Sodium-glucose cotransporter-2 inhibitors and risk of autoimmune rheumatic diseases: population based cohort study

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ABSTRACT

OBJECTIVE

To evaluate the use of sodium-glucose cotransporter-2 (SGLT-2) inhibitors and risk of autoimmune rheumatic diseases in adults with type 2 diabetes.

DESIGN

Retrospective cohort study.

SETTING

Nationwide healthcare database in South Korea, 2012-22.

PARTICIPANTS

2 032 157 adults aged ≥18 years with type 2 diabetes: 552 065 initiated SGLT-2 inhibitors and 1 480 092 initiated sulfonylureas.

MAIN OUTCOME MEASURES

The primary outcome was autoimmune rheumatic disease, defined using a validated algorithm incorporating diagnostic codes and registration in a disease specific nationwide programme. Secondary outcomes were individual types of autoimmune rheumatic diseases, including inflammatory arthritis and connective tissue diseases. Genital infections and herpes zoster were used as positive and negative control outcomes, respectively, to evaluate residual confounding. Hazard ratios and rate differences per 100 000 person years were estimated after normalised inverse probability treatment weighting based on propensity score.

RESULTS

After propensity score weighting, 1 030 088 initiators of SGLT-2 inhibitors (mean age 58.5 years; 59.9% men) and 1 002 069 initiators of sulfonylurea (mean age 58.5 years; 60.1% men) were included in the analysis. The weighted incidence rate per 100 000 person years was 51.90 and 58.41 in individuals initiating SGLT-2 inhibitors and sulfonylureas, respectively. Over a median of nine months' follow-up, SGLT-2 inhibitors were associated with an 11% lower risk of incident autoimmune rheumatic diseases compared with sulfonylureas (hazard ratio 0.89 (95% confidence interval (CI) 0.81 to 0.98); risk difference −6.50 (95% CI −11.86 to −1.14) per 100 000 person years). Findings were overall consistent among subgroups stratified by age, sex, type of SGLT-2 inhibitor, baseline cardiovascular disease, and obesity status. The hazard ratios for the control outcomes were 2.78 (2.72 to 2.83) for genital infections and 1.03 (1.01 to 1.05) for herpes zoster.

CONCLUSIONS

In this large cohort of adults with type 2 diabetes, SGLT-2 inhibitors were associated with an 11% lower risk of autoimmune rheumatic diseases compared with sulfonylureas. These results suggest that SGLT-2 inhibitors may contribute to reducing the risk of autoimmune diseases. This potential benefit, however, should be carefully weighed against known adverse events and concerns about tolerability. Replication in other populations and settings, as well as studies in patients with existing autoimmune rheumatic diseases, are warranted to confirm and extend these observations.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are considered one of the drug repurposing candidates for autoimmune diseases owing to their potential immunomodulatory properties

Whether the inhibitory effects of SGLT-2 inhibitors on critical cells and molecules in the development pathway, which are implicated in autoimmune pathogenesis, is clinically meaningful, remain unclear

WHAT THIS STUDY ADDS

In this large cohort of adults with type 2 diabetes, SGLT-2 inhibitors were associated with an 11% lower risk of autoimmune rheumatic diseases compared with sulfonylureas

Benefits were consistent among demographic and clinical subgroups, and among individual types of SGLT-2 inhibitors

Replication in other populations and settings, as well as studies in patients with existing autoimmune rheumatic diseases, are warranted to confirm and extend these observations

Introduction

Autoimmune rheumatic diseases represent a heterogeneous group of disorders characterised by chronic systemic inflammation primarily affecting the musculoskeletal system.[1] Diseases include disorders such as rheumatoid arthritis, psoriatic arthritis, spondyloarthritis, systemic lupus erythematosus, systemic sclerosis, and systemic vasculitis. Autoimmune rheumatic diseases affect more than 7% of the global population and are associated with substantial morbidity and mortality.[2 3] Since the early 2000s, although therapeutic advancements such as the development of biologics have substantially improved the prognosis of these conditions, challenges such as suboptimal responses for certain autoimmune rheumatic diseases and high treatment costs of biological agents highlight the need for the identification of alternative disease modifying treatments.[4-8]

Sodium-glucose cotransporter-2 (SGLT-2) inhibitors, such as dapagliflozin, empagliflozin, and canagliflozin, are a class of oral antidiabetic drugs that exerts hypoglycaemic effects by lowering the renal glucose excretion threshold, subsequently inhibiting renal glucose reabsorption. Evidence from large

scale randomised clinical trials has shown marked cardiovascular and kidney benefits of SGLT-2 inhibitors in addition to improving glycaemic control.[9] SGLT-2 inhibitors are now also considered one of the drug repurposing candidates for autoimmune diseases owing to their immunomodulatory properties, including reduction in pro-inflammatory markers, modulation of immune cell activity, and improvement in oxidative stress.[10-12] Preclinical studies have shown that dapagliflozin and empagliflozin can inhibit the accumulation of T cells and B cells and reduce the levels of key proinflammatory cytokines such as tumour necrosis factor alpha and interleukin 6.[13-18] In addition, in a previous clinical trial among patients with type 2 diabetes, treatment with empagliflozin for six months was shown to suppress T cell proliferation and production of interleukin 17.[19] However, whether the inhibitory effects of SGLT-2 inhibitors on critical cells and molecules in the development pathway, which are implicated in autoimmune pathogenesis, are clinically meaningful, remain unclear. Therefore, we conducted a large, population based cohort study to assess the association between use of SGLT-2 inhibitors and risk of autoimmune rheumatic diseases in adults with type 2 diabetes, leveraging a representative nationwide database of South Korea.

Methods

Study design and data source

In this active comparator, new user cohort study, we used the National Health Insurance Service-National Health Insurance Database from 2012 to 2022, which covers 98% of people in South Korea (data No NHIS-2025-04-1-020). This database provides deidentified individual level personal information and healthcare data collected from all medical institutions, including records of diagnoses using ICD-10 (international classification of diseases, 10th revision, clinical modification) codes, information on prescriptions (including name of drug, dose, route of administration, prescribed date, and days of supply), and procedures obtained from various healthcare settings (ie, inpatient, outpatient, and emergency department visits). The database also includes information on test results and lifestyle questionnaires (eg, alcohol intake and smoking status), which are collected through a government funded medical screening service. Mortality data, including information on date and cause of death, were available by linking with Statistics Korea. The study protocol has been registered and is publicly accessible through the Open Science Framework platform at https://osf.io/gaz4k.

Study population and drug use

We included adults (≥18 years) with a diagnosis of type 2 diabetes who received an SGLT-2 inhibitor or a sulfonylurea between 1 September 2014 (ie, the first date of reimbursement for SGLT-2 inhibitors in South Korea) and 31 December 2022. The index date was defined as the first date of administration of the SGLT-2 inhibitor or sulfonylurea. We chose sulfonylureas as comparator drugs because they are the most used second line oral glucose lowering agents in patients with similar stage of disease using SGLT-2 inhibitors and they share the same reimbursement criteria (see supplementary note 1). Additionally, sulfonylureas were not reported to be associated with autoimmune rheumatic disease; in contrast, other potential comparators, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and thiazolidinediones have been suggested to lower the risk.[20-24] We excluded people if they were younger than 18 years; had kidney failure,[25] which is contraindicated for the drugs of interest, within one year preceding the index date; had been prescribed the study drugs simultaneously on the index date; had been prescribed the study drugs within one year preceding the index date to ensure they are new users of study drugs; and had a diagnosis of any of the autoimmune rheumatic diseases any time before the index date. Supplementary table 1 provides detailed definitions of inclusion and exclusion criteria.

Outcome and follow-up

The primary outcome was autoimmune rheumatic diseases, identified using ICD-10 diagnosis codes along with the registration in the rare intractable disease registration (RIDR) programme (see supplementary table 2 for definitions). The South Korean government launched the RIDR programme in 2009 to provide additional financial support for patients with rare and intractable disease. Patients registered in the programme pay only 10% of their total medical costs, but to register, an official documentation is required from a doctor that includes an overall clinical assessment of the patient, including tests, radiological examinations, or biopsies according to established diagnostic criteria. Owing to high accuracy of diagnoses in the RIDR programme, they are considered reference standards in many validation studies.[26 27]

The secondary outcomes were inflammatory arthritis and connective tissue diseases.[28 29] We defined inflammatory arthritis as a composite of rheumatoid arthritis, psoriatic arthritis, or spondyloarthritis, and connective tissue diseases included systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis, polymyalgia rheumatica, mixed connective tissue disease, dermatomyositis/polymyositis, polyarteritis nodosa, and vasculitis.

Patients were followed under an as treated approach, from the index date until the earliest of occurrence of the outcomes of interest, discontinuation of the study drug, or at the time of initiation of the comparator drug, death, or end of study period (31 December 2022). We considered patients to have continued treatment if they had a prescription within 60 days of the expiration of the supply at the last fill.

Confounders

We considered a wide range of potential confounders at the index date or during the 365 days before the index date (see supplementary figure 1 for directed acyclic graph). Age, sex, income level, and calendar

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period were evaluated on the index date. As a proxy for severity of diabetes, we assessed types and number of antidiabetic drugs used, the level of antidiabetic treatment, diabetic complications (ie, retinopathy, neuropathy, and nephropathy), and fasting blood glucose level. Antidiabetic treatment was classified into three levels: the first level was no antidiabetic drug, or treatment with only one non-insulin antidiabetic drug; the second level was treatment with two or more different classes of non-insulin antidiabetic drugs; and the third level was treatment with insulin either alone or in combination with other antidiabetic drugs. We considered the Charlson comorbidity index, other comorbidities, and use of drugs measured 365 days before the index date. Healthcare utilisation was measured, including the number of hospital admissions, outpatient visits during the past year, and visits to a doctor in the previous 30 days. The body mass index (BMI), alcohol intake, smoking status, and most recent test results, including blood pressure, serum total cholesterol level, and glomerular filtration rate, were also evaluated. If test results were missing, we classified the values as unknown to use missing indicator methods. Supplementary table 3 shows the specific definitions of each confounder. The causal structure underlying potential confounders is illustrated using a directed acyclic graph (see supplementary figure 1).

Statistical analysis

To estimate the average treatment effect, we used the normalised inverse probability of treatment weighting method to adjust for confounders.[30] The propensity score was estimated using a multivariable logistic regression model that incorporated all the covariates. Adults receiving SGLT-2 inhibitors were assigned a weight of 1/propensity score, and individuals receiving sulfonylureas were given a weight of 1/(1−propensity score). We then normalised the calculated weights by dividing each weight by the mean of the weights to mitigate potential numerical instability caused by extreme weights. This approach ensures that the average weight across study population was 1.0, indicating that, on average, each participant represented one person in the weighted population, thereby mitigating inflation. We used the missing indicator method for those who did not complete the health examination in the primary analyses.[31] No other data were missing. We evaluated the balance of covariates between the treatment groups before and after weighting using absolute standardised differences, with a value <0.1 considered as sufficient balance.[32] We reported weighted number of events, incidence rates, and risk differences per 100 000 person years with 95% confidence intervals (CIs), estimated hazard ratios with 95% CIs using the Cox proportional hazards regression model, and plotted Kaplan-Meier curves to visualise the cumulative incidence of outcomes during follow-up. All statistical analyses were conducted using SAS Enterprise Guide version 7.1 (SAS Institute). The supplementary appendix includes the analytical codes used in this study and they are also publicly available at https://github.com/SKKUPEPV/SGLT2i-AIRD.git.

Subgroup and sensitivity analyses

Subgroup analyses were stratified by baseline age (<65 or ≥65 years), sex, type of SGLT-2 inhibitor (dapagliflozin, empagliflozin, ipragliflozin, or ertugliflozin), history of cardiovascular disease (yes or no), BMI (<25.0 or ≥25.0), and calendar period (2014-19 or 2020-22). For each subgroup, we re-estimated the propensity score and reperformed weighting.

To test the robustness of our findings, we conducted several sensitivity analyses. Firstly, to assess the potential influence of informative censoring, we followed patients under an intention-to-treat approach for a maximum of two years, regardless of treatment discontinuation or switching to the comparator class. Secondly, instead of using inverse probability treatment weighting to estimate the average treatment effect, we adjusted confounders using the 1:2 greedy nearest neighbour propensity score matching method to estimate the average treatment effect on treated participants. Thirdly, to handle potential residual confounding from missing test results, we restricted participants to those with test results only. Fourthly, we considered patients to have continued treatment if they had a prescription within 30 days or 90 days after the expiration of the supply of the last fill, rather than 60 days. Fifthly, to account for the competing risk of death, the Fine and Gray's proportional sub-hazards model was used.[33] Sixthly, to better ensure comparability in treatment stage and reduce confounding by indication, we restricted participants to those who were taking metformin alone and no other antidiabetic drugs any time before the index date. Seventhly, to assess the potential impact of informative censoring, we conducted an analysis applying time varying inverse probability of censoring weights, which were estimated at 90 day intervals throughout the follow-up period. Eighthly, we incorporated the use of other classes of antidiabetic drugs as time varying confounders, assessed at 90 day intervals, to account for potential confounding. Inverse probability of censoring weights was applied in this analysis as well. Ninthly, to account for the potential inclusion of patients with pre-existing autoimmune rheumatic disease, we conducted an analysis applying a 90 day lag period. Finally, we employed a positive control outcome (genital infection) and negative control outcome (herpes zoster) to assess residual confounding. Both genital infection and herpes zoster share common unmeasured confounders, such as frailty, with autoimmune rheumatic disease, and SGLT-2 inhibitors were associated with an increased risk of genital infection but not with risk of herpes zoster.[34-37] Thus, a positive association between SGLT-2 inhibitors and risk of genital infections was expected compared with sulfonylureas, whereas no association was expected for risk of herpes zoster.

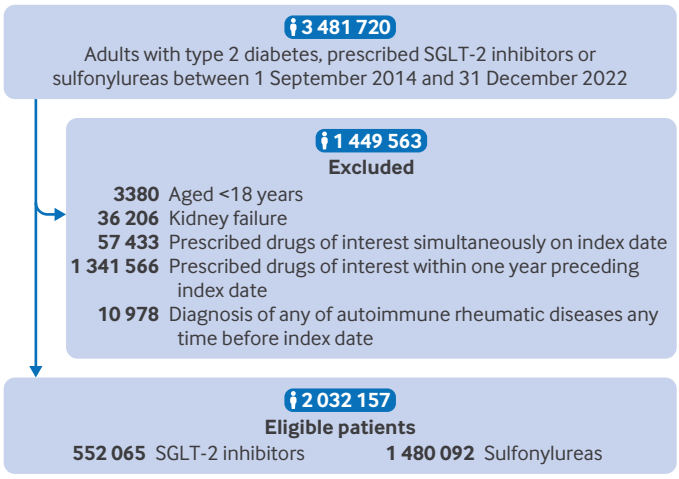

Fig 1 | Study flow chart. SGLT-2=sodium-glucose cotransporter-2

Exploratory analyses

We compared the incidence of autoimmune rheumatic diseases in new users of SGLT-2 inhibitors with those initiating other commonly prescribed second line or third line antidiabetic drug classes, including DPP-4 inhibitors, thiazolidinediones, and glucagon-like peptide-1 (GLP-1) receptor agonists, all of which showed potential immunomodulatory effects. The same inclusion and exclusion criteria, adjustment for confounders, and statistical methods were applied.

Patient and public involvement

No patients or members of the public were involved in the planning, design, or interpretation of the study. The dataset used was provided by the NHIS, a governmental institution in South Korea, and consisted of anonymised health information covering the entire national population. For security and confidentiality purposes, access to the data was restricted to authorised researchers, and direct involvement of patients or members of the public was not feasible. Furthermore, patient and public involvement was not a common practice in South Korea when we started the study. No funds or dedicated time was allocated for patient and public involvement activities. Nevertheless, the results of this study will be officially reported to the National Health Insurance Service.

Results

Baseline patient characteristics

Figure 1 shows the flow chart of the study cohort. We identified 552 065 new users of SGLT-2 inhibitors and 1 480 092 new users of sulfonylureas without a diagnosis of autoimmune rheumatic disease and with no use of study drugs at baseline. Before propensity score weighting, most baseline covariates, including diabetes complications, most comorbidities, use of other antidiabetic drugs, and healthcare utilisation were overall relatively well balanced, with an absolute standardised difference ≤0.1 (table 1). Some covariates, such as baseline use of other drugs, showed imbalance, with standardised differences >0.1, which were more prevalent among initiators of SGLT-2 inhibitors than among initiators of sulfonylureas (48.1% *v* 41.9% for angiotensin converting enzyme inhibitors or angiotensin receptor blockers, 59.2% *v* 50.2% for lipid lowering drugs, 6.8% *v* 4.2% for nitrates). After propensity score weighting, 1 030 088 initiators of SGLT-2 inhibitors and 1 002 069 initiators of sulfonylureas were included in the analysis (mean age 58.5 years, 60.0% male) (table 1). After propensity score weighting, baseline covariates, including diabetes complications, other comorbidities, concomitant use of other drugs, all test results (blood pressure, fasting blood glucose level, serum total cholesterol level, glomerular filtration rate), BMI, alcohol intake, and smoking status were well balanced. The most common antidiabetic agent used during the baseline period was metformin (64.4%), followed by DPP-4 inhibitors (49.1%). The most used type of SGLT-2 inhibitor was dapagliflozin (61.8%), followed by empagliflozin (31.9%) (see supplementary table 4). Supplementary table 5 and supplementary figure 2 show detailed distributions of the propensity score and corresponding weights, both before and after normalisation.

Risk of autoimmune rheumatic diseases

The median follow-up was 9.1 (interquartile range (IQR) 3.8-25.2) months for initiators of SGLT-2 inhibitors and 7.8 (3.1-23.5) months for initiators of sulfonylureas (see supplementary table 6 for distribution of reasons of censoring). The absolute incidence rates of autoimmune rheumatic disease were low in both treatment groups. A total of 790 and 840 adults with newly diagnosed autoimmune rheumatic disease were identified among initiators of SGLT-2 inhibitors and initiators of sulfonylureas, with incidence rates per 100 000 person years of 51.90 and 58.41, respectively. The corresponding risk difference per 100 000 person years was −6.50 (95% CI −11.86 to −1.14) and hazard ratio was 0.89 (0.81 to 0.98) (table 2). Cumulative incidence curves of autoimmune rheumatic disease for initiators of SGLT-2 inhibitors and sulfonylureas showed consistent results (fig 2). In analyses stratified on type of autoimmune rheumatic disease, the hazard ratio was 0.86 (0.77 to 0.97) for inflammatory arthritis and 0.95 (0.79 to 1.14) for connective tissue disease. Supplementary table 7 shows the risks of each specific autoimmune rheumatic disease comparing SGLT-2 inhibitors with sulfonylureas.

Subgroup analysis and sensitivity analyses

The lower risk of autoimmune rheumatic disease associated with SGLT-2 inhibitors was generally consistent across subgroups stratified by age, sex, type of SGLT-2 inhibitor, baseline cardiovascular disease, and BMI category (fig 3). Statistical significance was not, however, achieved for the subgroups with a relatively small number of outcomes (eg, those aged <65 years).

Most sensitivity analyses yielded point estimates and trends similar to those of the primary analysis,

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Table 1 | Baseline characteristics of adults with type 2 diabetes initiating SGLT-2 inhibitors and sulfonylureas. Values are number (percentage) unless stated otherwise

	Before propensity score weighting			After propensity score weighting		
Characteristics	SGLT-2 inhibitors (n=552 065)	Sulfonylureas (n=1 480 092)	Absolute standardised difference	SGLT-2 inhibitors (n=1 030 088)	Sulfonylureas (n=1 002 069)	Absolute standardised difference
Mean (SD) age (years)	55.1 (13.3)	60.0 (13.5)	0.365	58.5 (13.3)	58.5 (13.9)	0.003
Sex:						
Men	324 007 (58.7)	898 510 (60.7)	0.112	617 156 (59.9)	602 380 (60.1)	0.079
Women	228 058 (41.3)	581 582 (39.3)		412 931 (40.1)	399 690 (39.9)	
Income level:						
Low	195 895 (35.5)	566 889 (38.3)	0.065	389 811 (37.7)	376 845 (37.6)	0.001
Medium	207 988 (37.7)	549 011 (37.1)		384 591 (37.3)	373 696 (37.3)	
High	148 182 (26.8)	364 192 (24.6)		255 686 (24.8)	251 529 (25.1)	
Calendar year:						
2014	7018 (1.3)	72 590 (4.9)	0.647	49 970 (4.8)	39 393 (3.9)	0.056
2015	27 459 (5.0)	227 470 (15.4)		131 073 (12.7)	125 869 (12.6)	
2016	40 739 (7.4)	205 133 (13.9)		124 152 (12.1)	121 404 (12.1)	
2017	52 195 (9.5)	186 290 (12.6)		118 596 (11.5)	117 721 (11.8)	
2018	56 051 (10.2)	171 435 (11.6)		112 108 (10.9)	112 092 (11.2)	
2019	78 345 (14.2)	163 911 (11.1)		119 795 (11.6)	119 401 (11.9)	
2020	81 628 (14.8)	163 864 (11.1)		121 809 (11.8)	120 709 (12.1)	
2021	98 782 (17.9)	151 113 (10.2)		125 953 (12.2)	123 138 (12.3)	
2022	109 848 (19.9)	138 286 (9.3)		126 632 (12.3)	122 343 (12.2)	
Antidiabetic drug use:						
Metformin	322 991 (58.5)	959 278 (64.8)	0.13	675 772 (65.6)	633 659 (63.2)	0.049
DPP-4 inhibitor	196 980 (35.7)	754 739 (51.0)	0.313	524 476 (50.9)	174 155 (47.3)	0.072
Thiazolidinedione	33 690 (6.1)	104 014 (7.0)	0.037	78 540 (7.6)	69 065 (6.9)	0.028
Meglitinides	1607 (0.3)	11 560 (0.8)	0.067	7419 (0.7)	6528 (0.7)	0.008
α-glucosidase inhibitors	3517 (0.6)	17 930 (1.2)	0.06	13 009 (1.3)	10 698 (1.1)	0.018
Insulin	53 017 (9.6)	164 574 (11.1)	0.05	113 890 (11.1)	108 134 (10.8)	0.009
GLP-1 receptor agonists	1737 (0.3)	2174 (0.2)	0.035	2206 (0.2)	2112 (0.2)	0.001
Level of antidiabetic treatment:						
1	331 411 (60.0)	668 814 (45.2)	0.315	466 459 (45.3)	488 188 (48.7)	0.085
2	167 637 (30.4)	646 704 (43.7)		449 739 (43.7)	405 748 (40.5)	
3	53 017 (9.6)	164 574 (11.1)		113 890 (11.1)	108 134 (10.8)	
No of antidiabetic drugs:						
0-1	340 177 (61.6)	693 296 (46.8)	0.328	483 117 (46.9)	504 623 (50.4)	0.060
2-3	207 954 (37.7)	770 948 (52.1)		534 895 (51.9)	487 509 (48.7)	
≥4	3934 (0.7)	15 848 (1.1)		12 075 (1.2)	9938 (1.0)	
Charlson comorbidity index score:						
0	305 661 (55.4)	772 040 (52.2)	0.091	537 567 (52.2)	531 228 (53.0)	0.034
1	111 184 (20.1)	331 066 (22.4)		230 529 (22.4)	218 812 (21.8)	
2	89 321 (16.2)	221 386 (15.0)		153 551 (14.9)	152 683 (15.2)	
≥3	45 899 (8.3)	155 600 (10.5)		108 440 (10.5)	99 347 (9.9)	
Diabetes complications:						
Retinopathy	4110 (0.7)	12 780 (0.9)	0.013	9185 (0.9)	8352 (0.8)	0.006
Neuropathy	25 301 (4.6)	96 452 (6.5)	0.085	67 609 (6.6)	60 441 (6.0)	0.022
Nephropathy	18 079 (3.3)	48 481 (3.3)	0.000	32 949 (3.2)	32 782 (3.3)	0.004
Comorbidities:						
Hypertension	254 132 (46.0)	673 892 (45.5)	0.010	479 146 (46.5)	457 842 (45.7)	0.017
Cardiovascular disease	99 734 (18.1)	236 734 (16.0)	0.055	167 423 (16.3)	165 166 (16.5)	0.006
Chronic liver diseases	95 610 (17.3)	222 502 (15.0)	0.062	163 834 (15.9)	157 350 (15.7)	0.006
Chronic kidney diseases	7851 (1.4)	24 879 (1.7)	0.021	14 367 (1.4)	15 953 (1.6)	0.016
Chronic pulmonary diseases	47 871 (8.7)	153 596 (10.4)	0.058	105 202 (10.2)	99 533 (9.9)	0.009
Dyslipidaemia	243 051 (44.0)	539 094 (36.4)	0.156	395 717 (38.4)	385 697 (38.5)	0.002
Cancer	25 987 (4.7)	92 755 (6.3)	0.069	66 535 (6.5)	58 361 (5.8)	0.026
Concomitant drugs:						
Beta blockers	105 029 (19.0)	223 526 (15.1)	0.104	164 029 (15.9)	161 393 (16.1)	0.005
ACE inhibitor/ARB	265 628 (48.1)	620 801 (41.9)	0.124	451 329 (43.8)	436 402 (43.6)	0.005
Calcium channel blockers	201 165 (36.4)	513 916 (34.7)	0.036	367 488 (35.7)	352 595 (35.2)	0.010
Diuretics	112 959 (20.5)	325 519 (22.0)	0.037	229 284 (22.3)	216 259 (21.6)	0.016
Lipid lowering drugs	326 973 (59.2)	743 652 (50.2)	0.181	544 574 (52.9)	527 324 (52.6)	0.005
Nitrates	37 750 (6.8)	61 704 (4.2)	0.117	47 798 (4.6)	48 465 (4.8)	0.009
Anticoagulants	16 931 (3.1)	27 257 (1.8)	0.079	21 757 (2.1)	21 529 (2.2)	0.003
Antiplatelets	139 489 (25.3)	389 231 (26.3)	0.024	269 911 (26.2)	260 246 (26.0)	0.005
Corticosteroids	261 457 (47.4)	702 661 (47.5)	0.002	498 912 (48.4)	475 911 (47.5)	0.019
Antibiotics	336 917 (61.0)	914 516 (61.8)	0.016	645 514 (62.7)	618 455 (61.7)	0.020
NSAIDs	321 973 (58.3)	864 071 (58.4)	0.001	612 006 (59.4)	585 755 (58.5)	0.019

(Continued)

Table 1 | (Continued)

Characteristics	Before propensity score weighting			After propensity score weighting		
	SGLT-2 inhibitors (n=552 065)	Sulfonylureas (n=1 480 092)	Absolute standardised difference	SGLT-2 inhibitors (n=1 030 088)	Sulfonylureas (n=1 002 069)	Absolute standardised difference
Immunostimulants	662 (0.1)	6216 (0.4)	0.058	7190 (0.7)	3411 (0.4)	0.050
Immunosuppressants	4055 (0.7)	11 915 (0.8)	0.008	8221 (0.8)	7858 (0.8)	0.002
Hormonal replacement therapy	21 729 (3.9)	46 650 (3.2)	0.042	36 042 (3.5)	33 939 (3.4)	0.006
Healthcare utilisation:						
Mean (SD) No of hospital admissions	0.1 (0.8)	0.3 (1.5)	0.123	0.4 (3.3)	0.3 (1.3)	0.073
Mean (SD) No of outpatient visits	6.2 (7.1)	7.1 (8.7)	0.112	8.1 (15.6)	6.9 (8.3)	0.079
Visits to doctor 30 days before index date	412 409 (74.7)	1 139 169 (77.0)	0.053	788 643 (76.6)	765 609 (76.4)	0.004
Body mass index:						
Underweight or normal (<23.0)	41 941 (7.6)	217 480 (14.7)		135 072 (13.1)	127 750 (12.8)	
Overweight (23.0-24.9)	64 753 (11.7)	216 868 (14.7)		142 279 (13.8)	138 440 (13.8)	
Obesity I (25.0-29.9)	189 908 (34.4)	403 164 (27.2)	0.383	298 511 (29.0)	291 750 (29.1)	0.001
Obesity II (≥30.0 kg/m^2)	95 841 (17.4)	113 585 (7.7)		107 756 (10.5)	104 964 (10.5)	
Unknown	159 622 (28.9)	528 995 (35.7)		346 469 (33.6)	339 165 (33.8)	
Smoking:						
Never	220 632 (40.0)	531 306 (35.9)		382 117 (37.1)	371 039 (37.0)	
Former	82 248 (14.9)	186 400 (12.6)	0.136	135 676 (13.2)	132 121 (13.2)	0.001
Current	90 073 (16.3)	90 073 (15.8)		166 637 (16.2)	160 539 (16.0)	
Unknown	159 112 (28.8)	527 866 (35.7)		345 657 (33.5)	338 371 (33.8)	
Alcohol use (days/week):						
0	196 130 (35.5)	544 642 (36.8)		379 354 (36.8)	365 290 (36.4)	
1-2	140 019 (25.4)	267 717 (18.1)		204 964 (19.9)	201 289 (20.1)	
3-4	39 821 (7.2)	92 150 (6.2)	0.200	66 612 (6.5)	65 194 (6.5)	0.043
≥5	16 983 (3.1)	47 717 (3.2)		33 499 (3.2)	31 926 (3.2)	
Unknown	159 112 (28.8)	527 866 (35.7)		345 657 (33.6)	338 371 (33.8)	
Test results						
Blood pressure (mm Hg):						
Systolic <140 and diastolic <90	288 626 (52.3)	707 235 (47.8)		506 701 (49.2)	491 403 (49.0)	
Systolic ≥140 or diastolic ≥90	101 315 (18.3)	237 590 (16.0)	0.129	172 524 (16.7)	167 175 (16.7)	0.001
Unknown	162 214 (29.4)	535 267 (36.2)		350 863 (34.1)	343 491 (34.3)	
Fasting blood glucose level (mmol/L):						
<7.8	226 607 (41.0)	458 582 (31.0)		344 651 (33.5)	337 326 (33.7)	
7.8-11.1	113 678 (20.6)	301 035 (20.3)	0.242	210 205 (20.4)	204 596 (20.4)	0.024
>11.1	49 615 (9.0)	185 123 (12.5)		124 294 (12.1)	116 593 (11.6)	
Unknown	162 165 (29.4)	535 352 (36.2)		350 937 (34.0)	343 554 (34.3)	
Serum total cholesterol level (mmol/L):						
<5.2	139 386 (25.3)	421 858 (28.5)		288 317 (28.0)	276 683 (27.6)	
5.2-6.2	58 359 (10.6)	179 606 (12.1)	0.122	121 887 (11.8)	117 585 (11.7)	0.001
>6.2	39 536 (7.2)	112 063 (7.6)		76 191 (7.4)	74 800 (7.5)	
Unknown	314 784 (57.0)	766 565 (51.8)		543 692 (52.8)	533 033 (53.2)	
Glomerular filtration rate (mL/min/1.73m^2):						
<60	23 663 (4.3)	83 799 (5.7)		53 552 (5.2)	52 787 (5.3)	
60-89	177 085 (32.1)	439 542 (29.7)	0.179	313 898 (30.5)	303 717 (30.3)	0.001
≥90	188 179 (34.1)	416 532 (28.1)		308 470 (29.9)	299 127 (29.8)	
Unknown	163 138 (29.5)	540 219 (36.5)		354 167 (34.4)	346 439 (34.6)	

ACE=angiotensin converting enzyme; ARB=angiotensin receptor blocker; DPP-4=dipeptidyl peptidase-4; FBG, fasting blood glucose; GLP-1=glucagon-like peptide-1; NSAIDs=non-steroidal anti-inflammatory drugs; SD=standard deviation; SGLT-2=sodium-glucose cotransporter-2.

including the intention-to-treat analyses, with the use of propensity score matching to adjust for confounders, the inclusion of participants who underwent testing, the imposition of different grace periods to define discontinuation, application of Fine and Gray's model to account for risk of death, the restriction of participants who took metformin without any other antidiabetic drugs, and the consideration of time varying inverse probability of censoring weight and other antidiabetic drugs (see supplementary tables 8-16). An attenuated effect was found in the sensitivity analysis applying a 90 day lag period, although the direction of the association remained consistent with the primary analysis (hazard ratio 0.93, 95% CI 0.84 to 1.04) (see supplementary table 17). We found a 2.78-fold higher risk (hazard ratio 2.78, 95% CI 2.72 to 2.83) of genital infections and a 1.03-fold higher risk of herpes zoster (1.03, 1.01 to 1.05) associated with SGLT-2 inhibitors versus sulfonylureas (see supplementary table 18).

Exploratory analyses

The number of patients included in each cohort was: SGLT-2 inhibitors (n=440 842) versus DPP-4 inhibitors (n=2 923 797), SGLT-2 inhibitors (n=995 496) versus thiazolidinediones (n=830 134), and SGLT-2 inhibitors (n=1 193 587) versus GLP-1 receptor agonists (n=79 140). Compared with DPP-4

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Table 2 | Weighted results for primary and secondary outcomes comparing SGLT-2 inhibitors with sulfonylureas in adults with type 2 diabetes

	SGLT-2 inhibitors (n=1 030 088)		Sulfonylureas (n=1 002 069)		SGLT-2 inhibitors *v* sulfonylureas	
	No with event	Incidence rate/100 000 person years	No with event	Incidence rate/100 000 person years	Risk difference/100 000 person years (95% CI)	Hazard ratio (95% CI)
Primary outcome						
Autoimmune rheumatic diseases	790	51.90	840	58.41	−6.50 (−11.86 to −1.14)	0.89 (0.81 to 0.98)
Secondary outcomes						
Inflammatory arthritis	571	37.53	623	43.30	−5.78 (−10.37 to −1.19)	0.86 (0.77 to 0.97)
Connective tissue disease	222	14.58	225	15.61	−1.03 (−3.84 to 1.78)	0.95 (0.79 to 1.14)

CI=confidence interval; SGLT-2=sodium-glucose cotransporter-2.

inhibitors, SGLT-2 inhibitors were associated with a 21% lower risk (hazard ratio 0.79, 95% CI 0.74 to 0.84) (see supplementary table 19). The comparisons with GLP-1 receptor agonists and thiazolidinediones were not statistically significant, with hazard ratios of 1.61 (0.92 to 2.84) and 1.09 (0.96 to 1.23), respectively.

Discussion

In this large, population based cohort study in South Korea using a nationwide representative healthcare database, use of SGLT-2 inhibitors was associated with an 11% lower risk of autoimmune rheumatic disease compared with use of sulfonylureas. This finding was consistent across all predefined subgroup and sensitivity analyses. The results estimated for control outcomes (genital infections and herpes zoster) suggested that the association between SGLT-2 inhibitors and autoimmune rheumatic disease was highly unlikely biased by residual confounding.

Comparison with previous studies and interpretation of results

Although the underlying mechanisms vary across different autoimmune rheumatic diseases, many of these conditions share features of abnormal immune activation, immune system dysregulation, and chronic inflammation, which are thought to play central roles in disease development and progression.[38] In animal models, SGLT-2 inhibitors, such as dapagliflozin and empagliflozin, have been shown to reduce key proinflammatory cytokines, including interleukin 6, tumour necrosis factor alpha, and interleukin 1beta, independently of glucose control.[39-47] These agents also modulate immune cells by promoting macrophage polarisation towards an anti-inflammatory M2 phenotype, suppressing T cell and B cell accumulation, and shifting the balance between T helper 17 and T regulatory cells in a favourable direction.[14 18 44 48 49] In addition, a recent study of lupus prone mice showed that empagliflozin reduced anti-dsDNA (double stranded DNA) antibodies, proteinuria, and glomerular damage by enhancing podocyte autophagy and suppressing mTORC1 (mechanistic target of rapamycin complex 1) signalling, further supporting a direct anti-autoimmune role of SGLT-2 inhibition.[50] Clinical studies further supported the immunomodulatory and anti-inflammatory potential of SGLT-2 inhibitors. Treatment with SGLT-2 inhibitors has been shown to reduce CD80+ macrophages while increasing CD163+ monocytes, indicating a shift towards an anti-inflammatory state.[51] Additionally, SGLT-2 inhibitors inhibited T cell proliferation and interleukin 17 production and enhanced interleukin 10 levels, contributing to immune homoeostasis.[52] These effects were accompanied by a reduction in proinflammatory cytokines, such as interleukin 6, tumour necrosis factor alpha, and interleukin 1beta, as well as lower levels of high sensitivity C reactive protein and urinary monocyte MCP-1 (monocyte chemoattractant protein-1).[53-57] Furthermore, the marked metabolic benefits of SGLT-2 inhibitors, including improved glycaemic control, alleviation of ectopic fat deposition, insulin sensitising effect, and better lipid profiles, may reduce systemic inflammation and thereby mitigate autoimmune activation indirectly.[14 58-67]

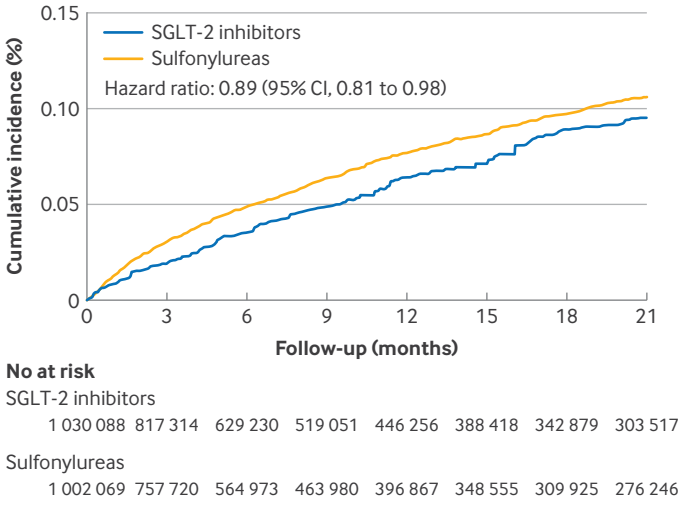

Fig 2 | Cumulative incidence curves of autoimmune rheumatic diseases comparing sodium-glucose cotransporter-2 (SGLT-2) inhibitors with sulfonylureas

Clinical implications

Our clinical study comprehensively investigated the association between use of SGLT-2 inhibitors and incidence of autoimmune rheumatic diseases using large scale real world data. The results suggest that the anti-inflammatory and immunomodulatory effects of SGLT-2 inhibitors, as suggested in previous studies, are clinically significant. Notably, while most large clinical trials of SGLT-2 inhibitors in chronic kidney or cardiovascular disease have predominantly enrolled

Variable	Incidence rate/ 100 000 person years: SGLT-2 inhibitors	Incidence rate/ 100 000 person years: Sulfonylureas	Risk difference/ 100 000 person years (95% CI)	Hazard ratio (95% CI)
Age (years)				
<65	43.11	45.43	-2.31 (-8.15 to 3.53)	0.95 (0.83 to 1.09)
≥65	70.05	83.87	-13.82 (-24.97 to -2.67)	0.82 (0.71 to 0.95)
Sex				
Men	38.22	41.95	-3.73 (-9.67 to 2.21)	0.91 (0.78 to 1.06)
Women	70.28	82.35	-12.07 (-21.98 to -2.16)	0.85 (0.75 to 0.97)
Drug				
Dapagliflozin	52.90	58.60	-5.70 (-11.40 to -0.01)	0.89 (0.81 to 0.99)
Empagliflozin	55.47	58.41	-2.94 (-10.79 to 4.91)	0.94 (0.73 to 1.22)
Ipragliflozin	47.85	59.04	-11.19 (-17.32 to -5.06)	0.77 (0.22 to 2.64)
Ertugliflozin	24.00	59.09	-35.09 (-40.56 to -29.62)	0.37 (0.06 to 2.26)
Cardiovascular disease				
Yes	65.06	72.33	-7.27 (-21.95 to 7.41)	0.91 (0.73 to 1.12)
No	48.82	55.42	-6.60 (-12.32 to -0.88)	0.88 (0.79 to 0.98)
Body mass index				
<25.0	59.16	71.83	-12.67 (-24.1 to -1.24)	0.78 (0.66 to 0.93)
≥25.0	45.95	50.38	-4.43 (-12.19 to 3.33)	0.92 (0.79 to 1.08)
Calendar period				
2014-19	51.29	56.43	-5.14 (-11.14 to 0.86)	0.90 (0.81 to 1.00)
2020-22	57.98	65.58	-7.60 (-19.84 to 4.64)	0.90 (0.74 to 1.10)

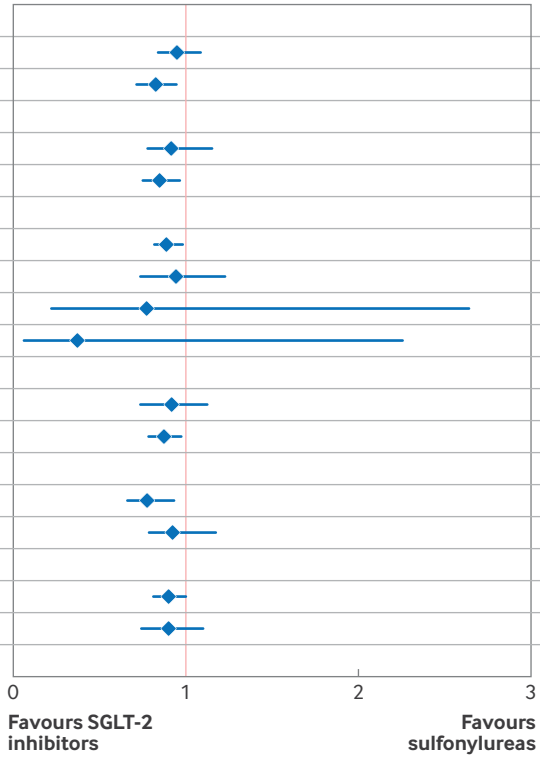

Fig 3 | Weighted results of primary outcomes comparing SGLT-2 inhibitors with sulfonylureas in each prespecified subgroup. CI=confidence interval; SGLT-2=sodium-glucose cotransporter-2

people in the overweight category (mean BMI around 30), our subgroup analyses indicate that the potential benefit of SGLT-2 inhibitors on autoimmune rheumatic diseases was evident even among individuals with lower BMI, with a more pronounced effect observed in those with a BMI <25.[2 68-71] This finding may further indirectly support the direct immunological benefits of SGLT-2 inhibitors that are independent of their metabolic effects, warranting further investigation.

In our exploratory analyses, use of SGLT-2 inhibitors was associated with a 21% lower risk of autoimmune rheumatic diseases compared with DPP-4 inhibitors, a drug class that has shown potential protective effects against autoimmune diseases. A previous observational study reported a reduced risk of a composite outcome that included rheumatoid arthritis, systemic lupus erythematosus, psoriasis, multiple sclerosis, or inflammatory bowel disease with the use of DPP-4 inhibitors (hazard ratio 0.68, 95% CI 0.52 to 0.89).[23] This finding may further underscore the potential immunomodulatory properties of SGLT-2 inhibitors—however, to further explore the repurposing potential of these drugs in the treatment of autoimmune rheumatic diseases, randomised controlled trials in patients with a diagnosis of autoimmune rheumatic diseases are required. Interestingly, repurposing an antidiabetic drug for the treatment of autoimmune rheumatic diseases has already been successful with metformin, which has shown anti-inflammatory and immunomodulatory effects, reducing the risk of rheumatoid arthritis in women and potentially mitigating the severity of autoimmune diseases such as multiple sclerosis.[72 73]

Additionally, our analysis comparing SGLT-2 inhibitors with GLP-1 receptor agonists suggested a potentially greater protective effect of GLP-1 receptor agonists (hazard ratio 1.61, 95% CI 0.92 to 2.84). However, this result should be interpreted with caution, given the limited sample size and few event in the GLP-1 receptor agonist group, which yielded a wide confidence interval. This is attributable to the low prescription rate of GLP-1 receptor agonists in South Korea, which differs from clinical prescribing patterns observed in other countries.[20 74] Notably, accumulating mechanistic evidence suggests that GLP-1 receptor agonists may exert anti-inflammatory or immunomodulatory effects, highlighting the need for further studies to assess their potential role in the treatment of autoimmune rheumatic diseases.[75-77]

Strengths and limitations of this study

This study has several strengths. Firstly, the nationwide database provided a large sample size, which enabled us to assess rare outcomes and investigate within

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important subgroups as well as by type of SGLT-2 inhibitor. Secondly, we applied rigorous methods, including the use of an active comparator new user cohort design and propensity score weighting. Furthermore, since we used strict definitions to identify the study outcomes, outcome misclassification was less likely.

This study also has limitations. Firstly, owing to the observational nature of our study, the possibility of unmeasured confounding cannot be ruled out, although we adjusted for numerous important confounders, including comorbidities and concomitant drug treatments, healthcare utilisation, test results (eg, fasting blood glucose, lipid profile, and renal function), and health behaviours (eg, alcohol intake and smoking status). In particular, information on family history of autoimmune diseases, a known risk factor for many autoimmune rheumatic diseases, was not available in our database and could not be accounted for in our analyses.[3] However, confounding by indication is less likely, as doctors are not expected to prescribe antidiabetic drugs for people with type 2 diabetes based on the future risk of autoimmune rheumatic diseases. Furthermore, results from control outcome analysis confirmed the internal validity of our findings.

Secondly, owing to the relatively high rate of treatment discontinuation, the median follow-up duration in our study was relatively short (about 8-9 months). The reasons for the high discontinuation could not be ascertained from claims data; however, this pattern was consistent with previous studies.[7,8] To assess potential bias resulting from differential discontinuation patterns, we conducted additional analyses using both an intention-to-treat approach and an inverse probability of censoring weighting. The results were consistent with those of the main analysis, suggesting that such bias is likely minimal. Therefore, our findings reflect real world clinical practice, where treatment discontinuation is common, making our findings representative of expected outcomes in such settings. Furthermore, we believe this timeframe is adequate to show the effect of SGLT-2 inhibitors, as mechanistic studies have shown rapid immunomodulatory and anti-inflammatory effects.[14,15,53]

Thirdly, we selected the missing indicator method as our primary approach for handling missing data. The proportion of missingness in test variables was not, however, negligible, ranging from 28.8% to 57.0% in both the SGLT-2 inhibitor and the sulfonylurea groups. Therefore, we conducted a sensitivity analysis using complete case data, which included participants without missing test results (see supplementary table 10). The results were consistent with the main findings, supporting the assumption that any bias introduced by the missing indicator method is likely minimal. Nevertheless, we acknowledge that bias arising from the exclusion of individuals with missing data cannot be ruled out. These considerations should be accounted for when interpreting the findings of our study.

Fourthly, we conducted various sensitivity analyses and found that the main findings were largely consistent across different settings, including drug use definitions, propensity score methodologies, study populations, grace periods for treatment discontinuation, time varying effects of censoring and concomitant antidiabetic drugs, and application of lag time. However, given the small number of events and the low incidence rate, the precision of the estimates may be limited, even when the direction of the association remains consistent. Therefore, caution is warranted when interpreting these results. Notably, the sensitivity analysis applying a lag period yielded a somewhat attenuated effect. This attenuation may be attributable to the conservative assumption that biologically plausible early events could have occurred before the index date, leading to the exclusion of individuals with follow-up durations shorter than 90 days. Consequently, participants who experienced the early onset of autoimmune rheumatic diseases were excluded from the analysis. This may have led to a potential dilution of the association by omitting clinically relevant early events and drug use. Furthermore, the reduced number of participants and outcome events after this lag likely limited statistical power, warranting cautious interpretation of this result.

Lastly, although our study broadly refers to SGLT-2 inhibitors, canagliflozin was not included in the analyses because it was not reimbursed during the study period in South Korea. Furthermore, as our study was restricted to the South Korean population, replication of these findings in other populations and healthcare settings is warranted to assess the generalisability of our findings.

Conclusion

In this large cohort of adults with type 2 diabetes, SGLT-2 inhibitors were associated with an 11% lower risk of autoimmune rheumatic diseases compared with sulfonylureas. These results suggest that SGLT-2 inhibitors may contribute to reducing the risk of autoimmune diseases. However, this potential benefit should be carefully weighed against known adverse events and concerns about tolerability. Replication in other populations and settings, as well as studies in patients with existing autoimmune rheumatic diseases, are warranted to confirm and extend these observations.

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Contributors: BH and HL contributed equally to the paper as joint first authors. All authors conceived and designed the study. JYS acquired the data. BH edited the study protocol. HL and KJ did the statistical analyses. All authors analysed and interpreted the data. BH wrote the manuscript, and all authors critically revised it. All authors approved the final version of the manuscript and agreed to be accountable for the accuracy of the work. JYS supervised the study and is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: This study was approved by the institutional review board of Sungkyunkwan University (SKKU 2024-11-008), and the requirement for informed consent was waived.

Data sharing The data that support the findings of this study are available from the National Health Insurance Service (NHIS) of South Korea, but restrictions apply to the availability of these data owing to domestic laws and regulations that prohibit the distribution or release of individual's data to the public and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the NHIS of South Korea. The analytical codes used in this study are provided in the supplementary appendix and are also publicly available in at https://github.com/SKKUPEPV/SGLT2i-AIRD.git.

Transparency: The lead author (JYS) affirms that the 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.

Dissemination to participants and related patient and public communities: Key findings will be disseminated through academic presentations, a press release, social media such as Facebook and X, and a plain language summary after publication to ensure broader accessibility and public engagement. The authors will also write a post on the official website of Sungkyunkwan University School of Pharmacy.

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Supplementary information: Note 1, tables 1-19, figures 1 and 2, and appendix