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Emulating a target trial using primary care electronic health records: SGLT-2i medications and Hemoglobin A1c

Sumeet Kalia[1,2], Olli Saarela[1], Braden O'Neill[1,2], Christopher Meaney[2], Rahim Moineddin[2], Frank Sullivan[3], Michelle Greiver[2]

[1] University of Toronto, Dalla Lana School of Public Health, Toronto, ON, M5T3M7, Canada

[2] University of Toronto, Department of Family and Community Medicine, Toronto, ON, M5G 1V7, Canada

[3] University of St Andrews, School of Medicine, St Andrews, United Kingdom

sumeet.kalia@utoronto.ca, olli.saarela@utoronto.ca, braden.oneill@unityhealth.to, christopher.meaney@utoronto.ca, rahim.moineddin@utoronto.ca, fms20@st-andrews.ac.uk, mgreiver@rogers.com

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Abstract

Substantial effort has been dedicated to conducting controlled experiments to generate clinical evidence for diabetes treatment. Randomized controlled experiments are the gold standard to establish cause and effect. However, due to their high-cost and time-commitment, large observational databases such as those comprised of electronic health record (EHR) data collected in routine primary care may provide an alternative source to address such causal objectives. We used a Canadian primary care repository housed at University of Toronto to emulate a randomized experiment. We estimated the effectiveness of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) medications for patients with diabetes using Hemoglobin A1c (HbA1c) as a primary outcome and marker for glycemic control. We assumed an intention-to-treat analysis for prescribed treatment, with analyses based on the

treatment assigned (i.e. drug prescription) rather than the treatment eventually received (i.e. drug dispensation). We defined the causal contrast of interest as the net change in HbA1c (%) between the group receiving standard of care versus the group receiving SGLT-2i medications. Using a counterfactual framework, marginal structural models demonstrated a reduction in mean HbA1c with the initiation of SGLT-2i medications. These findings provided similar effect sizes to those from earlier clinical trials on assessing the effectiveness of SGLT-2i medications.

Keywords: Randomized controlled trials; Marginal structural models; Electronic health records; Primary care; Diabetes; Glucose-lowering medications

1 Introduction

Randomized controlled experiments are the gold standard to establish the relationship between cause and effect. However, clinical trials are time consuming, expensive and prone to recruitment challenges with under-representation of racialized communities and rural regions [5, 8]. Under these circumstances, electronic health records (EHRs) may provide an alternative data source to assess the effectiveness of glucose lowering medications in diabetes population.

Diabetes is one of the most common chronic conditions; in this condition blood glucose levels are elevated due to the pancreas' inability to produce sufficient insulin (Type I) or an inability to properly metabolize glucose (Type II) [16]. More than 537 million adults live with diabetes worldwide as of 2021 [21], and the Center for Disease Control predict that the incidence of diabetes will continue to increase [22]. Type II diabetes accounts for 90% to 95% of all diabetes cases [22]. Elevated glucose in the form of chronic hyperglycemia can be regulated by manipulating the glucose re-absorption rate. For example, a healthy kidney can reabsorb up to 180g of glucose from glomerular filtration each day, and this mechanism can be inhibited using the sodium-glucose co-transporter located in the proximal tubules of the kidney [20]. The class of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) drugs may block 50% of the glucose re-absorption [20].

Hemoglobin A1c (HbA1c) is a marker for glycemic control, and optimal HbA1c levels are associated with reductions in diabetes-related complications and mortality [16]. According to clinical guidelines published by the American Diabetes Association [1], metformin and comprehensive lifestyle modifications are first line therapy for type II diabetes patients to achieve a target HbA1c $\leq$ 7%. Depending on the clinical profile of individual patients, a combination therapy of other glucose lowering medications can be recommended using several drug classes: SGLT-2i, Dipeptidyl Peptidase-4 inhibitors (DPP-4i), Glucagon-like Peptide 1 receptor agonists (GLP-1), sulfonylurea, and insulin [6].

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1.1 Knowledge gap

The safety and efficacy of SGLT-2i medications is well established [25]. However, this clinical evidence was gathered using clinical trials, and there is a knowledge gap for the effectiveness of SGLT-2i drugs using real-world data (e.g. primary care EHRs). It is necessary to develop approaches to ascertain the effectiveness of treatments using observational data, which has the potential to markedly reduce the resources required to identify effective treatments to improve health. Analysis of routinely collected EHR data may allow for potential opportunities in which we may assess the long-term adverse effects of diabetes treatment. EHR data may also allow us to assess for the presence of effect modification, which may not be feasible in randomized trials due to insufficient statistical power. The objective of this study is to emulate a target trial to assess the effectiveness of SGLT-2i using HbA1c as a marker for glycemic control.

2 Materials and Methods

The EHRs collected from different sources (including hospitals, specialist clinics, primary care providers, pharmacies, and laboratories) have the potential to serve as a complete lifetime record of a person's health history. The University of Toronto practice-based research network's (UTOPIAN) database contains de-identified medical information collected from EHRs of primary care practices across the greater Toronto region [23]. This repository is a rich source of de-identified patient-level data, including demographics, medical diagnoses, procedures, medications, immunizations, laboratory test results, vital signs and risk factors.

2.1 Conceptual framework

We used the directed acyclic graph (DAG), in Figure (1), to describe the causal relationship between SGLT-2i drugs and reduction in HbA1c. The dotted lines in Figure (1) describe the dependency that exist in primary care registry data, but we would not expect this dependency in a randomized trial. For example, a controlled experiment will administrate the initiation of a treatment for consenting patients, and thus the dotted line between drug prescription and drug initiation will cease to exist. We assume an intention-to-treat framework where the analyses are based on the treatment assignment (i.e. drug prescription) rather than the treatment eventually received (i.e. drug dispensation). The randomization procedure will ensure that the patient characteristics are balanced across treatment arms, and thereby breaking the empirical associations between treatment assignment (A_{ij}) and patient characteristics (X_{ij}). The baseline HbA1c (Y_{i0}) is assumed to encode the historical information on glycemic control. Other glucose lowering medications (X_{ij}) captures the use of monotherapy and combination therapy

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using several drug classes: (i) metformin, (ii) DPP-4i, (iii) GLP-1, (iv) sulfonylurea, (v) insulin, as detailed elsewhere [6]. The unmeasured factors (e.g. lifestyle factors) influence the HbA1c value while also influencing other patient characteristics (e.g. co-morbidities). With the exception of baseline patient characteristics (i.e. age, sex, income quintiles, rurality), we assume the patient characteristics (i.e. co-morbidities, other glucose-lowering medications) to be confounders. We include several co-morbidities with disease onset date as covariates X_{ij}: (i) chronic obstructive pulmonary disease (COPD), (ii) dementia, (iii) depression, (iv) dyslipidemia, (v) epilepsy, (vi) hypertension, (vii) osteoarthritis, (viii) Parkinson's disease, (ix) chronic kidney disease (CKD). These conditions have established phenotype definitions in UTOPIAN database, and further details are available online [3].

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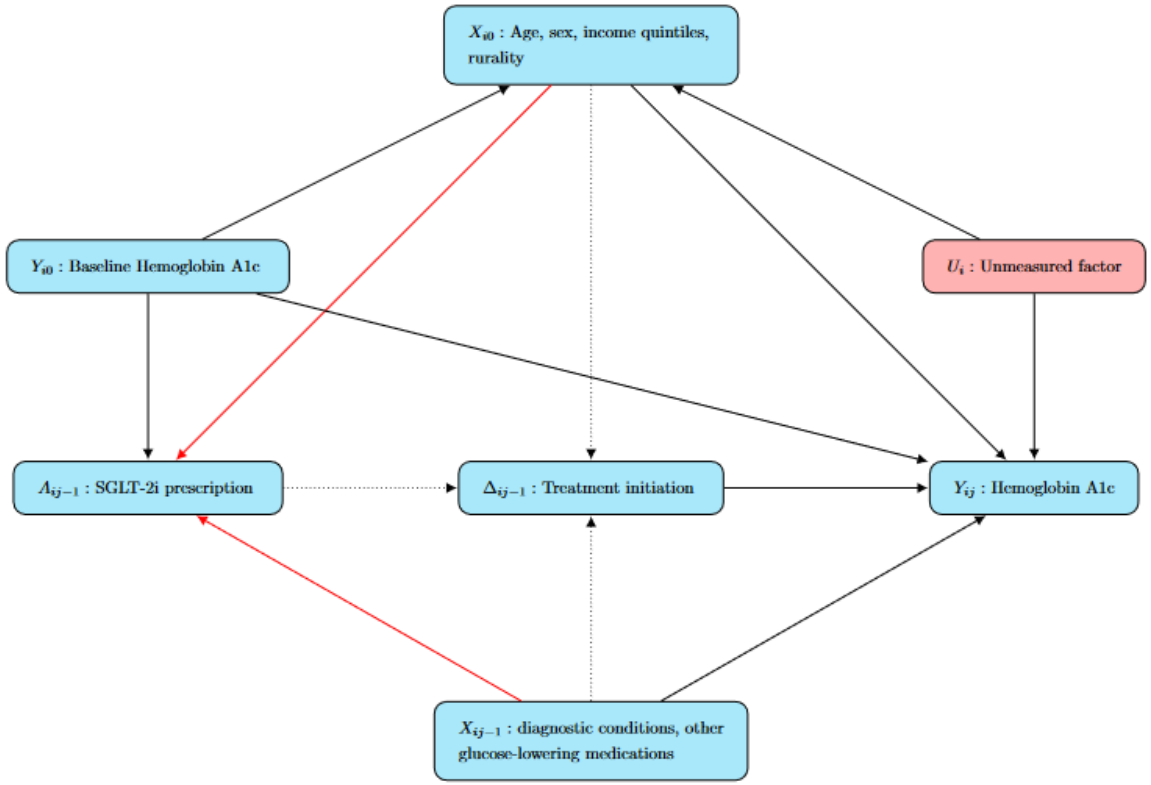

Figure 1: Directed acyclic graph for the treatment effect of sodium glucose co-transporter-2 inhibitors (SGLT-2i) prescriptions related to a change in Hemoglobin A1c (HbA1c). The red arrows depict the observational setting, and dotted arrows depict intention-to-treat analysis. The unmeasured factor U_i is time-invariant (subject-specific). Index i denotes unique individual and index j denotes discrete time-intervals (quarters).

2.2 Emulating a target trial

In similar spirit to Hernán and Robins [11], we describe a causal inference framework for emulating a randomized trial using a large observational data repository. We assume the following causal assumptions are satisfied: (i) exchangeability, (ii) postivity, (iii) consistency [12]. We describe the exchangeability assumption as "*no unmeasured confounding*" where the probability of treatment assignment is independent of the potential outcome conditioned on the observed covariates. We describe the positivity assumption as the non-zero probability of treatment assignment conditional on the observed covariates. The consistency assumption connects the potential (i.e. counterfactual) outcome to the observed outcome under the same observed treatment regimen.

We specify a target trial in which the start of study follow-up (i.e. time zero), eligibility and treatment assignment are synchronized to prevent immortal-time bias and selection bias [14]. We construct a repeated cross-sectional cohort in which the patients are enrolled when the following conditions are satisfied: (i) patient is at least 18 years of age; (ii) patient has diabetes [27], (iii) HbA1c $\geq$ 8.5% is recorded within the study period (January 01 2018 to December 31 2021). Patient follow-up starts when these eligibility criteria (i)-(iii) are met at the end of annual quarters. Patients are administratively censored at the end of study period (December 31, 2021) or mid-calendar year (June 30) when deceased year is recorded. The enrollment period is terminated on January 1 2021 while the study follow-up is terminated on December 31 2021. We exclude any patients who had an earlier prescription for SGLT-2i medication three years prior to the start of the study period (i.e. January 01, 2015 to December 31 2017). The three-year look back window reduces the possibility of selection bias by left truncating those individuals who initiated the SGLT-2i medications prior to meeting the eligibility criteria [14].

We define the causal contrast of interest as a net change in HbA1c (%) using the prescriptions for SGLT-2i medications versus standard care (defined as "routine diabetes care" without SGLT-2i medications). The net change in HbA1c is estimated in relation to the baseline eligibility of HbA1c $\geq$ 8.5% in treatment and control group. The discontinuation of SGLT-2i medications is defined using a combination of the information available in the medication table (in order of precedence): (i) stop date, (ii) total refills, and (iii) duration count. In the absence of stop date, medication length was determined as a product of `RefillCount`, `DurationCount` (standardized as "days") and `DurationUnit`, as further detailed in the data dictionary elsewhere [2]. Depending on the available information, SGLT-2i prescription may lead to minimum exposure of 30 days and maximum exposure of 365 days. If the start date and the stop date of SGLT-2i medication overlapped the last day of annual quarters (i.e. March 31; June 30; September 30; December 31) then we assumed the prescription was active and the patient was on the medication using the intention-to-treat analysis. The treatment A_{ij}, confounders X_{ij}, and primary

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Table 1: A summary of target trial to estimate the reduction in HbA1c† among SGLT-2i‡ users

Protocol component	Description
Follow-up period	Study follow-up starts on January 01, 2018 and terminated on December 31, 2021. Patient follow-up is defined with eligibility and censoring criteria.
Exclusion criteria	Exclude patients with three year look-back window for SGLT-2i prescriptions with respect to the start of the study period (January 01 2018).
Eligibility criteria	At least 18 years old patients with diabetes and elevated HbA1c ($\geq 8.5\%$).
Censoring criteria	Administratively censored on December 31, 2021 or mid-calendar year (June 30) when deceased year is recorded.
Treatment strategy	Prescription for SGLT-2i medication versus standard care (i.e. without SGLT-2i prescriptions).
Assignment procedures	Participants randomly assigned to either treatment strategy.
Outcome	Repeated-measures HbA1c (in %).
Causal contrast of interest	Cumulative SGLT-2i prescriptions versus standard care.
Adherence to treatment	Not available in primary care electronic health records.
Analysis plan	Intention-to-treat analysis.

† HbA1c= Hemoglobin A1c; ‡ SGLT-2i= Sodium-Glucose co-Transporter 2 Inhibitor.

outcome Y_{ij} are defined within each index quarter. In the case of multiple measurements within each quarter, positive values of A_{ij} and X_{ij} take precedence while an average value of Y_{ij} (Hemoglobin A1c) is computed for each patient within each quarter.

2.3 Marginal structural model

A marginal structural model using generalized estimating equations (AR-1 working correlation structure) with stabilized treatment weights is used to account for measured confounders. We formulate the marginal structural model as

$$\begin{aligned} E(Y_{ij}^a) = \theta_0 &+ \theta_1 \times \text{age group}_{ij} \\ &+ \theta_2 \times \text{sex}_i \\ &+ \theta_3 \times \text{income quintile}_i \\ &+ \theta_4 \times \text{rurality}_i \\ &+ \theta_5 \times \text{SGLT-2i prescription}_{ij-1} \\ &+ \theta_6 \times \text{baseline HbA1c}_i \end{aligned} \tag{1}$$

where Y_{ij}^a are the potential outcomes. The marginal structural model do not include confounders (i.e. co-morbidities and other glucose lowering medications) as they are

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accounted for using the stabilized weights. The effectiveness of glucose lowering medications is assessed among diabetes patients who are prescribed SGLT-2i drugs in a repeated cross-sectional design. We may describe the stabilizing weights for treatment A_{ij} as

$$SW_{ij}^{A} = \frac{Pr(A_{ij} \mid \text{age}_{ij}, \text{sex}_i)}{Pr(A_{ij} \mid \text{age}_{ij}, \text{sex}_i, X_{ij-1}, Y_{i0})} \tag{2}$$

where X_{ij-1} are the confounders measured prior to treatment A_{ij}, and Y_{i0} is the baseline HbA1c. The numerator describes the stabilizing factor with the exclusion of confounders X_{ij-1} and baseline HbA1c Y_{i0}, while the denominator describes the inverse probability of treatment assignment with the inclusion of confounders X_{ij-1} and baseline HbA1c Y_{i0}.

3 Results

3.1 Cohort description

The repeated cross-sectional cohort contained 7,552 diabetes patients (Figure 5). Table (2) described the patient characteristics with respect to the most recent HbA1c value (as of December 31, 2021). A higher proportion of patients with diabetes lived in neighborhoods in the lowest income quintile (27.4%) than those in the highest income quintile (17.6%). The mean HbA1c was higher in lowest income neighbourhoods in relation to more affluent neighbourhoods (8.40% v.s. 8.01%). A lower mean HbA1c was observed with the presence of SGLT-2i prescriptions (8.26% v.s. 7.99%). The overall prevalence of dyslipidemia was estimated as 70.9%, hypertension as 53.2%, CKD as 26.7%, osteoarthritis as 25.1%, and depression as 23.2%.

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Table 2: Glycemic control using Hemoglobin A1c in the diabetes cohort

Most recent Hemoglobin A1c (as of December 31, 2021)							
Patient characteristics	N patients	Percent %	Mean	Median	Std*	Q1**	Q3**
Age group (years)							
18-34 years	377	5.0%	8.92	8.70	2.13	7.22	10.40
35-49 years	1,120	14.8%	8.46	8.10	1.99	6.90	9.70
50-64 years	2,745	36.3%	8.25	7.90	1.81	7.00	9.13
65-79 years	2,343	31.0%	8.03	7.70	1.53	7.00	8.80
80+ years	967	12.8%	8.07	7.80	1.48	7.00	8.70
Sex							
Female	3,373	44.7%	8.30	8.00	1.77	7.10	9.20
Male	4,179	55.3%	8.16	7.80	1.73	6.90	9.00
Income quintiles							
1(=lowest)	2,076	27.5%	8.40	8.00	1.83	7.10	9.30
2	1,482	19.6%	8.14	7.80	1.69	6.90	9.00
3	1,271	16.8%	8.23	7.90	1.73	7.00	9.00
4	1,178	15.6%	8.14	7.80	1.76	6.90	9.00
5(=highest)	1,333	17.7%	8.01	7.70	1.58	6.90	8.80
Missing	212	2.8%	8.76	8.30	2.12	7.15	9.95
Region							
Rural	1,009	13.4%	8.32	8.00	1.73	7.10	9.30
Urban	6,401	84.8%	8.20	7.80	1.74	7.00	9.10
Missing	142	1.9%	8.66	8.30	2.06	7.00	9.70
SGLT-2i† prescription							
No	6574	87.0%	8.26	7.90	1.78	7.00	9.20
Yes	978	13.0%	7.99	7.60	1.51	7.00	8.60
Baseline Hemoglobin A1c							
8.5% - 9.0%	2,909	38.5%	7.90	7.70	1.31	7.00	8.60
9.0% - 10.0%	2,104	27.9%	8.12	7.90	1.57	7.00	9.10
10.0% or more	2,539	33.6%	8.69	8.20	2.18	6.90	10.30
Total	7,552	100.0%	8.22	7.90	1.75	7.00	9.10

*standard deviation; **Q1=1st quartile; Q3=3rd quartile

† SGLT-2i = sodium-glucose co-transporter 2 inhibitor

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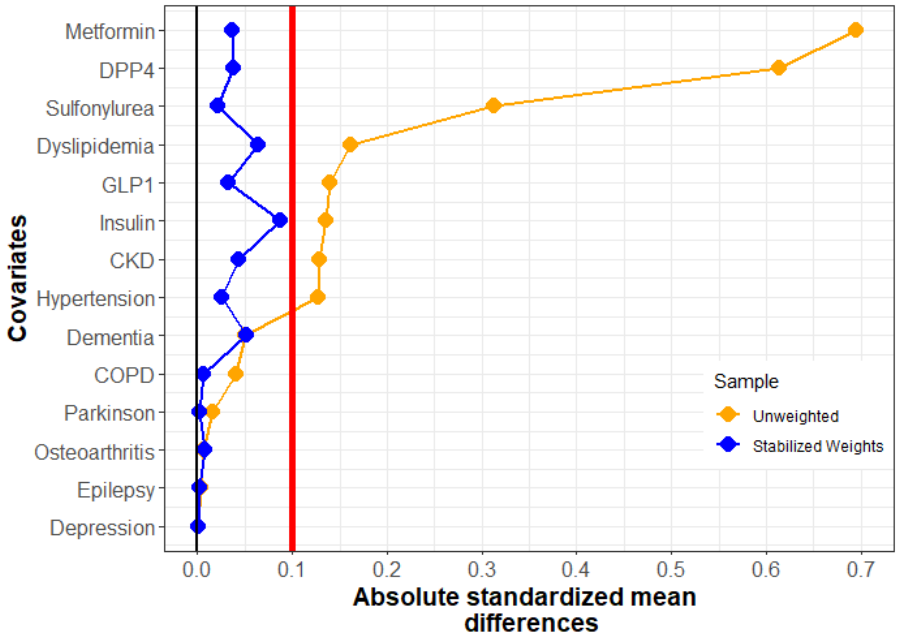
3.2 Covariate balance

We evaluated covariate balance using the stabilized treatment weights for SGLT-2i prescriptions in the repeated cross-sectional cohort by averaging over j discrete time intervals. The stabilized weights ranged from 0.119 to 2.99 with mean value of 0.957. All covariates including co-morbidities and other glucose lowering medications had absolute standardized mean difference lower than ± 0.1 for weighted sample, as shown in Figure (2). A reduction in absolute standardized mean difference was observed across multiple confounders in the weighted sample when compared with unweighted sample.

Figure 2: Covariate balance using stabilized treatment weights



3.3 Treatment assignment

Figure (3) describes the proportion of diabetes patients with quarterly prescription for SGLT-2i medications from 2018Q1 to 2021Q4. The prescription rates for SGLT-2i medications were gradually increasing with respect to age group, sex, income quintiles and rurality. The prescription rates were lower among young and old age groups, and among patient population residing in rural regions. Higher prescription rates were observed for patients with more elevated HbA1c at baseline.

3.4 Effectiveness of glucose lowering medications

The mean HbA1c was reduced by −0.53% (95% CI: −0.59% to −0.47%) with SGLT-2i prescription when compared to those without a SGLT-2i prescription, as shown in Figure (4). Older patients had lower HbA1c than younger patients (e.g. 65-79 years v.s. 18-34 years: −0.57% (95% CI: −0.72% to −0.42%)). The mean HbA1c was lower among males than females (−0.15% (95% CI: −0.21% to −0.10%)). The mean HbA1c was lower among patients residing in highest income quintile (5) compared with those in lowest income quintile (1) (−0.25% (95% CI: −0.33% to −0.18%)). Greater reduction in HbA1c was observed among patients with less elevated HbA1c at baseline (e.g. [8.5%-9.0%] v.s. [10% or more]: −1.05% (95% CI: −1.13% to −0.98%)).

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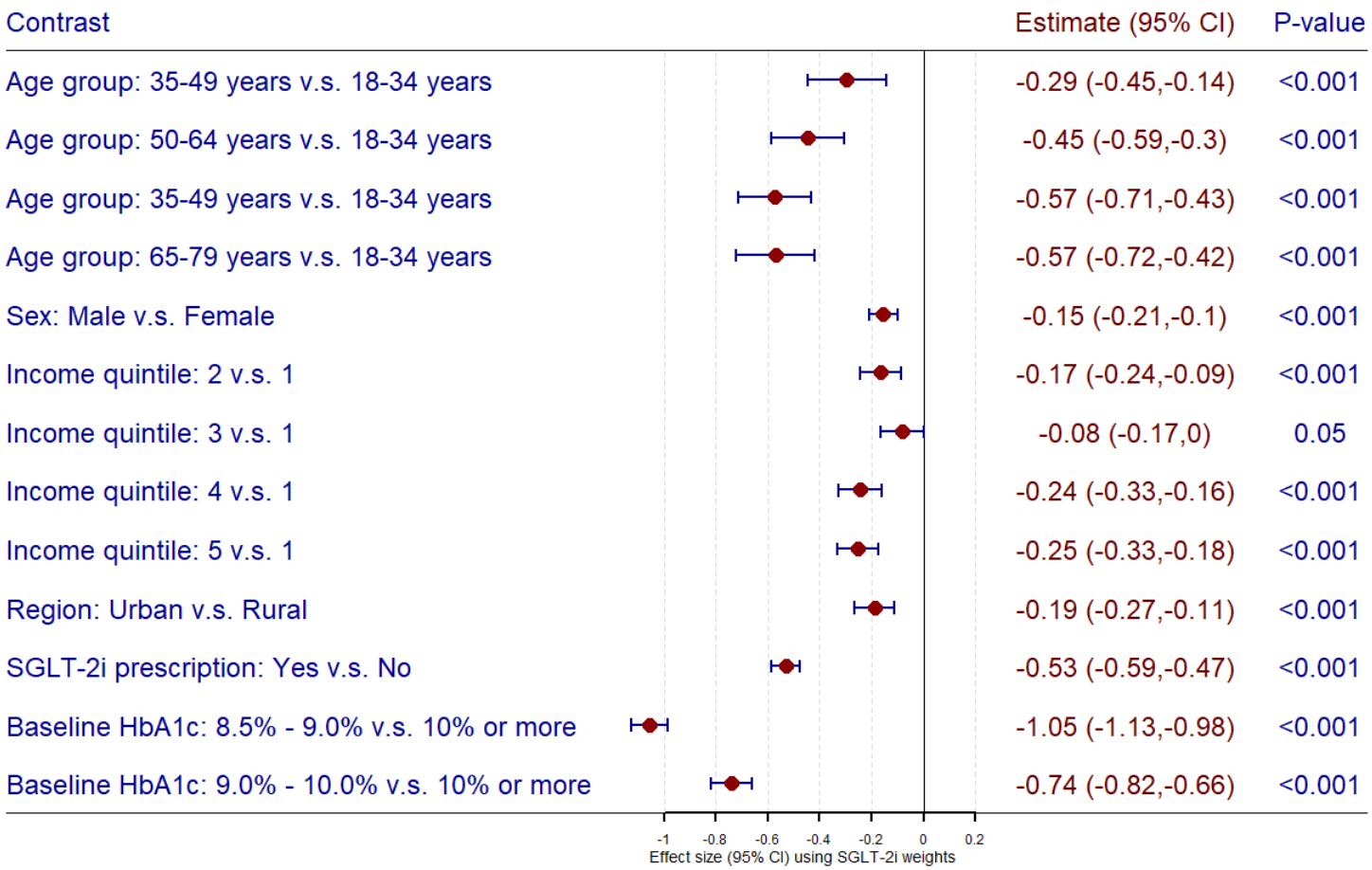
Figure 3: Prescription rates for sodium-glucose co-transporter 2 inhibitors (SGLT-2i) in the diabetes cohort

Figure 4: Net change in Hemoglobin A1c (%) using marginal structural models with stabilized treatment weights



4 Discussion

The marginal structural models demonstrated a reduction in mean HbA1c with SGLT-2i prescriptions using primary care EHRs. These findings corroborated the earlier results from a clinical trial [28], and from a meta-analysis of SGLT-2i medications [19]. For example, we found a reduction in mean HbA1c of −0.53% (95%: −0.59% to −0.47%) using intention-to-treat analysis for SGLT-2i prescriptions, while a clinical trial conducted by Zinman et al [28] reported −0.54% (95% CI: −0.58% to −0.49%) reduction in HbA1c using 10mg empagliflozin. Similarly, a meta-analysis conducted by Shyangda et al [19] reported −0.57% (95% CrI: −0.71% to −0.43%) reduction in HbA1c when comparing 10mg empagliflozin with placebo. We note that the clinical trials will still be required before drugs are introduced into clinical practice, but their effectiveness in real world settings provides an additional insight into their use for patients, physicians and policymakers.

With the advent of large clinical data repositories and computational power, there is emerging literature on emulating target trials using EHRs [11, 4]. Large healthcare repositories are becoming an attractive tool to evaluate interventions of public health significance [10]. However, it is necessary to consider several elements of emulating the target trial to reduce the possibility of generating incorrect conclusions [11]. In general, analysis based on comparative effectiveness research should not be performed on the basis of its feasibility [26], but after careful considerations of the quality of the information contained in large health care repositories [10]. Since primary care physicians provide front-line access to health care, a correct ascertainment was possible for several elements of the target trial using the primary care EHRs. For example, primary care providers are required by regulators to keep an updated medication list regardless of the source of the prescription. We believe that it was possible to reliably collect complete information on the exposure (i.e. prescriptions for glucose lowering medications) and the outcome (i.e. HbA1c) to characterize the longitudinal trajectories of glycemic control in diabetes population [6].

We employed the causal inference framework with counterfactual reasoning to emulate the target trial in this article. Hence, it is prudent to reflect on the validity of causal assumptions. We empirically validated the positivity assumption in the repeated cross-sectional cohort in which the probability of treatment assignment within each quarter was non-zero across all sub-strata (see Figure (3)). Our DAG (see Figure (1)) assumed that there were no unmeasured confounders when emulating this target trial. However, the violation of exchangeability assumption is possible in a case where the unmeasured factor is a common cause for the treatment process and the outcome process. This may lead to biased (or confounded) estimation of the treatment effect, and currently this is an active area of methodological research in causal inference literature [24]. We formulated the causal contrast of interest as a presence or absence of SGLT-2i prescriptions,

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and thereby ensuring the potential outcome framework with stable unit treatment value assumption (SUTVA) is well defined [18]. The validity of consistency assumption may become questionable for some common exposures in social epidemiology context including income quintiles, and other neighborhood characteristics such as rurality [17]. In addition we did not consider medication doses; depending on patients' clinical profile, primary care providers may prescribe low-dose or high-dose SGLT-2i medication. We acknowledge that we did not make this distinction, and this may violate the consistency assumption due to different dose response patterns for each patient.

Apart from causal assumptions, we also need to concern ourselves with other complex features of EHRs: measurement bias, data harmonization and standardization procedures, and other idiosyncratic coding practices across medical practitioners [15]. At the moment, we caution the reader that the estimated treatment effect in this article is prone to various methodological complexities including unmeasured confounders (e.g. joint determinants of exposure and outcome such as education), selection bias (e.g. convenience sampling frame of primary care practices), irregularities in longitudinal outcome (e.g. informative visit process), confounding by indication (e.g. diabetes severity). In spite of these methodological challenges, EHRs provide a possible avenue to emulate target trials which closely resembles an ideal trial with some compromises applied to the eligibility criteria and treatment strategies [11], and in spite of these potential challenges, the estimate of treatment effect obtained in this article was of similar magnitude as estimates obtained in other clinical trial [28], and meta-analytic setting [19].

In the future, we hope that primary care EHRs will foster the emulation of target trials to assess the long-term effects of glucose-lowering medications on adverse micro-vascular complications (e.g. diabetic retinopathy) and macro-vascular complications (e.g. coronary heart disease or stroke) of diabetes [9]. The primary care EHRs did not contain information on adherence to treatment to estimate the per-protocol treatment effect [13]. As an extension, future work (using population-level registry data) may allow for the identification of adherence to protocol based on the dispensation of glucose-lowering medications [7]. On a cautionary note, we hope that this article sheds more light on how we can embrace the complexities of EHRs (e.g. data heterogeneity, measurement bias, unmeasured confounders) while appreciating the on-going methodological developments in causal inference literature.

5 Research ethics statement

This project received Research Ethics Board (REB) approval from Health Sciences REB board at University of Toronto (RIS Protocol Number: 39268).

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7 Acroynms

- CKD = Chronic Kidney Disease
- COPD = Chronic Obstructive Pulmonary Disease
- DAG = Directed Acyclic Graph
- DPP-4i = Dipeptidyl Peptidase-4 inhibitor
- EHRs = Electronic Health Records
- eGFR = estimated Globular Filtration Rate
- GLP-1 = Glucagon-like Peptide 1 receptor agonists
- HbA1c = Hemoglobin A1c
- SGLT-2i = Sodium-Glucose co-Transporter 2 Inhibitor
- SUTVA = Stable Unit Treatment Value Assumption
- UTOPIAN = University of Toronto Practice Based Research Network

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8 Supplementary section

The CONSORT statement describes the checklist for emulating randomized trials using observational repositories [10]. The CONSORT diagram (Figure 5) describes the generation of longitudinal cohort. Table (3) describes the most recent HbA1c in the longitudinal cohort (as of December 31, 2021) with respect to co-morbidities and glucose lowering drug medications.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported
Title and abstract			
	1a	Identification as a randomised trial in the title	Yes
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Yes
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Yes
	2b	Specific objectives or hypotheses	Yes
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Yes
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Yes
Participants	4a	Eligibility criteria for participants	Yes
	4b	Settings and locations where the data were collected	Yes
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Yes
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Yes
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	NA
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Yes
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	NA

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Yes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Yes
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Yes
	13b	For each group, losses and exclusions after randomisation, together with reasons	Yes
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Yes
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Yes
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Yes
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Yes
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Yes
Other information			
Registration	23	Registration number and name of trial registry	NA
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	NSERC-CGS

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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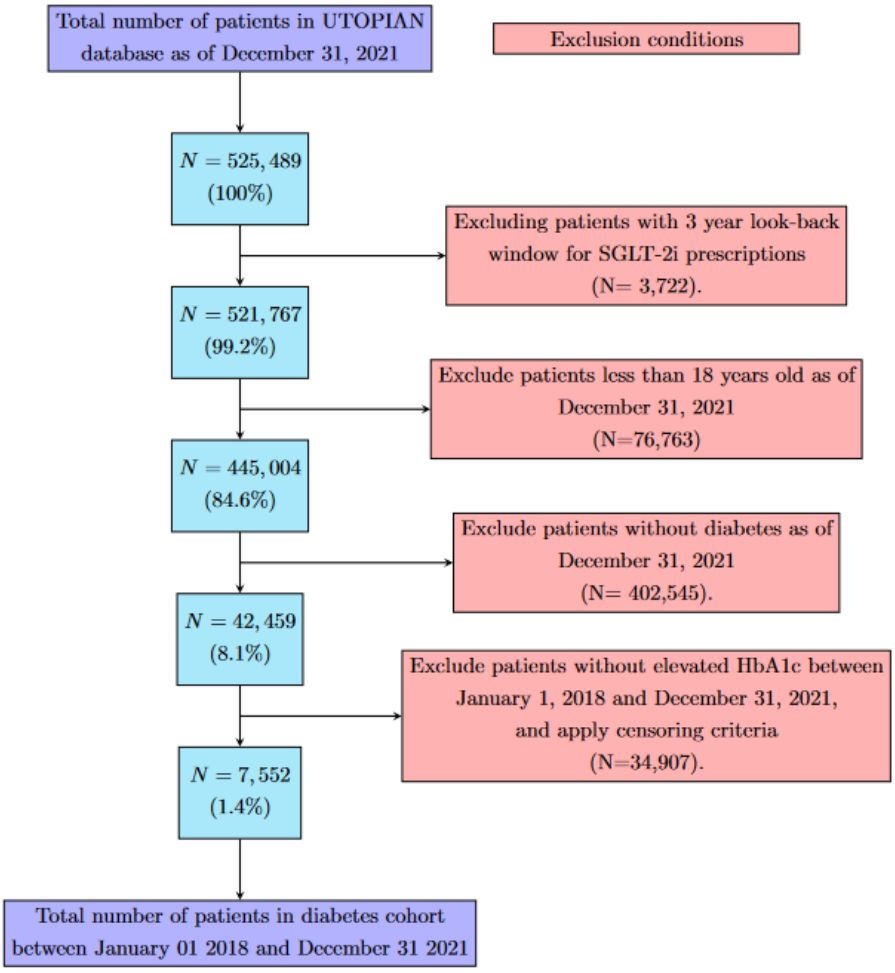

Figure 5: CONSORT diagram for the generation of longitudinal diabetes cohort (between January 01 2018 and December 31 2021) in the primary care repository of University of Toronto Practice Based Research Network (UTOPIAN).

Table 3: Mean hemoglobin A1c with respect to co-morbidities and glucose lowering medications

	Most recent Hemoglobin A1c (as of December 31, 2021)						
Patient characteristics	N patients	Column %	Mean	Median	Std*	Q1**	Q3**
Chronic Obstructive Pulmonary Disease							
No	7,081	93.8%	8.22	7.90	1.75	7.00	9.10
Yes	471	6.2%	8.30	7.90	1.72	7.00	9.20
Dementia							
No	7,092	93.9%	8.22	7.80	1.76	7.00	9.10
Yes	460	6.1%	8.28	8.10	1.65	7.10	9.20
Depression							
No	5,803	76.8%	8.20	7.80	1.74	7.00	9.00
Yes	1,749	23.2%	8.29	8.00	1.77	7.00	9.30
Dyslipidemia							
No	2,195	29.1%	8.29	8.00	1.75	7.10	9.20
Yes	5,357	70.9%	8.19	7.80	1.75	6.90	9.10
Epilepsy							
No	7,453	98.7%	8.22	7.90	1.75	7.00	9.10
Yes	99	1.3%	8.40	8.10	1.82	7.00	9.53
Hypertension							
No	3,532	46.8%	8.36	8.00	1.84	7.00	9.30
Yes	4,020	53.2%	8.11	7.80	1.66	6.96	8.90
Osteoarthritis							
No	5,654	74.9%	8.27	7.90	1.79	7.00	9.20
Yes	1,898	25.1%	8.08	7.80	1.63	6.95	8.85
Parkinson							
No	7,493	99.2%	8.23	7.90	1.75	7.00	9.10
Yes	59	0.8%	7.95	7.70	1.42	7.00	8.60
Chronic kidney disease							
No	5,535	73.3%	8.27	7.90	1.81	6.90	9.20
Yes	2,017	26.7%	8.09	7.80	1.57	7.00	8.80
Dipeptidyl Peptidase-4 inhibitor							
No	6,199	82.1%	8.18	7.80	1.73	6.90	9.10
Yes	1,353	17.9%	8.42	8.00	1.83	7.10	9.30
Glucagon-like Peptide 1 receptor agonists							
No	7,127	94.4%	8.21	7.90	1.74	7.00	9.10
Yes	425	5.6%	8.39	8.10	1.84	7.00	9.30
Sulfonylurea							
No	6,662	88.2%	8.18	7.80	1.74	6.90	9.00
Yes	890	11.8%	8.58	8.20	1.80	7.30	9.50
Insulin							
No	6,700	88.7%	8.12	7.80	1.70	6.90	8.90
Yes	852	11.3%	9.00	8.70	1.95	7.60	10.05
Metformin							
No	5,144	68.1%	8.17	7.80	1.69	7.00	9.00
Yes	2,408	31.9%	8.33	7.90	1.86	6.90	9.30
Total	7,552	100.0%	8.22	7.90	1.75	7.00	9.10

*standard deviation; **Q1=1st quartile; Q3=3rd quartile

† SGLT-2i = Sodium-Glucose co-Transporter 2 Inhibitor

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Dear reviewers,

We like to thank you for carefully reviewing our manuscript. Please see our response below.

05-Jul-2022

Re: AJE-00308-2022.R1
Emulating a target trial using primary care electronic health records: SGLT-2i medications and Hemoglobin A1c

Dear Mr Kalia:

Thank you for submitting your manuscript to the AJE and for your careful and thorough responses to the reviewers' comments. We would like to invite you to resubmit your manuscript and to respond to the additional minor comments made by one reviewer.

If you do submit a revision, please do so online at https://mc.manuscriptcentral.com/aje using the same number assigned the original submission. The on-line file will remain open for 60 days from the date of this letter, for submission of your revision. The original submission and instructions for uploading a revision will be located in the "Author" section of the account of the author who originally submitted the paper to our Journal. If you have any questions, please contact the Journal office prior to uploading your revised paper.

Be sure to respond to each of the reviewers' comments and the decision letter in the text box provided in the revision center. Please indicate and justify, any changes suggested that you have elected not to make, but DO NOT respond to the comments in your cover letter. Your 'point-by-point' response to the comments MUST BE PLACED IN THE TEXT BOX SO THAT THEY CAN BE VIEWED BY THE REVIEWERS if your article is sent out for re-review.

You are required to UPLOAD AN UNBLINDED COPY OF THIS MANUSCRIPT WHICH SHOWS THE CHANGES MADE (be sure that the title page lists all of the authors, along with your complete contact information (Name, degrees, phone, fax, email and complete mailing address)). This can be done by either using the Track Changes feature in Word or just by highlighting the changes (do not use color to show the changes; bolding is acceptable). IF USING TRACK CHANGES IN WORD, PLEASE TURN OFF THE BALLOON OPTION AND DO NOT TRACK FORMATTING CHANGES. Author Affiliations should be listed first under 'Acknowledgements' (AJE 'Instructions to Authors' have recently been

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modified). Please keep in mind the Journal's word limits for Original Contributions abstract (200) and text (3,500); Practice of Epidemiology abstract (200) and text (4,000).

Thank you for your interest in the Journal. I look forward to receiving your revised manuscript.

Sincerely,

Dr. Ellen Caniglia
Editor, AJE

American Journal of Epidemiology
https://mc.manuscriptcentral.com/aje

Reviewer: 1

Comments to the Author
(There are no comments.)

Reviewer: 2

Comments to the Author
I only have a few minor suggestion below:
- The example for macro-vascular complications should be changed from abnormal micro-albumin to coronary heart disease or stroke (page 14 line 38).

We modified the text as:

In the future, we hope that primary care EHRs will foster the emulation of target trials to assess the long-term effects of glucose-lowering medications on adverse micro-vascular (e.g. diabetic retinopathy) and macro-vascular complications (e.g. coronary heart disease or stroke) of diabetes.

- The new text around 'methodological complexities' in the Discussion should also be revised to replace 'biological mechanisms not captured in EHR' which is not a good example for confounding by something like 'joint determinants of exposure and treatment such as education' (Page 14 line 21).

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We modified the text as:

At the moment, we caution the reader that the estimated treatment effect in this article is prone to various methodological complexities including unmeasured confounders (e.g. joint determinants of exposure and outcome such as education), selection bias (e.g. convenience sampling frame of primary care practices), irregularities in longitudinal outcome (e.g. informative visit process), confounding by indication (e.g. diabetes severity).

Please kindly see the revised manuscript (with track changes) in Scholar One Portal.

Sincerely,

Kalia et al

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Emulating a target trial using primary care electronic health records: SGLT-2i medications and Hemoglobin A1c

Sumeet Kalia[1,2], Olli Saarela[1], Braden O'Neill[1,2], Christopher Meaney[2], Rahim Moineddin[2], Frank Sullivan[3], Michelle Greiver[2]

[1] University of Toronto, Dalla Lana School of Public Health, Toronto, ON, M5T3M7, Canada

[2] University of Toronto, Department of Family and Community Medicine, Toronto, ON, M5G 1V7, Canada

[3] University of St Andrews, School of Medicine, St Andrews, United Kingdom

sumeet.kalia@utoronto.ca, olli.saarela@utoronto.ca, braden.oneill@unityhealth.to, christopher.meaney@utoronto.ca, rahim.moineddin@utoronto.ca, fms20@st-andrews.ac.uk, mgreiver@rogers.com

July 7, 2022

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Abstract

Substantial effort has been dedicated to conducting controlled experiments to generate clinical evidence for diabetes treatment. Randomized controlled experiments are the gold standard to establish cause and effect. However, due to their high-cost and time-commitment, large observational databases such as those comprised of electronic health record (EHR) data collected in routine primary care may provide an alternative source to address such causal objectives. We used a Canadian primary care repository housed at University of Toronto to emulate a randomized experiment. We estimated the effectiveness of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) medications for patients with diabetes using Hemoglobin A1c (HbA1c) as a primary outcome and marker for glycemic control. We assumed an intention-to-treat analysis for prescribed treatment, with analyses based on the

treatment assigned (i.e. drug prescription) rather than the treatment eventually received (i.e. drug dispensation). We defined the causal contrast of interest as the net change in HbA1c (%) between the group receiving standard of care versus the group receiving SGLT-2i medications. Using a counterfactual framework, marginal structural models demonstrated a reduction in mean HbA1c with the initiation of SGLT-2i medications. These findings provided similar effect sizes to those from earlier clinical trials on assessing the effectiveness of SGLT-2i medications.

Keywords: Randomized controlled trials; Marginal structural models; Electronic health records; Primary care; Diabetes; Glucose-lowering medications

1 Introduction

Randomized controlled experiments are the gold standard to establish the relationship between cause and effect. However, clinical trials are time consuming, expensive and prone to recruitment challenges with under-representation of racialized communities and rural regions [5, 8]. Under these circumstances, electronic health records (EHRs) may provide an alternative data source to assess the effectiveness of glucose lowering medications in diabetes population.

Diabetes is one of the most common chronic conditions; in this condition blood glucose levels are elevated due to the pancreas' inability to produce sufficient insulin (Type I) or an inability to properly metabolize glucose (Type II) [16]. More than 537 million adults live with diabetes worldwide as of 2021 [21], and the Center for Disease Control predict that the incidence of diabetes will continue to increase [22]. Type II diabetes accounts for 90% to 95% of all diabetes cases [22]. Elevated glucose in the form of chronic hyperglycemia can be regulated by manipulating the glucose re-absorption rate. For example, a healthy kidney can reabsorb up to 180g of glucose from glomerular filtration each day, and this mechanism can be inhibited using the sodium-glucose co-transporter located in the proximal tubules of the kidney [20]. The class of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) drugs may block 50% of the glucose re-absorption [20].

Hemoglobin A1c (HbA1c) is a marker for glycemic control, and optimal HbA1c levels are associated with reductions in diabetes-related complications and mortality [16]. According to clinical guidelines published by the American Diabetes Association [1], metformin and comprehensive lifestyle modifications are first line therapy for type II diabetes patients to achieve a target HbA1c $\leq$ 7%. Depending on the clinical profile of individual patients, a combination therapy of other glucose lowering medications can be recommended using several drug classes: SGLT-2i, Dipeptidyl Peptidase-4 inhibitors (DPP-4i), Glucagon-like Peptide 1 receptor agonists (GLP-1), sulfonylurea, and insulin [6].

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1.1 Knowledge gap

The safety and efficacy of SGLT-2i medications is well established [25]. However, this clinical evidence was gathered using clinical trials, and there is a knowledge gap for the effectiveness of SGLT-2i drugs using real-world data (e.g. primary care EHRs). It is necessary to develop approaches to ascertain the effectiveness of treatments using observational data, which has the potential to markedly reduce the resources required to identify effective treatments to improve health. Analysis of routinely collected EHR data may allow for potential opportunities in which we may assess the long-term adverse effects of diabetes treatment. EHR data may also allow us to assess for the presence of effect modification, which may not be feasible in randomized trials due to insufficient statistical power. The objective of this study is to emulate a target trial to assess the effectiveness of SGLT-2i using HbA1c as a marker for glycemic control.

2 Materials and Methods

The EHRs collected from different sources (including hospitals, specialist clinics, primary care providers, pharmacies, and laboratories) have the potential to serve as a complete lifetime record of a person's health history. The University of Toronto practice-based research network's (UTOPIAN) database contains de-identified medical information collected from EHRs of primary care practices across the greater Toronto region [23]. This repository is a rich source of de-identified patient-level data, including demographics, medical diagnoses, procedures, medications, immunizations, laboratory test results, vital signs and risk factors.

2.1 Conceptual framework

We used the directed acyclic graph (DAG), in Figure (1), to describe the causal relationship between SGLT-2i drugs and reduction in HbA1c. The dotted lines in Figure (1) describe the dependency that exist in primary care registry data, but we would not expect this dependency in a randomized trial. For example, a controlled experiment will administrate the initiation of a treatment for consenting patients, and thus the dotted line between drug prescription and drug initiation will cease to exist. We assume an intention-to-treat framework where the analyses are based on the treatment assignment (i.e. drug prescription) rather than the treatment eventually received (i.e. drug dispensation). The randomization procedure will ensure that the patient characteristics are balanced across treatment arms, and thereby breaking the empirical associations between treatment assignment (A_{ij}) and patient characteristics (X_{ij}). The baseline HbA1c (Y_{i0}) is assumed to encode the historical information on glycemic control. Other glucose lowering medications (X_{ij}) captures the use of monotherapy and combination therapy

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using several drug classes: (i) metformin, (ii) DPP-4i, (iii) GLP-1, (iv) sulfonylurea, (v) insulin, as detailed elsewhere [6]. The unmeasured factors (e.g. lifestyle factors) influence the HbA1c value while also influencing other patient characteristics (e.g. co-morbidities). With the exception of baseline patient characteristics (i.e. age, sex, income quintiles, rurality), we assume the patient characteristics (i.e. co-morbidities, other glucose-lowering medications) to be confounders. We include several co-morbidities with disease onset date as covariates X_{ij}: (i) chronic obstructive pulmonary disease (COPD), (ii) dementia, (iii) depression, (iv) dyslipidemia, (v) epilepsy, (vi) hypertension, (vii) osteoarthritis, (viii) Parkinson's disease, (ix) chronic kidney disease (CKD). These conditions have established phenotype definitions in UTOPIAN database, and further details are available online [3].

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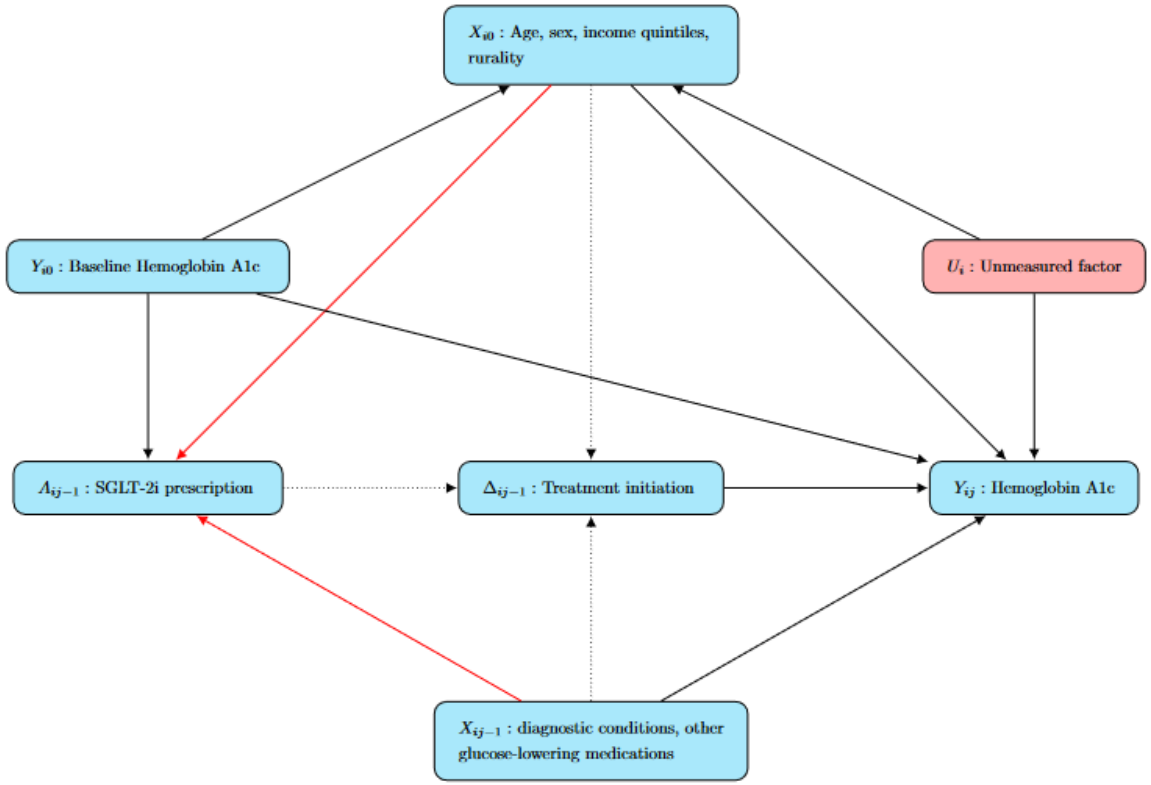

Figure 1: Directed acyclic graph for the treatment effect of sodium glucose co-transporter-2 inhibitors (SGLT-2i) prescriptions related to a change in Hemoglobin A1c (HbA1c). The red arrows depict the observational setting, and dotted arrows depict intention-to-treat analysis. The unmeasured factor U_i is time-invariant (subject-specific). Index i denotes unique individual and index j denotes discrete time-intervals (quarters).

2.2 Emulating a target trial

In similar spirit to Hernán and Robins [11], we describe a causal inference framework for emulating a randomized trial using a large observational data repository. We assume the following causal assumptions are satisfied: (i) exchangeability, (ii) postivity, (iii) consistency [12]. We describe the exchangeability assumption as "*no unmeasured confounding*" where the probability of treatment assignment is independent of the potential outcome conditioned on the observed covariates. We describe the positivity assumption as the non-zero probability of treatment assignment conditional on the observed covariates. The consistency assumption connects the potential (i.e. counterfactual) outcome to the observed outcome under the same observed treatment regimen.

We specify a target trial in which the start of study follow-up (i.e. time zero), eligibility and treatment assignment are synchronized to prevent immortal-time bias and selection bias [14]. We construct a repeated cross-sectional cohort in which the patients are enrolled when the following conditions are satisfied: (i) patient is at least 18 years of age; (ii) patient has diabetes [27], (iii) HbA1c $\geq$ 8.5% is recorded within the study period (January 01 2018 to December 31 2021). Patient follow-up starts when these eligibility criteria (i)-(iii) are met at the end of annual quarters. Patients are administratively censored at the end of study period (December 31, 2021) or mid-calendar year (June 30) when deceased year is recorded. The enrollment period is terminated on January 1 2021 while the study follow-up is terminated on December 31 2021. We exclude any patients who had an earlier prescription for SGLT-2i medication three years prior to the start of the study period (i.e. January 01, 2015 to December 31 2017). The three-year look back window reduces the possibility of selection bias by left truncating those individuals who initiated the SGLT-2i medications prior to meeting the eligibility criteria [14].

We define the causal contrast of interest as a net change in HbA1c (%) using the prescriptions for SGLT-2i medications versus standard care (defined as "routine diabetes care" without SGLT-2i medications). The net change in HbA1c is estimated in relation to the baseline eligibility of HbA1c $\geq$ 8.5% in treatment and control group. The discontinuation of SGLT-2i medications is defined using a combination of the information available in the medication table (in order of precedence): (i) stop date, (ii) total refills, and (iii) duration count. In the absence of stop date, medication length was determined as a product of `RefillCount`, `DurationCount` (standardized as "days") and `DurationUnit`, as further detailed in the data dictionary elsewhere [2]. Depending on the available information, SGLT-2i prescription may lead to minimum exposure of 30 days and maximum exposure of 365 days. If the start date and the stop date of SGLT-2i medication overlapped the last day of annual quarters (i.e. March 31; June 30; September 30; December 31) then we assumed the prescription was active and the patient was on the medication using the intention-to-treat analysis. The treatment A_{ij}, confounders X_{ij}, and primary

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Table 1: A summary of target trial to estimate the reduction in HbA1c† among SGLT-2i‡ users

Protocol component	Description
Follow-up period	Study follow-up starts on January 01, 2018 and terminated on December 31, 2021. Patient follow-up is defined with eligibility and censoring criteria.
Exclusion criteria	Exclude patients with three year look-back window for SGLT-2i prescriptions with respect to the start of the study period (January 01 2018).
Eligibility criteria	At least 18 years old patients with diabetes and elevated HbA1c ($\geq 8.5\%$).
Censoring criteria	Administratively censored on December 31, 2021 or mid-calendar year (June 30) when deceased year is recorded.
Treatment strategy	Prescription for SGLT-2i medication versus standard care (i.e. without SGLT-2i prescriptions).
Assignment procedures	Participants randomly assigned to either treatment strategy.
Outcome	Repeated-measures HbA1c (in %).
Causal contrast of interest	Cumulative SGLT-2i prescriptions versus standard care.
Adherence to treatment	Not available in primary care electronic health records.
Analysis plan	Intention-to-treat analysis.

† HbA1c= Hemoglobin A1c; ‡ SGLT-2i= Sodium-Glucose co-Transporter 2 Inhibitor.

outcome Y_{ij} are defined within each index quarter. In the case of multiple measurements within each quarter, positive values of A_{ij} and X_{ij} take precedence while an average value of Y_{ij} (Hemoglobin A1c) is computed for each patient within each quarter.

2.3 Marginal structural model

A marginal structural model using generalized estimating equations (AR-1 working correlation structure) with stabilized treatment weights is used to account for measured confounders. We formulate the marginal structural model as

$$\begin{aligned} E(Y_{ij}^a) = \theta_0 &+ \theta_1 \times \text{age group}_{ij} \\ &+ \theta_2 \times \text{sex}_i \\ &+ \theta_3 \times \text{income quintile}_i \\ &+ \theta_4 \times \text{rurality}_i \\ &+ \theta_5 \times \text{SGLT-2i prescription}_{ij-1} \\ &+ \theta_6 \times \text{baseline HbA1c}_i \end{aligned} \tag{1}$$

where Y_{ij}^a are the potential outcomes. The marginal structural model do not include confounders (i.e. co-morbidities and other glucose lowering medications) as they are

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accounted for using the stabilized weights. The effectiveness of glucose lowering medications is assessed among diabetes patients who are prescribed SGLT-2i drugs in a repeated cross-sectional design. We may describe the stabilizing weights for treatment A_{ij} as

$$SW_{ij}^{A} = \frac{Pr(A_{ij} \mid \text{age}_{ij}, \text{sex}_i)}{Pr(A_{ij} \mid \text{age}_{ij}, \text{sex}_i, X_{ij-1}, Y_{i0})} \tag{2}$$

where X_{ij-1} are the confounders measured prior to treatment A_{ij}, and Y_{i0} is the baseline HbA1c. The numerator describes the stabilizing factor with the exclusion of confounders X_{ij-1} and baseline HbA1c Y_{i0}, while the denominator describes the inverse probability of treatment assignment with the inclusion of confounders X_{ij-1} and baseline HbA1c Y_{i0}.

3 Results

3.1 Cohort description

The repeated cross-sectional cohort contained 7,552 diabetes patients (Figure 5). Table (2) described the patient characteristics with respect to the most recent HbA1c value (as of December 31, 2021). A higher proportion of patients with diabetes lived in neighborhoods in the lowest income quintile (27.4%) than those in the highest income quintile (17.6%). The mean HbA1c was higher in lowest income neighbourhoods in relation to more affluent neighbourhoods (8.40% v.s. 8.01%). A lower mean HbA1c was observed with the presence of SGLT-2i prescriptions (8.26% v.s. 7.99%). The overall prevalence of dyslipidemia was estimated as 70.9%, hypertension as 53.2%, CKD as 26.7%, osteoarthritis as 25.1%, and depression as 23.2%.

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Table 2: Glycemic control using Hemoglobin A1c in the diabetes cohort

Most recent Hemoglobin A1c (as of December 31, 2021)							
Patient characteristics	N patients	Percent %	Mean	Median	Std*	Q1**	Q3**
Age group (years)							
18-34 years	377	5.0%	8.92	8.70	2.13	7.22	10.40
35-49 years	1,120	14.8%	8.46	8.10	1.99	6.90	9.70
50-64 years	2,745	36.3%	8.25	7.90	1.81	7.00	9.13
65-79 years	2,343	31.0%	8.03	7.70	1.53	7.00	8.80
80+ years	967	12.8%	8.07	7.80	1.48	7.00	8.70
Sex							
Female	3,373	44.7%	8.30	8.00	1.77	7.10	9.20
Male	4,179	55.3%	8.16	7.80	1.73	6.90	9.00
Income quintiles							
1(=lowest)	2,076	27.5%	8.40	8.00	1.83	7.10	9.30
2	1,482	19.6%	8.14	7.80	1.69	6.90	9.00
3	1,271	16.8%	8.23	7.90	1.73	7.00	9.00
4	1,178	15.6%	8.14	7.80	1.76	6.90	9.00
5(=highest)	1,333	17.7%	8.01	7.70	1.58	6.90	8.80
Missing	212	2.8%	8.76	8.30	2.12	7.15	9.95
Region							
Rural	1,009	13.4%	8.32	8.00	1.73	7.10	9.30
Urban	6,401	84.8%	8.20	7.80	1.74	7.00	9.10
Missing	142	1.9%	8.66	8.30	2.06	7.00	9.70
SGLT-2i† prescription							
No	6574	87.0%	8.26	7.90	1.78	7.00	9.20
Yes	978	13.0%	7.99	7.60	1.51	7.00	8.60
Baseline Hemoglobin A1c							
8.5% - 9.0%	2,909	38.5%	7.90	7.70	1.31	7.00	8.60
9.0% - 10.0%	2,104	27.9%	8.12	7.90	1.57	7.00	9.10
10.0% or more	2,539	33.6%	8.69	8.20	2.18	6.90	10.30
Total	7,552	100.0%	8.22	7.90	1.75	7.00	9.10

*standard deviation; **Q1=1st quartile; Q3=3rd quartile

† SGLT-2i = sodium-glucose co-transporter 2 inhibitor

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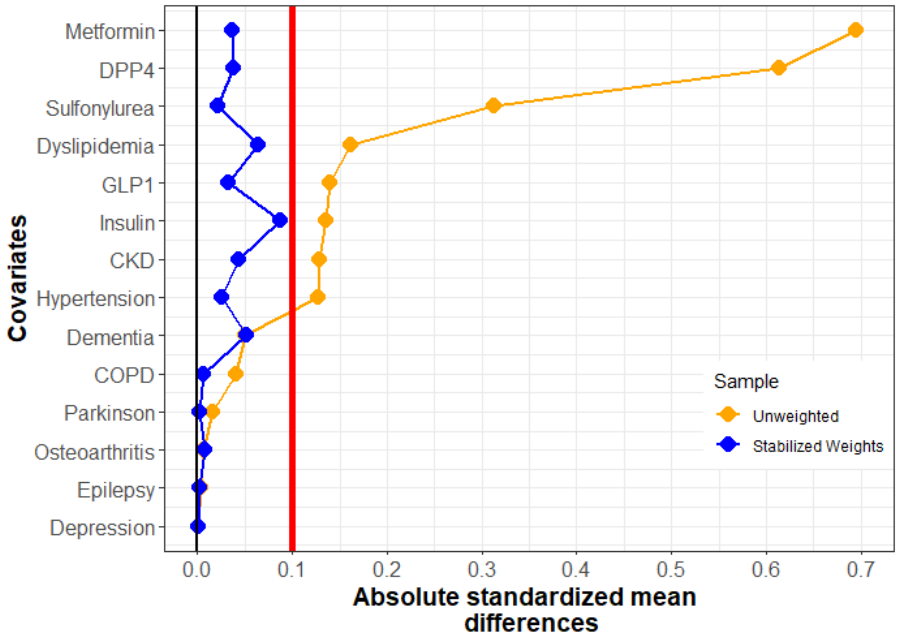
3.2 Covariate balance

We evaluated covariate balance using the stabilized treatment weights for SGLT-2i prescriptions in the repeated cross-sectional cohort by averaging over j discrete time intervals. The stabilized weights ranged from 0.119 to 2.99 with mean value of 0.957. All covariates including co-morbidities and other glucose lowering medications had absolute standardized mean difference lower than ± 0.1 for weighted sample, as shown in Figure (2). A reduction in absolute standardized mean difference was observed across multiple confounders in the weighted sample when compared with unweighted sample.

Figure 2: Covariate balance using stabilized treatment weights



3.3 Treatment assignment

Figure (3) describes the proportion of diabetes patients with quarterly prescription for SGLT-2i medications from 2018Q1 to 2021Q4. The prescription rates for SGLT-2i medications were gradually increasing with respect to age group, sex, income quintiles and rurality. The prescription rates were lower among young and old age groups, and among patient population residing in rural regions. Higher prescription rates were observed for patients with more elevated HbA1c at baseline.

3.4 Effectiveness of glucose lowering medications

The mean HbA1c was reduced by −0.53% (95% CI: −0.59% to −0.47%) with SGLT-2i prescription when compared to those without a SGLT-2i prescription, as shown in Figure (4). Older patients had lower HbA1c than younger patients (e.g. 65-79 years v.s. 18-34 years: −0.57% (95% CI: −0.72% to −0.42%)). The mean HbA1c was lower among males than females (−0.15% (95% CI: −0.21% to −0.10%)). The mean HbA1c was lower among patients residing in highest income quintile (5) compared with those in lowest income quintile (1) (−0.25% (95% CI: −0.33% to −0.18%)). Greater reduction in HbA1c was observed among patients with less elevated HbA1c at baseline (e.g. [8.5%-9.0%] v.s. [10% or more]: −1.05% (95% CI: −1.13% to −0.98%)).

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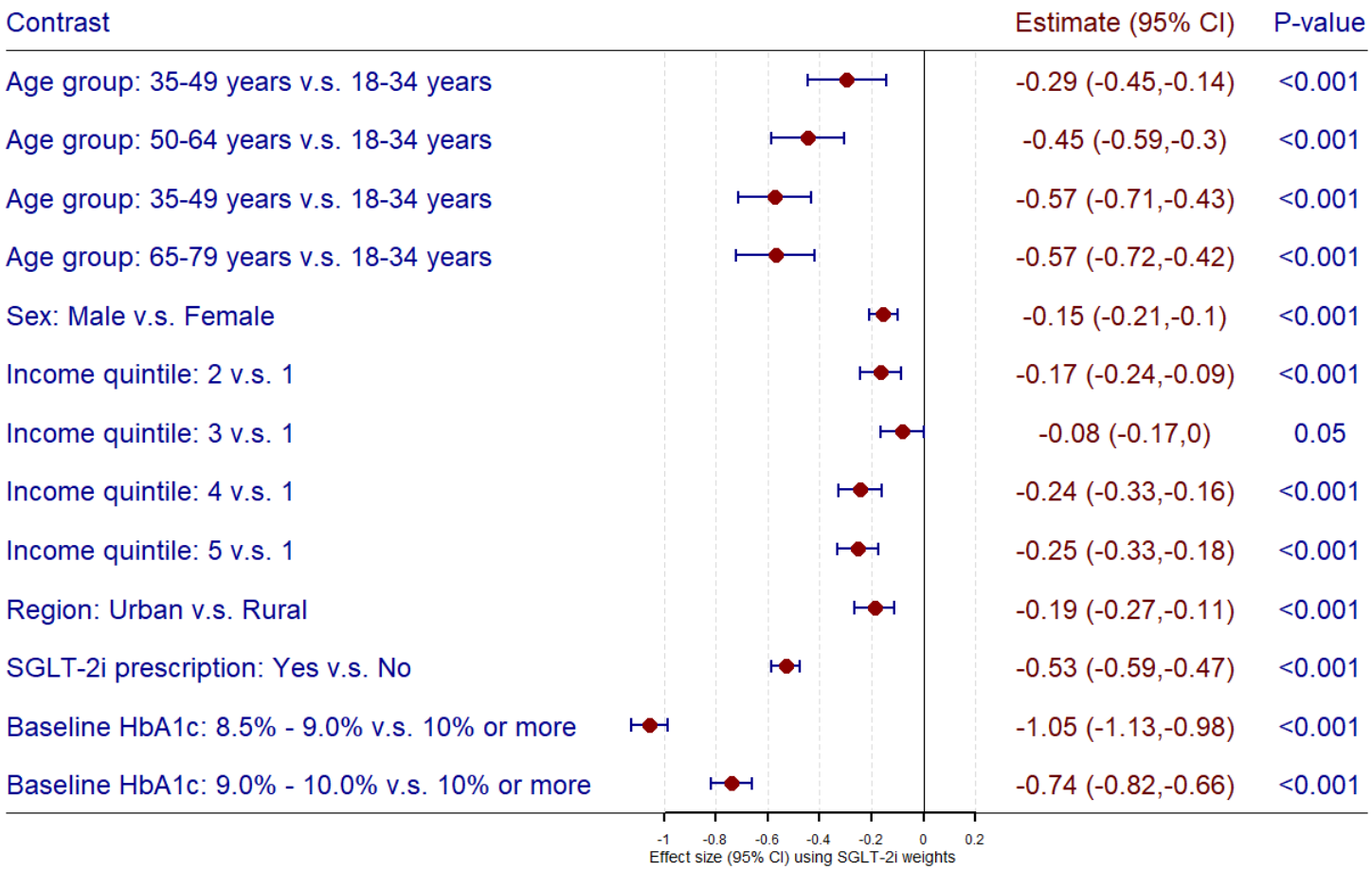
Figure 3: Prescription rates for sodium-glucose co-transporter 2 inhibitors (SGLT-2i) in the diabetes cohort

Figure 4: Net change in Hemoglobin A1c (%) using marginal structural models with stabilized treatment weights



4 Discussion

The marginal structural models demonstrated a reduction in mean HbA1c with SGLT-2i prescriptions using primary care EHRs. These findings corroborated the earlier results from a clinical trial [28], and from a meta-analysis of SGLT-2i medications [19]. For example, we found a reduction in mean HbA1c of −0.53% (95%: −0.59% to −0.47%) using intention-to-treat analysis for SGLT-2i prescriptions, while a clinical trial conducted by Zinman et al [28] reported −0.54% (95% CI: −0.58% to −0.49%) reduction in HbA1c using 10mg empagliflozin. Similarly, a meta-analysis conducted by Shyangda et al [19] reported −0.57% (95% CrI: −0.71% to −0.43%) reduction in HbA1c when comparing 10mg empagliflozin with placebo. We note that the clinical trials will still be required before drugs are introduced into clinical practice, but their effectiveness in real world settings provides an additional insight into their use for patients, physicians and policymakers.

With the advent of large clinical data repositories and computational power, there is emerging literature on emulating target trials using EHRs [11, 4]. Large healthcare repositories are becoming an attractive tool to evaluate interventions of public health significance [10]. However, it is necessary to consider several elements of emulating the target trial to reduce the possibility of generating incorrect conclusions [11]. In general, analysis based on comparative effectiveness research should not be performed on the basis of its feasibility [26], but after careful considerations of the quality of the information contained in large health care repositories [10]. Since primary care physicians provide front-line access to health care, a correct ascertainment was possible for several elements of the target trial using the primary care EHRs. For example, primary care providers are required by regulators to keep an updated medication list regardless of the source of the prescription. We believe that it was possible to reliably collect complete information on the exposure (i.e. prescriptions for glucose lowering medications) and the outcome (i.e. HbA1c) to characterize the longitudinal trajectories of glycemic control in diabetes population [6].

We employed the causal inference framework with counterfactual reasoning to emulate the target trial in this article. Hence, it is prudent to reflect on the validity of causal assumptions. We empirically validated the positivity assumption in the repeated cross-sectional cohort in which the probability of treatment assignment within each quarter was non-zero across all sub-strata (see Figure (3)). Our DAG (see Figure (1)) assumed that there were no unmeasured confounders when emulating this target trial. However, the violation of exchangeability assumption is possible in a case where the unmeasured factor is a common cause for the treatment process and the outcome process. This may lead to biased (or confounded) estimation of the treatment effect, and currently this is an active area of methodological research in causal inference literature [24]. We formulated the causal contrast of interest as a presence or absence of SGLT-2i prescriptions,

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and thereby ensuring the potential outcome framework with stable unit treatment value assumption (SUTVA) is well defined [18]. The validity of consistency assumption may become questionable for some common exposures in social epidemiology context including income quintiles, and other neighborhood characteristics such as rurality [17]. In addition we did not consider medication doses; depending on patients' clinical profile, primary care providers may prescribe low-dose or high-dose SGLT-2i medication. We acknowledge that we did not make this distinction, and this may violate the consistency assumption due to different dose response patterns for each patient.

Apart from causal assumptions, we also need to concern ourselves with other complex features of EHRs: measurement bias, data harmonization and standardization procedures, and other idiosyncratic coding practices across medical practitioners [15]. At the moment, we caution the reader that the estimated treatment effect in this article is prone to various methodological complexities including unmeasured confounders (e.g. ~~biological mechanism not captured in EHRs~~joint determinants of exposure and outcome such as education), selection bias (e.g. convenience sampling frame of primary care practices), irregularities in longitudinal outcome (e.g. informative visit process), confounding by indication (e.g. diabetes severity). In spite of these methodological challenges, EHRs provide a possible avenue to emulate target trials which closely resembles an ideal trial with some compromises applied to the eligibility criteria and treatment strategies [11], and in spite of these potential challenges, the estimate of treatment effect obtained in this article was of similar magnitude as estimates obtained in other clinical trial [28], and meta-analytic setting [19].

In the future, we hope that primary care EHRs will foster the emulation of target trials to assess the long-term effects of glucose-lowering medications on adverse micro-vascular complications (e.g. diabetic retinopathy) and macro-vascular complications (e.g. ~~abnormal micro-albumin~~coronary heart disease or stroke) of diabetes [9]. The primary care EHRs did not contain information on adherence to treatment to estimate the per-protocol treatment effect [13]. As an extension, future work (using population-level registry data) may allow for the identification of adherence to protocol based on the dispensation of glucose-lowering medications [7]. On a cautionary note, we hope that this article sheds more light on how we can embrace the complexities of EHRs (e.g. data heterogeneity, measurement bias, unmeasured confounders) while appreciating the on-going methodological developments in causal inference literature.

5 Research ethics statement

This project received Research Ethics Board (REB) approval from Health Sciences REB board at University of Toronto (RIS Protocol Number: 39268).

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6 Funding acknowledgement

This statistical research was supported by Natural Sciences and Engineering Research Council (NSERC) Canadian Graduate Scholarship (CGS: 534600).

7 Acroynms

- CKD = Chronic Kidney Disease
- COPD = Chronic Obstructive Pulmonary Disease
- DAG = Directed Acyclic Graph
- DPP-4i = Dipeptidyl Peptidase-4 inhibitor
- EHRs = Electronic Health Records
- eGFR = estimated Globular Filtration Rate
- GLP-1 = Glucagon-like Peptide 1 receptor agonists
- HbA1c = Hemoglobin A1c
- SGLT-2i = Sodium-Glucose co-Transporter 2 Inhibitor
- SUTVA = Stable Unit Treatment Value Assumption
- UTOPIAN = University of Toronto Practice Based Research Network

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8 Supplementary section

The CONSORT statement describes the checklist for emulating randomized trials using observational repositories [10]. The CONSORT diagram (Figure 5) describes the generation of longitudinal cohort. Table (3) describes the most recent HbA1c in the longitudinal cohort (as of December 31, 2021) with respect to co-morbidities and glucose lowering drug medications.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported
Title and abstract			
	1a	Identification as a randomised trial in the title	Yes
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Yes
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	Yes
	2b	Specific objectives or hypotheses	Yes
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Yes
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Yes
Participants	4a	Eligibility criteria for participants	Yes
	4b	Settings and locations where the data were collected	Yes
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Yes
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	Yes
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	NA
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	NA
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Yes
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	NA
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	NA
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	NA

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		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	Yes
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	Yes
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Yes
	13b	For each group, losses and exclusions after randomisation, together with reasons	Yes
Recruitment	14a	Dates defining the periods of recruitment and follow-up	Yes
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Yes
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Yes
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Yes
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	NA
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	NA
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	Yes
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Yes
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	Yes
Other information			
Registration	23	Registration number and name of trial registry	NA
Protocol	24	Where the full trial protocol can be accessed, if available	NA
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	NSERC-CGS

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

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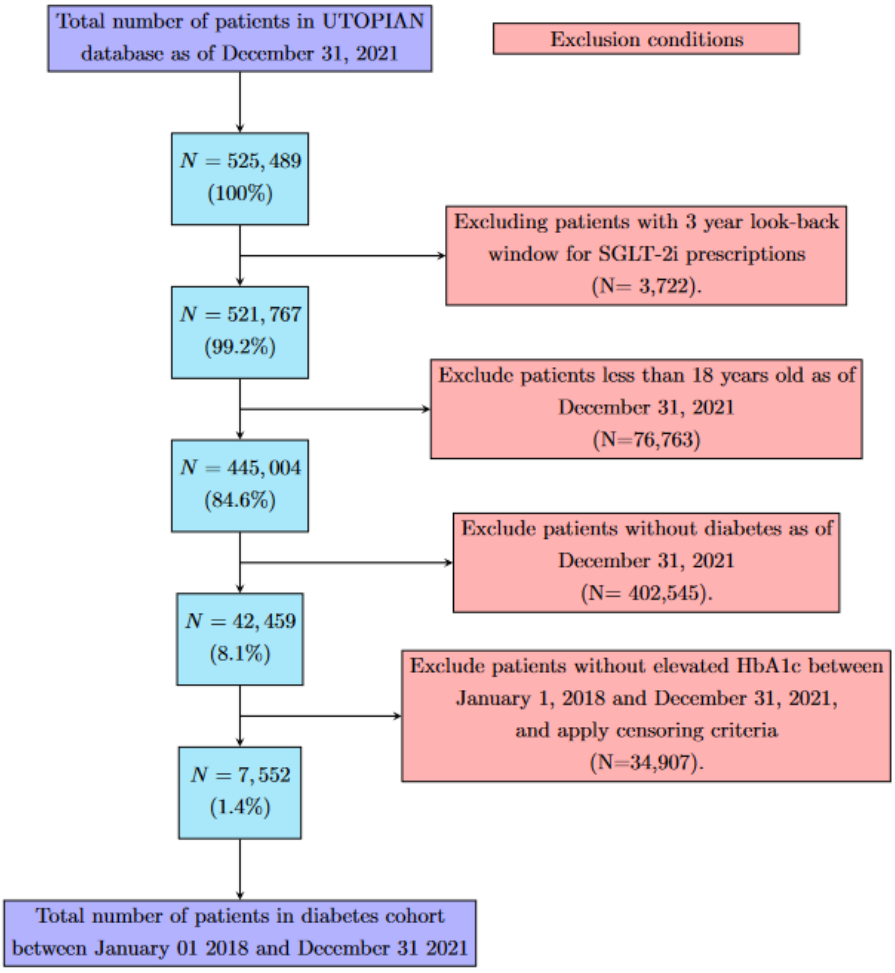

Figure 5: CONSORT diagram for the generation of longitudinal diabetes cohort (between January 01 2018 and December 31 2021) in the primary care repository of University of Toronto Practice Based Research Network (UTOPIAN).

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Table 3: Mean hemoglobin A1c with respect to co-morbidities and glucose lowering medications

Most recent Hemoglobin A1c (as of December 31, 2021)							
Patient characteristics	N patients	Column %	Mean	Median	Std*	Q1**	Q3**
Chronic Obstructive Pulmonary Disease							
No	7,081	93.8%	8.22	7.90	1.75	7.00	9.10
Yes	471	6.2%	8.30	7.90	1.72	7.00	9.20
Dementia							
No	7,092	93.9%	8.22	7.80	1.76	7.00	9.10
Yes	460	6.1%	8.28	8.10	1.65	7.10	9.20
Depression							
No	5,803	76.8%	8.20	7.80	1.74	7.00	9.00
Yes	1,749	23.2%	8.29	8.00	1.77	7.00	9.30
Dyslipidemia							
No	2,195	29.1%	8.29	8.00	1.75	7.10	9.20
Yes	5,357	70.9%	8.19	7.80	1.75	6.90	9.10
Epilepsy							
No	7,453	98.7%	8.22	7.90	1.75	7.00	9.10
Yes	99	1.3%	8.40	8.10	1.82	7.00	9.53
Hypertension							
No	3,532	46.8%	8.36	8.00	1.84	7.00	9.30
Yes	4,020	53.2%	8.11	7.80	1.66	6.96	8.90
Osteoarthritis							
No	5,654	74.9%	8.27	7.90	1.79	7.00	9.20
Yes	1,898	25.1%	8.08	7.80	1.63	6.95	8.85
Parkinson							
No	7,493	99.2%	8.23	7.90	1.75	7.00	9.10
Yes	59	0.8%	7.95	7.70	1.42	7.00	8.60
Chronic kidney disease							
No	5,535	73.3%	8.27	7.90	1.81	6.90	9.20
Yes	2,017	26.7%	8.09	7.80	1.57	7.00	8.80
Dipeptidyl Peptidase-4 inhibitor							
No	6,199	82.1%	8.18	7.80	1.73	6.90	9.10
Yes	1,353	17.9%	8.42	8.00	1.83	7.10	9.30
Glucagon-like Peptide 1 receptor agonists							
No	7,127	94.4%	8.21	7.90	1.74	7.00	9.10
Yes	425	5.6%	8.39	8.10	1.84	7.00	9.30
Sulfonylurea							
No	6,662	88.2%	8.18	7.80	1.74	6.90	9.00
Yes	890	11.8%	8.58	8.20	1.80	7.30	9.50
Insulin							
No	6,700	88.7%	8.12	7.80	1.70	6.90	8.90
Yes	852	11.3%	9.00	8.70	1.95	7.60	10.05
Metformin							
No	5,144	68.1%	8.17	7.80	1.69	7.00	9.00
Yes	2,408	31.9%	8.33	7.90	1.86	6.90	9.30
Total	7,552	100.0%	8.22	7.90	1.75	7.00	9.10

*standard deviation; **Q1=1st quartile; Q3=3rd quartile

† SGLT-2i = Sodium-Glucose co-Transporter 2 Inhibitor

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