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ORIGINAL ARTICLE

Inhibition of sodium-glucose cotransporter-2 and liver-related complications in individuals with diabetes: a Mendelian randomization and population-based cohort study

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Abstract

Background and Aims: No medication has been found to reduce liver-related events. We evaluated the effect of sodium-glucose cotransporter-2 inhibitor (SGLT2i) on liver-related outcomes.

Approach and Results: Single nucleotide polymorphisms associated with SGLT2 inhibition were identified, and a genetic risk score (GRS) was computed using the UK Biobank data (n = 337,138). Two-sample Mendelian randomization (MR) was conducted using the FinnGen (n = 218,792) database and the UK Biobank data. In parallel, a nationwide population-based study using the Korean National Health Insurance Service (NHIS) database was conducted. The development of liver-related complications (ie, hepatic

Abbreviations: aHR, adjusted hazard ratio; AMPK, adenosine monophosphate–activated protein kinase; DPP4i, dipeptidyl peptidase-4 inhibitor; GLP-1, glucagon-like peptide; GRS, genetic risk score; GWAS, genome-wide association study; IVW, inverse-variance weighted; MASLD, metabolic dysfunction–associated steatotic liver disease; MetALD, metabolic dysfunction associated and alcohol associated liver disease; MR, Mendelian randomization; NHIS, National Health Insurance Service; OAD, oral antidiabetic drug; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SLD, steatotic liver disease; T2DM, type 2 diabetes mellitus; UKB, UK Biobank.

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decompensation, HCC, liver transplantation, and death) was compared between individuals with type 2 diabetes mellitus and steatotic liver diseases treated with SGLT2i (n = 13,208) and propensity score–matched individuals treated with dipeptidyl peptidase-4 inhibitor (n = 70,342). After computing GRS with 6 single nucleotide polymorphisms (rs4488457, rs80577326, rs11865835, rs9930811, rs34497199, and rs35445454), GRS-based MR showed that SGLT2 inhibition (per 1 SD increase of GRS, 0.1% lowering of HbA1c) was negatively associated with cirrhosis development (adjusted odds ratio = 0.83, 95% CI = 0.70–0.98, $p = 0.03$) and this was consistent in the 2-sample MR (OR = 0.73, 95% CI = 0.60–0.90, $p = 0.003$). In the Korean NHIS database, the risk of liver-related complications was significantly lower in the SGLT2i group than in the dipeptidyl peptidase-4 inhibitor group (adjusted hazard ratio = 0.88, 95% CI = 0.79–0.97, $p = 0.01$), and this difference remained significant (adjusted hazard ratio = 0.72–0.89, all $p < 0.05$) across various sensitivity analyses.

Conclusions: Both MRs using 2 European cohorts and a Korean nationwide population-based cohort study suggest that SGLT2 inhibition is associated with a lower risk of liver-related events.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic diseases in the world, affecting 463 million people.[1] T2DM affects multiple organs including the heart, kidney,[2] and liver in the form of NAFLD.[3] In conjunction with the high prevalence of T2DM, NAFLD is one of the most common liver diseases worldwide, affecting ~34% of the global population.[3] Individuals with NAFLD may develop liver-related complications such as NASH, cirrhosis, and HCC.[4] NASH, which is an NAFLD complication with hepatic inflammation, has become one of the most prevalent indications for liver transplantation.[5] In an effort to better understand the metabolic impact of the liver and to further assess its interaction with other etiologies, the concept of steatotic liver disease (SLD), especially metabolic dysfunction–associated steatotic liver disease (MASLD) or increased metabolic dysfunction associated and alcohol associated liver disease (MetALD) was recently proposed and is now being used to describe individuals who have both SLD and metabolic diseases such T2DM.[6] Above all, there is an urgent need for new treatments for NAFLD, MASLD, and MetALD because no drug has yet been found to reduce long-term liver-related clinical problems in individuals with SLD.[7]

Among oral antidiabetic drugs (OADs), sodium-glucose cotransporter-2 inhibitor (SGLT2i) is reported to reduce the risk of several comorbidities associated with T2DM, including cardiovascular diseases and chronic kidney disease, based on evidence from randomized clinical trials.[8,9] Mendelian randomization (MR) also supports a causal relationship between SGLT2 inhibition and improved cardiovascular outcomes.[10] Considering the strong connection between T2DM, obesity, and the progression of NAFLD, the use of SGLT2i may offer substantial benefits. Studies have found that a significant proportion (30.5%) of individuals treated with dapagliflozin, an SGLT2i, experienced a weight loss of more than 5%.[11] The administration of SGLT2i has additionally been shown to improve liver biochemical parameters and reduce fat accumulation in the liver of individuals with NAFLD.[12]

The glucagon-like peptide-1 (GLP-1) receptor agonist[13,14] and glucose-dependent insulinotropic polypeptide/GLP-1 receptor dual agonist[15] have demonstrated encouraging outcomes for improving histologic conditions in individuals with NASH. Nevertheless, there is still a lack of studies that specifically focus on liver-related clinical outcomes in individuals with NAFLD, indicating a requirement for additional investigations in this field.[16] Thus, MR and population-based cohort studies using big data (eg, nationwide claims databases) have been employed to address issues that randomized trials are unable to clarify. Specifically, MR is used to examine causal relationships between various factors and outcomes in the general population.[17] Unlike other statistical approaches that

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are susceptible to confounders, MR is based on the assumption that particular genetic variations influence outcomes of interest only through the exposure of interest and independently of confounders.[17] On the other hand, population-based cohort studies with long-term follow-up of large samples of participants can enable findings that cannot be obtained using hospital-based cohorts with small sample sizes.[18] Moreover, unlike MR, seeking the association of multiple interventions within specific disease populations (eg, T2DM, MASLD, or MetALD) is possible in population-based cohort studies.[19]

This study aimed to confirm the association between SGLT2 inhibition and long-term liver-related complications using MR and long-term follow-up of a population-based cohort.

METHODS

MR analysis

Study population and outcome

Data were obtained from the UK Biobank (UKB) and FinnGen cohorts. UKB is a population-based cohort involving over 500,000 UK residents aged 40–69, recruited from 2006 to 2010.[20,21] FinnGen encompasses over 220,000 hospital-attended individuals with European ancestry independent of UKB, thereby enriching the disease endpoints.[22] After selecting a population of White British individuals who passed a quality control filter, clinical and genetic data were extracted from 337,138 participants (955 patients with cirrhosis and 336,183 controls) in the UKB cohort, and summary statistics were derived from 218,792 participants (1931 patients with cirrhosis and 216,861 controls) in the FinnGen cohort. The UKB database can be accessed following the approval of the UKB Consortium (application no. 53799), and the FinnGen database is accessible to the general public.

The primary outcome of the current MR analysis was the development of liver cirrhosis. Cirrhosis was identified using ICD-9 or ICD-10 diagnostic codes, as in another genome-wide association study (GWAS).[23]

Genetic instruments predicting SGLT2 inhibition

Single nucleotide polymorphisms associated with SGLT2 inhibition, which mimic the glucose-lowering effect of SGLT2i, were identified using previously described steps. In brief, SNPs associated with both low mRNA SLC5A2 expression[24] and a low HbA1c level (association p value $= 1\times10^{-4}$) were selected.[10] F-statistics were used to test the predictive strength of these SNPs. Two-sample MR was conducted to validate these SNPs, utilizing summary statistics from GWAS data of patients with T2DM from the FinnGen database. MR by the inverse-variance weighted (IVW) method revealed significant causal estimates between SGLT2 inhibition and a lower risk of T2DM (per 0.1% HbA1c decrease, OR = 0.95, 95% CI = 0.91–0.99, $p = 0.01$; Supplemental Table S1, http://links.lww.com/HEP/I337). These causal estimates remained significant in implemented MR sensitivity analyses.

Individual-level 1-sample MR

Using individual data from the UKB participants (n = 337,138), we conducted genetic risk score (GRS)-based 1-sample MR. Individuals with very high levels of heterozygosity or missing data, sex chromosomal aneuploidy, or excessive relatedness were excluded according to the criteria established by the UKB Consortium. We computed a GRS for the reduced SGLT2 activity (scaled to its HbA1c-lowering effect) by multiplying the gene dosage matrix with GWAS effect sizes (ie, the regressed βs) of the genetic instruments using PLINK 2.0 (version alpha 2.3, www.cog-genomics.org/plink/2.0/).[25] Reduced SGLT2 activity was represented as a decrease in the HbA1c levels and was scaled so that 1 SD of increase in GRS corresponded to a 0.1% decrease in HbA1c. Associations between the calculated GRS and binary cirrhosis outcome were analyzed using logistic regression, which was adjusted for factors such as age, sex, genotype measurement batch, hypertension, T2DM, BMI, waist circumference, and the first 10 principal components of the genetic factors.[26] We further stratified individuals based on GRS and compared the risk of liver-related complications between the higher 5% and lower 95% population using the Kaplan-Meier method. A Cox proportional hazard regression model was used to evaluate the effect of GRS on liver-related complication risk. The index date was established as the date on which baseline characteristics such as BMI and underlying comorbidities (eg, diabetes or hypertension) were obtained between 2006 and 2010. Individuals' follow-up time was calculated from the index date until the date of liver-related complications or the end of follow-up. The end of follow-up differed according to data type such as inpatient hospital data (March 2021), cancer registration data (July 2019), and mortality registry (March 2021). The liver-related complication was defined as the development of cirrhotic decompensation (eg, ascites, variceal bleeding, and HE), HCC, liver transplantation, or liver-related mortality.

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Summary-level 2-sample MR

Two-sample MR was conducted using SNPs associated with SGLT2 inhibition together with summary statistics from participants in the FinnGen cirrhosis GWAS cohort. None of the instrumented SNPs were excluded by this process. The IVW method with a fixed-effect model was used as the primary analytic approach.[10,27] As the IVW method involves the risk of bias due to directional pleiotropy, we also performed a sensitivity analysis to test for directional pleiotropy.[28] The simple median method was adopted as an additional sensitivity analysis, which offers reliable estimates despite the potential presence of invalid genetic instruments.[29] To evaluate whether an individual variant drove the overall result, leave-one-out analysis using the MR-Egger method was performed even though it lacks the statistical power to detect significance for a small number of SNPs. MR-PRESSO was performed to evaluate the outlier effect.[30]

Nationwide claims data analysis

Study population and treatment

For further validation of the relationship between SGLT2 inhibition and liver-related events, a nationwide cohort study was conducted. A cohort was designed using nationwide claims registered in the National Health Insurance Service (NHIS) of the South Korea database from January 1, 2013, to December 31, 2019.[31] Specific data obtained from each individual, including diagnosis codes, are provided in Supplemental Table S2, http://links.lww.com/HEP/I337. The NHIS regularly audits ICD-10 codes, procedure records, and prescription records to avoid unnecessary medical expenses, and the use of this database for research purposes is validated externally and internally[32–34] This study was approved by the institutional review boards of the NHIS (No. NHIS-2022-1-074) and Seoul National University Hospital (No. 2104-042-1209). Due to the retrospective nature and the anonymity of data, the requirement for informed consent was waived.

Individuals with either MASLD or MetALD who newly started either SGLT2i or dipeptidyl peptidase-4 inhibitor (DPP4i) as a second-line OAD for T2DM between September 2014 and December 2016 were eligible for inclusion. The main study population was restricted to individuals with both T2DM and SLD to evaluate the effect of SGLT2i among patients with an increased risk of liver-related events. SLD was defined as a fatty liver index of 30 or higher.[35] This definition was validated in the Korean population, where the AUROC was 0.87.[35] Based on this validation, this criterion has been widely used in numerous studies.[36,37] A total of 290,985 patients with previous and/or current malignancy, decompensated cirrhosis, and/or coadministration of SGLT2i and DPP4i were excluded. As a result, 13,227 individuals treated with SGLT2i and 136,294 treated with DPP4i were eligible for inclusion. To adjust for baseline variables, propensity score matching was applied, matching participants at a ratio of 1:6 using the nearest method and a caliper of 0.05.[38] Among SGLT2i individuals, 19 could not be matched with DPP4i individuals. All accessible factors (eg, demographic data, comorbidities, medications, and health check-up data) were included in propensity score matching as variables. The final analysis included 13,208 SGLT2i users and 70,342 DPP4i users (Supplemental Figure S1, http://links.lww.com/HEP/I337). The index date was the date of the first prescription of SGLT2i or DPP4i.

Outcomes

The primary outcome was the development of any liver-related complication, defined as cirrhosis-related complications (eg, ascites, variceal bleeding, and HE), HCC, liver transplantation, or liver-related mortality. Individuals were tracked till the data cutoff date (December 31, 2019), primary outcome, or the confirmation of death. The secondary outcome was the development of cirrhosis in patients without cirrhosis. Cirrhosis was defined as the diagnosis of cirrhosis in ICD-10 codes or the development of liver-related complications. The definition of liver-related complications and cirrhosis was considered based on other definitions of cirrhosis.[34]

Outcomes were also analyzed in each of MASLD and MetALD, but more stringent criteria were applied in differentiating between MASLD and MetALD. This is due to the possibility of bias arising from self-reported alcohol use,[39] a major cause of SLD. Specifically, for MASLD, it referred to individuals who self-reported total abstinence from alcohol, while for MetALD, it pertained to individuals who self-reported consuming alcohol a minimum of twice weekly. Outcomes that occurred within 6 months of the index date were excluded from the main analysis. Death data were extracted by matching patient information in the NHIS database with death status and diagnosis at the time of death from the National Statistical Office.

Statistical analysis

Chi-square tests were used to compare categorical variables, and Student *t* tests or Mann-Whitney *U* tests were used to compare continuous variables depending on the results of normality tests. Each outcome was compared using a Cox proportional hazard regression model and multivariable regression, and inverse

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probability of treatment weighting was additionally performed for some variables. T2DM increases mortality rates[40] and the risk of acquiring cardiovascular complications compared to the general population.[41] Thus, competing risk analysis, considering both overall mortality and cardiovascular complications as competing events, was conducted. Cardiovascular complications were defined as myocardial infarction, stroke, hospitalization due to heart failure, and cardiovascular-related mortality. To determine the significance of differences between subgroups in subgroup analyses, p values for interactions ($p_{interaction}$) were calculated. Analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc) and R 4.2.0 (R Foundation). All statistical tests were two-sided, and p values <0.05 were considered statistically significant.

RESULTS

MR analysis

Individual-level 1-sample MR using GRS

Six SNPs (rs4488457, rs80577326, rs11865835, rs9930811, rs34497199, and rs35445454) related to SGLT2 inhibition (per 1 SD increase of GRS, 0.1% lowering of HbA1c) were selected as genetic instruments (Supplemental Table S3, http://links.lww.com/HEP/I337).[10] These genetic instruments strongly predicted SGLT2 inhibitions (F-statistics = 24.6). Controlling for age, sex, and the first 10 principal components of genetic factors, the GRS for reduced SGLT2 activity was significantly associated with cirrhosis (per 0.1% HbA1c decrease, adjusted odds ratio = 0.83, 95% CI = 0.70–0.98, $p = 0.03$; Table 1) and this association persisted even after adjusting for age, sex, the first 10 principal components, T2DM, hypertension, BMI, and waist circumference (per 0.1% HbA1c decrease, adjusted odds ratio = 0.81, 95% CI = 0.68–0.96, $p = 0.01$). When we divided the individuals of the UKB population based on GRS, the top 5% of individuals had substantially fewer liver-related complications than the bottom 95% of individuals (adjusted hazard ratio [aHR] = 0.60, 95% CI = 0.37–0.97, $p = 0.038$; Figure 1). This relationship remained significant after adjusting for age, sex, the first 10 principal components, T2DM, hypertension, BMI, and waist circumference (aHR = 0.61, 95% CI = 0.38–1.00, $p = 0.048$).

Summary-level 2-sample MR

In the 2-sample MR using summary-level genetic data from the FinnGen GWAS database, MR by the IVW method revealed significant causal estimates between SGLT2 inhibition and a lower risk of cirrhosis (per 0.1% HbA1c decrease, OR = 0.73, 95% CI = 0.60–0.90, $p = 0.003$; Table 2). These causal estimates remained significant in all implemented MR sensitivity analyses. The casual estimate by the MR-Egger method was directionally consistent, and the MR-Egger intercept p value did not indicate significant directional pleiotropy (per 0.1% HbA1c decrease, OR = 0.76, 95% CI = 0.27–2.10, $p = 0.62$, intercept $p = 0.95$). The p from the MR-PRESSO method was consistent with that of the IVW method and the MR-PRESSO global test p value supported that there was no significant outlier effect (per 0.1% HbA1c decrease, OR = 0.73, 95% CI = 0.65–0.83, $p = 0.005$, global test $p = 0.86$). The leave-one-out analysis or single SNP analysis suggested the absence of a notable disproportionate effect from a given SNP in the causal estimates (Supplemental Table S4, http://links.lww.com/HEP/I337). A sensitivity analysis was conducted using the simple median method, yielding results that reported similar OR to previous studies.

Nationwide claims data analysis

Liver-related complications

A total of 83,550 individuals with either MASLD or MetALD were included, with a median follow-up period of 5.0 (IQR = 4.5–5.7) years in the DPP4i group and 4.9 (IQR = 4.3–5.4) years in the SGLT2i group. After applying propensity score matching, the study population was generally well-balanced including fasting glucose while the SGLT2i group had a significantly higher baseline BMI than the DPP4i group even after propensity score matching (Table 3).

During the follow-up period, 3089 patients (3.7%) experienced liver-related complications. The incidence

TABLE 1 Risk of cirrhosis according to GRS for SGLT2 reduced activity

Exposure and outcomes	Main analysis[a]		Sensitivity analysis[b]	
	Adjusted OR (95% CI)	p	Adjusted OR (95% CI)	p
GRS for reduced SGLT2 activity, per 1 SD increase in GRS, 0.1% lowering of HbA1c	0.83 (0.70–0.98)	0.03	0.81 (0.68–0.96)	0.01

[a]Adjusted for age, sex, and the first 10 principal components of genetic factors.
[b]Adjusted for age, sex, first 10 principal components, type 2 diabetes mellitus, hypertension, body mass index, and waist circumference.
Abbreviations: GRS, genetic risk score; SGLT2, sodium-glucose cotransporter-2.

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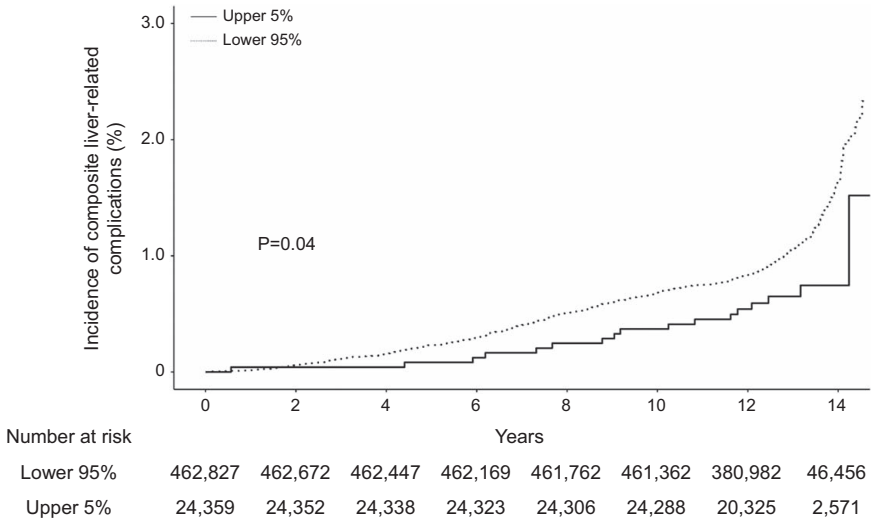

FIGURE 1 Cumulative incidence of liver-related complications in the UKB cohort. GRS was calculated using genetic instruments of SGLT2 inhibitions. Liver-related complications were defined as the development of cirrhosis-related complications (eg, ascites and variceal bleeding), HCC, liver transplantation, or liver-related mortality. Abbreviations: GRS, genetic risk score; SGLT2i, sodium-glucose cotransporter-2 inhibitor; UKB, UK Biobank.

was significantly lower in the SGLT2i group than in the DPP4i group (HR = 0.88, 95% CI = 0.79–0.97, $p = 0.01$; Figure 2A), with cumulative incidences of 0.66 (IQR = 0.60–0.73) per 100 person-years (SGLT2i) and 0.76 (IQR = 0.73–0.79) per 100 person-years (DPP4i) (Table 4). This significance remained after adjusting for baseline BMI and waist circumference (aHR = 0.88, 95% CI = 0.79–0.97, $p = 0.01$), and despite the absence of variation in the utilization of insulin, metformin, and other OADs, a consistent outcome was replicated when conducting a multivariable analysis that included these medications as covariates (aHR = 0.87, 95% CI = 0.79–0.97, $p = 0.01$). In addition, in subgroups of individuals with MASLD, the SGLT2i group had a significantly lower risk of liver-related events than the DPP4i group (HR = 0.81, 95% CI = 0.71–0.92, $p = 0.001$) and this was consistent in the multivariable analysis (aHR = 0.81, 95% CI = 0.71–0.92, $p = 0.002$). However, in individuals with MetALD, there was no significant difference between the 2 groups in both univariable (HR = 0.99, 95% CI = 0.81–1.21, $p = 0.93$) and multivariable (aHR = 0.99, 95% CI = 0.81–1.22, $p = 0.96$) analyses.

TABLE 2 Two-sample MR analysis using SGLT2 inhibition SNPs and summary statistics of FinnGen cirrhosis GWAS cohort (per 1 SD, 0.1% lower of HbA1c)

	OR (95% CI)	*p*
Inverse-variance weighted	0.73 (0.60–0.90)	0.003
MR-Egger	0.76 (0.27–2.10)	0.63
MR-PRESSO	0.73 (0.65–0.83)	0.005
Simple median	0.76 (0.58–0.99)	0.04

Abbreviations: GWAS, genome-wide association study; MR, Mendelian randomization; PRESSO, pleiotropy residual sum and outlier; SGLT2, sodium-glucose cotransporter-2.

For further analysis, we separated overall liver-related complications into liver-related mortality, transplantation, HCC, and cirrhosis-related complications and showed similar results (Table 5 and Figures 2B, C). When considering cirrhosis outcomes in individuals without cirrhosis, the SGLT2i group had a significantly lower chance of developing cirrhosis in both univariable (HR = 0.86, 95% CI = 0.78–0.95, $p = 0.003$) and multivariable (aHR = 0.86, 95% CI = 0.78–0.95, $p = 0.004$) analyses. Subgroup analyses were conducted based on the participant's demographic, anthropometric, and comorbidity characteristics. All subgroups exhibited similar tendencies.

Various sensitivity analyses supported our findings (Table 6). Liver-related complication events in the inverse probability of treatment weighted cohort showed consistent results (model 1: aHR = 0.88, 95% CI = 0.78–0.91, $p = 0.03$). Including liver-related outcomes within a 6-month lag period yielded similar results (model 2: aHR = 0.75, 95% CI = 0.68–0.83, $p < 0.001$). Applying stricter MASLD criteria (excluding patients with all liver diseases including chronic viral hepatitis B or C) did not change the result (model 3: aHR = 0.84, 95% CI = 0.74–0.96, $p = 0.005$). Censoring individuals after at least 1 month of medication cessation (SGLT2i or DPP4i) still showed SGLT2i users with a lower risk of liver-related complications than DPP4i users (model 4: aHR = 0.72, 95% CI = 0.60–0.88, $p = 0.001$). Including overall mortality and cardiovascular complications as competing risks, the SGLT2i group exhibited a significantly lower incidence of liver-related complications compared to the DPP4i group. This finding was supported by both univariable

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TABLE 3 Baseline characteristics of individuals in the South Korean NHIS database before and after propensity score matching

	Before PS matching					After PS matching				
Variable	Total (N = 149,521)	DPP4i (N = 136,294)	SGLT2i (N = 13,227)	*p*	SMD	Total (N = 83,550)	DPP4i (N = 70,342)	SGLT2i (N = 13,208)	*p*	SMD
Clinical characteristics										
Age, y	59.4 ± 11.4	59.8 ± 11.4	55.2 ± 10.9	< 0.001	0.40	56.2 ± 11.2	56.4 ± 11.2	55.3 ± 10.9	< 0.001	0.10
Male, N (%)	93,567 (62.6)	86,197 (63.2)	7370 (55.7)	< 0.001	0.15	47,856 (57.3)	40,491 (57.6)	7365 (55.8)	< 0.001	0.04
Residential area—urban, N (%)	97,652 (65.3)	88,648 (65.0)	9004 (68.1)	< 0.001	0.06	56,379 (67.5)	47,391 (67.4%)	8988 (68.1)	0.13	0.01
BMI, kg/m^2	26.9 ± 3.1	26.7 ± 3.0	28.2 ± 3.4	< 0.001	0.47	27.8 ± 3.2	27.7 ± 3.2	28.2 ± 3.4	< 0.001	0.16
Waist circumference, cm	90.2 ± 7.4	90.0 ± 7.3	92.2 ± 8.2	< 0.001	0.28	91.4 ± 7.8	91.3 ± 7.7	92.2 ± 8.2	< 0.001	0.11
Comorbidity, N (%)										
Hypertension	83,062 (55.6)	76,001 (55.8)	7061 (53.4)	< 0.001	0.05	44,836 (53.7)	37,782 (53.7)	7054 (53.4)	0.56	0.006
Dyslipidemia	106,425 (71.2)	96,995 (71.2)	9430 (71.3)	0.765	0.003	59,707 (71.5)	50,289 (71.5)	9418 (71.3)	0.67	0.004
Chronic kidney disease	15,237 (10.2)	14,333 (10.5)	904 (6.8)	< 0.001	0.03	6113 (7.3)	5210 (7.4)	903 (6.8)	0.02	0.004
Compensated cirrhosis	697 (0.5)	655 (0.5)	42 (0.3)	0.010	0.13	281 (0.3)	239 (0.3)	42 (0.3)	0.75	0.02
Viral hepatitis	3213 (2.2)	2926 (2.2)	287 (2.2)	0.887	0.002	1836 (2.2)	149 (2.2)	287 (2.2)	0.86	0.002
Alcoholic liver disease	42,361 (28.3)	38,924 (28.6)	3437 (26.0)	< 0.001	0.06	22,375 (26.8)	18,940 (26.9)	3435 (26.0)	0.03	0.02
Other liver disease	842 (0.6)	764 (0.6)	78 (0.6)	0.714	0.004	511 (0.6)	433 (0.6)	78 (0.6)	0.78	0.003
Prior heart failure	325 (0.2)	307 (0.2)	18 (0.1)	0.045	0.02	114 (0.1)	96 (0.1)	18 (0.14)	1.00	< 0.001
Prior myocardial infarction	653 (0.4)	606 (0.4)	47 (0.4)	0.156	0.01	303 (0.4)	256 (0.4)	47 (0.4)	0.95	0.001
Prior stroke	49 (0.03)	47 (0.03)	2 (0.02)	0.356	0.01	18 (0.02)	16 (0.02)	2 (0.02)	0.82	0.006
Laboratory findings										
Systolic BP, mm Hg	129.4 ± 14.5	129.4 ± 14.5	129.1 ± 14.2	0.016	0.02	129.1 ± 14.3	129.1 ± 14.3	129.1 ± 14.2	0.76	0.003
Diastolic BP, mm Hg	79.3 ± 9.6	79.3 ± 9.6	79.7 ± 9.6	< 0.001	0.04	79.5 ± 9.6	79.5 ± 9.6	79.7 ± 9.6	0.10	0.02
AST, IU/L	28.4 ± 11.5	28.3 ± 11.4	29.0 ± 11.8	< 0.001	0.06	28.9 ± 11.8	28.8 ± 11.8	29.0 ± 11.8	0.11	0.02
ALT, IU/L	33.1 ± 17.4	32.8 ± 17.2	35.2 ± 18.4	< 0.001	0.06	34.8 ± 18.3	34.7 ± 18.2	35.2 ± 18.5	0.002	0.01
Total cholesterol, mg/dL	196.5 ± 43.4	196.7 ± 43.3	194.2 ± 44.0	< 0.001	0.03	195.1 ± 43.6	195.3 ± 43.5	194.2 ± 44.0	0.01	0.006
Triglycerides, mg/dL	190.9 ± 89.6	191.3 ± 89.5	186.4 ± 90.0	< 0.001	0.006	187.5 ± 89.6	187.7 ± 89.5	186.4 ± 90.0	0.13	0.004
HDLc, mg/dL	48.2 ± 11.5	48.1 ± 11.5	48.5 ± 11.4	< 0.001	0.06	48.4 ± 11.4	48.4 ± 11.4	48.5 ± 11.4	0.53	0.02
LDLc, mg/dL	111.1 ± 39.1	111.3 ± 39.1	109.6 ± 39.5	< 0.001	0.13	110.2 ± 39.2	110.4 ± 39.2	109.6 ± 39.5	0.03	0.03
Fasting glucose, mg/dL	154.0 ± 49.9	154.0 ± 49.8	153.8 ± 50.0	0.54	0.04	154.0 ± 49.7	154.0 ± 50.0	153.8 ± 50.0	0.67	0.02
Hemoglobin, g/dL	15.0 ± 1.6	15.0 ± 1.6	14.5 ± 1.6	0.33	0.009	14.5 ± 1.6	14.5 ± 1.6	14.5 ± 1.6	0.35	0.009
Creatinine, mg/dL	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	< 0.001	0.19	0.9 ± 0.2	0.9 ± 0.2	0.9 ± 0.2	< 0.001	0.04
GFR, mL/min/1.73 m^2	85.7 ± 22.0	85.4 ± 22.0	89.3 ± 22.2	< 0.001	0.18	88.5 ± 22.1	88.4 ± 22.1	89.2 ± 22.2	< 0.001	0.04

TABLE 3. (*continued*)

Variable	Before PS matching					After PS matching				
	Total (N = 149,521)	DPP4i (N = 136,294)	SGLT2i (N = 13,227)	*p*	SMD	Total (N = 83,550)	DPP4i (N = 70,342)	SGLT2i (N = 13,208)	*p*	SMD
Medications, N (%)										
Aspirin	42,576 (28.5)	38,966 (28.6)	3610 (27.3)	0.002	0.02	23,192 (27.8)	19,585 (27.8)	3607 (27.3)	0.21	0.008
Statins	75,080 (50.2)	67,590 (49.6)	7490 (56.6)	< 0.001	0.09	46,320 (55.4	38,846 (55.2%)	7474 (56.6)	0.004	0.02
Antiviral agents	23,250 (15.6)	21,268 (15.6)	1982 (15.0)	0.06	0.14	12,722 (15.2)	10,742 (15.3)	1980 (15.0)	0.42	0.03
Insulin	2175 (1.5)	1886 (1.4)	289 (2.2)	< 0.001	0.03	1619 (1.9)	1334 (1.9)	285 (2.2)	0.05	0.01
Metformin	89,468 (59.8)	81,044 (59.5)	8424 (63.7)	< 0.001	0.20	52,356 (62.7)	43,950 (62.5)	8406 (63.6)	0.01	0.08
Thiazolidinedione	11,677 (7.8)	9898 (7.3)	1779 (13.5)	< 0.001	0.01	9395 (11.2)	7633 (10.9)	1762 (13.3)	< 0.001	0.009
Meglitinide	2047 (1.4)	1843 (1.4)	204 (1.5)	0.08	0.02	1202 (1.4)	998 (1.4)	204 (1.5)	0.28	0.01
GLP1ra	2 (0.00)	1 (0.00)	1 (0.01)	0.42	0.06	2 (0.00)	1 (0.00)	1 (0.01)	0.72	0.02
Sulfonylurea	62,186 (41.6)	56,860 (41.7)	5326 (40.3)	0.001	0.03	33,768 (40.4)	28,454 (40.5)	5314 (40.2)	0.65	0.004
Lifestyle, N (%)										
Alcohol consumption[a]				< 0.001	0.07				0.06	0.02
None	84,841 (56.7%)	77,283 (56.7%)	7,558 (57.1%)			47,513 (56.9%)	39,964 (56.8%)	7,549 (57.2%)		
Moderate	23,288 (15.6%)	20,987 (15.4%)	2,301 (17.4%)			14,121 (16.9%)	11,828 (16.8%)	2,293 (17.4%)		
Excessive	41,392 (27.7%)	38,024 (27.9%)	3,368 (25.5%)			21,916 (26.2%)	18,550 (26.4%)	3,366 (25.5%)		
Tobacco use				< 0.001	0.06				0.23	0.02
Never	77,868 (52.1)	70,646 (51.8)	7222 (54.6)			45,037 (53.9)	37,829 (53.8)	7208 (54.6)		
Past	33,896 (22.7)	31,086 (22.8)	2810 (21.2)			18,088 (21.7)	15,280 (21.7)	2808 (21.3)		
Current	37,757 (25.3)	34,562 (25.4)	3195 (24.2)			20,425 (24.5)	17,233 (24.5)	3192 (24.2)		
Exercise frequency				< 0.001	0.06				0.32	0.01
None	38,212 (25.6)	35,132 (25.8)	3080 (23.3)			19,866 (23.8)	16,789 (23.9)	3077 (23.3)		
1–2/wk	31,519 (21.1)	28,500 (20.9)	3019 (22.8)			18,798 (22.5)	15,785 (22.4)	3013 (22.8)		
≥ 3/wk	79,790 (53.4)	72,662 (53.3)	7128 (53.9)			44,886 (53.7)	37,768 (53.7)	7118 (53.9)		

Note: Data are reported as mean ± SD for continuous variables and n (%) for categorical variables. *p* values were calculated by Student *t* tests or Wilcoxon rank sum tests for continuous variables and chi-squared tests or Fisher exact tests for categorical variables as appropriate. All available variables were used in propensity score matching.

[a]Excessive alcohol consumption was defined as alcohol intake 2 or more times daily for males and 1 or more times daily for females.

Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitor; GFR, glomerular filtration rate; GLP1ra, glucagon-like peptide-1 receptor agonist; NHIS, National Health Insurance Service; PS, propensity score; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean difference.

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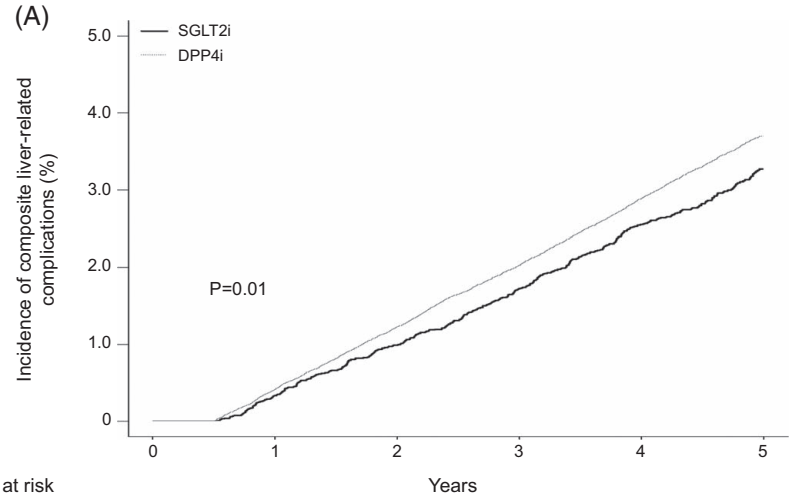
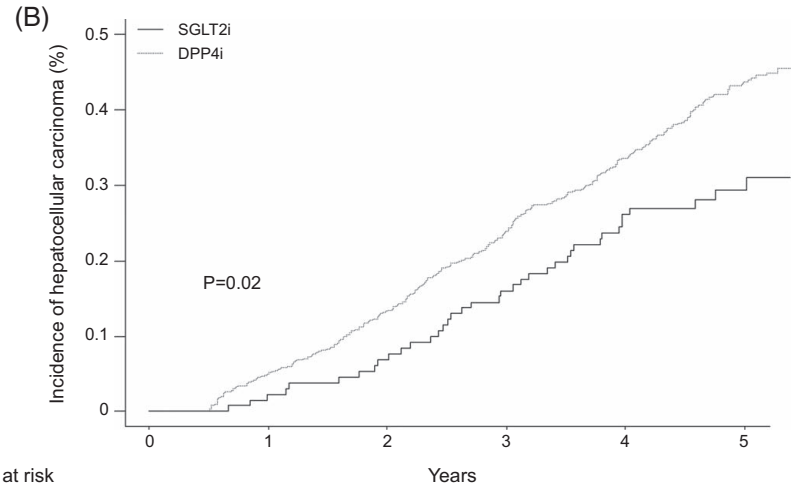
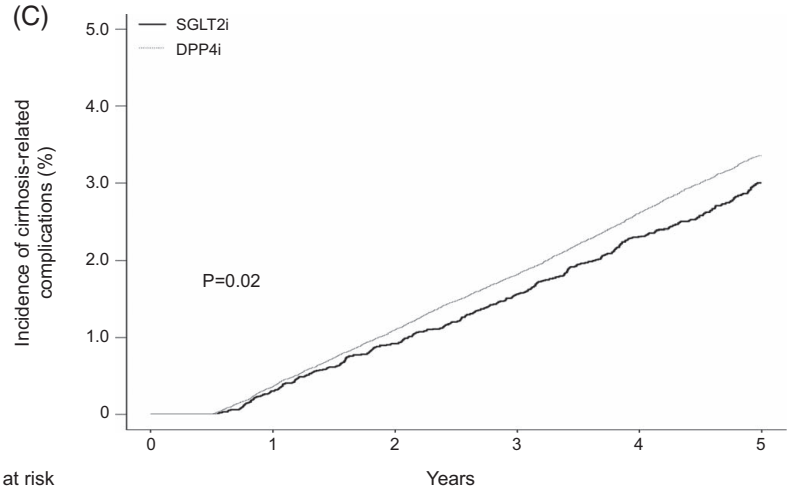


Number at risk						
DPP4i	70,342	69,749	68,766	67,824	66,784	36,537
SGLT2i	13,208	13,131	12,978	12,824	12,653	5,719



Number at risk						
DPP4i	70,342	69,993	69,474	68,953	68,354	37,638
SGLT2i	13,208	13,171	13,091	13,011	12,923	5,870



Number at risk						
DPP4i	70,342	69,778	68,829	67,917	66,905	36,622
SGLT2i	13,208	13,135	12,985	12,839	12,677	5,727

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FIGURE 2 Cumulative incidence of (A) liver-related complications, (B) HCC, and (C) cirrhosis-related complications in the Korean NHIS cohort. Analysis was performed after propensity score matching. Liver-related complications were defined as the development of cirrhosis-related complications (eg, ascites, variceal bleeding, HE, PVT, jaundice, peritonitis, hydrothorax, gastrointestinal hemorrhage, and hepatic failure), HCC, liver transplantation, or liver-related mortality. Abbreviations: DPP4i, dipeptidyl peptidase-4 inhibitor; NHIS, Nationwide Health Insurance Service; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

(subdistribution hazard ratio = 0.89, 95% CI = 0.80–0.99, $p = 0.03$) and multivariable (Model 5: adjusted subdistribution hazard ratio = 0.89, 95% CI = 0.80–0.99, $p = 0.03$) analyses.

DISCUSSION

MR analyses using 2 European cohorts (UKB and FinnGen) demonstrated that the genetically predicted effect of SGLT2 inhibition was associated with a lower risk of cirrhosis development. A parallel nationwide population-based cohort study using the Korean NHIS database showed that the liver-related complication risk was 12% lower in the SGLT2i group than in the DPP4i group among individuals with T2DM and SLD. Several sensitivity analyses further validated these results. This study provides comprehensive and robust evidence that SGLT2i can improve liver-related outcomes.

Both MR and nationwide population-based studies have inherent limitations, but their combined use may partially mitigate these constraints, albeit certain assumptions are necessary. In our MR study, we assessed the SGLT2 inhibition with regard to its effect on lowering HbA1c levels. However, this approach did not enable us to evaluate its influence on liver-related complications beyond diabetes management specifically. However, another study[42] suggests that both SGLT2i and DPP4i groups show a similar decrease in HbA1c levels. This indicates that in the Korean NHIS database, the prevention of liver-related complications may be more closely linked to SGLT2i itself rather than the effect of SGLT2i reducing HbA1c levels. Population-based cohort studies present inherent challenges, such as the potential for reverse causality or unexplained confounders, including increased BMI in the SGLT2i group, which may not be identifiable in the claims data.[43] MR analysis assists in resolving these concerns. Nevertheless, this method presupposes that the impact of SGLT2 inhibition on liver-related complications is consistent across different ethnicities, while the efficacy of MR is typically restricted to specific ethnic groups. However, the consistency of findings across numerous comparable outcomes in our study indicates that there might not be substantial ethnic discrepancies. In our analysis, 3 main assumptions of MR,[17] the relevance assumption, independence assumption, and exclusion-restriction assumption appeared to be adequately addressed. In an independent population, our genetic instruments were strongly associated with a decrease in HbA1c, as measured by high F-statistics values,[10] indicating that the assumption of relevance was met. Both MR-Egger and MR-PRESSO regression, which are considered to be less pleiotropy-biased, provided consistent results across our 2 MR data sets, indicating that the independence assumption was fulfilled. Although the exclusion-restriction assumption is untestable, weighted median analysis relaxed the exclusion-restriction assumption for as many as half of the genetic instruments. In addition, horizontal pleiotropy may be unlikely because all SNPs were in close proximity to the SLC5A2 gene. Thus, as most MR assumptions were supported, our MR analysis reveals a causal relationship between SGLT2 inhibition and cirrhosis prevention.

SGLT2 is located mainly in the apical membrane of the proximal convoluted tubule of the kidney and mediates glucose sodium cotransport throughout tubular cells.[44] SGLT2i blocks this SGLT2 channel, leading to multiple clinical effects such as glycosuria, weight loss, and the prevention of cardiovascular disease and chronic kidney disease.[44] SGLT2i might have affected the liver-related outcomes of individuals with both T2DM and SLD through 2 pathways. First, as suggested by our MR results, managing both hyperglycemia and obesity prevents the progression of hepatic fibrosis and cirrhosis development. Unlike DPP4i, SGLT2i promotes 2–5 kg of weight loss,[11] which improves insulin sensitivity and can further enhance glycemic control in individuals with T2DM.[45] Second, even after adjusting for multiple variables, including obesity, individual-level 1-sample MR showed that SGLT2 inhibition was associated with decreased cirrhosis development, suggesting other mechanisms of cirrhosis prevention besides weight loss, such as direct inhibition of the SGLT2 channel expressed in hepatocytes. Dapagliflozin decreases hepatic steatosis in murine models by activating adenosine monophosphate–activated protein kinase (AMPK).[46] AMPK suppresses lipogenesis and promotes fatty acid oxidation, and reactivation of AMPK suppresses hepatic steatogenesis in a murine model.[47] In addition to the relationship between SGLT2 and AMPK-mediated hepatic steatogenesis, the level of SGLT2 expression in hepatocytes is positively correlated with cell proliferation, survival, and apoptosis, which could be related to the development and progression of HCC.[48] A prior study established that levels of adiponectin, a substance known for inhibiting liver fibrosis and controlling cell growth through multiple

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TABLE 4 Liver-related complications and Cox proportional hazard analysis

	No. subjects	Person year	No. events	Follow-up duration, median (IQR)	Incidence rate, per 100 PY (IQR)	HR (95% CI)	*p*	aHR (95% CI)[a]	*p*
Composite liver-related complication									
DPP4i	70,342	351,022.1	2665	5.04 (4.52–5.68)	0.76 (0.73–0.79)	1 (Reference)		1 (Reference)	
SGLT2i	13,208	64,116.6	424	4.86 (4.34–5.41)	0.66 (0.60–0.73)	0.88 (0.79–0.97)	0.01	0.88 (0.79–0.97)	0.01
HCC									
DPP4i	70,342	356,013.3	307	5.08 (4.56–5.70)	0.09 (0.08–0.10)	1 (Reference)		1 (Reference)	
SGLT2i	13,208	64,897.5	38	4.89 (4.37–5.43)	0.06 (0.04–0.08)	0.68 (0.48–0.95)	0.02	0.68 (0.48–0.95)	0.02
Liver transplantation									
DPP4i	70,342	356,400.0	26	5.08 (4.57–5.70)	0.01 (0.00–0.01)	1 (Reference)		1 (Reference)	
SGLT2i	13,208	64,933.7	7	4.89 (4.37–5.44)	0.01 (0.00–0.02)	1.51 (0.65–3.48)	0.34	1.52 (0.66–3.51)	0.33
Cirrhosis-related complication									
DPP4i	70,342	351,426.1	2420	5.04 (4.52–5.68)	0.69 (0.66–0.72)	1 (Reference)		1 (Reference)	
SGLT2i	13,208	64,171.2	388	4.87 (4.34–5.41)	0.60 (0.55–0.67)	0.88 (0.79–0.98)	0.02	0.88 (0.79–0.98)	0.03
Liver-related mortality									
DPP4i	70,342	35,6451.9	133	5.08 (4.57–5.70)	0.04 (0.03–0.04)	1 (Reference)		1 (Reference)	
SGLT2i	13,208	64,950.1	15	4.90 (4.37–5.44)	0.02 (0.01–0.04)	0.63 (0.37–1.07)	0.09	0.63 (0.37–1.08)	0.10

[a]Adjusted for body mass index and waist circumference.

Abbreviations: aHR, adjusted hazard ratio; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.

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TABLE 5 Subgroup analyses

	DPP4i Case/Event	SGLT2i Case/Event	SGLT2i vs. DPP4i		SGLT2i vs. DPP4i		
			HR (95% CI)	*p*	aHR (95% CI)[a]	*p*	$p_{interaction}$[b]
Age							0.24
≤65	54,869/1644	10,841/296	0.95 (0.84–1.07)	0.407	0.95 (0.84–1.08)	0.44	
>65	15,473/1021	2367/128	0.83 (0.69–1.00)	0.049	0.83 (0.69–1.00)	0.05	
Sex							0.06
Female	29,851/1155	5843/172	0.78 (0.66–0.91)	0.002	0.78 (0.66–0.91)	0.002	
Male	40,491/1510	7365/252	0.95 (0.84–1.09)	0.50	0.96 (0.84–1.10)	0.56	
BMI (kg/m^2)							0.63
≤25	13,942/582	2172/81	0.93 (0.73–1.17)	0.51	0.93 (0.73–1.17)	0.51	
>25	56,400/2083	11,036/343	0.87 (0.78–0.97)	0.02	0.87 (0.77–0.97)	0.01	
Waist circumference (cm)							0.12
Male ≤90, Female ≤85	21,362/741	3521/118	1.01 (0.83–1.22)	0.96	1.01 (0.83–1.23)	0.93	
Male >90, Female >85	48,980/1924	9687/306	0.83 (0.73–0.93)	0.002	0.83 (0.74–0.94)	0.003	
Hypertension							0.33
No	32,560/1068	6154/181	0.93 (0.79–1.09)	0.35	0.93 (0.79–1.09)	0.34	
Yes	37,782/1597	7054/243	0.84 (0.73–0.96)	0.01	0.85 (0.74–0.97)	0.02	
Dyslipidemia							0.94
No	20,053/858	3790/138	0.88 (0.74–1.06)	0.17	0.89 (0.74–1.06)	0.19	
Yes	50,289/1807	9418/286	0.87 (0.77–0.99)	0.03	0.87 (0.77–0.99)	0.04	

[a]Adjusted for body mass index and waist circumference.
[b]$p_{interaction}$ was calculated between SGLT2i and DPP4i users.
Abbreviations: aHR, adjusted hazard ratio; DPP4i, dipeptidyl peptidase-4 inhibitor; $p_{interaction}$, *p* value for interaction; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SMD, standardized mean difference.

pathways,[49] rise notably when patients are treated with empagliflozin, a type of SGLT2i.[50] As adiponectin levels increase with the use of SGLT2i, this suggests a potential role of these inhibitors in preventing the advancement of hepatic fibrosis and preventing cancer development, including HCC.

TABLE 6 Sensitivity analyses

	HR (95% CI)	*p*	aHR (95% CI)	*p*
Model 1: Inverse probability of treatment weighting[a]				
DPP4i	1 (Reference)		1 (Reference)	
SGLT2i	0.88 (0.79–0.99)	0.04	0.88 (0.78–0.91)	0.03
Model 2: Including events occurred within 6 months[b]				
DPP4i	1 (Reference)		1 (Reference)	
SGLT2i	0.73 (0.66–0.80)	<0.001	0.75 (0.68–0.83)	<0.001
Model 3: Strict MASLD individuals[c]				
DPP4i	1 (Reference)		1 (Reference)	
SGLT2i	0.84 (0.74–0.95)	0.005	0.84 (0.74–0.95)	0.005
Model 4: Censor after 30 days of discontinuation of medications				
DPP4i (patients without cirrhosis)	1 (Reference)		1 (Reference)	
SGLT2i (patients without cirrhosis)	0.73 (0.60–0.88)	0.001	0.72 (0.60–0.88)	0.001
Model 5: Competing risk analysis[d]	SHR (95% CI)	*p*	aSHR (95% CI)	*p*
DPP4i (patients without cirrhosis)	1 (Reference)		1 (Reference)	
SGLT2i (patients without cirrhosis)	0.89 (0.80–0.99)	0.03	0.89 (0.80–0.99)	0.03

[a]Age, sex, BMI, waist circumference, cirrhosis, LDL, the use of antiviral agents, and the use of metformin were adjusted in inverse probability of treatment weight, and age, BMI, and waist circumference were adjusted in multivariable analysis.
[b]Adjusted for BMI and waist circumference.
[c]Patients with viral hepatitis or alcohol consumption were excluded.
[d]Cardiovascular complications and mortality were considered as competing events.
Abbreviations: aHR, adjusted hazard ratio; aSHR, adjusted subdistribution hazard ratio; DPP4i, dipeptidyl peptidase-4 inhibitor; MASLD, metabolic dysfunction–associated steatotic liver disease; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SHR, subdistribution hazard ratio.

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To evaluate the true effect of SGLT2i, it may be ideal to compare individuals who were or were not prescribed SGLT2i. However, retrospective study designs entail a high risk of multiple biases, such as immortal time bias and selection bias.[34,51] To minimize these biases, we compared individuals using SGLT2i to those taking another second-line OAD. Unfortunately, due to the limited number of individuals available at the time of the study, the GLP-1 agonist, a potent SLD treatment,[13] was unable to serve as a comparator. This is owing to the fact that GLP-1 agonists were mostly not covered by insurance for second-line OADs in the Korean health care system. However, DPP4i, which lowers serum glucose levels by inhibiting DPP4—an enzyme that cleaves GLP-1 or glucose-dependent insulinotropic polypeptide—was available and widely used as a second-line OAD in Korea.[52] As DPP4i has been commonly used as a second-line OAD since 2008,[53] similar to SGLT2i, both immortal time bias and selection bias are reduced, as the discrepancy between SGLT2i users and nonusers was minimal. In addition, prior studies demonstrate that DPP4i improved liver enzyme levels and the noninvasive liver fibrosis index in individuals with NAFLD.[54] Sulfonylurea, another common second-line OAD, promotes insulin secretion and weight gain, adversely impacting NAFLD progression.[55] On the other hand, DPP4i suppresses the elevated plasma DPP4 level reported in individuals with NAFLD.[56] As DPP4 secreted by hepatocytes is related to insulin resistance or adipose inflammation,[57] DPP4i could improve, or at least not worsen, liver-related outcomes in individuals with NAFLD. For example, omarigliptin, a DPP4i, decreases liver enzyme levels and improves the noninvasive hepatic fibrosis index in individuals with NAFLD.[54] However, we found that SGLT2i users showed better liver-related outcomes than DPP4i users, suggesting that SGLT2i is preferable to DPP4i for individuals with both NAFLD and T2DM.

There are several limitations of this study. First, we may only speculate on the mechanism by which SGLT2 inhibition prevents cirrhosis, and additional translational research is needed to bridge this knowledge gap. Second, the relatively healthy study population of the Korea NHIS database with health examination data and the UKB database could have caused selection bias or prescription bias. Third, the definitions of MASLD and MetALD heavily rely on accurately assessing alcohol consumption. In the Korean NHIS database, the brevity of the alcohol habit–related questionnaire items makes it challenging to precisely gauge alcohol intake. To manage this limitation, we proceeded with our analysis by conducting sensitivity analyses, using different definitions of excessive alcohol intake. Fourth, as we have previously highlighted, the use of MR to explore the effects of multiple interventions within specific disease cohorts (eg, T2DM, MASLD, or MetALD) faces significant hurdles, including the risk of collider bias.[19] In response to these challenges, our study opted for a population-based cohort study approach. This methodology enabled us to employ a range of definitions and analytical techniques, providing a nuanced understanding of the impact of SGLT2i usage across these targeted disease populations. Nonetheless, it is important to acknowledge that this choice of study design may not fully mitigate the inherent limitations associated with observational research, including potential residual confounding. Lastly, cirrhosis and liver-related outcomes were identified using diagnostic codes (along with procedural and prescription codes), not direct diagnostic tools such as liver biopsy or liver elastography; consequently, liver-related outcomes (including cirrhosis) may be less accurate than other outcomes such as malignancy or death. Yet, the definitions used in this study have been used in other population-based studies,[23,58] which report consistent results. Furthermore, in the present study, consistent results were found across diverse ethnic populations and in multiple sensitivity analyses, which together suggest that SGLT2 inhibition reduces the risk of liver-related events or cirrhosis.

In conclusion, MR using 2 European cohorts and a nationwide cohort study using Korean claim data collectively suggest that SGLT2i treatment was associated with a lower risk of liver-related outcomes. In individuals with T2DM and with either MASLD or MetALD, the use of SGLT2i as a second-line OAD should be encouraged to prevent further liver-related complications.

AUTHOR CONTRIBUTIONS

The corresponding authors (Yoon Jun Kim and Jeong-Hoon Lee) had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. Conceptualization and methodology: Sung Won Chung, Heejin Cho, Hey-Sung Moon, Hyein Han, Hyunjae Shin, Sehoon Park, Jeong-Hoon Lee, and Yoon Jun Kim. Software: Sung Won Chung, Heejin Cho, Hye-Sung Moon, and Hyein Han. Validation: Jeong-Hoon Lee and Yoon Jun Kim. Formal analysis: Sung Won Chung, Hyunjae Shin, Heejin Cho, Hye-Sung Moon, Hyein Han, and Sehoon Park. Data curation and investigation: Sung Won Chung, Heejin Cho, Hyunjae Shin, Jeayeon Park, Moon Haeng Hur, and Sehoon Park. Resources: Min Kyung Park, Yun Bin Lee, Eun Ju Cho, Jeong-Hoon Lee, Su Jong Yu, Yoon Jun Kim, and Jung-Hwan Yoon. Writing—original draft preparation: Sung Won Chung, Hye-Sung Moon, Hyunjae Shin, and Sehoon Park. Writing—review and editing: Heejin Cho, Jeong-Hoon Lee, and Yoon Jun Kim. Visualization: Sung Won Chung, Hyunjae Shin, and Heejin Cho. Supervision:

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CONFLICTS OF INTEREST

Yun Bin Lee received grants from Samjin Pharmaceuticals and Yuhan Pharmaceuticals. Su Jong Yu received grants from Yuhan Pharmaceuticals and Daewoong Pharmaceuticals. Jung-Hwan Yoon received grants from Bayer, Bukwang Pharmaceuticals, and Daewoong Pharmaceuticals. Jeong-Hoon Lee received grants from Yuhan Pharmaceuticals. He is on the speakers' bureau for Daewoong Pharmaceuticals, Gilead, and Green-Cross Cell. Yoon Jun Kim advises and is on the speakers' bureau for Bayer. He is on the speakers' bureau and received grants from Bukwang Pharmaceuticals, Handok Pharmaceuticals, and Yuhan Pharmaceuticals. He consults for Etnova. He is on the speakers' bureau for CJ Pharmaceuticals, Gilead, MSD Korea, and Samil Pharmaceuticals. He received grants from AstraZeneca, Boston Scientific, Bristol-Myers Squibb, Celltrion, JW Creagene, Hanmi Pharmaceuticals, PharmaKing, and Roche. The remaining authors have no conflicts to report.

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REFERENCES

1. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. Diabetes Res Clin Pract. 2019;157:107843.
2. Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Phys Ther. 2008; 88:1254–64.
3. Riazi K, Azhari H, Charette JH, Underwood FE, King JA, Afshar EE, et al. The prevalence and incidence of NAFLD worldwide: A systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2022;7:851–61.
4. Pinyopornpanish K, Khoudari G, Saleh MA, Angkurawaranon C, Pinyopornpanish K, Mansoor E, et al. Hepatocellular carcinoma in nonalcoholic fatty liver disease with or without cirrhosis: A population-based study. BMC Gastroenterol. 2021; 21:394.
5. Wong RJ, Singal AK. Trends in liver disease etiology among adults awaiting liver transplantation in the United States, 2014-2019. JAMA Netw Open. 2020;3:e1920294.
6. Rinella ME, Lazarus JV, Ratziu V, Francque SM, Sanyal AJ, Kanwal F, et al. A multi-society Delphi consensus statement on new fatty liver disease nomenclature. Hepatology. 2023;78: 1966–86.
7. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64:1388–402.
8. Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2019;380:347–57.
9. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–28.
10. Xu M, Zheng J, Hou T, Lin H, Wang T, Wang S, et al. SGLT2 inhibition, choline metabolites, and cardiometabolic diseases: A mediation Mendelian randomization study. Diabetes Care. 2022; 45:2718–28.
11. Bolinder J, Ljunggren Ö, Kullberg J, Johansson L, Wilding J, Langkilde AM, et al. Effects of dapagliflozin on body weight, total fat mass, and regional adipose tissue distribution in patients with type 2 diabetes mellitus with inadequate glycemic control on metformin. J Clin Endocrinol Metab. 2012;97:1020–31.
12. Chehrehgosha H, Sohrabi MR, Ismail-Beigi F, Malek M, Reza Babaei M, Zamani F, et al. Empagliflozin improves liver steatosis and fibrosis in patients with non-alcoholic fatty liver disease and type 2 diabetes: A randomized, double-blind, placebo-controlled clinical trial. Diabetes Ther. 2021;12:843–61.
13. Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, et al. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med. 2021;384: 1113–24.
14. Park MJ, Kim H, Kim MG, Kim K. Comparison of glucagon-like peptide-1 receptor agonists and thiazolidinediones on treating nonalcoholic fatty liver disease: A network meta-analysis. Clin Mol Hepatol. 2023;29:693–704.

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15. Hartman ML, Sanyal AJ, Loomba R, Wilson JM, Nikooienejad A, Bray R, et al. Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of nonalcoholic steatohepatitis in patients with type 2 diabetes. Diabetes Care. 2020;43:1352–5.
16. Chang Y, Jeong SW, Jang JY. Recent updates on pharmacologic therapy in non-alcoholic fatty liver disease. Clin Mol Hepatol. 2024;30:129–33.
17. Davies NM, Holmes MV, Davey Smith G. Reading Mendelian randomisation studies: A guide, glossary, and checklist for clinicians. BMJ. 2018;362:k601.
18. Song SO, Jung CH, Song YD, Park CY, Kwon HS, Cha BS, et al. Background and data configuration process of a nationwide population-based study using the Korean National Health Insurance System. Diabetes Metab J. 2014;38:395–403.
19. Munafò MR, Tilling K, Taylor AE, Evans DM, Davey Smith G. Collider scope: When selection bias can substantially influence observed associations. Int J Epidemiol. 2018;47:226–35.
20. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK Biobank: An open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12:e1001779.
21. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of sociodemographic and health-related characteristics of UK Biobank participants with those of the general population. Am J Epidemiol. 2017;186:1026–34.
22. Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, et al. FinnGen provides genetic insights from a well-phenotyped isolated population. Nature. 2023;613:508–18.
23. Emdin CA, Haas M, Ajmera V, Simon TG, Homburger J, Neben C, et al. Association of genetic variation with cirrhosis: A multitrait genome-wide association and gene-environment interaction study. Gastroenterology. 2021;160:1620–633.e1613.
24. Võsa U, Claringbould A, Westra HJ, Bonder MJ, Deelen P, Zeng B, et al. Large-scale cis- and trans-eQTL analyses identify thousands of genetic loci and polygenic scores that regulate blood gene expression. Nat Genet. 2021;53:1300–10.
25. Chang CC, Chow CC, Tellier LC, Vattikuti S, Purcell SM, Lee JJ. Second-generation PLINK: Rising to the challenge of larger and richer datasets. GigaScience. 2015;4:7.
26. Price AL, Patterson NJ, Plenge RM, Weinblatt ME, Shadick NA, Reich D. Principal components analysis corrects for stratification in genome-wide association studies. Nat Genet. 2006;38:904–9.
27. Lin Z, Deng Y, Pan W. Combining the strengths of inverse-variance weighting and Egger regression in Mendelian randomization using a mixture of regressions model. PLoS Genet. 2021;17:e1009922.
28. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: Effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44:512–25.
29. Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. Genet Epidemiol. 2016;40:304–14.
30. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet. 2018;50:693–8.
31. Shin DW, Cho B, Guallar E. Korean National Health Insurance Database. JAMA Intern Med. 2016;176:138.
32. Seo HJ, Oh IH, Yoon SJ. A comparison of the cancer incidence rates between the national cancer registry and insurance claims data in Korea. Asian Pac J Cancer Prev. 2012;13:6163–8.
33. Lee CK, Ha HJ, Oh SJ, Kim JW, Lee JK, Kim HS, et al. Nationwide validation study of diagnostic algorithms for inflammatory bowel disease in Korean National Health Insurance Service database. J Gastroenterol Hepatol. 2020;35:760–8.
34. Lee DH, Chung SW, Lee J-H, Kim HY, Chung GE, Kim MS, et al. Association of chronic hepatitis B infection and antiviral treatment with the development of the extrahepatic malignancies: A nationwide cohort study. J Clin Oncol. 2022;40:3394–405.
35. Lee YH, Bang H, Park YM, Bae JC, Lee BW, Kang ES, et al. Non-laboratory-based self-assessment screening score for non-alcoholic fatty liver disease: Development, validation and comparison with other scores. PLoS One. 2014;9:e107584.
36. Lee H, Lee HW, Kim SU, Chang Kim H. Metabolic dysfunction-associated fatty liver disease increases colon cancer risk: A nationwide cohort study. Clin Transl Gastroenterol. 2022;13:e00435.
37. Park JH, Hong JY, Shen JJ, Han K, Park JO, Park YS, et al. Increased risk of young-onset digestive tract cancers among young adults age 20-39 years with nonalcoholic fatty liver disease: A nationwide cohort study. J Clin Oncol. 2023;41:3363–73.
38. Lunt M. Selecting an appropriate caliper can be essential for achieving good balance with propensity score matching. Am J Epidemiol. 2013;179:226–35.
39. Gilligan C, Anderson KG, Ladd BO, Yong YM, David M. Inaccuracies in survey reporting of alcohol consumption. BMC Public Health. 2019;19:1639.
40. Li S, Wang J, Zhang B, Li X, Liu Y. Diabetes mellitus and cause-specific mortality: A population-based study. Diabetes Metab J. 2019;43:319–41.
41. Dal Canto E, Ceriello A, Rydén L, Ferrini M, Hansen TB, Schnell O, et al. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. Eur J Prev Cardiol. 2019;26:25–32.
42. Fang HSA, Gao Q, Tan WY, Lee ML, Hsu W, Tan NC. The effect of oral diabetes medications on glycated haemoglobin (HbA1c) in Asians in primary care: A retrospective cohort real-world data study. BMC Med. 2022;20:22.
43. Chubak J, Boudreau DM, Wirtz HS, McKnight B, Weiss NS. Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. J Natl Cancer Inst. 2013;105:1456–62.
44. DeFronzo RA, Norton L, Abdul-Ghani M. Renal, metabolic and cardiovascular considerations of SGLT2 inhibition. Nat Rev Nephrol. 2017;13:11–26.
45. Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus—Mechanisms and treatments. Nat Rev Gastroenterol Hepatol. 2021;18:599–612.
46. Li L, Li Q, Huang W, Han Y, Tan H, An M, et al. Dapagliflozin alleviates hepatic steatosis by restoring autophagy via the AMPK-mTOR pathway. Front Pharmacol. 2021;12:589273.
47. Boudaba N, Marion A, Huet C, Pierre R, Viollet B, Foretz M. AMPK re-activation suppresses hepatic steatosis but its down-regulation does not promote fatty liver development. EBioMedicine. 2018;28:194–209.
48. Jojima T, Wakamatsu S, Kase M, Iijima T, Maejima Y, Shimomura K, et al. The SGLT2 inhibitor canagliflozin prevents carcinogenesis in a mouse model of diabetes and non-alcoholic steatohepatitis-related hepatocarcinogenesis: Association with SGLT2 expression in hepatocellular carcinoma. Int J Mol Sci. 2019;20:5237.
49. Gamberi T, Magherini F, Modesti A, Fiaschi T. Adiponectin signaling pathways in liver diseases. Biomedicines. 2018;6:52.
50. Kahl S, Gancheva S, Straßburger K, Herder C, Machann J, Katsuyama H, et al. Empagliflozin effectively lowers liver fat content in well-controlled type 2 diabetes: A randomized, double-blind, phase 4, placebo-controlled trial. Diabetes Care. 2020;43:298–305.
51. Giobbie-Hurder A, Gelber RD, Regan MM. Challenges of guarantee-time bias. J Clin Oncol. 2013;31:2963–9.

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52. Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes. 1998; 47:1663–70.
53. Hur KY, Moon MK, Park JS, Kim SK, Lee SH, Yun JS, et al. 2021 clinical practice guidelines for diabetes mellitus of the Korean Diabetes Association. Diabetes Metab J. 2021;45: 461–81.
54. Hattori S, Nomoto K, Suzuki T, Hayashi S. Beneficial effect of omarigliptin on diabetic patients with non-alcoholic fatty liver disease/non-alcoholic steatohepatitis. Diabetol Metab Syndr. 2021;13:28.
55. Mazzotti A, Caletti MT, Marchignoli F, Forlani G, Marchesini G. Which treatment for type 2 diabetes associated with non-alcoholic fatty liver disease? Dig Liver Dis. 2017;49: 235–40.
56. Baumeier C, Schlüter L, Saussenthaler S, Laeger T, Rödiger M, Alaze SA, et al. Elevated hepatic DPP4 activity promotes insulin resistance and non-alcoholic fatty liver disease. Mol Metab. 2017;6:1254–63.
57. Ghorpade DS, Ozcan L, Zheng Z, Nicoloro SM, Shen Y, Chen E, et al. Hepatocyte-secreted DPP4 in obesity promotes adipose inflammation and insulin resistance. Nature. 2018;555:673–7.
58. Younossi ZM, Paik JM, Al Shabeeb R, Golabi P, Younossi I, Henry L. Are there outcome differences between NAFLD and metabolic-associated fatty liver disease? Hepatology. 2022;76: 1423–37.

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