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Five comparative cohorts to assess the risk of genital tract infections associated with sodium-glucose cotransporter-2 inhibitors initiation in type 2 diabetes mellitus

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Abstract

Aim: To assess the association between SGLT-2 inhibitors initiation and genital tract infections (GTIs) among patients with type 2 diabetes.

Methods: A population-based cohort study using administrative healthcare data from Alberta, Canada, and primary care data from the UK's Clinical Practice Research Datalink (CPRD). Among new metformin users, we identified new users of SGLT-2 inhibitors and five active comparator cohorts (new users of dipeptidyl peptidase-4 (DPP-4) inhibitors, sulfonylureas (SU), glucagon-like peptide-1 receptor agonists (GLP-1 RA), thiazolidinediones (TZD) and insulin). The outcome of interest was a composite GTI outcome. In each cohort, we used high-dimensional propensity score matching to adjust for confounding and conditional Cox proportional hazards regression to estimate the hazard ratios (HR). We used random-effects meta-analysis to combine aggregate data across databases.

Results: The risk of GTI was higher for SGLT-2 inhibitors users compared with DPP4inhibitor users (pooled HR 2.68, 95% CI 2.19 3.28), SU users (3.29, 2.62–4.13), GLP1-RA users (2.51, 1.90–3.31), TZD users (4.17, 2.46–7.08) and insulin users (1.86, 1.27–2.73).

Conclusion: In five comparative cohorts, SGLT-2 inhibitors initiation is associated with a higher risk of GTIs. These findings from real-world data are consistent with placebo-controlled randomized controlled trials.

KEYWORDS

SGLT-2 Inhibitors, Genital tract infections, Cohort, Comparative safety

1 | INTRODUCTION

The sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a class of antihyperglycaemic agents that lower blood glucose in a novel insulin-independent mechanism.[1] Specifically, SGLT-2 inhibitors work by preventing glucose reabsorption and facilitating its excretion in urine by inhibiting the SGLT-2 proteins in the proximal

convoluted tubule in the kidneys.[1] These co-transporters are responsible for glucose reabsorption and inhibiting them has been proven to be an effective approach for glycaemic control.[2,3] This unique mechanism of action that complements existing antihyperglycaemic agents, in addition to their protective role in cardiovascular disease, chronic kidney disease and heart failure, placed SGLT-2 inhibitors in a favoured position in the newest clinical diabetes guidelines.[4,5] However, the induced glucosuria can increase susceptibility to additional growth of commensal genital microorganisms and increase the risk of genital tract infections (GTIs).[6-8] Thus, SGLT-2 inhibitors are hypothesized to aggravate an existing high risk of genital infections associated with diabetes, wherein those with diabetes were found to be more likely to experience infections compared to those without diabetes.[9]

Four SGLT-2 inhibitor agents have been approved in both the United Kingdom and Canada: canagliflozin, dapagliflozin, empagliflozin and ertugliflozin. After their approval, signals from post-marketing case reports indicated a potential increased risk of genital infections after SGLT-2 inhibitor initiation, some of which were considered serious, such as Fournier's gangrene.[10,11] Eventually, the Food and Drug administration (FDA) issued a safety warning concerning the reoccurrence of serious genital infections associated with SGLT-2 inhibitors.[12] Data from several randomized controlled trials (RCTs) and systematic reviews support such findings.[13-15] Specifically, large RCTs have found between a 3- to 5-fold increase in risk of GTIs.[13-15] Additionally, several observational studies using a variety of data sources, GTI definitions, and exposure contrasts have supported an increased risk associated with SGLT-2 inhibitors,[16-24] albeit only one of which used Canadian data and was limited to those 65 years and older.[18]Moreover, several of these studies did not have a comparator group[21-23] were limited to specific or small populations[18,20,22] and follow-up periods of 6 months or less.[18,20,24]

Therefore, the aim of this study is to provide additional population based real-world evidence on the risk of GTI associated with the initiation of SGLT-2 inhibitors compared with clinically relevant active comparators.

Novelty Statement:

- In five comparative cohorts, new use of SGLT-2 inhibitors was associated with two to four times higher risk of genital tract infections compared with other classes of antihyperglycemic classes.
- In three stratified analyses, findings show that all SGLT-2 inhibitor agents (canagliflozin, dapagliflozin and empagliflozin) were associated with an increased risk of genital tract infections compared to DPP-4 inhibitors.
- There was no evidence of effect modification of the risk of SGLT-2 inhibitors on genital tract infections by age, sex, HbA1c level, or diabetes duration.
- These results were consistent across a range of sensitivity analyses.

2 | METHODS

2.1 | Study design, setting and population

This was a population-based cohort study using administrative healthcare data from Alberta, Canada, and primary care clinical data from the United Kingdom's Clinical Practice Research Datalink (CPRD) GOLD. Alberta's administrative databases contain data from healthcare system encounters for all Alberta residents (>4 million). The CPRD contains data collected from more than 950 primary care practices, providing a representative sample of about 5% of the UK population.[25-29] Data from both sources are de-identified individual-level longitudinal data that have been validated and used extensively for research.[26,27]

From these data sources, we identified a base cohort of new users of metformin monotherapy, between January 1, 2012 and March 30, 2018, in Alberta and January 1, 2005 and November 29, 2018, in CPRD. We defined new metformin use as first use without a prescription record for any antihyperglycaemic drug, including insulin, in the previous 365 days. Included users were adults (≥18 years) with at least 1 year of continuous data before the first metformin prescription.

2.2 | Exposure

From the new metformin users cohort, we identified the primary study cohort that included new users of an SGLT-2 or a dipeptidyl peptidase-4 (DPP-4) inhibitor between January 1, 2013, in the United Kingdom and May 1, 2014, in Canada (market entry date) and October 31, 2019, in CPRD and March 31, 2018, in Alberta (study end date). Dispensing records from Alberta and prescription records from CPRD were used to capture outpatient medication use. We defined index date as the date of initiation of SGLT-2 inhibitor or DPP-4 inhibitor and used an as-treated exposure definition. Specifically, person-time exposure began at the index date and exposure discontinuation was

calculated as the end date of the last SGLT-2 or DPP-4 inhibitor prescription plus a 30-day grace period. Gaps in therapy were allowed for our primary exposure definition. Other exposure definitions were considered in our sensitivity analyses.

Using the same base cohort and time period, we also identified four other secondary new user cohorts: SGLT-2 inhibitor versus sulfonylurea (SU) users; SGLT-2 inhibitor versus thiazolidinedione (TZD) users; SGLT-2 inhibitor versus glucagon-like peptide-1 receptor agonist (GLP1-RA) users, and SGLT-2 inhibitor versus insulin users.

For our main analysis, we excluded users with a high risk of GTI. Specifically, those with a previous hospitalization record of balanitis, vulvovaginal candidiasis, genital candidiasis, vulvovaginitis, vaginal thrush, bacterial vaginitis, vulvitis and vulval abscess, phimosis, paraphimosis and Fournier gangrene. We also excluded users with a history of regular oral corticosteroid use (>9 prescriptions in a 12-month period) regular antibiotic use (>9 prescriptions in a 12-month period) or any biologics or antirejection drug use, within 365 days before index date.

2.3 | Outcome

We used hospital, emergency department (Alberta only) and physician visit records to define a composite GTI outcome, which included any of balanitis, vulvovaginal candidiasis, genital candidiasis, vulvovaginitis, vaginal thrush, bacterial vaginitis, vulvitis, and vulval abscess, phimosis, paraphimosis and Fournier gangrene. We retrieved hospital-based diagnoses using International Classification of Diseases, 10th revision (ICD-10) codes and medical diagnoses using ICD-9 in Alberta and READ codes in CPRD. A detailed list of all diagnostic codes used is available in Table S1.

2.4 | Statistical analysis

First, we matched SGLT-2 inhibitor new users to an active comparator (i.e. DPP-4 inhibitors new users in the primary cohort) based on the logit of high-dimensional propensity scores (hd-ps) in a 1-to-1 nearest-neighbour greedy match.[30-32] The hd-ps was estimated by a multivariable logistic regression using variables derived from five dimensions (hospitalizations, procedures, medical diagnoses, prescription medication and laboratory records) during the year before index date. For the Alberta analysis, emergency department visits, were also added as a sixth dimension. From each dimension, the most prevalent 200 variables were identified, of which 500 were included in the final logistic model, along with several predefined variables, such as sex, age, year of cohort entry, prescription drug use, co-morbidities, laboratory values (HbA1c, eGFR, lipid levels), physiological (BMI in CPRD), lifestyle indicators (smoking status in CPRD) and socioeconomic status based on the index of multiple deprivation from CPRD only. We assessed balance of baseline covariates after matching using standardized differences with >10% considered as unbalanced.[33]

Second, we used standard descriptive statistics to compare the characteristics of new SGLT-2 inhibitor users with their matched comparator. Third, we followed patients from their exposure index date until the earliest of experiencing the outcome, switching from SGLT-2 inhibitor to comparator, switching from comparator to SGLT-2 inhibitor, death, or cohort end date. Fourth, we used a conditional Cox proportional hazards regression model, that is, stratified by matched pair, to compare risk of each outcome in the hd-ps matched cohort (matched model). Fifth, we further adjusted for age, sex, and the use of other antihyperglycaemic agents in the year prior to index date (matched adjusted model). Sixth, we added interaction terms between the exposure variable and age, sex, diabetes duration and A1C level, to assess for any effect modification. A p-value below 0.05 was considered statistically significant. Last, we used random effects model to meta-analyse aggregate data from each database.[34]

As a subgroup analysis, we stratified the primary cohort (SGLT-2 inhibitors matched to DPP-4 inhibitors) based on individual SGLT-2 inhibitor agents (canagliflozin, dapagliflozin and empagliflozin).

We conducted four types of sensitivity analyses to test the robustness of our findings. First, we reran our primary comparator analysis using different exposure definitions:(1) as-treated exposure definition, whereby exposure was stopped at a person's first gap with a gap being considered more than 30 days between the last day supply of the previous prescription; (2) intention to treat exposure definitions with a maximum follow-up of 180, 365 and 730 days; (3) time-varying exposure definition. Second, we reran our primary and secondary comparator analyses analysis using a restricted CPRD GOLD cohort of those eligible for Hospital Episodes Statistics (HES) and death certificate records through the Office of National Statistics (ONS) or HES/ONS linkage. (i.e. patients with hospital and death certificate records). Third, we repeated the main analysis for the primary and secondary cohorts without excluding those with a previous hospitalization record indicating a GTI or those who have used antibiotics or oral corticosteroids regularly or any biologics or anti-rejection medications within 365-days prior to index date. Fourth, we ran a Cox regression model for the primary and secondary cohorts without the hd-ps

matching approach. This model was adjusted for age, sex, diabetes duration, HbA1c and eGFR.

3 | RESULTS

3.1 | Study population

In the primary cohort (SGLT-2 vs. DPP-4 inhibitors users) we identified 7744 new SGLT-2 inhibitor users and 12,996 new DPP-4 inhibitor users in Alberta (Figure 1A) and 8032 new SGLT2 inhibitor users and 21,338 new DPP-4 inhibitor users in CPRD (Figure 1B) over the study period. Of those, we matched 7538 SGLT-2 inhibitor users in Alberta and 7471 in CPRD to DPP-4 inhibitor users. Matching resulted in two groups in both Alberta and CPRD that are well-balanced on baseline patient characteristics (Table 1). Flow diagrams of all secondary cohorts are reported in Figures S1–S4. Hd-ps matching resulted in balanced groups in the four secondary cohorts (Tables S2–S5).

3.2 | Incidence of genital tract infection

For the primary cohort in Alberta, the crude incidence rates (95% CI) per 1000 person-years of GTI in SGLT-2 inhibitor users was 33.39 (29.40, 37.77) versus 14.31 (12.48, 16.34) in DPP-4 inhibitor users. After hd-ps matching, there were 249 GTI events over a mean of 2.70 survival years in the SGLT-2 inhibitor group and 120 events over 3.12 years in the DPP-4 inhibitor group. The matched incidence rates (95% CI) per 1000 person-years of GTI were 33.58 (29.54, 38.02) for SGLT-2 inhibitors versus 16.42 (13.61, 19.33) for DPP-4 inhibitors.

For the primary cohort in CPRD, the crude incidence rates (95%CI) per 1000 person-years in SGLT2 users was 36.08 (32.70, 39.71) versus 11.19 (10.16, 12.30) in DPP-4

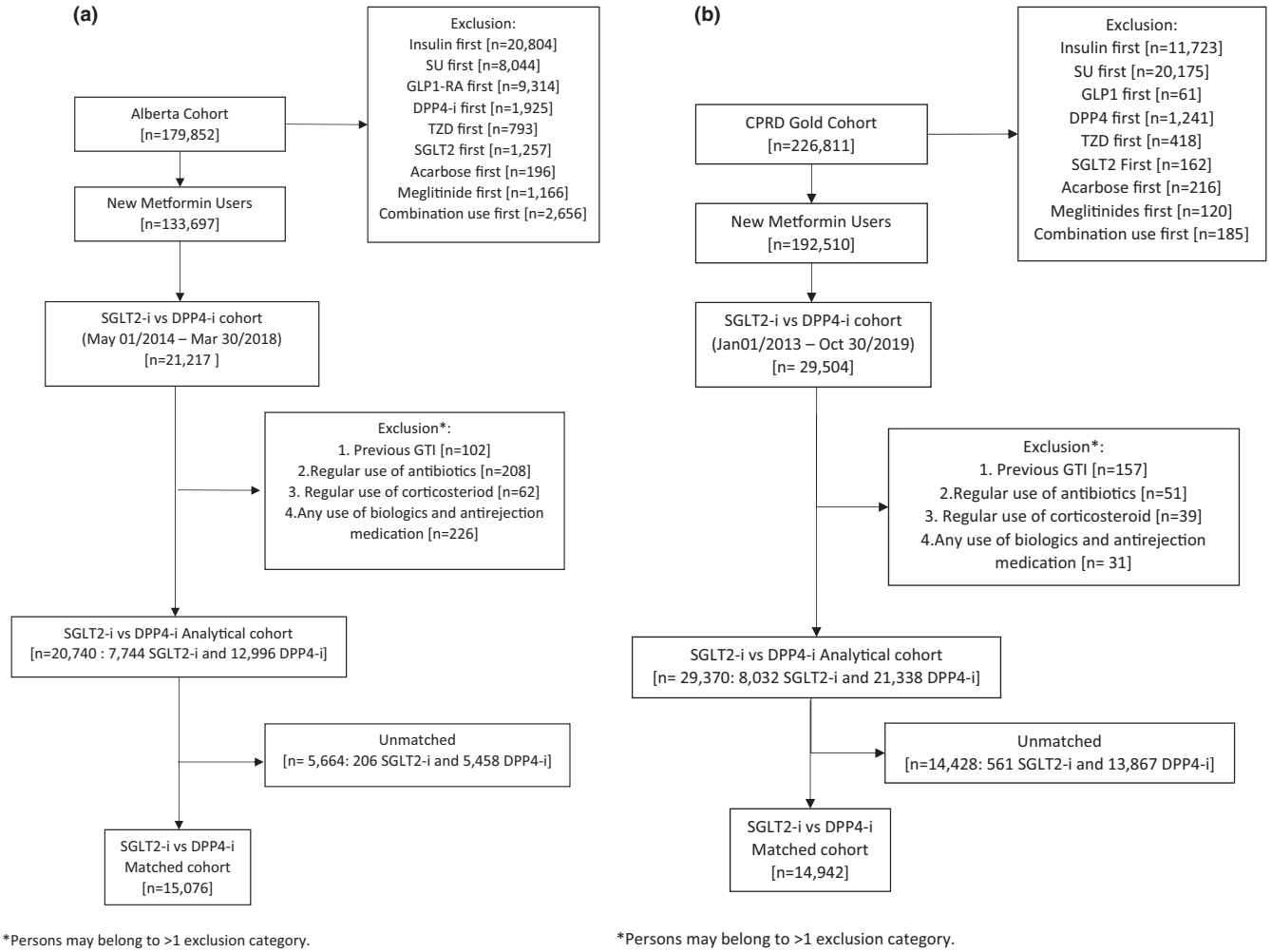

FIGURE 1 (a) Flow diagram to identify new users of sodium glucose co-transporter-2 inhibitor (SGLT2-i) inhibitors and dipeptidyl peptidase-4 inhibitor (DPP4-i) inhibitors in Alberta. (b) Flow diagram to identify new users of sodium glucose co-transporter-2 inhibitor (SGLT2-i) inhibitors and dipeptidyl peptidase-4 inhibitor (DPP4-i) inhibitors in Clinical Practice Research Datalink

inhibitor users. After hd-ps matching, there were 392 GTI events over a mean 4.59 survival years in the SGLT-2 inhibitor group and 141 events over 4.94 years in the DPP-4 inhibitor group. The matched incidence rates (95% CI) per 1000 person-years of GTI were 35.66 (32.22, 39.37) for SGLT-2 inhibitors vs 13.31 (11.20, 15.70) for DPP-4 inhibitors.

For all secondary cohorts, the crude and matched incidence rates of GTI are reported in Table 2.

3.3 | Risk of GTI in SGLT-2 inhibitors compared with other antihyperglycaemic classes

Compared with DPP-4 inhibitors, results summarized in Figure 2 show that SGLT-2 inhibitors were associated with an increase in the risk for GTI (pooled HR, 2.68 [CI, 2.19 to 3.28]). The risk of GTI in SGLT-2 inhibitor users remained significantly higher than DPP-4 inhibitor users after further adjustment for age, sex, and previous use of other antihyperglycemic agents (pooled HR, 2.60 [CI, 1.88 to 3.58]) (Figure 3). This increased risk was also observed after varying the exposure definition (Table 3). No evidence of effect modification by age (P-value for the interaction term in CPRD; Alberta were = (0.310; 0.491), sex (0.644; 0.900), HbA1c (0.990; 0.535) or diabetes duration (0.528; 0.392) were observed.

Our stratified analysis shows that all SGLT-2 inhibitor agents were significantly associated with an increased risk of GTI compared with DPP-4 inhibitors: canagliflozin (pooled HR, 3.99 [CI, 2.14 to 7.42]) and dapagliflozin (pooled HR, 2.40 [CI, 1.68 to 3.43]) and empagliflozin (pooled HR, 2.32 [CI, 0.97 to 5.57]), albeit the lower limit of the confidence interval for empagliflozin is marginally below 1.

Compared with other antihyperglycaemic comparators, Figure 2 shows that the risk of GTI was also significantly higher for the SGLT-2 inhibitor group in the SU cohort (pooled HR, 3.29 [CI, 2.62 to 4.13]), TZD cohort (pooled HR, 4.17 [CI, 2.46 to 7.08]), GLP1-RA cohort (pooled HR, 2.51 [CI, 1.90 to 3.31]) and insulin cohort (pooled HR, 1.86 [CI, 1.27 to 2.73]). The overall associations for most cohorts were not affected by further adjustments of age, sex and previous use of other antihyperglycaemic agents (Figure 3).

Compared with all comparators, results did not differ when we restricted the CPRD GOLD cohort to those eligible for HES/ONS linkage, albeit with wider confidence intervals in the CPRD analysis due to the smaller population (Figure 4). Similarly, the inclusion of those with a history of GTI, chronic use of corticosteroids or antibiotics or any use of biologics/antirejection medications led to similar overall results (Figure S5). Lastly, the use of a more simplified Cox model also showed a higher risk of GTI associated with SGLT-2 inhibitors used in all comparator cohorts; however, with slightly lower estimates compared with the hd-ps matched model (Figure S6).

4 | DISCUSSION

We examined the GTI risk associated with the initiation of SGLT-2 inhibitors among metformin new users in Alberta and the United Kingdom, compared with five clinically relevant active comparators. Our analysis shows that the initiation of SGLT-2 inhibitors is associated with an increased risk of GTI compared with DPP-4 inhibitors, SU, TZD, GLP1-RA and insulin across two databases.

Our analysis suggests a potential for intra-class variability in risk across agents, wherein the point estimate for dapagliflozin was slightly lower compared with canagliflozin. The estimate for empagliflozin was the lowest and did not reach statistical significance, albeit with a lower confidence limit marginally less than 1. Risk differences among the SGLT-2 inhibitor agents have been reported in a systematic review and meta-analysis of RCTs, wherein a subgroup analysis by type of individual SGLT-2 inhibitors showed a statistically significant difference in GTIs (relative risk [95%CI] 4.45 [3.49, 5.67] for canagliflozin; 3.22 [1.95, 5.32] for dapagliflozin; 3.14 [2.29, 4.30] for empagliflozin.[14]

Biological hypotheses indicate a possible effect modification by sex due to the activity of oestrogen on the vaginal mucosa in women of reproductive age or women using oral contraceptive or hormone replacement therapy , which can increase candida growth conditions, predisposing colonization and infection.[7,21] A cohort study found an increased risk of genitourinary infections associated with the use of SGLT-2 inhibitors compared with DPP-4 inhibitors in women.[21] This increased risk was predicted by younger age and oestrogen therapy.[21] However, our results did not support an effect modification by sex. This is consistent with evidence from RCTs[14] and another observational study.[18]

Our analysis is the first to use population-based Canadian data, without any age restrictions,[18] to assess the association between SGLT-2 inhibitors and a broad definition of GTIs. Furthermore, the use of primary care data from the UK allowed for further adjustment of physiological and life-style indicators, such as BMI and smoking. Further, this analysis differs from other observational studies in the availability of lab measurement data, which can capture unique proxies of confounding, such HbA1c, kidney function test, and lipid levels. Moreover, we have used a broad GTI definition that is

TABLE 1 Baseline characteristics of individuals included into the cohort of new users of SGLT2 inhibitors and DPP-4 inhibitors after high dimensional propensity score matching

	Alberta cohort					Clinical practice research datalink cohort				
	SGLT−2 inhibitor		DPP−4 inhibitor			SGLT−2 inhibitor		DPP−4 inhibitor		
	N, mean or median	% or SD	*N*, mean or median	% or SD	Standardized difference	*N*, mean or median	% or SD	*N*, mean or median	% or SD	Standardized difference
Number of individuals	7538	50.00	7538	50.00	0.00	7471	50.00	7471	50.00	0.00
Age at index date (years), mean (SD)	56.73	1.08	56.73	1.10	0.01	57.22	10.54	57.88	11.63	−0.06
Female, *n* (%)	2958	39.24	2939	38.99	0.01	3177	42.52	3121	41.77	0.02
Diabetes mellitus duration (years), mean (SD)	2.25	1.73	2.24	1.71	0.01	4.38	3.42	4.25	3.31	0.04
No. of distinct drugs in 100 days before index date, median (IQR)	4	5.00	4	4.00	0.00	7	6.00	7	6.00	0.00
No. of outpatient physician visits in year before index date, median (IQR)	12	15.00	12	15.00	0.00	18	14.00	18	14.00	0.00
Number of hospitalizations in year before index date, n (%)										
Zero	6874	91.19	6934	91.99	−0.03	7032	94.12	7036	94.18	<0.01
One	512	6.79	462	6.13	0.03	30	0.40	32	0.43	<0.01
Two	120	1.59	108	1.43	0.01	39	0.52	34	0.46	0.01
Three or more	32	0.42	34	0.45	0.00	370	4.95	369	4.94	<0.01
Calendar year of cohort entry date										
2013	NA	NA	NA	NA	NA	173	2.32	167	2.24	0.01
2014	158	2.10	150	1.99	0.01	635	8.50	702	9.40	−0.03
2015	1481	19.65	1540	20.43	−0.02	1079	14.44	1221	16.34	−0.05
2016	2412	32.00	2417	32.06	0.00	1343	17.98	1419	18.99	−0.03
2017	2693	35.73	2661	35.30	0.01	1567	20.97	1526	20.43	0.01
2018	794	10.53	770	10.21	0.01	1539	20.60	1453	19.45	0.03
2019	NA	NA	NA	NA	NA	1135	15.19	983	13.16	0.06
Comorbidities in year before index date, n(%)										

TABLE 1 (Continued)

	Alberta cohort					Clinical practice research datalink cohort				
	SGLT−2 inhibitor		DPP−4 inhibitor			SGLT−2 inhibitor		DPP−4 inhibitor		
	N, mean or median	% or SD	*N*, mean or median	% or SD	Standardized difference	*N*, mean or median	% or SD	*N*, mean or median	% or SD	Standardized difference
Acute myocardial infarction	79	1.05	75	0.99	0.01	45	0.60	44	0.59	<0.01
Stroke	103	1.37	96	1.27	0.01	32	0.43	36	0.48	−0.01
Dyslipidaemia	907	12.03	869	11.53	0.02	131	1.75	139	1.86	−0.01
Heart failure	131	1.74	106	1.41	0.03	53	0.71	53	0.71	0.00
Hypertension	3880	51.47	3844	50.99	0.01	1123	15.03	1157	15.49	−0.01
Chronic kidney disease	17	0.23	16	0.21	0.00	27	0.36	27	0.36	<0.01
Use of medications in year before index date, n(%)										
Metformin	6732	89.31	6622	87.85	0.05	7022	93.99	6944	92.95	0.04
Acarbose	7	0.09	11	0.15	−0.02	[a]	0.04	[a]	0.05	−0.01
GLP1-RA	379	5.03	143	1.90	0.17	543	7.27	86	1.15	0.31
TZD	34	0.45	47	0.62	−0.02	329	4.40	235	3.15	0.07
Insulin	664	8.81	374	4.96	0.15	398	5.33	105	1.41	0.22
Meglitinides	221	2.93	230	3.05	−0.01	7	0.09	[a]	0.05	0.01
SU	1793	23.79	2050	27.20	−0.08	2249	30.10	2520	33.73	−0.08
ACE inhibitors	2640	35.02	2604	34.54	0.01	3174	42.48	3196	42.78	−0.01
ARBs	1681	22.30	1650	21.89	0.01	1096	14.67	1093	14.63	<0.01
Statins	3873	51.38	3830	50.81	0.01	5246	70.22	5310	71.07	−0.02
Loop diuretics	303	4.02	290	3.85	0.01	482	6.45	512	6.85	−0.02
Thiazide diuretics	565	7.50	546	7.24	0.01	1082	14.48	1101	14.74	−0.01
Beta blockers	1133	15.03	1088	14.43	0.02	1575	21.08	1579	21.14	<0.01
CCB	1182	15.68	1189	15.77	0.00	1976	26.45	2005	26.84	−0.01
Other antihypertensives	78	1.03	78	1.03	0.00	407	5.45	405	5.42	<0.01

[a]suppressed number < 5.

TABLE 2 Crude and matched incidence rate (IR) and 95% confidence intervals (95%CI) per 1,000 person-years of genital tract infection

	Alberta cohort				Clinical practice research datalink cohort			
	Crude estimates		Matched estimates		Crude estimates		Matched estimates	
Exposure cohort	IR	95% CI	IR	95% CI	IR	95% CI	IR	95% CI
SGLT-2 inhibitors	33.39	29.40–37.77	33.58	29.54–38.02	36.08	32.70 – 39.71	35.66	32.27 – 39.37
DPP-4 inhibitors	14.21	12.48–16.34	16.42	13.61–19.33	11.19	10.16 – 12.30	13.31	11.21 – 15.70
SGLT-2 inhibitors	33.42	29.54–37.67	32.40	28.46–36.74	36.81	33.48 – 40.38	33.67	30.23 – 37.39
SU	15.38	13.65–17.27	13.30	10.78–16.25	10.70	9.70 – 11.77	11.73	9.75 – 13.99
SGLT-2 inhibitors	34.10	30.95–37.48	31.17	18.47–49.26	35.40	33.03 – 37.90	29.50	23.95 – 35.96
TZD	16.92	7.31–33.35	11.23	3.65–26.21	10.16	7.04 – 14.20	9.45	6.17 – 13.85
SGLT-2 inhibitors	32.05	28.85–35.50	41.29	34.35–49.23	34.54	32.19 – 37.02	37.50	31.90 – 43.80
GLP1-RA	20.67	15.95–26.34	18.88	13.87–25.10	16.58	12.90 – 20.98	15.83	12.02 – 20.47
SGLT-2 inhibitors	32.37	29.09–35.96	33.14	28.25–38.63	26.77	25.03 – 28.60	27.16	23.86 – 30.79
Insulin	22.69	19.56–26.18	20.50	16.85–24.70	17.13	14.91 – 19.60	14.89	14.13 – 18.09

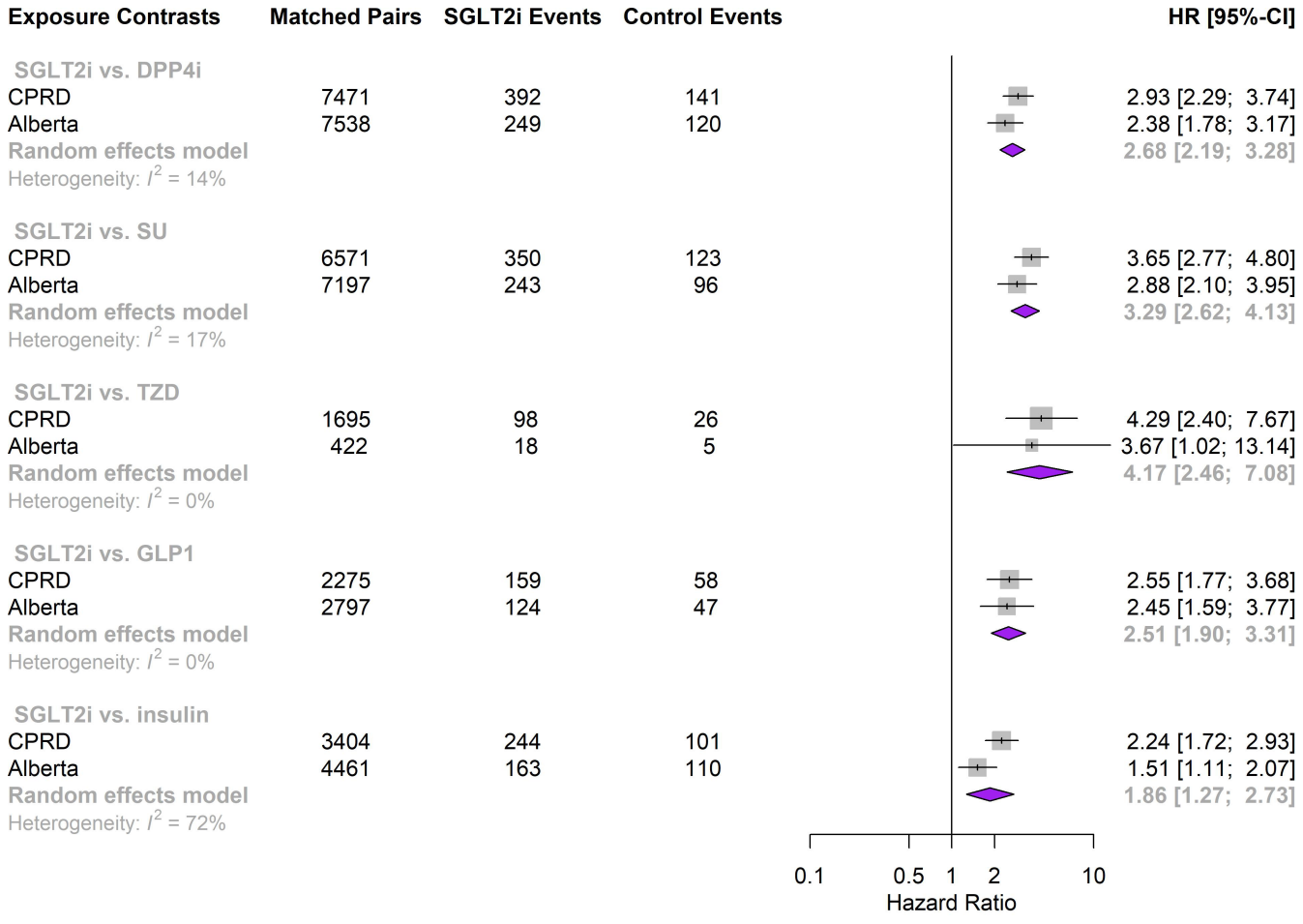

FIGURE 2 Pooled hazard ratio for genital tract infections across databases, using matched only Cox model without further adjustments. Abbreviations: DPP4-i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones; GLP1, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; CI, confidence interval

not restricted to severe infections leading to hospital admission. Although the primary exposure contrast of SGLT-2 inhibitor versus DPP-4 inhibitor has been used in other observational studies,[16-18] this analysis provides estimates using four other antihyperglycaemic agents. The twofold increase in the risk of GTI associated with

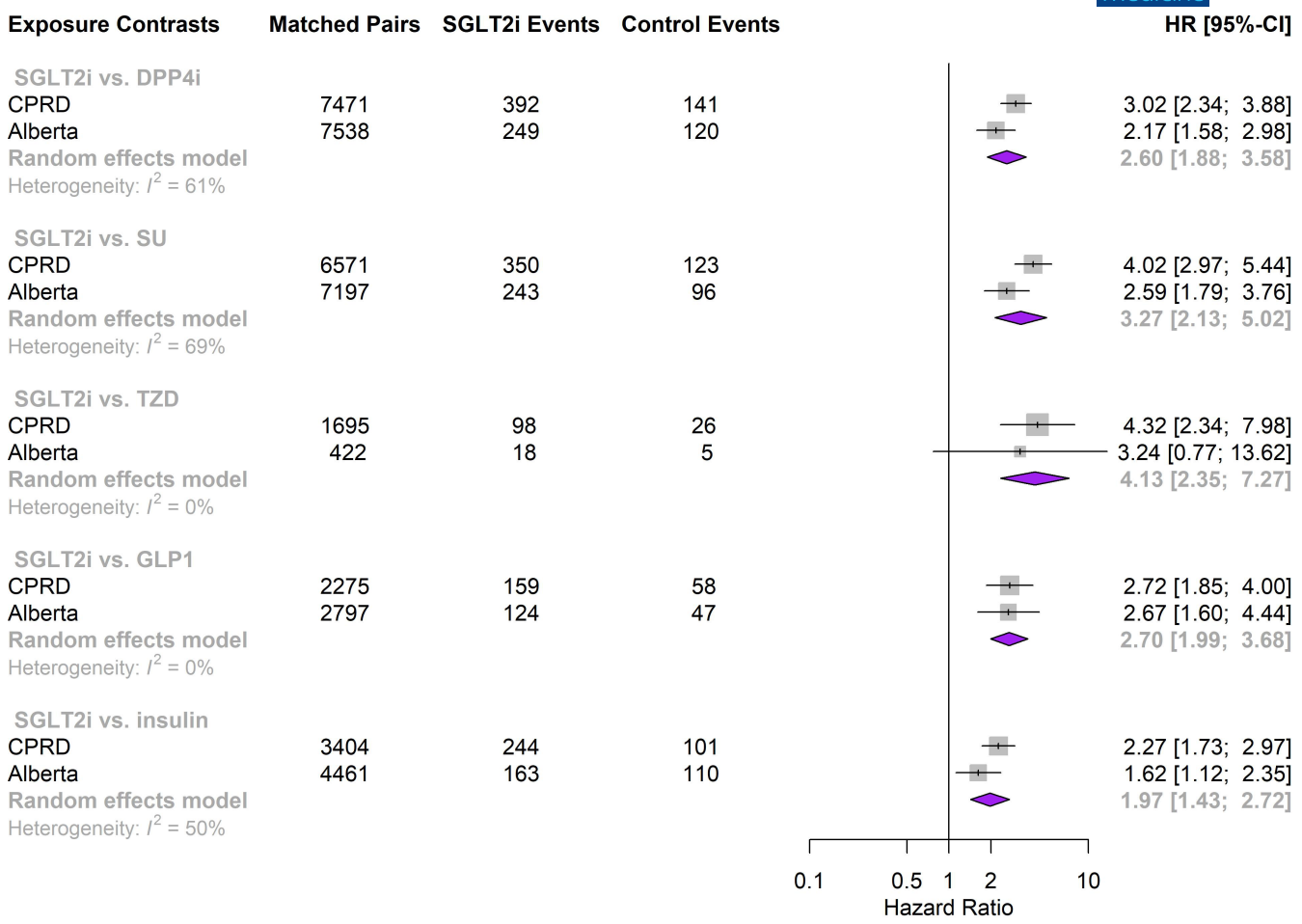

FIGURE 3 Pooled hazard ratio for genital tract infections across databases, using matched Cox model with further adjustment for age, sex and previous use of other diabetes medications. Abbreviations: DPP4-i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium glucose co-transporter-2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones; GLP1, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; CI, confidence interval

TABLE 3 Random effects pooled hazard ratios for genital tract infection among SGLT-2 inhibitor users compared with DPP-4 inhibitor users, using matched only Cox model without further adjustment and Cox model adjusted for age, sex and use of other diabetes medications, after varying the exposure definition

	Matched only		Adjusted	
Exposure definition	**Pooled HR**	**95% CI**	**Pooled HR**	**95% CI**
As-treated exposure definition without allowing any gaps in exposure	2.97	2.23–3.96	2.89	1.90–4.40
Intention to treat exposure definitions with a maximum follow-up of 180 days	2.82	1.97–4.03	2.74	1.77–4.24
Intention to treat exposure definitions with a maximum follow-up of 365 days	2.58	1.91–3.50	2.58	1.84–3.63
Intention to treat exposure definitions with a maximum follow-up of 730 days	2.49	2.05–3.04	2.45	1.89–3.19
Time-varying exposure definition	2.87	2.38–3.46	2.64	1.99–3.52

the use of SGLT-2 inhibitors compared with DPP-4 inhibitors observed in our analysis is consistent with results from previous observational studies, wherein the risk estimates ranged between a two- to threefold increased risk.[16-18] This not only complements the already existing evidence but also provides clinicians with additional safety data regarding GTI compared with other clinically relevant active comparators.

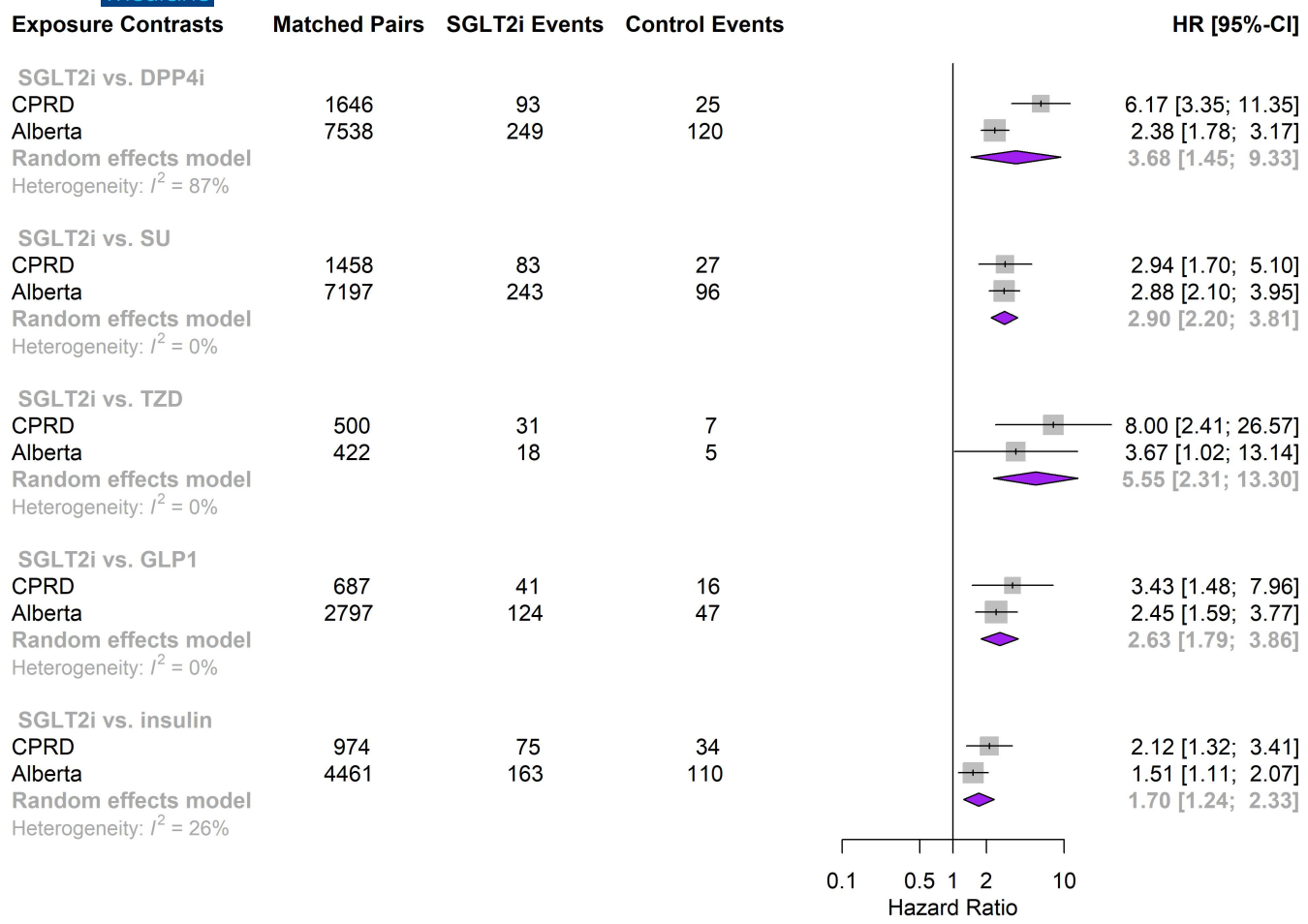

FIGURE 4 Pooled hazard ratio for genital tract infections across databases, using matched only Cox model without further adjustments using the HES/ONS linked population in Clinical Practice Research Datalink. Abbreviations: DPP4-i, Dipeptidyl peptidase-4 inhibitor; SGLT2i, Sodium glucose co-transporter-2 inhibitor; SU, Sulfonylurea; TZD, Thiazolidinediones; GLP1, Glucagon-Like Peptide 1 Receptor Agonist; HR, Hazard ratio; CI, confidence interval

Although this study supports existing evidence of increased GTI risk among SGLT-2 inhibitors, it has limitations. Misclassification of drug exposure that was based on prescription (CPRD) and dispensing (AB) records is possible. Misclassification of the outcome is also possible since the outcome definition used has not been validated in either Alberta or CPRD, albeit the diagnostic codes were used in existing literature. Nevertheless, the use of READ codes in CPRD can possibly impact the ability to optimally capture GTI events. Additionally, self-managed GTIs wherein medical care was not sought are not captured. However, if present these non-differential misclassifications of the exposure or the outcome would bias results toward the null. The influence of unmeasured confounding cannot be ruled out, despite our restrictive active comparator new user design among new users of metformin and high dimensional propensity score matching. Lastly, our study had limited power to detect a narrow definition of GTI based on hospitalizations only. Future analysis using larger data sets to explore the stratified risk of each type of GTI as well as the potential impact on antibiotic use will be useful.

5 | CONCLUSIONS

Using real-world data from two sources, we found an increased risk of GTI associated with the initiation of SGLT-2 inhibitors compared to DPP-4 inhibitors, SU, TZD, GLP1-RA and insulin initiation. Minimal intraclass variation in the magnitude of the increased risk was observed with the initiation of different SGLT-2 agents. These findings from real world data are consistent with those from placebo-controlled RCTs.

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as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. Copyright © (2021), re-used with the permission of The Health & Social Care Information Centre. All rights reserved. The OPCS Classification of Interventions and Procedures, codes, terms and text is Crown copyright (2016) published by Health and Social Care Information Centre, also known as NHS Digital and licensed under the Open Government Licence available at www.nationalarchives.gov.uk/doc/open-government-licence/open-government-licence.htm". This study is based on data provided by The Alberta Strategy for Patient Orientated Research (ABSPOR) SUPPORT unit, Alberta Health, and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta, Alberta Health Services, nor ABSPOR. Neither the Government of Alberta, Alberta Health Services, nor ABSPOR expresses any opinion in relation to this study. The data that support the findings of this study are available from the ABSPOR (https://absporu.ca). We had full permission to use these data, however, restrictions apply to the public availability of these data, which are under data access agreements for the current study.

CONFLICT OF INTEREST

None to declare.

AUTHOR CONTRIBUTIONS

JMG, DTE and AZ conceived the study idea, and all authors contributed to the study design. WA and JMS conducted all analyses. WA and JMG wrote the first draft of the manuscript. All authors contributed to and approved the final version of the article. JMG affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

ETHICS APPROVAL

The study protocol was approved by the University of Alberta's Human Research Ethics Board (#84111), University of Waterloo's Research Ethics Board (#31928) and the CPRD's Independent Scientific Advisory Committee (ISAC 18_205).

DATA SHARING

No additional data available.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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