Glucagon-Like Peptide 1 Receptor Agonists and Sodium–Glucose Cotransporter 2 Inhibitors and Risk of Nonalcoholic Fatty Liver Disease Among Patients With Type 2 Diabetes

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OBJECTIVE
To determine whether glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter 2 (SGLT-2) inhibitors, separately, are associated with a decreased risk of nonalcoholic fatty liver disease (NAFLD) compared with dipeptidyl peptidase 4 (DPP-4) inhibitors among patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS
We assembled two new-user, active comparator cohorts using the U.K. Clinical Practice Research Datalink. The first included 30,291 and 225,320 new users of GLP-1 RA and DPP-4 inhibitors, respectively. The second included 41,184 and 148,421 new users of SGLT-2 inhibitors and DPP-4 inhibitors, respectively. Cox proportional hazards models weighted using propensity score fine stratification were fit to estimate hazard ratios (HRs) with 95% CIs of NAFLD. We also determined whether the study drugs were associated with a decreased risk of hepatic transaminase elevation within restricted subcohorts.

RESULTS
GLP-1 RA were associated with a lower incidence of NAFLD with a wide CI compared with DPP-4 inhibitors (3.9 vs. 4.6 per 1,000 person-years, respectively; HR 0.86, 95% CI 0.73–1.01). SGLT-2 inhibitors were associated with a decreased risk of NAFLD (5.4 vs. 7.0 per 1,000 person-years, respectively; HR 0.78, 95% CI 0.68–0.89). In the restricted subcohorts, both GLP-1 RA and SGLT-2 inhibitors were associated with a decreased risk of hepatic transaminase elevation (HR 0.89, 95% CI 0.83–0.95, and HR 0.66, 95% CI 0.61–0.71).

CONCLUSIONS
SGLT-2 inhibitors, and possibly GLP-1 RA, may be associated with a decreased incidence of NAFLD and hepatic transaminase elevation among patients with type 2 diabetes.
Patients with type 2 diabetes have a high burden of nonalcoholic fatty liver disease (NAFLD), a condition resulting from the accumulation of hepatic fat (1). Type 2 diabetes also increases the risk of developing the aggressive form of NAFLD, nonalcoholic steatohepatitis (NASH), and its potentially fatal complications, including cirrhosis, end-stage liver disease, and hepatocellular carcinoma (2–4). Overall, NAFLD has been shown to increase all-cause mortality, associated with up to 7.5% of all deaths in the U.S. (1,5,6).

There has been a growing interest in the effects of second-line antidiabetes drugs, such as glucagon-like peptide 1 receptor agonists (GLP-1 RA) and sodium–glucose cotransporter 2 (SGLT-2) inhibitors, on reducing hepatic fat content (7,8). In randomized controlled trials (RCTs), GLP-1 RAs have been associated with the resolution of established NASH compared with placebo (9,10). Similarly, SGLT-2 inhibitors compared with placebo reduced hepatic fat in RCTs among patients with type 2 diabetes and NAFLD (11,12). On the other hand, DPP-4 inhibitors were not associated with a reduction in hepatic fat (13,14). Indeed, possible reasons for GLP-1 RA and SGLT-2 inhibitors to have this potentially beneficial role in hepatic steatosis, as opposed to DPP-4 inhibitors, include their weight-reducing and anti-inflammatory effects (15–18). While the findings of these RCTs suggest a possible role for these drugs in the treatment of NAFLD, it remains unknown whether they can prevent early hepatic fat deposition and decrease the incidence of NAFLD. To date, studies assessing this association in the real-world setting have been limited. Indeed, in one study, thiazolidinediones, but not GLP-1 RA, were associated with a decreased NAFLD risk compared with sulfonylureas and insulin (19). However, to our knowledge, no real-world studies have been conducted to assess whether novel antidiabetes drugs, such as SGLT-2 inhibitors, are associated with a decreased risk of NAFLD.

Given the increasing liver-related mortality among patients with type 2 diabetes (20), we conducted a population-based cohort study to determine whether GLP-1 RA and SGLT-2 inhibitors, separately, are associated with a decreased risk of NAFLD compared with dipeptidyl peptidase 4 (DPP-4) inhibitors among patients with type 2 diabetes.

**RESEARCH DESIGN AND METHODS**

**Data Source**

We conducted this study with the U.K. Clinical Practice Research Datalink (CPRD), using the GOLD and Aurum databases. The CPRD is a population-based database containing the clinical records of >50 million patients across >2,000 primary care general practices. Diagnoses and procedures are recorded using the Read code or SNOMED-CT classification, and prescriptions written by general practitioners are coded with the U.K. Prescription Pricing Authority dictionary. The CPRD also includes information on lifestyle variables (e.g., smoking, alcohol use, BMI), clinical measures (e.g., blood pressure), and laboratory test results (e.g., hemoglobin A1c, liver enzymes). These variables have been validated, with a median positive predictive value of 89% (21–23), and the data and practices are audited regularly to ensure high quality.

The study protocol was approved by the Independent Scientific Advisory Committee of the CPRD (protocol 21_000458) and by the Research Ethics Board of the Jewish General Hospital, Montreal, Canada.

**Study Population**

We assembled two new-user, active comparator cohorts. The first cohort consisted of new users of GLP-1 RA (dulaglutide, exenatide, liraglutide [except the 3 mg/0.5 mL formulation indicated for weight loss], lixisenatide, semaglutide) and new users of DPP-4 inhibitors (albiglutin, linaglutin, saxagliptin, sitagliptin, vildagliptin) from 1 January 2007 (the year the first incretin-based drugs entered the U.K. market) through 30 April 2020. The second cohort consisted of new users of SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) and new users of DPP-4 inhibitors from 1 January 2013 (the year the first SGLT-2 inhibitor entered the U.K. market) through 30 April 2020. Cohort entry was defined as the date of the first-ever prescription for one of the drugs of interest (GLP-1 RA, SGLT-2 inhibitors) or DPP-4 inhibitors during the study period.

In both cohorts, we excluded patients <40 years of age (given that the mean age of patients diagnosed with NAFLD is ~54 years in the U.K. (24)) and those with <1 year of medical history in the CPRD before cohort entry. The latter served as a minimum washout period to ensure the identification of new users. In addition, we excluded those who were concomitantly prescribed the study drugs at cohort entry, as well as those who previously used one of the study drugs at any time before cohort entry (i.e., SGLT-2 inhibitors in the GLP-1 RA vs. DPP-4 inhibitor cohort and GLP-1 RA in the SGLT-2 inhibitor vs. DPP-4 inhibitor cohort). We also excluded patients diagnosed with end-stage renal disease at any time before cohort entry, as GLP-1 RA and SGLT-2 inhibitors are contraindicated in these patients. Finally, we excluded patients previously diagnosed with fatty liver disease (alcoholic and nonalcoholic) and those diagnosed with alcohol-related disorders and chronic liver diseases (including chronic hepatitis, fibrosis, cirrhosis, end-stage liver disease, and hepatocellular cancer) at any time before cohort entry.

We selected DPP-4 inhibitors as the active comparator because they do not reduce hepatic steatosis (13,14), they have neutral effects on body weight, and they constitute immediate theraeutic alternatives to GLP-1 RA and SGLT-2 inhibitors (25,26). This contrasts with other possible comparators, such as metformin, sulfonylureas, thiazolidinediones, and insulin. Metformin is a first-line drug used at the early stages of type 2 diabetes (25), and given the association between type 2 diabetes and NAFLD, its use can introduce confounding by indication (27). As for sulfonylureas and insulin, they are unlikely to have neutral effects, as they promote weight gain, affect insulin signaling pathways, and have been associated with profibrotic changes in the liver (25,28). Likewise, thiazolidinediones are unlikely to have neutral effects, as they have been associated with NAFLD resolution (29), and their use decreased over the years because of their effects on weight gain and possible association with cancers (26).

**Follow-up Period**

All patients were followed while continuously exposed to the study drugs with use of an on-treatment approach. Continuous use was defined as the duration...
of one prescription overlapping the date of the next prescription, with a 60-day grace period in the event of nonoverlap. Thus, patients were followed from cohort entry until an incident diagnosis of NAFLD (Supplementary Table 1), discontinuation or switching to one of the study drugs, death from any cause, end of registration with the CPRD, or end of the study period (31 July 2020)—whichever occurred first.

Potential Confounders
We considered a wide range of potential confounders, all measured before or at cohort entry. These included age (modeled using cubic splines with five interior knots) (30), sex, BMI, smoking status, and calendar year (entered as a categorical variable). We also included proxies for diabetes severity, including hemoglobin A1c, diabetes duration (defined with the date of the first of hemoglobin A1c ≥6.5%, diagnosis of type 2 diabetes, or prescription for any antidiabetes drug, modeled using cubic splines with five interior knots), microvascular complications (nephropathy, retinopathy, macular degeneration, retinopathy, and peripheral neuropathy), microvascular complications (myocardial infarction, stroke, and peripheral neuropathy), and previous use of antidiabetes drugs in the year before and including cohort entry. The models also included comorbidities—cancer, chronic heart failure, hypothyroidism, sleep apnea, and depression—and common comedications: lipid-lowering drugs, antihypertensive drugs, and antplatelet drugs. Finally, we considered drugs known to induce fatty liver disease (methotrexate, griseofulvin, tamoxifen, glucocorticoids, valproate, amiodarone, oral contraceptives, hormone replacement therapy, and androgen deprivation therapy) and markers of health-seeking behavior (uptake of cancer screening [fecal occult blood testing or colonoscopy, mammography, prostate-specific antigen testing] and influenza and pneumococcal vaccinations), all measured in the year before cohort entry.

Statistical Analysis
We used propensity score fine stratification to adjust for confounding (31). In each new-user cohort, we estimated the predicted probability of receiving the drugs of interest (GLP-1 RA or SGLT-2 inhibitor) versus a DPP-4 inhibitor using multivariable logistic regression models conditional on the covariates listed above. Patients in the nonoverlapping regions of the propensity score distributions were trimmed from the cohorts. We then created 50 strata based on the propensity score distribution of the patients receiving the drugs of interest (GLP-1 RA or SGLT-2 inhibitors). Within each stratum, GLP-1 RA or SGLT-2 inhibitor users received a weight of 1, while users of DPP-4 inhibitors were weighted in proportion to the number exposed in the corresponding stratum (31). With this method we aimed to balance the covariate distribution within each stratum. By creating strata based on the smaller exposure group, we ensured minimal loss of information and avoided extreme weights; this method is thus useful in scenarios of low exposure prevalence. The estimator generated with this approach is the average treatment effect among the treated.

We used descriptive statistics to summarize the characteristics of the exposure groups before and after propensity score weighting. Standardized differences were used to assess covariate balance between the exposure groups, with differences <0.10 indicating good balance (32). Incidence rates of NAFLD, with 95% CIs based on the Poisson distribution, were calculated for each exposure group. Weighted Kaplan-Meier curves were plotted to display the cumulative incidence of NAFLD for each exposure group over the follow-up period. Weighted Cox proportional hazards models were fit to estimate hazard ratios (HRs) with 95% CIs of incident NAFLD, comparing GLP-1 RA and SGLT-2 inhibitors, separately, with DPP-4 inhibitors. Finally, we calculated the number needed to treat to prevent one NAFLD event after 1 and 5 years of use with the Kaplan-Meier method (33).

Secondary Analyses
We conducted three secondary analyses. First, we assessed whether there was a duration-response relation between the use of GLP-1 RA and SGLT-2 inhibitors and the incidence of NAFLD. For this analysis, duration of use was updated at every risk set (i.e., a time-varying fashion), allowing patients to contribute to different duration categories. This variable was modeled on the continuous scale with use of restricted cubic splines with five interior knots to allow for potential violations of the linearity assumption. Second, we assessed whether the association varied with individual drugs within each class. Third, we examined possible effect measure modification by age (<=75 and >=75 years, given the age-based differences in prognosis of NAFLD) (34), sex (given that NAFLD is more common among males) (35), metformin use (as it has been associated with weight loss) (36), thiazolidinediones use (as they have been shown to resolve NASH in patients with type 2 diabetes) (29), and lipid-lowering drugs use (as they have been associated with improvement of liver enzymes in patients with NAFLD) (37) and according to BMI category at cohort entry (<=24.9, 25.0-29.9, >=30 kg/m²). We tested effect measure modification by including interaction terms between the exposures and these variables in the models.

Sensitivity Analyses
We conducted four sensitivity analyses to assess the robustness of the findings. First, we repeated the analyses by varying the grace period between consecutive prescriptions to 30 and 90 days. Second, we used time-varying inverse probability of censoring weighting to account for potential informative censoring due to 1) discontinuation or switching between the exposure groups, 2) administrative censoring (end of the study period and end of registration with the general practice), and 3) competing risk by death (38-40). This involved taking the product of the weights calculated from the conditional probabilities of treatment discontinuation or switching, administrative censoring, and death using the covariates listed above. Third, we conducted an intention-to-treat analysis with follow-up censored at 1 year (to minimize the effects of exposure misclassification). Finally, we repeated the analyses using a more restrictive algorithm, where the outcome had to be accompanied by supporting clinical events within 3 months of the NAFLD diagnosis. These included abdominal imaging, transaminase elevations, liver biopsy, and referrals to gastroenterology, in the absence of other acute and chronic liver disease diagnoses (which may lead to fatty changes in the liver) (Supplementary Fig. 1). This was done using the
definition of the American Association for the Study of Liver Diseases for identifying NAFLD using electronic health data (41).

**Restricted Subcohort Analysis**
We assembled restricted subcohorts (42) to assess the impact of residual confounding and the possibility that some patients in the cohorts had undiagnosed NAFLD. This entailed further restricting the cohorts described above to patients with at least one laboratory value of hepatic transaminases (ALT or AST) in the year before cohort entry and then excluding those with values above the reference range (ALT or AST >50 IU/L) (43). Thus, those remaining in the cohorts were patients with no evidence of liver abnormalities at any time before cohort entry and with normal hepatic transaminases levels in the year before cohort entry.

We conducted two analyses within each of the restricted subcohorts. The first was analogous to the primary analysis and included assessment of whether GLP-1 RA and SGLT-2 inhibitors are associated with a decreased risk of NAFLD. In the second, we evaluated whether GLP-1 RA and SGLT-2 inhibitors are associated with decreased risk of elevation in hepatic transaminases, as NAFLD is associated with elevation in hepatic transaminases by more than one to three times the reference range (that is, >50 IU/L in either ALT or AST) (44,45). For this analysis, patients were followed from cohort entry until an incident elevation in hepatic transaminases, discontinuation or switching to one of the study drugs, death from any cause, end of registration with the CPRD, or end of study period (31 July 2020)—whichever occurred first. All analyses were conducted with SAS, version 9.4 (SAS Institute, Cary, NC).

**RESULTS**
During the study period, the incidence of NAFLD increased nearly fourfold, from 1.2 per 1,000 person-years in 2007 to 4.5 per 1,000 person-years in 2019 (Supplementary Fig. 2). This pattern mirrored the prescribing rates of GLP-1 RA, DPP-4 inhibitors, and SGLT-2 inhibitors, which also increased during the study period (Supplementary Fig. 2).

**GLP-1 RA Versus DPP-4 Inhibitors**
The first cohort included 30,291 new users of GLP-1 RA and 225,320 new users of DPP-4 inhibitors (Supplementary Fig. 3). Before weighting, GLP-1 RA users were younger and more likely to be obese and have microvascular complications of diabetes compared with DPP-4 inhibitor users (Table 1). After weighting, the baseline covariates were well-balanced between the exposure groups (Table 1). There were 2,144 NAFLD events during a median follow-up of 1.4 years (interquartile range 0.5–3.1).

Table 3 presents the results of the primary analyses. The use of GLP-1 RA was associated with a lower incidence of NAFLD compared with DPP-4 inhibitors, although the CI included the null value (3.9 vs. 4.6 per 1,000 person-years, respectively; HR 0.86, 95% CI 0.73–1.01) (Table 3). The cumulative incidence curves diverged after 4 years of use, with a lower cumulative incidence of NAFLD among GLP-1 RA users than DPP-4 inhibitor users (Supplementary Fig. 5). In secondary analyses, the CI of the HR included the null value throughout the duration of use (Supplementary Fig. 6). The number needed to treat at 1 and 5 years of use was 1,371 and 348.

The association between GLP-1 RA and NAFLD was not modified by age, sex, use of lipid-lowering drugs, or prior use of metformin or thiazolidinediones (Supplementary Fig. 7). Among the individual drugs, exenatide users had a significantly lower incidence of NAFLD compared with DPP-4 inhibitors (Supplementary Fig. 7). The sensitivity analyses generated consistent results, with the exception of the more restrictive outcome definition in which the use of GLP-1 RA was associated with a 23% decreased risk of NAFLD compared with DPP-4 inhibitors (HR 0.77, 95% CI 0.63–0.94) (Supplementary Fig. 8).

**SGLT-2 Inhibitors Versus DPP-4 Inhibitors**
The second cohort included 41,184 new users of SGLT-2 inhibitors and 148,421 new users of DPP-4 inhibitors (Supplementary Fig. 4). Before weighting, SGLT-2 inhibitor users were younger, more likely to be obese, and less likely to have microvascular complications than DPP-4 inhibitor users (Table 2). After weighting, all covariates were well-balanced between the exposure groups (Table 2). Overall, there were 1,507 NAFLD events over a median follow-up of 1.1 years (interquartile range 0.5–2.5).

The use of SGLT-2 inhibitors was associated with a 22% decreased risk of NAFLD compared with DPP-4 inhibitors (5.4 vs. 7.0 per 1,000 person-years, respectively; HR 0.78, 95% CI 0.68–0.89) (Table 3). The cumulative incidence curves diverged after 4 months of use, where a lower cumulative incidence of NAFLD was observed with SGLT-2 inhibitors (Supplementary Fig. 9). In secondary analyses, the lowest HR for the association between SGLT-2 inhibitors and NAFLD was observed at ~1.3 years of use (HR 0.64, 95% CI 0.50–0.81); however, it gradually increased with increasing duration of use but with wider CIs after ~2.5 years (Supplementary Fig. 10). The number needed to treat at 1 and 5 years of use was 552 and 166, respectively.

There was no effect measure modification by age, sex, BMI, use of lipid-lowering drugs, or prior use of metformin or thiazolidinediones (Supplementary Fig. 11). In the individual drugs-based analysis, dapagliflozin was associated with a lower risk of NAFLD (Supplementary Fig. 11). Overall, the findings remained consistent in sensitivity analyses where we varied the grace period, reweighted using inverse probability of censoring weights, used an intention-to-treat approach, and used an alternative outcome definition of NAFLD (Supplementary Fig. 12).

**Restricted Subcohorts**
The first restricted subcohort included 20,676 new users of GLP-1 RA and 175,091 new users of DPP-4 inhibitors (Supplementary Fig. 13). Overall, GLP-1 RA were not associated with a decreased risk of NAFLD, while an 11% decreased risk was observed with elevated hepatic transaminase levels (Table 4 and Supplementary Fig. 14).

The second restricted subcohort included 30,639 new users of SGLT-2 inhibitors and 116,520 new users of DPP-4 inhibitors in the second cohort (Supplementary Fig. 15). SGLT-2 inhibitors were associated with a 21% decreased risk of NAFLD and a 34% decreased risk of elevated hepatic transaminase levels (Table 4 and Supplementary Fig. 16).
Table 1—Baseline characteristics of the GLP-1 RA versus DPP-4 inhibitor exposure groups before and after propensity score weighting

|                               | Before weighting | Standardized difference | After weighting | Standardized difference |
|--------------------------------|------------------|-------------------------|-----------------|-------------------------|
| **Total, n**                   | GLP-1 RA         | DPP-4 inhibitors        | GLP-1 RA        | DPP-4 inhibitors        |
|                                | 30,291           | 225,320                 | 30,291          | 225,320                 |
| Age, years, mean (SD)          | 58.0 (9.6)       | 65.3 (12.1)             | 58.0 (9.6)      | 58.2 (9.7)              |
| Male, n (%)                    | 15,861 (52.4)    | 127,965 (56.8)          | 15,861 (52.4)   | 115,928 (51.5)          |
| BMI 
24.9 kg/m², n (%)           | 202 (0.7)        | 70,691 (31.4)           | 202 (0.7)       | 13,829 (6.1)            |
| BMI ≥30.0 kg/m², n (%)        | 27,550 (91.0)    | 124,441 (55.7)          | 27,550 (91.0)   | 204,585 (90.8)          |
| Smoking status, n (%)         | 24,626 (81.3)    | 178,726 (79.3)          | 24,626 (81.3)   | 182,965 (81.2)          |
| Hemoglobin A1c, n (%)         | 10,860 (35.9)    | 14,502 (6.4)            | 10,860 (35.9)   | 78,836 (35.0)           |
| Type of antidiabetes drugs, n (%) | 27,282 (90.1) | 199,582 (88.6) | 27,282 (90.1) | 201,797 (89.6) |
| Metformin                      | 15,155 (50.0)    | 110,817 (49.2)          | 15,155 (50.0)   | 118,576 (52.6)          |
| Thiazolidinedione              | 7,240 (23.9)     | 28,921 (12.8)           | 7,240 (23.9)    | 58,221 (25.8)           |
| Meglitinides                   | 349 (1.2)        | 1,727 (0.8)             | 349 (1.2)       | 2,830 (1.3)             |
| α-Glucosidase inhibitors       | 242 (0.8)        | 981 (0.4)               | 242 (0.8)       | 2,032 (0.9)             |
| Insulin                        | 10,860 (35.9)    | 14,502 (6.4)            | 10,860 (35.9)   | 78,836 (35.0)           |
| Peripheral vascular disease, n (%) | 2,943 (9.7)     | 20,939 (8.9)            | 2,943 (9.7)     | 21,782 (9.7)            |
| Stroke, n (%)                  | 1,168 (3.9)      | 13,400 (5.9)            | 1,168 (3.9)     | 8,962 (4.0)             |
| Myocardial infarction, n (%)   | 2,330 (7.7)      | 19,028 (8.4)            | 2,330 (7.7)     | 17,660 (7.8)            |
| Renal disease, n (%)           | 4,738 (15.6)     | 50,732 (22.5)           | 4,738 (15.6)    | 36,585 (16.2)           |
| Retinopathy, n (%)             | 12,090 (39.9)    | 81,472 (36.2)           | 12,090 (39.9)   | 88,887 (39.4)           |
| Neuropathy, n (%)              | 8,548 (28.2)     | 53,659 (23.8)           | 8,548 (28.2)    | 62,674 (27.8)           |
| Cancer, n (%)                  | 1,738 (5.7)      | 21,092 (9.4)            | 1,738 (5.7)     | 13,358 (5.9)            |
| Heart failure, n (%)           | 1,322 (4.4)      | 11,858 (5.3)            | 1,322 (4.4)     | 10,165 (4.5)            |
| Hypothyroidism, n (%)          | 3,610 (11.9)     | 25,027 (11.1)           | 3,610 (11.9)    | 27,103 (12.0)           |
| Sleep apnea, n (%)             | 2,810 (9.3)      | 7,351 (3.3)             | 2,810 (9.3)     | 20,806 (9.2)            |
| Depression, n (%)              | 13,334 (44.0)    | 71,773 (31.9)           | 13,334 (44.0)   | 99,597 (44.2)           |
| Antiplatlet, n (%)             | 1,925 (6.4)      | 16,838 (7.5)            | 1,925 (6.4)     | 14,664 (6.5)            |
| Statins, n (%)                 | 25,017 (82.6)    | 181,778 (80.7)          | 25,017 (82.6)   | 184,992 (82.1)          |
| Fibrates, n (%)                | 1,221 (4.0)      | 5,119 (2.3)             | 1,221 (4.0)     | 8,539 (3.8)             |
| ACE inhibitors, n (%)          | 16,516 (54.5)    | 107,882 (47.9)          | 16,516 (54.5)   | 122,149 (54.2)          |
| Angiotensin II receptor blockers, n (%) | 6,804 (22.5) | 44,497 (19.7) | 6,804 (22.5) | 50,731 (22.5) |

Continued on p. 6
| Before weighting | GLP-1 RA | DPP-4 inhibitors | Standardized difference | After weighting | GLP-1 RA | DPP-4 inhibitors | Standardized difference |
|------------------|---------|-----------------|------------------------|----------------|---------|-----------------|------------------------|
| B-Blockers, n (%)| 7,821 (25.8) | 60,514 (26.9) | 0.02 | 7,821 (25.8) | 58,916 (26.1) | 0.01 |
| Calcium channel blockers, n (%) | 10,220 (33.7) | 74,978 (33.3) | 0.01 | 10,220 (33.7) | 76,199 (33.8) | 0.00 |
| Diuretics, n (%) | 8,718 (28.8) | 54,193 (24.1) | 0.11 | 8,718 (28.8) | 65,373 (29.0) | 0.01 |
| Renin inhibitors, n (%) | 52 (0.2) | 202 (0.1) | 0.02 | 52 (0.2) | 417 (0.2) | 0.00 |
| Methotrexate, n (%) | 248 (0.8) | 1,802 (0.8) | 0.00 | 248 (0.8) | 1,938 (0.9) | 0.00 |
| Griseofulvin, n (%) | 2 (0.0)* | 18 (0.0) | 0.00 | 2 (0.0)* | 12 (0.0) | 0.00 |
| Tamoxifen, n (%) | 61 (0.2) | 647 (0.3) | 0.02 | 61 (0.2) | 516 (0.2) | 0.01 |
| Steroids, n (%) | 14,064 (46.4) | 94,393 (41.9) | 0.11 | 14,064 (46.4) | 105,507 (46.8) | 0.01 |
| Valproate, n (%) | 237 (0.8) | 1,602 (0.7) | 0.01 | 237 (0.8) | 1,857 (0.8) | 0.00 |
| Amiodarone, n (%) | 136 (0.4) | 1,105 (0.5) | 0.01 | 136 (0.4) | 1,162 (0.5) | 0.01 |
| Oral contraceptives, n (%) | 896 (3.0) | 2,928 (1.3) | 0.12 | 896 (3.0) | 6,919 (3.1) | 0.01 |
| Hormone replacement therapy, n (%) | 920 (3.0) | 4,512 (2.0) | 0.07 | 920 (3.0) | 7,305 (3.2) | 0.01 |
| Androgen deprivation therapy, n (%) | 94 (0.3) | 1,547 (0.7) | 0.05 | 94 (0.3) | 735 (0.3) | 0.00 |
| Fecal occult blood testing or colonoscopy, n (%) | 2,463 (8.1) | 26,388 (11.7) | 0.12 | 2,463 (8.1) | 18,555 (8.2) | 0.00 |
| Mammography, n (%) | 2,591 (8.6) | 14,660 (6.5) | 0.08 | 2,591 (8.6) | 19,672 (8.7) | 0.01 |
| Prostate-specific antigen testing, n (%) | 1,616 (5.3) | 18,978 (8.4) | 0.12 | 1,616 (5.3) | 12,147 (5.4) | 0.00 |
| Influenza vaccination, n (%) | 13,171 (43.5) | 58,341 (25.9) | 0.38 | 13,171 (43.5) | 97,245 (43.2) | 0.01 |
| Pneumococcal vaccination, n (%) | 1,273 (4.2) | 9,880 (4.4) | 0.01 | 1,273 (4.2) | 9,363 (4.2) | 0.00 |
| Year of cohort entry, n (%) | | | | | | |
| 2007 | 328 (1.1) | 838 (0.4) | 0.08 | 328 (1.1) | 2,619 (1.2) | 0.01 |
| 2008 | 2,172 (7.2) | 4,262 (1.9) | 0.26 | 2,172 (7.2) | 15,009 (6.7) | 0.02 |
| 2009 | 3,874 (12.8) | 10,923 (4.8) | 0.28 | 3,874 (12.8) | 26,310 (11.7) | 0.03 |
| 2010 | 4,528 (14.9) | 20,484 (9.1) | 0.18 | 4,528 (14.9) | 34,328 (15.2) | 0.01 |
| 2011 | 3,349 (11.1) | 19,528 (8.7) | 0.08 | 3,349 (11.1) | 26,170 (11.6) | 0.02 |
| 2012 | 3,587 (11.8) | 21,117 (9.4) | 0.08 | 3,587 (11.8) | 27,317 (12.1) | 0.01 |
| 2013 | 2,299 (7.6) | 19,759 (8.8) | 0.04 | 2,299 (7.6) | 17,575 (7.8) | 0.01 |
| 2014 | 1,796 (5.9) | 19,537 (8.7) | 0.11 | 1,796 (5.9) | 13,909 (6.2) | 0.01 |
| 2015 | 1,754 (5.8) | 21,482 (9.5) | 0.14 | 1,754 (5.8) | 13,279 (5.9) | 0.00 |
| 2016 | 1,377 (4.5) | 22,332 (9.9) | 0.21 | 1,377 (4.5) | 10,290 (4.6) | 0.00 |
| 2017 | 1,370 (4.5) | 21,585 (9.6) | 0.20 | 1,370 (4.5) | 9,900 (4.4) | 0.01 |
| 2018 | 1,438 (4.7) | 20,582 (9.1) | 0.17 | 1,438 (4.7) | 10,514 (4.7) | 0.00 |
| 2019 | 1,841 (6.1) | 17,989 (8.0) | 0.07 | 1,841 (6.1) | 13,735 (6.1) | 0.00 |
| 2020 | 578 (1.9) | 4,902 (2.2) | 0.02 | 578 (1.9) | 4,365 (1.9) | 0.00 |

*Cells with less than 5 observations are suppressed as per the confidentiality policies of the Clinical Practice Research Datalink.
Table 2—Baseline characteristics of the SGLT-2 inhibitor versus DPP-4 inhibitor exposure groups before and after propensity score weighting

|                          | Before weighting | Standardized difference | After weighting | Standardized difference |
|--------------------------|------------------|-------------------------|----------------|-------------------------|
|                          | SGLT-2 inhibitors | DPP-4 inhibitors        |                | SGLT-2 inhibitors        | DPP-4 inhibitors        |
| Age, years, mean (SD)    | 58.7 (9.7)       | 66.4 (12.4)             | 0.69           | 58.7 (9.7)              | 58.8 (9.8)              |
| Male, n (%)              | 24,198 (58.8)    | 84,417 (56.9)           | 0.04           | 24,198 (58.8)           | 87,122 (58.7)           |
| BMI                      |                  |                         |                |                         |                         |
| ≤24.9 kg/m², n (%)       | 2,220 (5.4)      | 19,820 (13.4)           | 0.28           | 2,220 (5.4)             | 8,276 (5.6)             |
| 25.0–29.9 kg/m², n (%)   | 9,629 (23.4)     | 48,477 (32.7)           | 0.21           | 9,629 (23.4)            | 34,821 (23.5)           |
| ≥30.0 kg/m², n (%)       | 28,946 (70.3)    | 78,516 (52.9)           | 0.36           | 28,946 (70.3)           | 103,838 (70.0)          |
| Unknown                  | 389 (0.9)        | 1,608 (1.1)             | 0.01           | 389 (0.9)               | 1,486 (1.0)             |
| Smoking status, n (%)    |                  |                         |                |                         |                         |
| Ever                     | 31,292 (76.0)    | 116,995 (78.8)          | 0.07           | 31,292 (76.0)           | 112,678 (75.9)          |
| Never                    | 9,865 (24.0)     | 31,324 (21.1)           | 0.07           | 9,865 (24.0)            | 35,641 (24.0)           |
| Unknown                  | 27 (0.1)         | 102 (0.1)               | 0.00           | 27 (0.1)                | 102 (0.1)               |
| Hemoglobin A₁c, n (%)    |                  |                         |                |                         |                         |
| ≤7.0%                    | 2,403 (5.8)      | 14,072 (9.5)            | 0.14           | 2,403 (5.8)             | 8,802 (5.9)             |
| 7.1–8.0%                 | 9,649 (23.4)     | 42,594 (28.7)           | 0.12           | 9,649 (23.4)            | 34,440 (23.2)           |
| >8.0%                    | 28,969 (70.3)    | 90,901 (61.2)           | 0.19           | 28,969 (70.3)           | 104,542 (70.4)          |
| Unknown                  | 163 (0.4)        | 854 (0.6)               | 0.03           | 163 (0.4)               | 637 (0.4)               |
| Diabetes duration, years, mean (SD) | 7.9 (6.1) | 9.1 (6.6) | 0.19 | 7.9 (6.1) | 7.9 (6.1) |
| Type of antidiabetes drugs, n (%) |          |                         |                |                         |                         |
| Metformin                | 38,398 (93.2)    | 129,534 (87.3)          | 0.20           | 38,398 (93.2)           | 138,466 (93.3)          |
| Sulfonylureas            | 14,510 (35.2)    | 64,435 (43.4)           | 0.17           | 14,510 (35.2)           | 52,657 (35.5)           |
| Thiazolidinedione        | 2,772 (6.7)      | 9,093 (6.1)             | 0.02           | 2,772 (6.7)             | 9,193 (6.7)             |
| Meglitinides             | 122 (0.3)        | 498 (0.3)               | 0.01           | 122 (0.3)               | 474 (0.3)               |
| α-Glucosidase inhibitors | 46 (0.1)         | 315 (0.2)               | 0.03           | 46 (0.1)                | 178 (0.1)               |
| Insulin                  | 5,127 (12.4)     | 10,002 (6.7)            | 0.19           | 5,127 (12.4)            | 18,068 (12.2)           |
| Peripheral vascular disease, n (%) | 2,564 (6.2) | 13,876 (9.3) | 0.12 | 2,564 (6.2) | 9,304 (6.3) |
| Stroke, n (%)            | 1,365 (3.3)      | 9,724 (6.6)             | 0.15           | 1,365 (3.3)             | 5,033 (3.4)             |
| Myocardial infarction, n (%) | 2,677 (6.5) | 12,879 (8.7) | 0.08 | 2,677 (6.5) | 9,635 (6.5) |
| Renal disease, n (%)     | 2,462 (6.0)      | 35,550 (24.0)           | 0.52           | 2,462 (6.0)             | 9,311 (6.3)             |
| Retinopathy, n (%)       | 13,138 (31.9)    | 54,556 (36.8)           | 0.10           | 13,138 (31.9)           | 46,475 (31.3)           |
| Neuropathy, n (%)        | 6,784 (16.5)     | 33,427 (22.5)           | 0.15           | 6,784 (16.5)            | 24,318 (16.4)           |
| Cancer, n (%)            | 2,440 (5.9)      | 15,382 (10.4)           | 0.16           | 2,440 (5.9)             | 8,784 (6.0)             |
| Heart failure, n (%)     | 1,012 (2.5)      | 8,551 (5.8)             | 0.17           | 1,012 (2.5)             | 3,791 (2.6)             |
| Hypothyroidism, n (%)    | 4,430 (10.8)     | 17,595 (11.9)           | 0.03           | 4,430 (10.8)            | 16,026 (10.8)           |
| Sleep apnea, n (%)       | 2,321 (5.6)      | 5,230 (3.5)             | 0.10           | 2,321 (5.6)             | 8,385 (5.6)             |
| Depression, n (%)        | 15,330 (37.2)    | 48,329 (32.6)           | 0.10           | 15,330 (37.2)           | 54,909 (37.0)           |
| Antiplatelet, n (%)      | 2,394 (5.8)      | 12,381 (8.3)            | 0.10           | 2,394 (5.8)             | 8,631 (5.8)             |
| Statins, n (%)           | 31,031 (75.3)    | 117,382 (79.1)          | 0.09           | 31,031 (75.3)           | 111,163 (74.9)          |
| Fibrates, n (%)          | 755 (1.8)        | 2,899 (2.0)             | 0.01           | 755 (1.8)               | 2,607 (1.8)             |
| ACE inhibitors, n (%)    | 18,270 (44.4)    | 68,305 (46.0)           | 0.03           | 18,270 (44.4)           | 65,438 (44.1)           |
| Angiotensin II receptor blockers, n (%) | 6,564 (15.9) | 28,166 (19.0) | 0.08 | 6,564 (15.9) | 23,488 (15.8) |
| β-Blockers, n (%)        | 8,487 (20.6)     | 41,053 (27.7)           | 0.17           | 8,487 (20.6)            | 30,589 (20.6)           |
|                         | 11,835 (28.7)    | 50,019 (33.7)           | 0.11           | 11,835 (28.7)           | 42,742 (28.8)           |
CONCLUSIONS

The results of this large population-based study indicate that the use of SGLT-2 inhibitors, and possibly GLP-1 RA, is associated with a decreased risk of NAFLD compared with the use of DPP-4 inhibitors. In addition, both GLP-1 RA and SGLT-2 inhibitors were associated with a decreased risk of hepatic transaminase elevations. Overall, these results remained consistent in sensitivity analyses.

In several small-scale RCTs investigators have examined the efficacy of GLP-1 RA and SGLT-2 inhibitors in patients with established NAFLD, both with and without type 2 diabetes (8). In these RCTs, GLP-1 RA and SGLT-2 inhibitors were associated with reduced hepatic fat and resolution of inflammatory histologic changes associated with NAFLD (9,10,12). In addition, in one RCT with examination of the effect of SGLT-2 inhibitors in patients with well-controlled diabetes with or without NAFLD, investigators found a reduction in hepatic fat content irrespective of the presence of NAFLD (11).

To date, only one observational study has included examination of the association between GLP-1 RA and the incidence of NAFLD in patients with type 2 diabetes (19). In that study, GLP-1 RA were not associated with a decreased incidence of NAFLD compared with insulin (HR 1.22, 95% CI 0.91–1.63) (19). In contrast, we found GLP-1 RA were associated with a decreased incidence of NAFLD, although the CI included the null value. We also found that GLP-1 RA were associated with a decreased risk of new-onset hepatic transaminase elevation. Finally, our findings suggest that SGLT-2 inhibitors may reduce both the incidence of NAFLD and elevations in hepatic transaminase. These novel findings will need

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| Table 2—Continued |
|-------------------|
|                  | Before weighting | Standardized difference | After weighting | Standardized difference |
| Calcium channel blockers, n (%) | SGLT-2 inhibitors | DPP-4 inhibitors | SGLT-2 inhibitors | DPP-4 inhibitors |
| Diuretics, n (%) | 6,324 (15.4) | 35,416 (23.9) | 0.22 | 6,324 (15.4) | 22,975 (15.5) | 0.00 |
| Renin inhibitors, n (%) | 11 (0.0) | 46 (0.0) | 0.00 | 11 (0.0) | 49 (0.0) | 0.00 |
| Methotrexate, n (%) | 329 (0.8) | 1,255 (0.8) | 0.01 | 329 (0.8) | 1,185 (0.8) | 0.00 |
| Griseofulvin, n (%) | 1 (0.0)* | 9 (0.0) | 0.01 | 1 (0.0)* | 4 (0.0)* | 0.00 |
| Tamoxifen, n (%) | 104 (0.3) | 412 (0.3) | 0.00 | 104 (0.3) | 366 (0.2) | 0.00 |
| Steroids, n (%) | 16,155 (39.2) | 62,405 (42.0) | 0.06 | 16,155 (39.2) | 58,185 (39.2) | 0.00 |
| Valproate, n (%) | 299 (0.7) | 1,211 (0.8) | 0.00 | 299 (0.7) | 1,101 (0.7) | 0.00 |
| Amiodarone, n (%) | 75 (0.2) | 766 (0.5) | 0.06 | 75 (0.2) | 281 (0.2) | 0.00 |
| Oral contraceptives, n (%) | 1,081 (2.6) | 1,933 (1.3) | 0.10 | 1,081 (2.6) | 3,847 (2.6) | 0.00 |
| Hormone replacement therapy, n (%) | 988 (2.4) | 2,931 (2.0) | 0.03 | 988 (2.4) | 3,523 (2.4) | 0.00 |
| Androgen deprivation therapy, n (%) | 134 (0.3) | 1,105 (0.7) | 0.06 | 134 (0.3) | 480 (0.3) | 0.00 |
| Fecal occult blood testing or colonoscopy, n (%) | 6,732 (16.3) | 22,790 (15.4) | 0.03 | 6,732 (16.3) | 24,306 (16.4) | 0.00 |
| Mammography, n (%) | 3,301 (8.0) | 9,326 (6.3) | 0.07 | 3,301 (8.0) | 11,971 (8.1) | 0.00 |
| Prostate-specific antigen testing, n (%) | 2,855 (6.9) | 13,154 (8.9) | 0.07 | 2,855 (6.9) | 10,377 (7.0) | 0.00 |
| Influenza vaccination, n (%) | 594 (1.4) | 4,427 (3.0) | 0.10 | 594 (1.4) | 2,156 (1.5) | 0.00 |
| Pneumococcal vaccination, n (%) | 2,467 (6.0) | 6,333 (4.3) | 0.08 | 2,467 (6.0) | 8,739 (5.9) | 0.00 |
| Year of cohort entry, n (%) | 483 (1.2) | 19,415 (13.1) | 0.48 | 483 (1.2) | 1,883 (1.3) | 0.01 |
| 2013 | 2,343 (5.7) | 19,580 (13.2) | 0.26 | 2,343 (5.7) | 8,157 (5.5) | 0.01 |
| 2015 | 4,668 (11.3) | 21,564 (14.5) | 0.10 | 4,668 (11.3) | 16,307 (11.0) | 0.01 |
| 2016 | 5,627 (13.7) | 22,500 (15.2) | 0.04 | 5,627 (13.7) | 20,257 (13.6) | 0.00 |
| 2017 | 6,584 (16.0) | 21,721 (14.6) | 0.04 | 6,584 (16.0) | 23,657 (15.9) | 0.00 |
| 2018 | 7,854 (19.1) | 20,689 (13.9) | 0.14 | 7,854 (19.1) | 28,508 (19.2) | 0.00 |
| 2019 | 10,116 (24.6) | 18,040 (12.2) | 0.32 | 10,116 (24.6) | 36,733 (24.7) | 0.00 |
| 2020 | 3,509 (8.5) | 4,912 (3.3) | 0.22 | 3,509 (8.5) | 12,919 (8.7) | 0.01 |

*Cells with less than 5 observations are suppressed as per the confidentiality policies of the Clinical Practice Research Datalink.*
to be corroborated in future studies. Furthermore, additional studies will be needed to directly compare the effectiveness of GLP-1 RA and SGLT-2 inhibitors in reducing the risk of NAFLD and new-onset hepatic transaminase elevation.

Several possible biological mechanisms can explain the decreased risk of NAFLD observed with GLP-1 RA and SGLT-2 inhibitors. First, these drugs are known to induce weight loss (15,16). Such weight loss can prevent hepatic fat accumulation when hepatic steatosis has not yet developed or reverse early fat accumulation, thus reducing NAFLD incidence. Second, these drugs have been shown to have anti-inflammatory effects (17,18), reduce blood pressure (17,46), and improve lipid imbalances (18,47), all of which are beneficial in metabolic syndrome, of which NAFLD is considered to be the hepatic manifestation (48).

In this study, the use of GLP-1 RA and SGLT-2 inhibitors was also associated with a decreased risk of new-onset hepatic transaminase elevation in a cohort with no history of NAFLD. Hepatic transaminases are the most common biochemical abnormality in patients with NAFLD (44) and are used in early detection and management of this condition (45). Systemically, elevated hepatic transaminases are associated with increased systemic proinflammatory biomarkers such as C-reactive protein (49) and are independent predictors of adverse cardiovascular outcomes (50). In the liver, they have been found to correlate with the extent of hepatocyte inflammation in NAFLD (51,52), with several studies reporting higher hepatic transaminase in NASH (4,52). While RCTs of GLP-1 RA and SGLT-2 inhibitors have reported reductions in hepatic transaminases among patients with elevated baseline levels, our study is the first to report that these drugs may be associated with a decreased risk of new-onset hepatic transaminase elevation (8). Future studies should examine whether the decreased risk of hepatic transaminase elevation associated with the use of these drugs translates into delaying systemic complications of NAFLD.

This study has several strengths. First, we assembled large cohorts of patients using GLP-1 RA, SGLT-2 inhibitors, and DPP-4 inhibitors using the CPRD, a representative primary care database from the U.K. Second, we used a new-user, active comparator design, which helped reduce confounding by indication and time-related biases (53), while generating clinically relevant findings based on an active comparator for which there is clinical equipoise (25). Lastly, we conducted several sensitivity analyses addressing different sources of bias; these generated highly consistent results. This study has some limitations. First, exposure misclassification is possible given that the CPRD does not record prescriptions written by specialists. However, in the U.K., type 2 diabetes is primarily managed by general practitioners, and thus this exposure misclassification is likely to have been minimal and nondifferential between the exposure groups. Second, the incidence of NAFLD was lower in the GLP-1 RA versus DPP-4 inhibitor cohort than in the SGLT-2 inhibitor versus DPP-4 inhibitor cohort. This can be explained by the fact that the latter cohort was assembled after 2013, which coincided with the highest NAFLD incidence rates during the study period (Supplementary Fig. 2). This phenomenon has previously been described and has been attributed to an increasing prevalence of predisposing conditions such as diabetes and obesity, increasing awareness of NAFLD, and increasing monitoring of long-term conditions using imaging and blood tests (24). Importantly, previous U.K. studies have reported that NAFLD may be underdiagnosed in the primary care setting (24,54). While this may have affected the sensitivity of the outcome definition, a previous study suggested a good specificity of the diagnosis with use of U.K. primary care databases; patients with a diagnosis of NAFLD in the primary care database were shown to have clinical characteristics similar to those of patients diagnosed with imaging (55). Thus, a nondifferential misclassification of the outcome should bias the results toward the null, indicating that our findings might be conservative estimates of the true beneficial effects. Interestingly, the use of an alternative, potentially more specific, outcome definition yielded protective results for both GLP-1 RA and SGLT-2 inhibitors. Third, the

**Table 3—HRs for NAFLD in comparing GLP-1 RA and SGLT-2 inhibitors with DPP-4 inhibitors**

| Exposure                     | No. of patients | No. of events | Person-years | Weighted incidence rate (95% CI)* | Crude HR | Weighted HR (95% CI)† |
|------------------------------|-----------------|---------------|--------------|-----------------------------------|----------|-----------------------|
| GLP-1 RA vs.                  |                 |               |              |                                   |          |                       |
| DPP-4 inhibitor cohort        | 225,320         | 1,883         | 488,964      | 4.6 (4.4–4.8)                     | 1.00     | 1.00 (reference)      |
| GLP-1 RA                     | 30,291          | 261           | 66,580       | 3.9 (3.5–4.4)                     | 1.02     | 0.86 (0.73–1.01)      |
| SGLT-2 vs. DPP-4 inhibitor   |                 |               |              |                                   |          |                       |
| SGLT-2 inhibitors            | 148,421         | 1,202         | 267,648      | 7.0 (6.7–7.4)                     | 1.00     | 1.00 (reference)      |
| SGLT-2 inhibitors            | 41,184          | 305           | 55,975       | 5.4 (4.9–6.1)                     | 1.14     | 0.78 (0.68–0.89)      |

*Per 1,000 person-years. †The models were weighted with use of propensity score fine stratification.
CPRD does not collect information on physical exercise and diet, factors known to be associated with NAFLD progression (56). However, our propensity score models included BMI, a variable shown to be strongly associated with these lifestyle variables (57,58). Fourth, residual confounding is possible, as with any observational study. However, we used an active comparator used at a similar stage of the disease as GLP-1 RAs and SGLT-2 inhibitors. We also considered a wide range of potential confounders in the propensity score models, chieving excellent balance in the weighted cohorts. Finally, some of the secondary analyses were based on fewer exposed events and should thus be interpreted with caution.

In summary, the findings of this study indicate that in comparison with DPP-4 inhibitors, SGLT-2 inhibitors, and possibly GLP-1 RA, may be associated with a decreased risk of NAFLD. In addition, these drugs were associated with a decreased risk of elevation in hepatic transaminase enzymes. These findings are significant given the limited pharmacologic options available to prevent NAFLD (59). Given the increased risk of all-cause, liver-related, and cardiovascular mortality associated with NAFLD (5,6), and the potential irreversibility of its late-stage complications (8), therapeutic strategies including SGLT-2 inhibitors and GLP-1 RA may reduce the burden of NAFLD among patients with type 2 diabetes.

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**Author Contributions.** All authors conceived and designed the study. L.A. acquired data. R.P., H.Y., and L.A. did the statistical analyses. All authors analyzed and interpreted data. R.P. 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. L.A. supervised the study. L.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Table 4—HRs for NAFLD and hepatic transaminase elevation in comparing GLP-1 RA and SGLT-2 inhibitors with DPP-4 inhibitors in the restricted subcohort**

| Exposure                                      | No. of patients | No. of events | Person-years | Weighted incidence rate (95% CI)* | Crude HR | Weighted HR (95% CI)* |
|-----------------------------------------------|-----------------|---------------|--------------|----------------------------------|----------|-----------------------|
| NAFLD                                         |                 |               |              |                                  |          |                       |
| GLP-1 RA vs. DPP-4 inhibitor cohort           |                 |               |              |                                  |          |                       |
| DPP-4 inhibitors                              | 175,091         | 1,005         | 381,306      | 3.1 (2.9–3.3)                    | 1.00     | 1.00 (Reference)      |
| GLP-1 RA                                      | 20,676          | 115           | 44,979       | 2.6 (2.1–3.1)                    | 0.97     | 0.83 (0.66–1.04)      |
| SGLT-2 vs. DPP-4 inhibitor cohort             |                 |               |              |                                  |          |                       |
| DPP-4 inhibitors                              | 116,520         | 650           | 211,559      | 4.4 (4.1–4.7)                    | 1.00     | 1.00 (Reference)      |
| SGLT-2 inhibitors                             | 30,639          | 142           | 41,154       | 3.5 (2.9–4.1)                    | 1.08     | 0.79 (0.64–0.96)      |

**Hepatic transaminase elevation**

| Exposure                                      | No. of patients | No. of events | Person-years | Weighted incidence rate (95% CI)* | Crude HR | Weighted HR (95% CI)* |
|-----------------------------------------------|-----------------|---------------|--------------|----------------------------------|----------|-----------------------|
| GLP-1 RA vs. DPP-4 inhibitor cohort           |                 |               |              |                                  |          |                       |
| DPP-4 inhibitors                              | 175,091         | 12,185        | 359,009      | 41.9 (41.2–42.6)                 | 1.00     | 1.00 (Reference)      |
| GLP-1 RA                                      | 20,676          | 1,593         | 42,152       | 37.8 (36.0–39.7)                 | 1.11     | 0.89 (0.83–0.95)      |
| SGLT-2 vs. DPP-4 inhibitor cohort             |                 |               |              |                                  |          |                       |
| DPP-4 inhibitors                              | 116,520         | 6,800         | 202,260      | 40.5 (39.5–41.6)                 | 1.00     | 1.00 (Reference)      |
| SGLT-2 inhibitors                             | 30,639          | 1,065         | 40,039       | 26.6 (25.0–28.2)                 | 0.75     | 0.66 (0.61–0.71)      |

*Per 1,000 person-years. †The models were weighted with use of propensity score fine stratification.

**References**

1. Tilg H, Moschen AR, Roden M. NAFLD and diabetes mellitus. Nat Rev Gastroenterol Hepatol 2017;14:32–42
2. Younossi ZM, Gramlich T, Matteoni CA, Boparai N, McCullough AJ. Nonalcoholic fatty liver disease in patients with type 2 diabetes. Clin Gastroenterol Hepatol 2004;2:262–265
3. Younossi ZM, Tampi RP, Racila A, et al. Economic and clinical burden of nonalcoholic steatohepatitis in patients with type 2 diabetes in the U.S. Diabetes Care 2020;43:283–289
4. Sheka AC, Adeyi O, Thompson J, Hamed B, Crawford PA, Ikrumuddin S. Nonalcoholic steatohepatitis: a review. JAMA 2020;323:1175–1183
5. Mantovani A, Scorletti E, Mosca A, Allsi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism 2020;111:154170
6. Alvarez CS, Graubard BI, Thistle JE, Petrick JL, McGlynn KA. Attributable fractions of non-alcoholic fatty liver disease for mortality in the United States: results from the third National Health and Nutrition Examination Survey with 27 years of follow-up. Hepatology 2020;72:430–440
7. Vincent RK, Williams DM, Evans M. A look to the future in non-alcoholic fatty liver disease: are glucagon-like peptide-1 analogues or sodium-glucose co-transporter-2 inhibitors the answer? Diabetes Obes Metab 2020;22:2227–2240
8. Dougherty JA, Guirguis E, Thornbay K-A. A systematic review of newer antidiabetic agents in the treatment of nonalcoholic fatty liver disease. Ann Pharmacother 2021;55:65–79
9. Newsome PN, Buchholtz K, Cusi K, et al.; NN9931-4296 Investigators. A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. N Engl J Med 2021;384:1113–1124
