compared to adherent patients. Using administrative claim data in the US, Lau et al have shown that the risk of being admitted to hospital was approximately 1.5 times higher in patients non-adherent to anti-hyperglycemic medication.⁶ Other than hospitalization, the rate of outpatient care visits^{7,8} and emergency room (ER) visits⁸ are also remarkably higher in non-adherent diabetes patients than adherent patients. A systematic review of economic impact of medication adherence has suggested that poor adherence to anti-hyperglycemic medication was associated with increased cost in almost every aspect of healthcare, especially in care of patients with related complications.⁹

While adherence to anti-hyperglycemic medication has noticeable benefit for diabetes control and management, poor adherence is documented to be common among patients with diabetes. A meta-analysis of 70 observational studies has estimated that the prevalence of adhering to anti-hyperglycemic medication was ranged from 38% to 93% in patients with diabetes¹⁰ and the average medication possession rate (MPR) was approximately 75% over a 12-month period for diabetes patients.¹¹ More importantly, adherence to anti-hyperglycemic medication should be a continuing effort for disease management and maintaining drug adherence over time is essential for achieving better long-term outcomes for diabetes patients.¹²

Research on health behaviors and associated factors have suggested the ongoing and time-varying nature of medication adherence.^{12,13} However, only a few studies have documented the trajectory of anti-hyperglycemic medication status, including the time-varying nature of drug adherence,^{12,14,15} and very few have characterized its long-term (>2 years) relationship with health outcomes for patients with diabetes.^{4,16,17} Moreover, only few, if any, have been able to account for lifestyle factors in their analysis. In this study, we used data from Alberta's Tomorrow Project (ATP), a population-based cohort study of chronic diseases in Alberta, Canada, linked with Alberta Health (AH) administrative healthcare and medication dispense databases, to characterize the longitudinal pattern of potentially time-varying adherence to anti-hyperglycemic drugs and its relationship with healthcare utilization for patients with diabetes, over 15 years following the diagnosis.

Methods

Study Design

We conducted a longitudinal cohort study to characterize the association between time-varying anti-hyperglycemic medication adherence and healthcare utilization for patients with diabetes, using data from ATP and the linked administrative healthcare data. We also structured our manuscript and reported our results following the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines.¹⁸ [Supplementary Figure S1](#) shows the study design and the timeline of time-varying exposure (medication adherence status) and outcome (healthcare utilization) measurement. ATP participants with diabetes were followed from the date of diagnosis (index date) to March 31, 2018 (or until death).

Study Participants

In 2000–2008, ATP randomly recruited a total of 29,876 participants aged 35–69 years, living in Alberta, Canada, with no history of cancer other than non-melanoma skin cancer at the time of enrollment, to explore how lifestyle, genetics and environment influence the health and wellbeing of Albertans. All these 29,876 ATP participants had completed the ATP baseline health and lifestyle questionnaires and provided valid written consent to data linkage to administrative healthcare data and use of the linked health data in research at the time of enrollment. For this study, 2467 incident cases of diabetes (ie, diabetes diagnosed after enrollment in ATP) were identified in this ATP cohort, among which 2155 incident cases with at least 24 months of follow-up after diagnosis until March 31, 2018 (the end of the study) were included in the final analysis.

Data Sources

Alberta Health (AH) administrative datasets utilized in this study include all drug dispense records from Alberta Blue Cross (ABC) and Pharmaceutical Information Network (PIN) and health services records from Ambulatory Care, Inpatient and Practitioner/Physician Claims datasets. Detailed descriptions of AH administrative datasets for research can be obtained from Alberta Health (<http://www.health.alberta.ca/initiatives/health-research.html>). Individual-level AH administrative data from October 1, 2000–March 31, 2018 were linked to the ATP cohort using the unique identifier Personal Health Number (PHN) provided by participants during the consent process. After data linkage, AH healthcare data were de-identified before release to the authors of this study.

Other than the linked AH healthcare data, a wide range of information on exposures and risk factors for chronic diseases, including sociodemographic and socio-economic factors, anthropometrics and lifestyle behaviors (eg, diet history and physical activities), were self-reported by the ATP participants using well-validated questionnaire, including the Canadian Dietary History Questionnaire (CDHQ)¹⁹ and Past-Year Total Physical Activity Questionnaire (PYTPAQ),²⁰ at time of enrollment. Detailed information on the ATP self-administered questionnaires can be found at www.myATP.ca.

Diabetes Cases

Diabetes cases were identified using a modified version of the well-validated Canadian National Diabetes Surveillance System (NDSS) algorithm:²¹

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 contribute to the case definition. Cases were identified as “incident” only if the index date was more than 6 months after ATP enrollment to ensure true incident cases were identified for the study.

Anti-Hyperglycemic Drug Adherence

We used drug prescription records to compute proportion of days covered (PDC) as measurement of drug adherence.²² Specifically, anti-hyperglycemic drug prescription records were identified using the ATC code of A10 in the linked ABC and PIN datasets. For each chemical class of drugs (lowest level of ATC code), PDC was calculated as a ratio of the number of days covered by the medication (based on days supplied) divided by the total number of days within the specified time window (eg, in the past 12 months or in the cumulative number of months since index date).²² A gap of less than 60 days was allowed for being considered as persistent treatment.²³ The mean PDC was obtained by dividing the summed PDC of each anti-hyperglycemic drug class over the total number of drug classes.²⁴ A dichotomized variable was generated based on the value of mean PDC to indicate adherence ($PDC \geq 0.8$) vs non-adherence ($PDC < 0.8$) as is routinely done in health services research.²⁵ A third category of “no medication” was also used for individuals who were patients with diabetes but did not have anti-hyperglycemic medication records (eg, some patients may have used diet and lifestyle efforts to control diabetes). As medication adherence may potentially change over time, we estimated adherence using a time-varying approach. Specifically, the patient’s anti-hyperglycemic medication status (no medication, adherent or non-adherent) was updated every 12 months, beginning from the date of diagnosis (index date), for each year following the diagnosis. The estimated medication adherence was then used to predict the subsequent rate of healthcare utilization.

Healthcare Utilization Variables

All-cause hospitalization was defined as any hospital admission within the linked hospital discharge abstract data (DAD). Diabetes-specific hospitalization was identified by ICD code of diabetes (ICD-9: 250 or ICD-10: E10-E14) as the most responsible condition for hospitalization. Hospitalization for ambulatory care sensitive (ACS) conditions was identified by ICD codes of a set of 28 ACS conditions.²⁶ ED visit was identified using Alberta Management Information System (MIS) codes (71310, 71313 and 71314) in the linked AH ambulatory care dataset. Primary care visits were identified using specialty group codes in Practitioner/Physician Claims data for a visit to a general practitioner (GP) or a specialist in an outpatient environment (eg, at physician’s office). The rate of healthcare utilization was calculated as a ratio of the number of health services encounters divided by the total person-years for a subsequent period. Specifically, we evaluated whether anti-hyperglycemic medication adherence was associated with healthcare utilization within the subsequent period (eg, 12 months) of follow-up in a rolling time-varying manner (ie, year 1 adherence was used to predict year 2 healthcare utilization, then year 2 adherence was used to predict year 3 healthcare utilization).

Statistical Analysis

The baseline characteristics of study participants and rate of healthcare utilization were summarized based on participants’ anti-hyperglycemic medication adherence status (no medication, adherent or no adherent). 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’s *t*-test for continuous variables and χ^2 test for categorical variables and incidence rates.

The association between the time-varying anti-hyperglycemic medication adherence status and rate of healthcare utilization was examined using generalized estimating equation (GEE) model, with medication status as the time-varying exposure variable, the number of health services encounters in the subsequent 12 months as the outcome variable, and person-year as the offset variable. In our study, the outcome variables were measured repeatedly in every 12 months for each patient, which potentially leads to “within-subject” correlation for the outcome. Therefore, we chose to use GEE model, a semiparametric model with Huber–White “sandwich” estimator, to estimate the population average effect after controlling the “within-subject” correlation.²⁷ In addition, given a large number of patients with no events (ie, zero inflated count data with over-dispersion), a negative binomial distribution was assumed in the GEE model.

Incident rate ratio (IRR) and 95% CIs were computed after adjusting for the following covariates in the GEE model: age at diagnosis (35–44 years, 45–64 years, 65+ years), sex (male/female), ethnicity (Caucasian vs other), living in rural vs urban areas, education attainment (secondary or less, some post-secondary, post-secondary), body mass index (BMI) categories (under/normal weight ≤ 24.9 kg/m², overweight 25.0–29.9 kg/m², obese ≥ 30.0 kg/m²), smoking status (yes/no), physically active (yes/no, based on whether or not accumulating at least 210 min moderate-to-vigorous intensity recreational physical activities per week in the past 12 months),²⁸ tertiles of Healthy Eating Index for diet quality assessment,²⁹ and time-varying covariates (healthcare utilization and Elixhauser comorbidities [0, 1–2, 2+] in the past 12 months).³⁰ For participants who had missing values in these covariates ([Supplementary Table S1](#)), a “missing indicator” category was created to ensure all participants were included and results were minimally affected by missing values.

We also undertook several additional analyses to evaluate the robustness of our main results: 1) instead of measuring adherence in the past 12 months, PDC was calculated over the cumulative number of months for each year after diagnosis (eg, adherence over years 1–5 following diagnosis were used to predict year 6 adherence as opposed to just 12 months prior); 2) assessing the impact of drug adherence on subsequent healthcare utilization for a longer period (eg, 36 or 60 months vs 12 months in the primary analysis) with a subgroup of patients with at least 72 months of follow-up; 3) other than unadjusted and fully adjusted models, relevant covariates were progressively adjusted in the regression analysis, from basic demographic factors (age, sex, urban/rural) and standard administrative health records (comorbidities and prior healthcare use) to difficult-to-capture patient characteristics (ethnicity, education attainment and BMI) and lifestyle factors (smoking, physical activity, and diet quality), to evaluate the relative potential of confounding effect, including the healthy user bias. All statistical analyses, with significant level at $\alpha=0.05$, were conducted using STATA[®]14 software.

Results

Characteristics of Study Participants

This longitudinal cohort study included 2155 incident cases of diabetes with an average (SD) follow-up of 7.3 (3.7) years (range 2.0–16.2 years) from diagnosis to March 31, 2018 (or death). The baseline characteristics of study participants were summarized based on anti-hyperglycemic medication adherence status in the first 12 months of diagnosis ([Supplementary Table S1](#)). The average (SD) age at incidence was 59.6 (9.3) years and 51.0% of the participants are women. The majority (87.1%) of participants self-reported as being of Caucasian ethnicity and 27.2% of the participants lived in rural areas. Overall, there was a higher percentage of non-adherent patients living in rural areas, with more comorbid conditions and higher rates of hospitalization, ED visits and GP visits in the first 12 months following diagnosis ([Supplementary Table S1](#)).

Anti-Hyperglycemic Drug Adherence Profile

During the follow-up period after diagnosis (up to 16 years), the percentage of patients taking anti-hyperglycemic medications increased over time (p-value <0.01 for trend test), from 47.6% in the first 12 months up to 77.3% in the final year of follow-up ([Figure 1](#)). In addition, in patients who took anti-hyperglycemic medications, the average PDC and the ratio of adherent vs non-adherent patients did not significantly change over time after diagnosis ([Figure 1](#)).

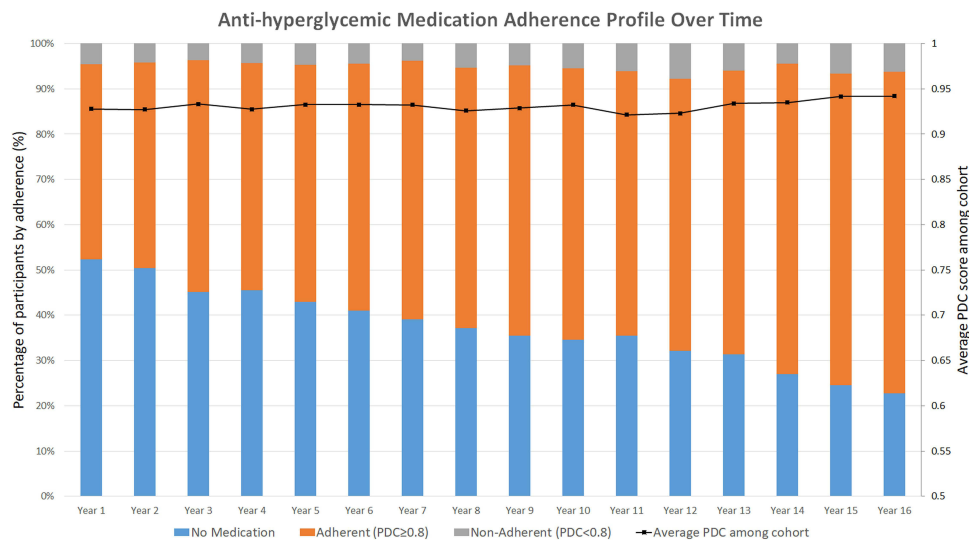


Figure 1 Anti-hyperglycemic medication adherence profile after diagnosis. Patients were grouped based on whether or not taking anti-hyperglycemic medication and adherence levels by proportion of days covered (PDC) categories (adherent: PDC ≥ 0.8, non-adherent: PDC < 0.8). The percentage of patients taking anti-hyperglycemic medication and the average PDC score were summarized for each year from diagnosis (Year 1) to Year 16.

Anti-Hyperglycemic Drug Adherence and Healthcare Utilization

Even though the adherence to anti-hyperglycemic drugs may change over time (Figure 1), patients with diabetes who did not take any anti-hyperglycemic medications in the past 12 months had a significantly lower (*p*-value < 0.01) rate of healthcare utilization in the subsequent 12 months, compared to patients who did take the medications (except for all-cause hospitalization, Table 1). In unadjusted analyses, compared to the adherent patients, non-adherent patients had a significantly higher rate of all-cause hospitalization (0.260 vs 0.162 per person-year), diabetes-specific hospitalization (0.030 vs 0.004 per person-year), hospitalization for ACS conditions (0.052 vs 0.021 per person-year), ED visits (1.042 vs 0.729 per person-year) and GP visits (8.684 vs 7.800 per person-year); all *p*-values < 0.01 (Table 1). Similar to the 12 months results, non-adherent patients also had higher rates of health services utilization compared to adherent patients in the subsequent 36 (or 60) months (Supplementary Tables S2).

In multivariable regression models, any use of anti-hyperglycemic drugs during the past 12 months, irrespective of adherence status, was associated with higher rates of healthcare utilization in the subsequent 12 months (Table 2). In addition, compared to adherent patients, non-adherent patients had substantially higher rates of all-cause hospitalization

Table 1 Rate of Healthcare Utilization in the Subsequent 12 Months by Anti-Hyperglycemic Medication Status (n=2155)[†]

	No Medication			Adherent			Non-Adherent		
	Freq.	P-Y	IR	Freq.	P-Y	IR	Freq.	P-Y	IR
All-cause hospitalization	1049	6092.1	0.172	1193	7342.3	0.162	176	676.5	0.260**
DM-specific hospitalization	10	6092.1	0.002*	26	7342.3	0.004	20	676.5	0.030**
ACS hospitalization	111	6092.1	0.018*	156	7342.3	0.021	35	676.5	0.052**
ED visits	4155	6092.1	0.682*	5349	7342.3	0.729	705	676.5	1.042**
GP visits	44,061	6092.1	7.232*	57,271	7342.3	7.800	5875	676.5	8.684**

Notes: [†]Patients were grouped based on whether or not they were taking anti-hyperglycemic medication and by adherence levels (via proportion of days covered [PDC] categories, adherent: PDC ≥ 0.8, non-adherent: PDC < 0.8); due to the time-varying nature of drug adherence, patient' data was segmented by every 12 months. Frequency was computed as the accumulated number of healthcare utilization events of each drug adherence category over the total follow-up of 15 years for all the segments; person-year (P-Y) is the accumulated person-years of each drug adherence category over the total follow-up of 15 years for all segments. *Statistically significant (*p*<0.05) difference between patients with no anti-hyperglycemic medication (reference group) vs adherent or non-adherent patients; **Statistically significant (*p*<0.05) difference between adherent vs non-adherent patients.

Abbreviations: P-Y, person-years; IRR, incidence rate ratio; DM, diabetes; ACS, ambulatory care sensitive conditions; ED, emergency department; GP, general practitioner.

Table 2 Association Between Anti-Hyperglycemic Medication, Drug Adherence and Healthcare Utilization in the Subsequent 12 Months in Patients with Diabetes: Results from Multivariable Negative Binomial Regression Analysis*

	IRR	95% CI	p-value	IRR	95% CI	p-value
n=2155	All-cause hospitalization					
Medication status**						
No medication	Ref	-	-	-	-	-
Adherent	1.09	0.99–1.22	0.08	Ref	-	-
Non-adherent	1.62	1.33–1.97	<0.001	1.48	1.22–1.79	<0.001
	DM-specific hospitalization					
Medication status**						
No medication	Ref	-	-	-	-	-
Adherent	2.62	1.20–5.72	0.02	Ref	-	-
Non-adherent	12.39	5.23–29.33	<0.001	4.73	2.38–9.40	<0.001
	ACS hospitalization					
Medication status**						
No medication	Ref	-	-	-	-	-
Adherent	1.46	1.10–1.94	0.008	Ref	-	-
Non-adherent	2.94	1.88–4.60	<0.001	2.01	1.31–3.07	<0.001
	ED visits					
Medication status**						
No medication	Ref	-	-	-	-	-
Adherent	1.10	1.03–1.18	0.003	Ref	-	-
Non-adherent	1.43	1.26–1.63	<0.001	1.30	1.15–1.47	<0.001
	GP visits					
Medication status**						
No medication	Ref	-	-	-	-	-
Adherent	1.14	1.09–1.19	<0.001	Ref	-	-
Non-adherent	1.34	1.23–1.45	<0.001	1.17	1.08–1.27	<0.001

Notes: *Incident rate ratio (IRR) was estimated using multivariable negative binomial regression models, after adjusting for age at diagnosis (35–44yr, 45–64yr, 65+yr), sex (male/female), ethnicity (Caucasian vs other), rural vs urban, education attainment (secondary or less, some post-secondary, post-secondary), BMI categories (under/normal, overweight, obesity), current smoking status (yes/no), physically active (yes/no, based on whether or not accumulating at least 210 min 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, previous healthcare utilization after diagnosis, and Elixhauser comorbidities (0, 1–2, 2+); **Patients were grouped based on whether or not they were taking anti-hyperglycemic medication and by adherence levels (via proportion of days covered [PDC] categories, adherent: PDC≥0.8, non-adherent: PDC <0.8).

Abbreviations: P-Y, person-years; IRR, incidence rate ratio; CI, confidence interval; DM, diabetes; ACS, ambulatory care sensitive conditions; ED, emergency department; GP, general practitioner.

(IRR=1.48, 95% CI=1.22–1.79), diabetes-specific hospitalization (IRR=4.73, 95% CI=2.38–9.40), hospitalization for ACS conditions (IRR=2.01, 95% CI=1.31–3.07), ED visits (IRR=1.30, 95% CI=1.15–1.47) and GP visits (IRR=1.17, 95% CI=1.08–1.27) in the subsequent 12 months (Table 2).

Additional analyses using PDC calculated from a cumulative number of months since diagnosis showed similar results, compared to the main analysis with PDC calculated within any of the time segments of past 12 months. Moreover, in a sub-cohort study of patients with at least 72 months of follow-up, rates of healthcare utilization in the subsequent 36 or 60 months was still significantly higher in patients using anti-hyperglycemic medication compared to patients not taking medications (data available upon request). However, in examining the relationship between drug adherence and healthcare utilization in the subsequent 36 or 60 months, the observed associations were weaker (eg

Table 3 Past 12 Months Drug Adherence and Healthcare Utilization in the Subsequent 12, 36 and 60 Months: Sub-Group Analysis of Patients with at Least 72 Months of Follow-Up*

	Subsequent 12 Months			Subsequent 36 Months			Subsequent 60 Months		
	IRR	95% CI	p-value	IRR	95% CI	p-value	IRR	95% CI	p-value
n=1477	All-cause hospitalization								
PDC levels									
≥0.8	Ref	-	-	Ref	-	-	Ref	-	-
<0.8	1.75	1.36–2.27	0.002	1.18	0.98–1.39	0.07	1.05	0.94–1.18	0.35
	DM-specific hospitalization								
PDC levels									
≥0.8	Ref	-	-	Ref	-	-	Ref	-	-
<0.8	6.01	2.21–16.35	<0.001	3.21	1.63–6.33	0.001	3.01	1.83–4.94	<0.001
	ACS hospitalization								
PDC levels									
≥0.8	Ref	-	-	Ref	-	-	Ref	-	-
<0.8	2.32	1.35–43.99	0.002	1.25	0.86–1.81	0.25	1.14	0.88–1.47	0.31
	ED visits								
PDC levels									
≥0.8	Ref	-	-	Ref	-	-	Ref	-	-
<0.8	1.43	1.20–1.69	<0.001	1.12	0.99–1.27	0.06	1.07	0.96–1.18	0.21
	GP visits								
PDC levels									
≥0.8	Ref	-	-	Ref	-	-	Ref	-	-
<0.8	1.23	1.10–1.38	<0.001	1.12	1.01–1.22	0.03	1.08	0.99–1.16	0.07

Notes: *Incident rate ratio (IRR) was estimated using multivariable negative binomial regression models, after adjusting for age at diagnosis (35–44yr, 45–64yr, 65+yr), sex (male/female), ethnicity (Caucasian vs other), rural vs urban, education attainment (secondary or less, some post-secondary, post-secondary), BMI categories (under/normal, overweight, obesity), current smoking status (yes/no), physically active (yes/no, based on whether or not accumulating at least 210 min 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, previous healthcare utilization after diagnosis, and Elixhauser comorbidities (0, 1–2, 2+).

Abbreviations: P-Y, person-years; IRR, incidence rate ratio; CI, confidence interval; DM, diabetes; ACS, ambulatory care sensitive conditions; ED, emergency department; GP, general practitioner.

IRR=1.18 [0.98–1.39] and 1.05 [0.94–1.18] for all-cause hospitalization and IRR=1.12 [0.99–1.27] and 1.07 [0.96–1.18] for ED visits in the subsequent 36 months and 60 months, respectively) (Table 3). In multivariable regression analyses with covariates progressively adjusted in the model, no appreciable changes were observed in IRR, although there was a relative smaller IRR when lifestyle factors (eg, physical activities and diet quality) and other difficult-to-capture patient characteristics (eg, BMI and education attainment) were adjusted (Supplementary Figure S2).

Discussion

This longitudinal cohort study showed that after taking into account the potential time-varying impact, poor adherence to anti-hyperglycemic medication was still associated with substantially higher rates of healthcare utilization, including hospitalization, ED visits and GP visits, in the subsequent 12 months. However, this association became much weaker over longer period of follow-up (eg, 36 or 60 months). This observation may be related to the notion that tighter glycemic

control has not shown to prevent downstream complications of diabetes during the long term (unless HbA1c is maintained to the level of <6.5% or 48 mmol/mol).³¹

In the previous studies in the literature, for the short-term impact (typically 12 months), similar to our study, many observational investigations have shown a significant protective effect of anti-hyperglycemic drug adherence.^{3,6,32–34} However, mixed results have been reported on the long-term impact of anti-hyperglycemic drug adherence and outcomes of diabetes. A randomized trial study conducted by the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study group showed that compared to standard therapy, intensive anti-glycemic therapy, which requires high medication adherence, can achieve better control of glycated hemoglobin levels, but did not significantly reduce major cardiovascular events (hazard ratio=0.90, 95% CI: 0.78–1.04) over a period of 3.5 years.³¹ A longer-term follow-up (~9 years) of the surviving ACCORD participants also showed that there was a neutral effect of intensive anti-glycemic treatment on the composite outcome and all-cause mortality (hazard ratio=1.01, 95% CI: 0.92–1.10) in the long run. Conversely, during 30 years of follow-up in Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study, intensive anti-diabetic treatment significantly reduced incidence of cardiovascular diseases by 30% (95% CI: 0.07–0.48) in type 1 diabetes. Moreover, a national cohort study of type 2 diabetes patients in Sweden showed that the risk of all-cause mortality was similar between patients with different levels of drug adherence, although the risk of cardiovascular diseases was lower in adherent patients.³⁵ These studies, including ours, suggest that the beneficial impact of anti-hyperglycemic medications, including good adherence to medications, could be diminished over the long term; other factors, such as developing related complications (eg, cancer and cardiovascular diseases)^{36,37} and potential therapeutic inertia,^{38,39} may weaken the effectiveness of anti-hyperglycemic medications. Given the potential decline of the degree of benefit from anti-hyperglycemic treatment over time reported in our study, continuing effort of monitoring HbA1c level, timely intensification of anti-hyperglycemic treatment and effective control of related complications (such as CVD), should be enhanced in practice to gain better outcomes for patients with diabetes in the long run.

We also postulate that the reported short-term effect^{3,6,32–34} may be due to some uncontrolled confounding factors, potentially the healthy-user effect.⁴⁰ Our data showed that patients adherent to anti-hyperglycemic medications, were more physically active, with higher diet quality, tended to be non-smokers and with fewer comorbid conditions and healthcare encounters at the baseline, compared to the non-adherent group, indicating adherent patients might be healthy users. However, in our multivariable regression models, in addition to socio-demographic factors (eg, age and sex) and standard clinical records from administrative data (eg, prior healthcare use and comorbidities), factors that potentially lead to healthy user bias, including education attainment and lifestyle behaviors (smoking status, physical activities and diet quality), were fully controlled to reduce bias from these confounders. Thus, healthy-user bias is less likely a factor in the results observed in the study, although it is still possible that some unknown/unmeasured patient's characteristics or life events, which we could not control for, were influencing patient's subsequent healthcare utilization.

The strength of our study includes linking and co-analyzing population-based cohort data with administrative healthcare data in characterizing the longitudinal impact of anti-glycemic drug adherence on healthcare utilization over 15 years. Compared to previous similar studies,^{3,6,32,33} this study, with difficult-to-capture lifestyle and other patient data (eg, education attainment and BMI) from the ATP, was able to control a wider range of confounding effects, including the potential healthy user bias, to make a more accurate estimation of the association. Another strength of our study is to consider drug adherence as a time-varying exposure variable when examining the association between drug adherence and subsequent healthcare utilization, which helps to avoid person-time related misclassification of exposure variables.⁴¹

Despite these strengths, there are several limitations in our study. First, although ATP participants were randomly recruited from Alberta's general population, compared to the general population in Alberta, the ATP participants are older, with more women and living a relative healthy lifestyle.⁴² Results of our study might not be generalized to general populations in Canada. However, given the high internal validity (eg, fairly large number of participants and adjusting for a wide range of potential confounders), our study provides a better understanding of the longitudinal relationship between anti-hyperglycemic drug adherence and subsequent healthcare utilization. Secondly, while administrative health data is a useful data source for drug prescription records and related epidemiology studies, prescription records-based calculation of PDC is considered as an indirect measurement of drug adherence. However, compared to direct measures (eg, pill counts), prescription records-based measurement is more objective and reliable.⁴³ In addition, potential data linkage and

secondary analysis of these prescription records makes it more feasible to study drug adherence for large population-based cohort, compared to direct measures.

Conclusions

By linking administrative health data to the ATP cohort, our study shows that adherence to anti-hyperglycemic medications was substantially associated with reduced healthcare utilization in short term (12 months); however, this association becomes weaker for a longer period of follow-up (36–60 months). Results of this study, which will benefit not only the ATP participants, provide a cautionary new piece of evidence in the literature on how anti-hyperglycemic medications would affect outcomes of diabetes. Future research exploring why the beneficial effect of anti-hyperglycemic medication seems to be plateaued over a longer term is warranted.

Abbreviations

ABC, Alberta Blue Cross; ACCORD, Action to Control Cardiovascular Risk in Diabetes; ACS, Ambulatory Care Sensitive; AH, Alberta Health; ATC, Anatomical Therapeutic Chemical Classification; ATP, Alberta's Tomorrow Project; BMI, body mass index; CI, confidence interval; DAD, discharge abstract data; DCCT, diabetes control and complications trial; ED, emergency department; EDIC, epidemiology of diabetes interventions and complications; GEE, generalized estimating equation; GP, general practitioner; IRR, incident rate ratio; MIS, management information system; NDSS, National Diabetes Surveillance System; PDC, proportion of days covered; PHN, personal health number; PIN, pharmaceutical information network; SD, standard deviation.

Data Sharing Statement

To comply with the Alberta Health (AH) Health Information Policy and Alberta Tomorrow Project (ATP) data disclosure guidelines, datasets used in this study are not available for readers.

Ethics Statement and Consent to Participate

This study was approved by the Health Research Ethics Board of the University of Alberta (study ID Pro00058561). This study also complied with the Declaration of Helsinki. All participants of this study have 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.

Consent for Publication

All authors of this study have read the manuscript, accepted responsibility for the content of manuscript, consented for publication.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically

reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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