Archival Report

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Glucagon-Like Peptide-1 Receptor Agonists and Alcohol Use: A Real-Word Observational Study in a Large, Integrated Health Care System

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ABSTRACT

BACKGROUND: Growing research suggests that glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduce alcohol consumption, positioning them as new potential pharmacotherapies for alcohol use disorder. However, human studies examining alcohol consumption measures in generalizable samples have been limited.

METHODS: In this cohort study, we analyzed electronic health records from a large, integrated health care system (Kaiser Permanente Northern California) to examine the association between new prescriptions of GLP-1RAs and change in alcohol use among adults. Propensity score matching was utilized to account for differences in baseline characteristics between GLP-1RA–treated (n = 1214) and untreated (n = 1063) individuals. Changes in average drinks consumed per week (drinks/week) from baseline to follow-up (up to 1 year) were compared between groups using difference-in-differences (D-I-D) analysis. Stratified analyses examined treatment effect variation by sex, obesity, and baseline alcohol use risk level.

RESULTS: Both GLP1-RA–treated and untreated groups reduced their drinks/week from baseline to follow-up (mean change [95% CI] = −1.81 [−2.11 to −1.51] and −1.38 [−1.70 to −1.06], respectively); the group difference did not reach statistical significance (D-I-D [95% CI] = −0.43 [−0.87 to 0.01]). Among individuals with low-risk baseline alcohol use, including 1126 (92.8%) GLP-1RA–treated and 996 (93.7%) untreated individuals, receipt of GLP-1RAs was associated with significantly greater reductions in drinks/week (D-I-D [95% CI] = −0.32 [−0.64 to −0.01]). Treatment effects did not vary by sex or obesity.

CONCLUSIONS: GLP-1RAs may be effective in reducing average weekly alcohol consumption, even in individuals with low-risk use. The small subsample of individuals with high-risk use limited our ability to estimate associations in this group.

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Approximately 28.9 million people met criteria for alcohol use disorder (AUD) in the United States in 2023 (1). AUD treatment includes psychosocial and pharmacological interventions, although uptake of the medications approved by the U.S. Food and Drug Administration (FDA)—disulfiram, acamprosate, oral and injectable naltrexone—remains low, with <2% of adults with AUD being prescribed them (1). Repurposing medications used to treat other common conditions may be a promising strategy to increase AUD treatment options and utilization.

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), FDA approved for type 2 diabetes mellitus (T2DM) and obesity, have garnered attention for their potential to reduce alcohol craving and use (2–4). Preclinical studies indicate that GLP-1RAs reduce alcohol consumption in rodents and nonhuman primates (5–10), possibly through mechanisms related to reward processing (11–13), stress (14,15), and/or cognition (16,17). Observational human studies have also shown an association between the GLP-1 system and alcohol-related phenotypes (18–20). Randomized controlled trials (RCTs) have been limited (21). One RCT found that exenatide reduced alcohol intake in individuals with obesity but not in those with normal weight (22). Another recent RCT found that a low dose of semaglutide significantly reduced alcohol craving and use (23).

Electronic health record (EHR)–based studies have found beneficial effects with GLP-1RAs on alcohol-related outcomes, including reduced hospitalizations and incidence/recurrence of AUD diagnoses (24–29). However, studies examining GLP-1RAs' effects on the quantity of alcohol intake, for example self-reported data that are collected during routine clinical care, have been limited. Previous EHR-based studies examining the effects of GLP-1RAs on alcohol intake have primarily been conducted in well-characterized, but less generalizable, samples (e.g., mainly older male patients in the U.S. Department of Veterans Affairs [VA]); more research that can leverage self-reported alcohol use data in more diverse and generalizable samples is needed. Additionally, differential

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treatment response (e.g., by sex, obesity, and baseline alcohol use) and the relationships between treatment dose/duration and alcohol-related outcomes have been examined less often.

In the current study, we investigated the relationship between GLP-1RAs and alcohol use using EHR data from a real-world sample of individuals who received care at Kaiser Permanente Northern California (KPNC). Specifically, we examined the association between initiation of GLP-1RAs and changes in self-reported alcohol use collected in the EHR during routine clinical care. We also investigated whether the associations differed by sex, obesity, and baseline alcohol use risk level. We hypothesized that individuals who received GLP-1RAs would report greater reductions in alcohol use compared with a matched untreated group and that treatment response would be greater among those with high-risk baseline alcohol use and obesity but would not differ by sex. We also conducted exploratory dose-response analyses with semaglutide, given promising results with this agent in animal studies (6,7), human observational studies (25,27), and a recent RCT (23).

METHODS AND MATERIALS

Data Source and Setting

We utilized EHR data from KPNC, a large, integrated health care system providing comprehensive care to 4.6 million members, representing approximately one-third of the region. KPNC members are diverse and reflect the general U.S. population with access to care (30). Members enroll through employer-based plans, health insurance exchanges, and federal programs such as Medicare and Medicaid. The EHR data encompass detailed medical and pharmacy information, including sociodemographic information, clinical diagnoses and procedures, laboratory results, and self-reported data. Most KPNC members use internal pharmacies, ensuring nearly complete capture of prescription fills (31).

KPNC began a universal alcohol screening program, Alcohol as a Vital Sign, in adult primary care in June 2013 and has screened about 81% of all adult members (32). Using National Institute on Alcohol Abuse and Alcoholism (NIAAA) evidence-based screening instruments, patients are asked a single question about heavy drinking days in the preceding 3 months ("How many times in the past three months have you had 5 or more drinks containing alcohol in a day?" for men ages 18–65 years or ≥4 drinks in a day for men age ≥66 years and women ≥18 years) (33) and 2 questions to calculate average weekly consumption: ("On average, how many days per week do you have an alcoholic drink?" and "On a typical drinking day, how many drinks do you have?"). Responses are recorded in the EHR along with other vital sign information. Drinking that exceeds NIAAA recommended daily and/or weekly limits is considered a positive screening (33). Clinicians offer patients who screen positive a brief intervention and referral to outpatient substance use treatment, if needed. The EHR issues best-practice alerts to complete alcohol screenings annually or every 6 months if the patient screened positive previously until they screen negative.

This study was approved by the KPNC Institutional Review Board with a waiver of informed consent and preregistered on Open Science Framework (https://osf.io/qcjh6).

Study Design

The study design was a new-user, retrospective cohort study (Figure 1). Individuals entered the study between June 1, 2013, and June 30, 2023, on their respective index date: the first GLP-1RA dispensation date (treated group) or a randomly selected outpatient visit (control group). Individuals were followed until their first alcohol screening during a 365-day follow-up or were censored at the earliest of the following: disenrollment from the health plan, death, 365 days postindex, or at the end of the study period (June 30, 2024). Consistent with an intention-to-treat approach, discontinuation of GLP-1RAs was not considered a censoring factor for the treated group.

We initially designed our study to include an active comparator group of new users of DPP-4 inhibitors (DPP-4Is), another class of FDA-approved medications for T2DM that blocks the degradation of endogenous GLP-1; however, we found that the small sample size would have limited the generalizability of study findings. Additionally, since the inception of this work, new data in rodents and humans indicate that DPP-4Is do not reduce alcohol consumption (29).

Study Sample

For the GLP-1RA–treated group, we identified adults (≥18 years) who were new users of FDA-approved GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, or semaglutide) through outpatient pharmacy data. Individuals with at least 60 days of continuous medication exposure were included. Treatment duration was based on the days' supply indicated on at least 1 dispensation, with no more than a 7-day gap between dispensations. A 120-day washout period was applied to identify new users of GLP-1RAs. Individuals prescribed both a GLP-1RA and a DPP-4I on the same index date were excluded to avoid possible confounding. Individuals who were prescribed drug coformulations (e.g., GLP-1RA and insulin) were also excluded.

For the untreated control group, we identified adults with at least 1 outpatient encounter in primary care or endocrinology (where GLP-1RAs are typically prescribed) and excluded those who had any dispensations of GLP-1RAs or DPP-4Is between June 1, 2013, and June 30, 2023. A random outpatient encounter was chosen as the index date for each untreated individual.

From both groups, we also excluded individuals with noncontinuous health insurance membership or drug coverage in the year before index (allowing up to 60-day gaps), individuals with no baseline alcohol screening in the year before index, individuals who reported no alcohol use at their baseline screening, and individuals with missing neighborhood deprivation index.

Exposures

The primary exposure was new use of GLP-1RAs (≥60 days). Among individuals who received subcutaneous semaglutide only, we also calculated cumulative and average weekly doses. Cumulative dose represented the total milligrams dispensed during the follow-up period and was categorized based on the cohort's distribution (4 to 10, >10 to 18, >18 to 32, and >32 mg). Average weekly dose was calculated by dividing the cumulative dose by total number of weeks

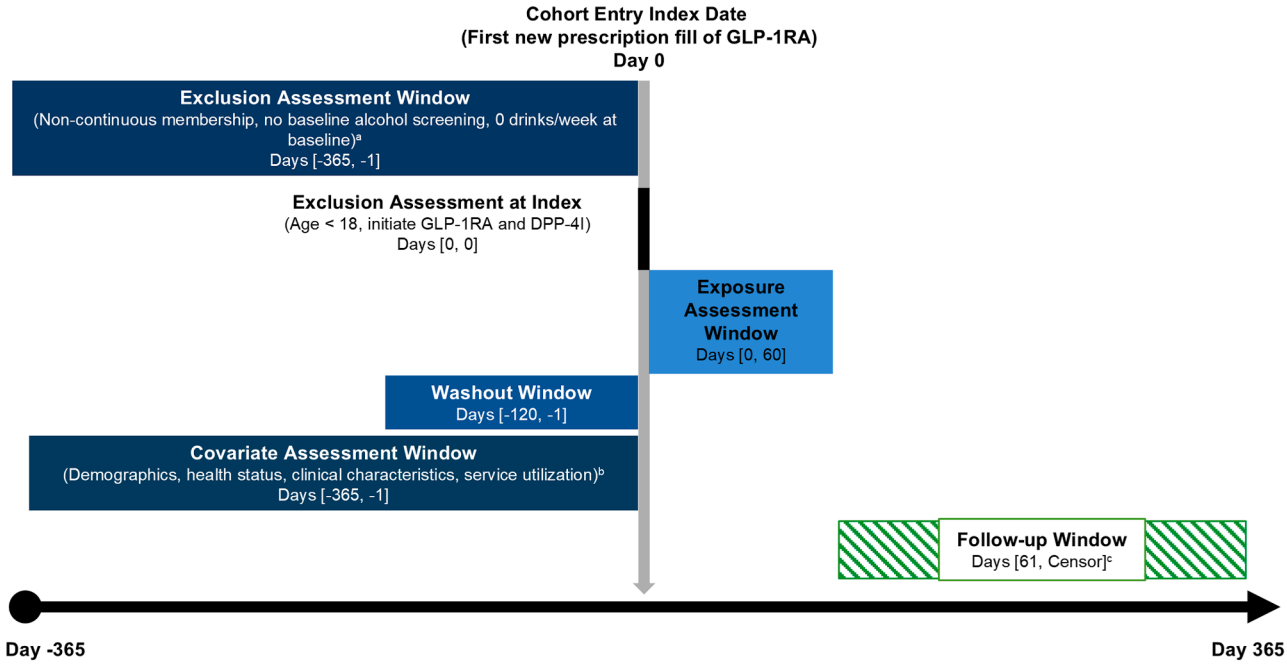

Figure 1. Study design schematic for the GLP-1RA–treated group. [a]Individuals were excluded for noncontinuous health plan membership and pharmacy benefits in the 365 days before their first new prescription fill; up to a 60-day gap was allowed. [b]Health status covariates included obesity, glycemic control, and decreased kidney function. Clinical characteristics included alcohol use disorder, atherosclerotic cardiovascular disease, chronic kidney disease, chronic liver disease, history of bariatric surgery, hyperlipidemia, substance use disorders, type 2 diabetes mellitus, and Charlson comorbidity index. Service utilization included substance use disorder treatment visit, any alcohol pharmacotherapy, number of outpatient visits, any inpatient visit, number of emergency department visits, and number of outpatient prescriptions filled. [c]Individuals were followed until the earliest of the following: subsequent alcohol screening, disenrollment, death, 365 days postindex, or the end of the study period (June 30, 2024). GLP-1RA, glucagon-like peptide-1 receptor agonist.

prescribed and categorized based on common doses dispensed as well as the cohort's distribution (0.25 to 0.5, >0.5 to 1, and >1 mg/week).

Propensity Score Matching

Propensity score matching (PSM) was performed to account for potential confounding bias. PSM ensures comparability by matching on the probability of receiving treatment, conditional on baseline covariates hypothesized to be confounders of the exposure-outcome relationship and/or associated with the outcome (34). Propensity scores were estimated by fitting a logistic regression model with GLP-1RA exposure as the outcome. Based on literature review and data availability, covariates included sex (female, male); age group (18–34, 35–49, 50–64, ≥65 years); race and ethnicity (Asian or Pacific Islander, Black, Latino/Hispanic, White, other/unknown race); the neighborhood deprivation index, a measure of socioeconomic status based on geocoded census data (categorized into quartiles based on the KPNC membership) (35); index year; baseline alcohol use risk level (low risk: 1–7 drinks/week for females or 1–14 drinks/week for males; high risk: ≥8 drinks/week for females or ≥15 drinks/week for males) (33); tobacco smoking status (never/former, current); obesity (body mass index [BMI] ≥ 30) (36); glycemic control (HbA1c < 7%); decreased kidney function (estimated glomerular filtration rate < 60 mL/min/1.73 m^2); history of bariatric surgery (37); prior-year clinical diagnoses based on ICD-9-CM and ICD-10-CM codes (AUD, atherosclerotic cardiac disease, chronic kidney disease, hyperlipidemia, substance use disorder, T2DM); the Charlson comorbidity index, an overall measure of disease burden (38); and prior-year health service utilization (substance use disorder treatment visit, any alcohol pharmacotherapy, number of outpatient visits, number of emergency department visits, any inpatient visits, and number of outpatient prescription fills). Alcohol pharmacotherapy included dispensations of FDA-approved medications for AUD (acamprosate, disulfiram, oral/injectable naltrexone), promising medications used off label (gabapentin, topiramate, varenicline) (39,40), and medications associated with decreased alcohol use (spironolactone) (41,42).

We conducted 1:1 matching using a greedy nearest-neighbor algorithm on the logit of the propensity score, requiring matches to be within a caliper distance of 0.2 SD (43,44). Exact matching on sex, obesity (BMI ≥ 30), and baseline alcohol use risk level (low risk: 1–7 drinks/week for females or 1–14 drinks/week for males; high risk: ≥8 drinks/week for females or ≥15 drinks/week for males) was also performed to ensure comparability within each subgroup for stratified analyses (45).

Distributions of the covariates in the GLP-1RA–treated and untreated groups were compared, before and after PSM, by calculating the standardized mean difference (SMD); covariates with absolute SMD values <0.1 were considered to be well balanced (46).

Outcomes

The primary outcome was the difference-in-differences (D-I-D) of the average number of drinks consumed per week (drinks/week) from baseline (the latest alcohol screening within 365 days prior to or on the index date) to follow-up (the first alcohol screening during the 365-day follow-up), comparing the GLP-1RA–treated and untreated groups. Sex, obesity, and baseline alcohol use risk level were examined as potential moderators of D-I-D. Individuals were censored if they did not have a follow-up alcohol screening during the 365-day observation window, consistent with standard approaches in observational pharmacoepidemiology studies using real-world data (47). Covariate balance was reassessed after PSM among those retained for analysis (34,48).

We originally planned to also examine the percentage of individuals with 1- or 2-level reductions in the World Health Organization drinking risk levels and the percentage of individuals with no heavy drinking days (49,50), but sample sizes of individuals reporting high-risk drinking levels and >0 heavy drinking days at baseline were too small to conduct these analyses.

Statistical Analysis

Mixed-effects regression models with an interaction term between time and treatment group were fit to estimate the mean number of drinks/week and 95% CIs at baseline, follow-up, change over time within each treatment group, and the D-I-D. The D-I-D represents the average treatment effect on the treated individuals (34). We also conducted stratified analyses by fitting mixed-effects regression models within each subgroup by sex, obesity, and baseline alcohol use risk level.

We conducted several sensitivity analyses to examine the robustness of findings with respect to 1) residual confounding, 2) attrition bias, and 3) censoring criteria. To examine the potential of residual confounding, we refit the final outcome model by adding covariates (i.e., AUD diagnosis) that became imbalanced after censoring to estimate the adjusted D-I-D. To address potential attrition bias, we applied inverse probability of censoring weighting (IPCW). This weighting procedure creates a pseudopopulation in which covariates are no longer associated with censoring by upweighting retained individuals with characteristics associated with a higher likelihood of censoring (51). Inverse-probability censoring weights were estimated by fitting a logistic regression model with no censoring as the outcome, including all covariates in addition to the exposure variable. We compared the distributions of covariates in the groups retained and lost to follow-up by calculating the SMDs, before and after IPCW. Finally, we fit the final outcome models, weighted by IPCW, and used the robust standard error estimator (34). To examine the potential impact of medication discontinuation on the study findings, we also censored GLP-1RA–treated individuals who did not have an alcohol screening up to at least 90 days after medication discontinuation.

Among individuals who received subcutaneous semaglutide only, we conducted an exploratory analysis to examine the relationship between cumulative and average weekly dose with changes in alcohol use by fitting mixed-effects regression models. For these models, the D-I-D represents the differential mean change in the number of drinks/week reported from baseline to follow-up, comparing each dose category with the lowest dose category as the reference.

Analyses were conducted using SAS software version 9.4 (SAS Institute Inc.). Statistical significance was set at $p < .05$ (2 tailed).

RESULTS

Study Sample

We identified 2546 GLP-1RA–treated and 802,161 untreated individuals meeting eligibility criteria (Figure S1). One GLP-1RA–treated individual was unable to be matched to an untreated individual through PSM; therefore, the matched sample included 2545 GLP-1RA–treated individuals and 2545 untreated matches. Prior to PSM, the GLP-1RA–treated group differed from the untreated group on nearly all baseline characteristics; as expected, the GLP-1RA–treated group had a higher prevalence of obesity (84.8% vs. 26.5%), atherosclerotic cardiovascular disease (23.6% vs. 11.7%), chronic kidney disease (19.9% vs. 4.1%), chronic liver disease (10.6% vs. 2.9%), hyperlipidemia (43.3% vs. 21.8%), history of bariatric surgery (6.1% vs. 0.6%), and T2DM (62.3% vs. 6.0%) (Table S1). PSM sufficiently balanced all characteristics between GLP-1RA–treated and untreated groups (Figure 2 and Table S1). Of the matched sample, 1331 GLP-1RA–treated and 1482 untreated individuals were censored due to not having a follow-up alcohol screening. All covariates remained balanced after censoring except for AUD diagnosis (SMD = 0.102) (Table 1 and Figure 2).

The final analytical sample included 1214 GLP-1RA–treated and 1063 untreated individuals. The GLP-1RA–treated and untreated groups were 52.6% and 53.3% female and 57.3% and 57.8% White, with a mean (SD) age of 55.5 (12.9) and 56.7 (13.9) years, respectively (Table 1). Most of the participants had low-risk baseline alcohol use (92.8% of GLP-1RA–treated and 93.7% of untreated groups), obesity (85.6% and 84.5%, respectively), and index years between 2020 and 2023 (96.5% and 97.3%, respectively).

Subcutaneous semaglutide and liraglutide were the most-prescribed GLP-1RAs (Table 2). The mean (SD) duration of GLP-1RA treatment was 173 (84) days. GLP-1RAs were primarily prescribed for T2DM (54.7%) and weight management (34.3%). Approximately 60.1% of the GLP-1RA–treated group had their follow-up alcohol screening while they were still taking the GLP-1RA medication, 16.0% had a 1- to 90-day gap between medication discontinuation and follow-up screening, and 24.0% had a >90-day gap.

D-I-D of Average Drinks per Week

The GLP-1RA–treated and untreated groups reduced alcohol use by −1.81 (95% CI, −2.11 to −1.51) and −1.38 (95% CI, −1.70 to −1.06) drinks/week on average, respectively, from baseline to follow-up, resulting in a D-I-D of −0.43 (95% CI, −0.87 to 0.01) (Table 3 and Figure S2). No differential patterns were observed after stratifying by sex or obesity. Among individuals with low-risk baseline alcohol use, those treated with GLP-1RAs had a significantly greater reduction in drinks/week than the untreated group (D-I-D = −0.32 [95%

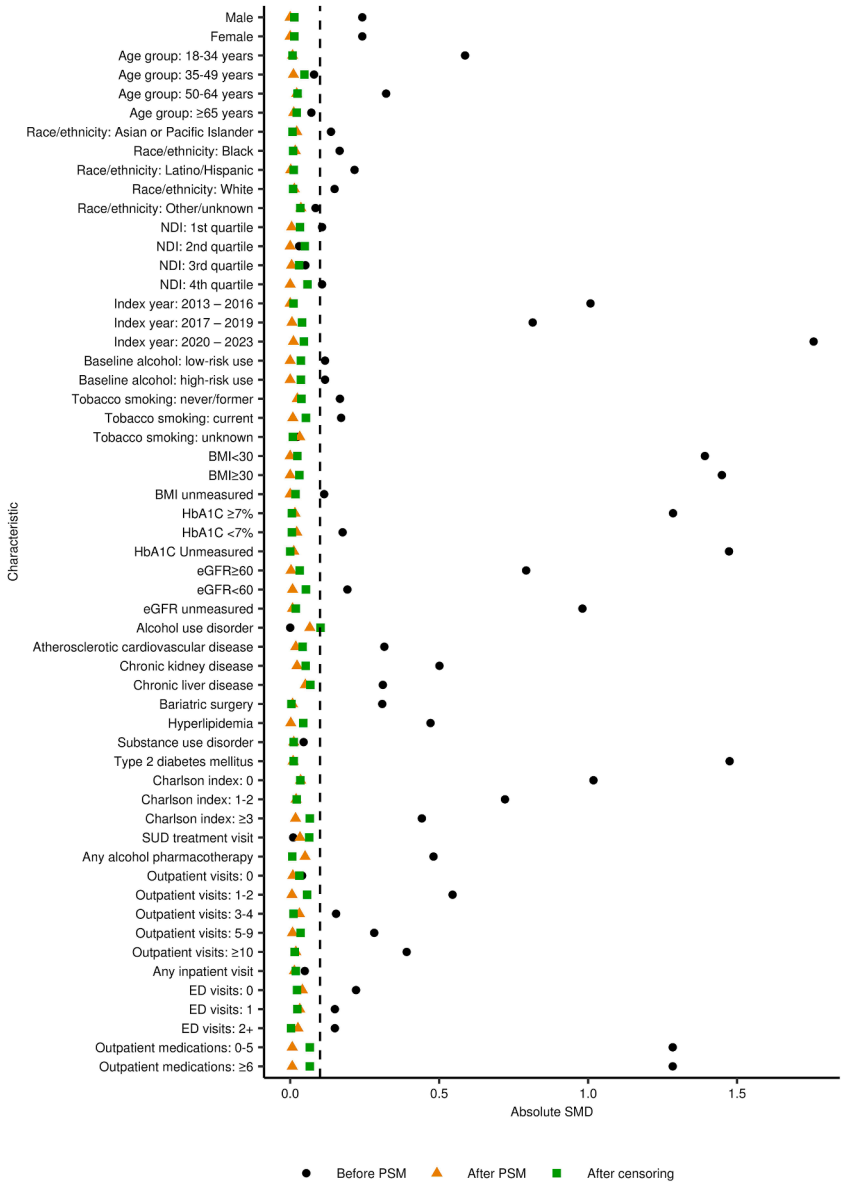

Figure 2. Covariate balance before PSM, after PSM, and after censoring. Absolute SMDs comparing covariates between glucagon-like peptide-1 receptor agonist–treated and untreated cohorts. SMDs <0.1 were considered well balanced. BMI, body mass index; ED, emergency department; eGFR, estimated glomerular filtration rate; NDI, neighborhood deprivation index; PSM, propensity score matching; SMD, standardized mean difference; SUD, substance use disorder.

CI, −0.64 to −0.01]). While the D-I-D estimate was greater among individuals with high-risk baseline alcohol use, the difference did not reach statistical significance, likely due to the small sample size of this subgroup.

Results of sensitivity analyses did not differ meaningfully from the main analysis (Tables S2 and S3).

Exploratory Dose-Response Analyses

Among the 711 GLP-1RA–treated individuals who received subcutaneous semaglutide only, the distribution of baseline characteristics, including drinking risk level, varied by cumulative dose (Table S4) and average weekly dose (Table S5). In unadjusted analyses, higher cumulative and average weekly doses appeared to be associated with smaller reductions in average drinks/week; however, the observed differences did not reach statistical significance (Table 4).

DISCUSSION

In this cohort study using real-world data, a group of adults with GLP-1RA dispensations and low-risk alcohol use had significantly greater reductions in alcohol use than matched untreated control adults. Previous research suggests greater treatment response in people with higher severity of alcohol use (29); however, the small sample size of high-risk drinkers in the current study limited the precision of estimates in this subgroup (although reductions were numerically greater than among low-risk drinkers). The lack of a significant group difference in the overall sample could be related to the increased

Table 1. Baseline Characteristics of the GLP-1RA–Treated and Untreated Groups

Characteristic	GLP-1RA Treated, *n* = 1214	Untreated, *n* = 1063	SMD[a]
Demographics			
Sex			
Female	638 (52.6%)	567 (53.3%)	−0.014
Male	576 (47.4%)	496 (46.7%)	0.014
Age Group			
18–34 years	73 (6.0%)	62 (5.8%)	0.008
35–49 years	325 (26.8%)	263 (24.7%)	0.048
50–64 years	473 (39.0%)	427 (40.2%)	−0.025
≥65 years	343 (28.3%)	311 (29.3%)	−0.022
Race/Ethnicity			
Asian or Pacific Islander	89 (7.3%)	76 (7.1%)	0.008
Black	117 (9.6%)	99 (9.3%)	0.010
Latino/Hispanic	289 (23.8%)	248 (23.3%)	0.012
White	696 (57.3%)	614 (57.8%)	−0.010
Other/unknown	23 (1.9%)	26 (2.4%)	−0.034
Neighborhood Deprivation Index Quartile			
First quartile, lowest	281 (23.1%)	260 (24.5%)	−0.033
Second quartile	404 (33.3%)	330 (31.0%)	0.049
Third quartile	326 (26.9%)	272 (25.6%)	0.030
Fourth quartile, highest	203 (16.7%)	201 (18.9%)	−0.058
Year of Index Date			
2013–2016	11 (0.9%)	8 (0.8%)	0.011
2017–2019	31 (2.6%)	21 (2.0%)	0.040
2020–2023	1172 (96.5%)	1034 (97.3%)	−0.046
Substance Use			
Baseline Alcohol Use Risk Level[b]			
Low risk	1126 (92.8%)	996 (93.7%)	−0.036
High risk	88 (7.2%)	67 (6.3%)	0.036
Tobacco Smoking Status			
Never/former	1137 (93.7%)	1006 (94.6%)	−0.038
Current	62 (5.1%)	43 (4.0%)	0.053
Unknown	15 (1.2%)	14 (1.3%)	−0.009
Health Status			
Obesity, Body Mass Index ≥30			
No	143 (11.8%)	134 (12.6%)	−0.024
Yes	1039 (85.6%)	898 (84.5%)	0.031
Unmeasured	32 (2.6%)	31 (2.9%)	−0.018
Glycemic Control, HbA1c <7%			
No	613 (50.5%)	540 (50.8%)	−0.006
Yes	534 (44.0%)	465 (43.7%)	0.006
Unmeasured	67 (5.5%)	58 (5.5%)	0
Decreased Kidney Function, eGFR <60 mL/min/1.73 m^2			
No	1052 (86.7%)	910 (85.6%)	0.032
Yes	100 (8.2%)	103 (9.7%)	−0.053
Unmeasured	62 (5.1%)	50 (4.7%)	0.019
Clinical Characteristics			
Alcohol Use Disorder Diagnosis	24 (2.0%)	9 (0.8%)	0.102
Atherosclerotic Cardiovascular Disease	341 (28.1%)	319 (30.0%)	−0.042
Chronic Kidney Disease	242 (19.9%)	234 (22.0%)	−0.052
Chronic Liver Disease	144 (11.9%)	104 (9.8%)	0.068
History of Bariatric Surgery	78 (6.4%)	69 (6.5%)	−0.004
Hyperlipidemia	562 (46.3%)	516 (48.5%)	−0.044
Substance Use Disorder Diagnosis	8 (0.7%)	8 (0.8%)	−0.012
Type 2 Diabetes Mellitus	762 (62.8%)	661 (62.2%)	0.012
Charlson Comorbidity Index			
0	435 (35.8%)	364 (34.2%)	0.034
1–2	535 (44.1%)	457 (43.0%)	0.022
≥3	244 (20.1%)	242 (22.8%)	−0.066
Prior-Year Health Service Utilization			
Substance Use Disorder Treatment Visit	15 (1.2%)	6 (0.6%)	0.064
Any Alcohol Pharmacotherapy	275 (22.7%)	244 (23.0%)	−0.007
Number of Outpatient Visits			
0	13 (1.1%)	9 (0.8%)	0.031
1–2	131 (10.8%)	97 (9.1%)	0.057
3–4	184 (15.2%)	157 (14.8%)	0.011
5–9	452 (37.2%)	413 (38.9%)	−0.035
≥10	434 (35.7%)	387 (36.4%)	−0.015
Any Inpatient Visit	57 (4.7%)	54 (5.1%)	−0.019
Number of Emergency Department Visits			
0	884 (72.8%)	784 (73.8%)	−0.023
1	213 (17.5%)	176 (16.6%)	0.024
≥2	117 (9.6%)	103 (9.7%)	−0.003
Number of Outpatient Prescriptions Filled			
0–5	250 (20.6%)	191 (18.0%)	0.066
≥6	964 (79.4%)	872 (82.0%)	−0.066

Values are presented as *n* (%).

eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; SMD, standardized mean difference.

[a]After propensity score matching and censoring, the SMD for each variable was calculated to determine whether the distribution was balanced between the GLP-1RA–treated and untreated groups. Variables with absolute SMDs <0.1 were considered well balanced.

[b]Baseline alcohol use risk level was defined based on national guidelines (low risk: ≤7 drinks/week for females and ≤14 drinks/week for males; high risk: ≥8 drinks/week for females and ≥15 drinks/week for males).

variance when averaging across baseline alcohol use risk levels. We observed an expected reduction in alcohol use over time among the untreated group as well, possibly due to alcohol screening and brief intervention (52) and/or worsening health (53). Most GLP-1RA dispensations in this study occurred between 2020 to 2023, overlapping with the COVID-19 pandemic, which might have also influenced our study findings (54). However, the reductions in alcohol use observed among low-risk drinkers were greater for those treated with GLP-1RAs than for untreated individuals, suggesting a potential treatment effect.

Findings of the current study expand the current literature by showing that even among people classified as low-risk drinkers, GLP-1RAs may help reduce alcohol intake. These results are consistent with previous studies indicating that GLP-1RAs are associated with reductions in alcohol use and

Table 2. Characteristics of the GLP-1RA–Treated Group (*n* = 1214)

Characteristic	Mean (SD) or *n* (%)
Duration of Treatment, Days	173 (84)
Medications Dispensed	
Dulaglutide only	2 (0.2%)
Exenatide only	30 (2.5%)
Liraglutide only	361 (29.7%)
Oral semaglutide only	3 (0.3%)
Subcutaneous semaglutide only	711 (58.6%)
Dulaglutide and exenatide	1 (0.1%)
Exenatide and liraglutide	2 (0.2%)
Exenatide and subcutaneous semaglutide	2 (0.2%)
Liraglutide and subcutaneous semaglutide	102 (8.4%)
Prescription Indications	
Type 2 diabetes	664 (54.7%)
Weight management	417 (34.3%)
Prediabetes	33 (2.7%)
Other/unknown	100 (8.2%)
Gap Between Medication Discontinuation and Follow-Up Screening	
0 days, follow-up occurred while taking medication	729 (60.1%)
1–90 days	194 (16.0%)
>90 days	291 (24.0%)

GLP-1RA, glucagon-like peptide-1 receptor agonist.

Table 3. Changes in Self-Reported Average Number of Drinks per Week From Baseline to Follow-Up, Comparing the GLP-1RA–Treated and Untreated Groups, Overall and by Sex, Obesity, and Baseline Alcohol Use Risk Level

Group	GLP-1RA Treated	Untreated
Overall	*n* = 1214	*n* = 1063
Baseline	4.54 (4.26 to 4.82)	4.62 (4.33 to 4.92)
Follow-Up	2.73 (2.45 to 3.01)	3.24 (2.95 to 3.54)
Change	−1.81 (−2.11 to −1.51)	−1.38 (−1.70 to −1.06)
D-I-D	−0.43 (−0.87 to 0.01); *p* = .053	
By Sex		
Female	*n* = 638	*n* = 567
Baseline	3.51 (3.23 to 3.79)	3.77 (3.47 to 4.06)
Follow-up	1.94 (1.66 to 2.22)	2.47 (2.18 to 2.77)
Change	−1.57 (−1.88 to −1.26)	−1.29 (−1.62 to −0.97)
D-I-D	−0.28 (−0.73 to 0.17); *p* = .219	
Male	*n* = 576	*n* = 496
Baseline	5.68 (5.19 to 6.16)	5.60 (5.08 to 6.13)
Follow-up	3.60 (3.12 to 4.09)	4.12 (3.60 to 4.65)
Change	−2.07 (−2.60 to −1.54)	−1.48 (−2.05 to −0.91)
D-I-D	−0.60 (−1.37 to 0.18); *p* = .134	
By Obesity		
BMI <30	*n* = 143	*n* = 134
Baseline	5.05 (4.22 to 5.88)	5.37 (4.51 to 6.22)
Follow-up	3.20 (2.37 to 4.02)	4.10 (3.25 to 4.96)
Change	−1.85 (−2.68 to −1.02)	−1.26 (−2.12 to −0.40)
D-I-D	−0.59 (−1.78 to 0.60); *p* = .329	
BMI ≥30	*n* = 1039	*n* = 898
Baseline	4.49 (4.19 to 4.79)	4.52 (4.20 to 4.85)
Follow-up	2.63 (2.33 to 2.93)	3.10 (2.78 to 3.42)
Change	−1.86 (−2.18 to −1.53)	−1.42 (−1.77 to −1.07)
D-I-D	−0.44 (−0.91 to 0.04); *p* = .073	
By Baseline Alcohol Use Risk Level[a]		
Low risk	*n* = 1126	*n* = 996
Baseline	3.53 (3.33 to 3.73)	3.76 (3.55 to 3.97)
Follow-up	2.38 (2.19 to 2.58)	2.94 (2.73 to 3.15)
Change	−1.14 (−1.36 to −0.93)	−0.82 (−1.05 to −0.59)
D-I-D	−0.32 (−0.64 to −0.01); *p* = .045	
High Risk	*n* = 88	*n* = 67
Baseline	17.48 (15.37 to 19.59)	17.45 (15.03 to 19.87)
Follow-up	7.15 (5.04 to 9.26)	7.78 (5.36 to 10.20)
Change	−10.33 (−12.90 to −7.76)	−9.67 (−12.62 to −6.72)
D-I-D	−0.66 (−4.57 to 3.26); *p* = .740	

Values are presented as mean (95% CI) or D-I-D (95% CI).

BMI, body mass index; D-I-D, difference-in-differences; GLP-1RA, glucagon-like peptide-1 receptor agonist.

[a]Baseline alcohol use risk level was defined based on national guidelines (low risk: ≤7 drinks/week for females and ≤14 drinks/week for males; high risk: ≥8 drinks/week for females and ≥15 drinks/week for males).

other alcohol-related outcomes. Our study also complements the literature by analyzing a direct, self-reported, quantitative measure of alcohol use collected during routine screening in a diverse sample that is representative of the U.S. population with access to care. As a comparison, a previous study at the VA among a primarily male (93%) and White (71%) sample found that GLP-1RAs were associated with a greater reduction in Alcohol Use Disorder Identification Test - Consumption (AUDIT-C) scores (29). While RCTs remain the gold standard for causal inference, real-world studies allow for heterogeneous samples, including those with comorbidities, and may help detect potential predictors of response to GLP-1RAs. We successfully used PSM to adjust for confounding bias and performed several sensitivity analyses to ensure the robustness of the results. These sensitivity analyses showed that residual confounding due to imbalanced covariates, attrition, and medication discontinuation likely did not influence our findings.

We had hypothesized that obesity would moderate the effects of GLP-1RAs on alcohol drinking, given post hoc analysis of an RCT that found that exenatide reduced alcohol intake in individuals with obesity (BMI > 30) but not in those with lower BMI (22). However, our results did not show differential treatment effects by obesity, consistent with another recent pharmacoepidemiologic study (29). Contrary to the exenatide RCT mentioned above (22), an earlier nicotine exenatide RCT and a recent alcohol semaglutide RCT suggest greater GLP-1RA response in alcohol-related outcomes in people without obesity (23,55). While the existing evidence is inconclusive, future research should continue to explore whether/how obesity and/or related metabolic factors moderate the effects of GLP-1RAs on alcohol intake, especially because AUD and obesity have considerable epidemiologic and mechanistic overlap (56,57).

While we found that males had higher baseline alcohol use and thus greater reductions in alcohol use from baseline to follow-up, GLP-1RA–treated and untreated groups did not

Table 4. Dose-Response Analysis of Subcutaneous Semaglutide on Changes in Self-Reported Average Number of Drinks per Week (*n* = 711)

	Cumulative Dose			
	4–10 mg	>10–18 mg	>18–32 mg	>32 mg
All patients	*n* = 206	*n* = 166	*n* = 173	*n* = 166
Baseline	4.97 (4.30 to 5.64)	4.45 (3.71 to 5.19)	3.68 (2.95 to 4.41)	4.33 (3.58 to 5.07)
Follow-up	2.68 (2.01 to 3.35)	2.60 (1.86 to 3.35)	2.31 (1.58 to 3.03)	3.22 (2.47 to 4.00)
Change	−2.29 (−3.09 to −1.49)	−1.85 (−2.74 to −0.96)	−1.36 (−2.25 to −0.50)	−1.11 (−2.00 to −0.22)
D-I-D	REF	0.44 (−0.75 to 1.64); *p* = .469	0.92 (−0.27 to 2.10); *p* = .129	1.18 (−0.01 to 2.38); *p* = .053
	Average Weekly Dose			
	0.25–0.5 mg/Week	>0.5-1 mg/Week,	>1 mg/Week	
All patients	*n* = 314	*n* = 282	*n* = 115	
Baseline	4.86 (4.32 to 5.39)	3.96 (3.39 to 4.53)	4.13 (3.24 to 5.02)	
Follow-up	2.86 (2.32 to 3.40)	2.45 (1.88 to 3.02)	2.85 (1.96 to 3.75)	
Change	−2.00 (−2.65 to −1.35)	−1.51 (−2.19 to −0.82)	−1.28 (−2.35 to −0.21)	
D-I-D	REF	0.49 (−0.45 to 1.43); *p* = .309	0.72 (−0.53 to 1.97); *p* = .258	

Values are presented as mean (95% CI) or D-I-D (95% CI).
D-I-D, difference-in-differences; REF, reference group.

differ significantly in alcohol use reductions when analyses were stratified by sex. Previous studies with both rodents and humans have not shown strong evidence of sex differences in GLP-1RA effects on alcohol use (4,24,25). Nevertheless, given some reports, future research should continue to include both male and female participants to monitor sex differences (or lack of) in GLP-1/addiction studies (58,59).

The optimal dose and duration of treatment with GLP-1RAs that is safe and effective in reducing alcohol use is an important clinical question, but to our knowledge, it has not been systematically investigated. The FDA recommends that semaglutide dosing should begin at 0.25 mg/week and proceed with incremental doses every 4 weeks (at least) up to 2.0 or 2.4 mg/week for T2DM or obesity, respectively, if needed. A recent RCT found that treatment with low-dose semaglutide reduced alcohol craving and drinking in people with AUD (23). While exploratory and preliminary, our dose-response analyses showed greater alcohol reductions in individuals who received lower doses of semaglutide, suggesting that higher doses may not be needed or may not be as beneficial in reducing alcohol use. One possible explanation is that desensitization of GLP-1R after chronic stimulation by GLP-1RAs, as evidenced by in vitro studies (60–64), may lead to tachyphylaxis (tolerance or diminished response) of appetite suppression, reduced gastric motility, and weight loss; notably, glucose-lowering effects of GLP-1RAs are less prone to tachyphylaxis (64–69). Additionally, a previous study with rodents found that higher doses of liraglutide were not more effective in preventing opioid seeking than lower doses, suggesting tolerance to the protective effect of GLP-1RA treatment (70). Another possible explanation is that the low-dose groups in our study had higher baseline alcohol use (Tables S4 and S5) and thus greater room to decrease drinking. We did not perform additional analyses examining the effects of high versus low doses given the relatively small sample of individuals prescribed the same GLP-1RA (subcutaneous semaglutide), as aggregating dose across different medications would be impossible. Well-controlled prospective studies with sufficient sample size are needed to determine clinically safe and effective regimens of GLP-1RAs for the treatment of AUD, especially given previous human studies suggesting changes in the endogenous GLP-1 system as a function of alcohol exposure and AUD (18–20,71).

Our study had several limitations and strengths. We used EHR data to capture exposure and acknowledge that this may not guarantee adherence. While most KPNC members utilize internal pharmacies, our data do not capture GLP-1RA use obtained through external telehealth or direct-to-consumer programs. Therefore, misclassification of the exposure is possible but would likely be nondifferential, which would bias effect estimates toward the null. Real-world data such as these are subject to potential confounding by indication and channeling bias; patients prescribed GLP-1RAs might have had different characteristics or health behaviors compared with control participants, which could influence the likelihood of receiving GLP-1RAs and/or alcohol use, independent of treatment effects. We used PSM, including many potential confounders (e.g., health status variables, comorbidities, and health service utilization), to minimize this bias; however, residual confounding is still possible due to unmeasured variables. The timing of alcohol screenings in this study depended on clinical workflows and patient engagement with primary care, introducing variability in follow-up duration, which is a common limitation in observational studies. While our aim was to examine changes in alcohol use from baseline to a single follow-up screening, consistent with a quasi-experimental approach commonly used in pharmacoepidemiology (72), our study did not examine longitudinal trends over multiple follow-ups, which would require a longer observation window as screening typically occurs once per year. Our study period included the onset of the COVID-19 pandemic, when alcohol screening workflows in the health care system were disrupted (32); however, our sensitivity analyses to address potential biases related to attrition and censoring were largely consistent with the main analysis. The ability to examine self-reported quantity of alcohol use from a well-established

screening program with EHR data is a notable strength as many other claims-based studies are limited to diagnostic codes. Lastly, the study was restricted to insured patients; thus, the findings may not generalize to uninsured populations.

Conclusions

Our findings suggest that GLP-1RAs help people reduce alcohol intake and could be repurposed to treat alcohol problems. Additional studies, especially RCTs, are needed to further test the safety and efficacy of GLP-1RAs for decreasing alcohol use, especially in individuals with high-risk alcohol use and AUD.

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The datasets of the current study are not publicly available due to potentially identifiable information (e.g., dates of diagnoses) and KPNC privacy regulations. They are available upon reasonable request, contingent on appropriate human subjects approval and data use agreements.

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