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Association of Semaglutide With Tobacco Use Disorder in Patients With Type 2 Diabetes

Target Trial Emulation Using Real-World Data

William Wang; Nora D. Volkow, MD; Nathan A. Berger, MD; Pamela B. Davis, MD, PhD; David C. Kaelber, MD, PhD, MPH; and Rong Xu, PhD

Background: Reports of reduced desire to smoke in patients treated with semaglutide, a glucagon-like peptide receptor agonist (GLP-1RA) medication for type 2 diabetes mellitus (T2DM) and obesity, have raised interest about its potential benefit for tobacco use disorders (TUDs).

Objective: To examine the association of semaglutide with TUD-related health care measures in patients with comorbid T2DM and TUD.

Design: Emulation target trial based on a nationwide population-based database of patient electronic health records.

Setting: United States, 1 December 2017 to 31 March 2023.

Participants: Seven target trials were emulated among eligible patients with comorbid T2DM and TUD by comparing the new use of semaglutide versus 7 other antidiabetes medications (insulins, metformin, dipeptidyl-peptidase-4 inhibitors, sodium-glucose cotransporter-2 inhibitors, sulfonylureas, thiazolidinediones, and other GLP-1RAs).

Measurements: The TUD-related health care measures (medical encounter for diagnosis of TUD, smoking cessation medication prescriptions, and smoking cessation counseling) that occurred within a 12-month follow-up were examined using Cox proportional hazards and Kaplan–Meier survival analyses.

Results: The study compared 222 942 new users of antidiabetes medications including 5967 of semaglutide. Semaglutide was associated with a significantly lower risk for medical encounters for TUD diagnosis compared with other antidiabetes medications, and was strongest compared with insulins (hazard ratio [HR], 0.68 [95% CI, 0.63 to 0.74]) and weakest but statistically significant compared with other GLP-1RAs (HR, 0.88 [CI, 0.81 to 0.96]). Semaglutide was associated with reduced smoking cessation medication prescriptions and counseling. Similar findings were observed in patients with and without a diagnosis of obesity. For most of the group comparisons, the differences occurred within 30 days of prescription initiation.

Limitation: Documentation bias, residual confounding, missing data on current smoking behavior, body mass index, and medication adherence.

Conclusion: Semaglutide was associated with lower risks for TUD-related health care measures in patients with comorbid T2DM and TUD compared with other antidiabetes medications including other GLP-1Ras, primarily within 30 days of prescription. These findings suggest the need for clinical trials to evaluate semaglutide's potential for TUD treatment.

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Tobacco use is the leading preventable risk factor for premature deaths worldwide, accounting for an estimated 7.7 million annual deaths globally (1). Mortality from tobacco use reflects its contribution to various types of cancer and pulmonary, cardiac, and vascular diseases including stroke and diabetes, among others. Despite global trends in the reduction of tobacco use, the prevalence of smokers is still very high. In the United States in 2021, among adults aged 18 years or older, 11.5% were current cigarette smokers (2). Though there are effective medications for smoking cessation, not every smoker responds to them and the relapse rates are high (3). Thus, alternative medications for smoking cessation are needed.

See also:

Web-Only
Supplement

Clinical anecdotes that patients treated with semaglutide, a glucagon-like peptide-1 receptor agonist (GLP-1RA) approved for type 2 diabetes mellitus (T2DM) in 2017 and for obesity in 2021, reported reduced desire to smoke have attracted attention about its potential benefit for smoking cessation. Furthermore, we recently reported that semaglutide was associated with lower risks for both incidence and relapse of cannabis use disorder (4), which is frequently associated with cigarette smoking (up to 90% use both drugs) (5). Meanwhile, a small clinical trial in patients with a diagnosis of obesity or prediabetes ($n = 80$) that compared exenatide with placebo as an adjunct to nicotine replacement therapy (NRT)

for smoking cessation reported increased rates of abstinence (6). One small, phase 2, placebo-controlled trial is currently evaluating the effects of semaglutide on nicotine intake in smokers (7). Currently, limited data are available from real-world populations. Here, we used an emulation target trial using a large electronic health record (EHR) database to conduct a nationwide multicenter retrospective cohort study in patients with comorbid T2DM and tobacco use disorder (TUD) to determine whether semaglutide was associated with changes in health care use measures related to TUD (visits to clinician for TUD diagnosis, smoking cessation medication prescriptions and counseling). These measures were further assessed in subpopulations with and without a diagnosis of obesity.

METHODS

Specification of the Target Trials

Study Overview

We used a target trial emulation framework (8–10) to evaluate the comparative effectiveness of the new use of semaglutide versus the new use of other antidiabetes medications on TUD-related health care measures in 3 study populations: patients with comorbid T2DM and TUD, patients with comorbid T2DM and TUD who had a diagnosis of obesity, and those who did not have a diagnosis of obesity. Supplement Table 1 (available at Annals.org) lists the key protocol components. For each study population, 7 separate target trials were specified in comparing semaglutide with each of the 7 antidiabetes medications: insulins, metformin, dipeptidyl-peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter-2 inhibitors (SGLT2i), sulfonylureas (SUs), thiazolidinediones (TZDs), and other GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide). The target trials are specified as follows.

This study analyzed deidentified and population-based EHR data within the TriNetX Analytics platform. The TriNetX platform aggregates, and Health Insurance Portability and Accountability Act (HIPAA) deidentifies, data contributed from the EHRs of participating health care organizations. The built-in analytics within the TriNetX Analytic platform analyzed patient-level data; however, only population-level results are reported to users. Based on the deidentification methods used by TriNetX, as per HIPAA privacy and security rules (11), TriNetX sought and obtained expert attestation that TriNetX data are HIPAA deidentified: thus, access to protected health information is not allowed (and, therefore, there is no risk for protected health information disclosure); thus, institutional review board review was not required.

Eligibility Criteria

For all target trials, eligibility criteria included patients who had a diagnosis of T2DM and a diagnosis of TUD, had medical encounters with health care organizations between December 2017 and March 2023, had no use of any antidiabetes medications within the past year, and had at least 1 of the diseases based on the prescription guideline for semaglutide (12) (obesity, hypertension, hypercholesterolemia, hyperlipidemia, heart diseases, or stroke). Exclusion criteria included a history of bariatric surgery, pancreatitis, type 1 diabetes, thyroid cancer, or gastroparesis based on contraindications, warnings, and limited use information for semaglutide in patients with T2DM (12). For target trials in the subpopulation of patients with comorbid T2DM and TUD who had a diagnosis of obesity, an additional inclusion criterion was a diagnosis of obesity (based on International Classification of Diseases, 10th Revision [ICD-10] codes for obesity or body mass index [BMI] ≥30). For target trials in the subpopulation of patients with comorbid T2DM and TUD who had no diagnosis of obesity, patients with a preexisting diagnosis of obesity were excluded. Details of eligibility criteria are in Supplement Table 2 (available at Annals.org).

Treatment Strategies

For each of the 7 target trials, the treatment strategies were the initiation of semaglutide use at baseline (index event) versus the initiation of comparison antidiabetes medication use at baseline (index event). All treatment strategies included not initiating more than 1 of the 8 studied treatment strategies at baseline (that is, no coprescription of semaglutide and the comparison medication). For all treatment strategies, initiation of use is defined as the first prescription for the drug, consistent with an intention-to-treat design. The treatment strategy is assigned at baseline, regardless of medication use adherence or medication switch or add-on.

Study Outcomes

Outcomes of interest included 3 health care measures related to TUD: medical encounters for TUD diagnosis, smoking cessation medication prescriptions, and smoking cessation counseling. One non-TUD–related health care measure was used for sensitivity analyses: overall medical encounters. Each health care measure was analyzed separately. Each eligible patient was followed from the index event until the occurrence of the measure, death, loss to follow-up, or 12 months after the index event, whichever occurred first.

Analysis Approach

The causal estimates of interest represent the intention-to-treat effect of being assigned to the treatment strategies. Cumulative incidences were estimated using the Kaplan–Meier survival analysis in patients who were propensity-score matched (1:1 using nearest neighbor greedy matching with a caliper of 0.25 times the SD) for baseline covariates. Cox proportional hazards analyses were used to compare rates of time-to-events daily during the follow-up time after

the index event. Hazard ratios (HRs) and 95% CIs were calculated. Risk difference was calculated, which is the difference in risk between treatment strategies, with 95% CI calculated with the *Z* test (null hypothesis: risk difference equals 0). All models are adjusted for confounders at baseline by propensity-score matching baseline covariates.

Emulation of the Target Trials

We explicitly emulated the target trials described in the previous sections using data and built-in analytic functions on the TriNetX Analytics platform (more details are in **Supplement Tables 1** to **4** and **Supplement Figure 1**, available at Annals.org).

TriNetX is a global, federated, health research network providing access to deidentified and aggregated EHRs from approximately 113 million patients in 64 large health care organizations covering diverse geographic regions, age, race and ethnicity, income and insurance groups, and clinical settings (13) (for more details, see the **Supplement**, available at Annals.org). The TriNetX platform has been successfully used in retrospective cohort studies (14–24) including evaluations of risk and outcomes of COVID-19 in patients with substance use disorders including TUD (14); associations of semaglutide with suicidal ideation (25), cannabis use disorder (4), and alcohol use disorder (26); and for associations of GLP-1RAs with cancer risks (27, 28).

Available data elements of EHRs include extensive information on demographics, diagnoses (ICD-10, medications [Anatomical Therapeutic Chemical (ATC) codes], and medical prescription normalized medical prescription [RxNorm]), procedures (Current Procedural Terminology [CPT]), laboratory tests (Logical Observation Identifiers Names and Codes [LOINC]), genomics, visits, and socioeconomic and lifestyle information. Self-reported sex, race, and ethnicity data from contributing health care systems are mapped by TriNetX according to Office of Management and Budget (OMB) standards into 1) race (Asian, American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race) and 2) ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown Ethnicity). All covariates are either binary, categorical, or continuous but essentially guaranteed to exist. Missing sex values are represented using "Unknown Sex." The missing data for race and ethnicity are presented as "Unknown Race" or "Unknown Ethnicity." For other variables including medical conditions, procedures, laboratory tests, and socioeconomic determinants of health, the value is either present or absent, so "missing" is not pertinent.

Each component of the target trial was emulated using EHRs from the TriNetX Analytics platform. Patients were classified into drug treatment groups—semaglutide versus other antidiabetes medications (insulins, metformin, DPP-4i, SGLT2i, SU, TZD, and other GLP-1RAs) based on the first prescription in the study period (December 2017 to March 2023), which was the baseline or index event. Eligibility criteria and 70 baseline covariates were evaluated at baseline. The semaglutide group and each of the 7 comparison treatment groups were separately propensity-score matched for covariates at the baseline to emulate randomization. After propensity-score matching, the semaglutide group and its corresponding comparison group were balanced.

Statistical Analysis

The data were collected and analyzed on 22 April 2024 within the TriNetX Analytics platform. All of the statistical analyses in this study including propensity-score matching, Kaplan–Meier survival analysis, Cox proportional hazards analysis, and risk difference were done using built-in functions within the TriNetX Analytics platform that are implemented using Survival 3.2-3 in R 4.0.2 and libraries and utilities for data science and statistics in Python 3.7 and Java 11.0.16. Details of clinical codes for eligibility criteria, treatment strategies, outcomes, and baseline covariates are in **Supplement Table 4**.

Role of the Funding Source

The funding source had no role in the design of this study and did not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

RESULTS

Study Populations

Figure 1 is a flow chart of the cohort construction. The study included 222 942 new users of antidiabetes medications including 5967 new users of semaglutide and 216 975 new users of other antidiabetes medications, with sample size ranging from 4231 for TZD to 213 225 for insulin. Semaglutide was separately compared with each of the 7 antidiabetes medication classes in patients with comorbid T2DM and TUD. Before propensity matching, the insulin and semaglutide groups differed by age, sex, race and diagnosis of obesity, some mental or behavioral health conditions and some cardiovascular conditions, and by prior smoking cessation medication prescriptions and counseling (**Table**). Some of these factors also differed between semaglutide and other noninsulin comparators (metformin, DPP-4i, SGLT2i, SU, TZD, and other GLP-1RAs). After propensity-score matching, comparison groups were largely balanced (**Table**; **Supplement Tables 5–10**, available at Annals.org).

Association of Semaglutide With Medical Encounters for TUD Diagnosis in Patients With T2DM and TUD

In patients with T2DM and TUD, semaglutide was associated with a significantly lower risk for medical encounters for TUD diagnosis compared with all 7 antidiabetes medications, with the strongest effect compared with insulins (HR, 0.68 [95% CI, 0.63 to 0.74]) and

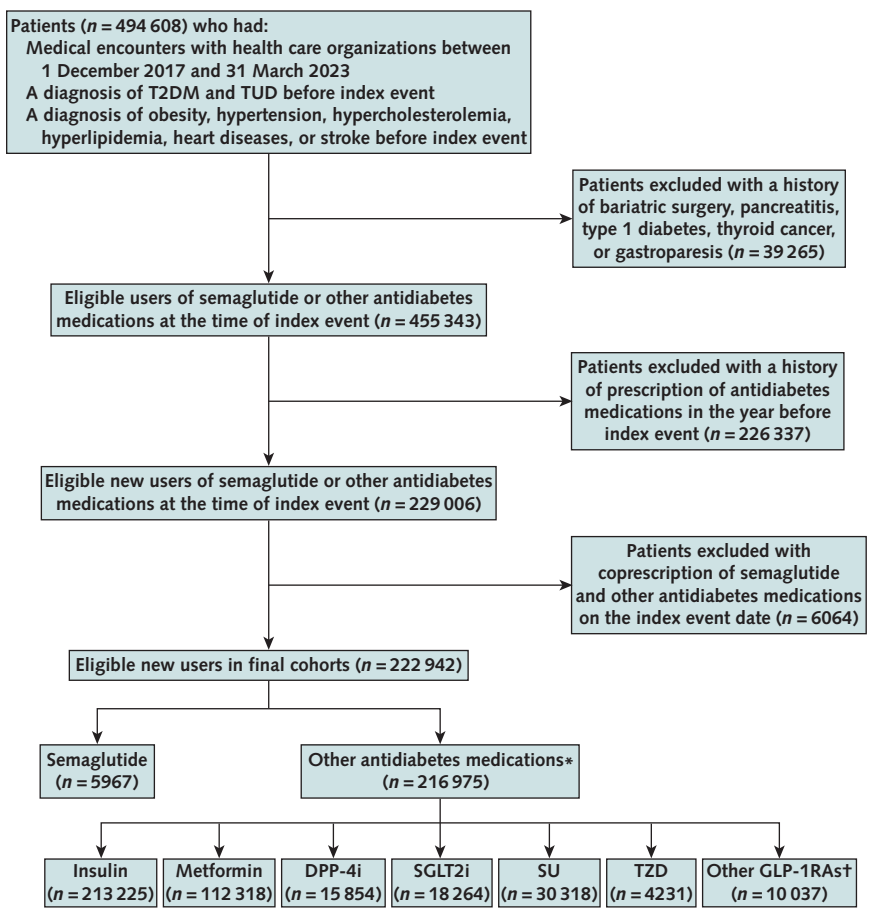
the weakest but statistically significant effect compared with other GLP-1RAs (HR, 0.88 [CI, 0.81 to 0.96]) (**Figure 2**). The 12-month cumulative incidence curves comparing semaglutide with each of the 7 antidiabetes medications are shown in **Figure 3**. The separation between the curves for many of the comparisons was most prominent within the first 30 days and continued to diverge more modestly (except for comparison with insulins) until approximately day 180, plateauing thereafter.

Among patients with T2DM and TUD who had no diagnosis of obesity, semaglutide was associated with a significantly lower risk for medical encounters for TUD diagnosis compared with other antidiabetes medications except for other GLP-1RAs, with HRs ranging from 0.60 for insulin and 0.78 for TZD. Compared with other GLP-1RAs, semaglutide was associated with a lower though not statistically significant risk (HR, 0.85 [CI, 0.71 to 1.02]) (**Figure 2**). Among patients with T2DM and TUD who had a prior diagnosis of obesity, semaglutide was associated with a significantly lower risk for medical encounters for TUD diagnosis compared with all 7 antidiabetes medications (**Supplement Figure 2**, available at Annals.org).

Association of Semaglutide With Smoking Cessation Medication Prescriptions in Patients With T2DM and TUD

Semaglutide was associated with a significantly lower risk for smoking cessation medication prescriptions compared with other antidiabetes medications, and was strongest compared with insulins (HR, 0.32 [CI, 0.28 to 0.38]) and weakest compared with other GLP-1RAs (HR, 0.62 [CI, 0.52 to 0.74]) (**Figure 4**). Similar statistically significant reductions were observed in patients without a diagnosis of obesity (**Figure 4**) and in patients with a diagnosis of obesity (**Supplement Figure 3**, available at Annals.org). The 12-month cumulative incidences of smoking cessation medication prescriptions comparing semaglutide with each of the 7 antidiabetes medications are in **Supplement Figure 4** (available at Annals.org). The separation for many of the curves is evident within the first 30 days and continues thereafter,

Figure 1. Study flow diagram.



DPP-4i = dipeptidyl-peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TUD = tobacco use disorder; TZD = thiazolidinedione.
* The combined total of patients (*n* = 216 975) is not a sum of the patients from each of the 7 comparison antidiabetes medication cohorts because a patient could be prescribed more than 1 antidiabetes medication during the study period.
† Other GLP-1RAs included albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

Table. Characteristics of the Semaglutide Versus Insulin Groups Before and After Propensity-Score Matching for Baseline Covariates for the Study Population of Patients With Comorbid T2DM and TUD

Characteristic	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	Insulin	SMD	Semaglutide	Insulin	SMD
Total, *n*	5967	213 225	–	5954	5954	–
Mean age at index event (SD), *y*	58.5 (11.9)	64.6 (13.0)	0.48*	58.5 (11.9)	58.6 (13.4)	0.004
Sex, %						
Female	50.4	37.2	0.27*	50.4	50.8	0.008
Male	41.5	57.4	0.32*	41.5	41.1	0.009
Unknown	8.1	5.4	0.11*	8.1	8.1	<.001
Ethnicity, %						
Hispanic/Latinx	4.4	6.6	0.10*	4.4	4.2	0.008
Not Hispanic/Latinx	77.7	74.4	0.08	77.7	77.9	0.005
Unknown	17.9	19.1	0.03	17.9	17.9	<.001
Race, %						
Asian	3.5	3.6	0.007	3.5	3.6	0.009
Black	11.8	19.0	0.20*	11.8	11.8	0.002
White	69.1	62.3	0.14*	69.0	69.0	0.001
Unknown	11.9	11.2	0.02	12.0	12.0	0.001
Marital status, %						
Never married	11.7	14.8	0.09	11.7	12.0	0.01
Divorced	7.9	7.7	0.007	7.9	7.5	0.02
Widowed	5.3	8.9	0.14*	5.3	5.5	0.007
Adverse socioeconomic determinants of health, %	6.4	5.7	0.03	6.4	6.2	0.01
Problems related to lifestyle, %	21.9	13.6	0.22*	21.8	20.8	0.03
Preexisting diagnoses of medical conditions, %						
Obesity diagnoses						
Severe obesity due to excess calories	40.9	16.1	0.57*	40.8	41.3	0.01
Severe obesity with alveolar hypoventilation	1.8	1.5	0.02	1.8	1.9	0.01
Obesity due to excess calories	45.2	17.3	0.63*	45.1	45.5	0.008
Other obesity	1.7	0.5	0.11*	1.7	1.8	0.009
Obesity, unspecified	53.5	28.7	0.52*	53.4	55.2	0.04
BMI 30.0–30.9	6.6	4.0	0.12*	6.6	6.9	0.01
BMI 31.0–31.9	7.0	3.9	0.14*	7.0	7.3	0.01
BMI 32.0–32.9	7.9	3.9	0.17*	7.9	7.5	0.02
BMI 33.0–33.9	8.7	3.8	0.21*	8.7	8.7	0.001
BMI 34.0–34.9	9.1	3.7	0.22*	9.0	8.9	0.005
BMI 35.0–35.9	9.9	3.8	0.24*	9.9	9.4	0.02
BMI 36.0–36.9	9.2	3.5	0.24*	9.2	9.3	0.003
BMI 37.0–37.9	8.9	3.1	0.25*	8.9	9.0	0.002
BMI 38.0–38.9	8.7	2.9	0.25*	8.7	8.8	0.005
BMI 39.0–39.9	8.3	2.4	0.26*	8.2	8.5	0.01
BMI 40.0–44.9	21.0	7.5	0.39*	20.9	21.3	0.009
BMI 45.0–49.9	12.9	3.9	0.33*	12.8	12.3	0.02
BMI 50.0–59.9	9.0	2.7	0.27*	9.0	9.0	0.002
BMI 60.0–69.9	2.7	0.8	0.15*	2.7	2.8	0.006
BMI ≥70	0.7	0.4	0.05	0.7	0.7	0.004
Mental/behavioral health conditions						
Depression	35.0	23.9	0.25*	34.9	34.8	0.002
Major depression, recurrent	11.3	4.5	0.25*	11.2	10.5	0.02
Mood disorders	40.1	28.1	0.26*	40.0	40.0	0.001
Anxiety disorders	43.0	26.0	0.36*	42.9	43.0	0.003
Psychotic disorders	2.5	4.4	0.11*	2.5	2.4	0.004
Behavioral disorders	9.6	3.0	0.27*	9.6	9.4	0.007
Disorders of adult personality and behavior	1.8	1.6	0.02	1.8	1.6	0.02
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	4.3	1.4	0.17*	4.2	4.0	0.008
Conduct disorders	0.4	0.4	<0.001	0.4	0.4	0.008
Symptoms and signs involving emotional state	6.5	5.9	0.02	6.5	6.1	0.02
Alcohol use disorder	5.5	9.3	0.15*	5.5	5.7	0.009
Opioid use disorder	3.4	3.9	0.03	3.4	3.3	0.002
Cannabis use disorder	2.8	4.4	0.09	2.8	2.5	0.02
Cocaine use disorder	1.4	3.2	0.12*	1.4	1.0	0.04
Other stimulant disorders	1.1	1.8	0.06	1.1	1.0	0.02
Other psychoactive substance-related disorders	2.7	3.9	0.07	2.7	2.2	0.03

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Table–Continued

Characteristic	Before Propensity-Score Matching			After Propensity-Score Matching		
	Semaglutide	Insulin	SMD	Semaglutide	Insulin	SMD
Cardiovascular and other risk/conditions						
Hypertension	84.1	88.1	0.12*	84.1	84.7	0.02
Disorders of lipoprotein metabolism and other lipidemias	81.1	69.4	0.27*	81.1	82.2	0.03
Hyperlipidemia	67.7	61.3	0.13*	67.7	69.1	0.03
Hypercholesterolemia	30.0	21.4	0.20*	29.9	30.2	0.007
Ischemic heart diseases	31.1	45.6	0.30*	31.1	32.6	0.03
Other forms of heart disease	41.4	54.7	0.27*	41.5	41.9	0.009
Cerebral infarction	4.9	10.7	0.22*	4.9	4.9	0.002
Cerebrovascular diseases	12.7	22.3	0.26*	12.7	12.9	0.007
Cancer	44.7	32.2	0.26*	44.6	44.6	<0.001
Chronic pain	36.0	21.2	0.33*	36.0	35.7	0.006
Preexisting medical procedures and medication prescriptions, %						
Hospitalizations	27.0	35.7	0.19*	27.0	27.7	0.02
Tobacco abuse counseling	4.4	2.5	0.10*	4.4	4.1	0.01
Smoking and tobacco use cessation counseling visit	5.4	3.1	0.12*	5.4	5.5	0.004
Smoking cessation education	0.2	0.1	0.01	0.2	0.2	<0.001
Drugs used in nicotine dependence	17.6	12.5	0.14*	17.5	17.3	0.004
NRT	12.9	11.6	0.04	12.9	13.0	0.004
Varenicline	7.9	1.9	0.28*	7.8	7.5	0.01
Bupropion	15.9	4.5	0.38*	15.8	14.6	0.03
Nortriptyline	2.4	1.2	0.09	2.4	2.2	0.01

BMI = body mass index; NRT = nicotine replacement therapy; SMD = standardized mean difference.
* SMD greater than 0.1, a threshold indicating cohort imbalance. Adverse socioeconomic determinants of health (International Classification of Diseases, 10th Revision [ICD-10] codes Z55 to Z65: "Persons with potential health hazards related to socioeconomic and psychosocial circumstances") include problems related to education and literacy, employment and unemployment, housing and economic circumstances, social environment, upbringing, primary support group including family circumstances, certain psychosocial circumstances, and other psychosocial circumstances. Problems with lifestyle (ICD-10 code Z72: "Problems related to lifestyle") included tobacco use, lack of physical exercise, inappropriate diet and eating habits, high-risk sexual behavior, gambling and betting, and other problems related to lifestyle including antisocial behavior and sleep deprivation. For propensity-score matching for "adverse socioeconomic determinants of health" and "problems related to lifestyle," the parent codes (Z55 to Z65 and Z72) instead of individual child codes were matched due to the small number for each child code.

though with attenuated divergence between the groups, which plateaued by day 180.

Association of Semaglutide With Smoking Cessation Counseling in Patients With T2DM and TUD

Semaglutide was associated with a lower risk for smoking cessation counseling compared with other antidiabetes medications with HRs ranging from 0.69 to 0.85, which was statistically significant when compared with insulins, metformin, and DPP-4i. Among patients with no diagnosis of obesity, semaglutide was associated with decreased risk for smoking cessation counseling, which was significant compared with metformin and SU. Among patients with a diagnosis of obesity, semaglutide was associated with reduced but not significant risk for smoking cessation counseling compared with insulins, metformin, DPP-4i, SU, and other GLP-1RAs (**Supplement Figures 5** and **6**, available at Annals.org).

Sensitivity Analysis

Among patients with T2DM and TUD, those who used semaglutide were more likely to have medical encounters compared with those who used insulin but less likely when compared with patients who received other antidiabetes medications. The associations were statistically significant but not strong, with HRs ranging from 0.81 to 1.15. Similar findings were observed in patients with a diagnosis of obesity. Among patients with no diagnosis of obesity, semaglutide was not significantly associated with having medical encounters compared with other antidiabetes medications except for insulins (**Supplement Figure 7**, available at Annals.org).

DISCUSSION

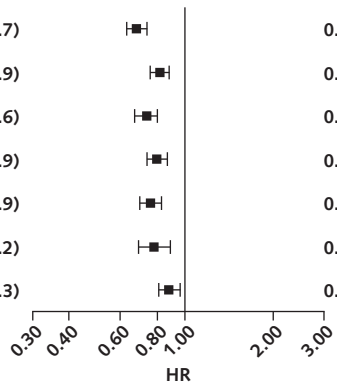
In our study of real-world populations of patients with comorbid T2DM and TUD, we found that semaglutide was associated with a lower risk for TUD-related health care utilization–including use that would indicate smoking cessation efforts–compared with other antidiabetes medications. Comparators studied included insulin, other non-insulin/non-GLP-1RAs, and other GLP-1RAs. Similar effects were observed in subpopulations without and with a diagnosis of obesity. For many comparisons, the cumulative incidence curves separated most prominently by day 30 and, although they continued to diverge, the divergence rate was much more modest and plateaued by day 180.

The comparison antidiabetes medications are not known to be associated with harmful effects on TUD. Rather, studies suggest that some of the comparison medications including insulin, metformin, and other GLP-1RAs have beneficial effects on reducing nicotine's rewarding effects in both rodents and in human smokers (29–35). The lower risks for TUD-related measures at follow-up for patients who were prescribed semaglutide are consistent with preclinical and preliminary clinical

Figure 2. Comparison of risk and hazard rate of medical encounters for TUD diagnosis in patients with T2DM and TUD between propensity-score matched semaglutide and other antidiabetes medication groups.

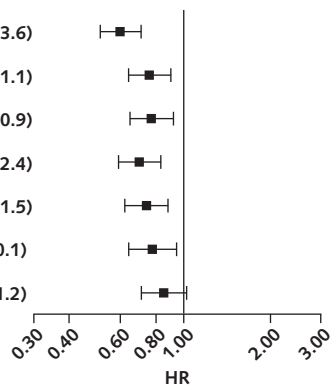
Medical Encounters for TUD Diagnosis in Patients With T2DM and TUD (Comparison Between Matched Semaglutide vs. Other Antidiabetes Medication Cohorts)

Size/Cohort, *n*	Exposure	Comparison	Cases, Overall Risk, *n* (%)		RD (95% CI), %	HR (95% CI)
			Exposure	Comparison		
5954	Semaglutide	Insulins	1168 (19.6)	1479 (24.8)	−5.2 (−6.7 to −3.7)	0.68 (0.63 to 0.74)
5955	Semaglutide	Metformin	1170 (19.6)	1372 (23.0)	−3.4 (−4.9 to −1.9)	0.82 (0.76 to 0.88)
4831	Semaglutide	DPP-4i	923 (19.1)	1174 (24.3)	−5.2 (−6.8 to −3.6)	0.74 (0.67 to 0.80)
5325	Semaglutide	SGLT2i	1046 (19.6)	1232 (23.1)	−3.5 (−5.0 to −1.9)	0.80 (0.74 to 0.87)
5388	Semaglutide	SU	1042 (19.3)	1283 (23.8)	−4.5 (−6.0 to −2.9)	0.76 (0.70 to 0.83)
2659	Semaglutide	TZD	462 (17.4)	551 (20.7)	−3.3 (−5.5 to −1.2)	0.78 (0.69 to 0.89)
5337	Semaglutide	Other GLP-1RAs*	1051 (19.7)	1149 (21.5)	−1.9 (−3.4 to −0.3)	0.88 (0.81 to 0.96)



Medical Encounters for TUD Diagnosis in Patients With T2DM and TUD (Without Obesity) (Comparison Between Matched Semaglutide vs. Other Antidiabetes Medication Cohorts)

Size/Cohort, *n*	Exposure	Comparison	Cases, Overall Risk, *n* (%)		RD (95% CI), %	HR (95% CI)
			Exposure	Comparison		
1302	Semaglutide	Insulins	238 (18.3)	326 (25.0)	−6.8 (−9.9 to −3.6)	0.60 (0.51 to 0.71)
1305	Semaglutide	Metformin	240 (18.4)	295 (22.6)	−4.2 (−7.3 to −1.1)	0.76 (0.64 to 0.90)
1283	Semaglutide	DPP-4i	237 (18.5)	289 (22.5)	−4.1 (−7.2 to −0.9)	0.77 (0.65 to 0.92)
1293	Semaglutide	SGLT2i	238 (18.4)	310 (24.0)	−5.6 (−8.7 to −2.4)	0.70 (0.59 to 0.83)
1292	Semaglutide	SU	237 (18.3)	297 (23.0)	−4.6 (−7.8 to −1.5)	0.74 (0.62 to 0.88)
1033	Semaglutide	TZD	188 (18.2)	223 (21.6)	−3.4 (−6.8 to 0.1)	0.78 (0.64 to 0.94)
1268	Semaglutide	Other GLP-1RAs*	232 (18.3)	256 (20.2)	−1.9 (−5.0 to 1.2)	0.85 (0.71 to 1.02)

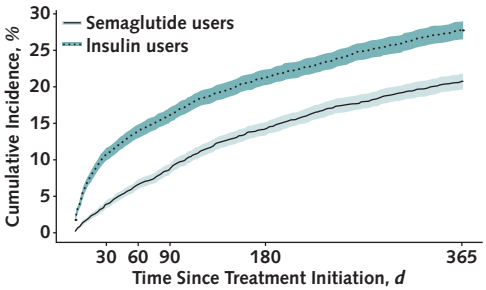


DPP-4i = dipeptidyl-peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; RD = risk difference; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TUD = tobacco use disorder; TZD = thiazolidinedione. Results for (*top*) the whole cohort and (*bottom*) the cohort without a diagnosis of obesity. Each eligible patient in the matched groups was followed from the index event until the occurrence of the health care measure, death, loss to follow-up, or 12 months after the index event, whichever occurred first. Hazard rates were calculated using a Cox proportional hazards model with censoring applied.
* Other antidiabetes GLP-1RAs included albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

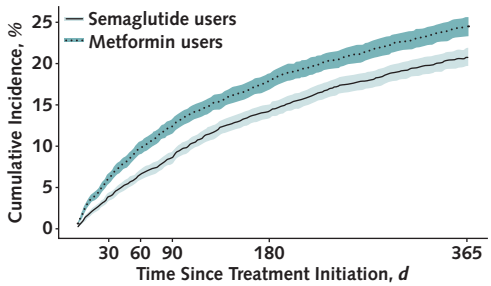
evidence in support of its potential beneficial effects as well as that of other GLP-1RA medications for the treatment of TUD (6, 36).

Our study used EHR data and did not measure current nicotine intake and smoking lapse and does not contain granular information on the number of cigarettes consumed per day, change in cigarette craving, and duration of time to smoking reinstatement. What we examined was the clinical codes for 3 TUD-related health care use measures including medical encounters that specified a TUD diagnosis, smoking cessation medication prescriptions, and smoking cessation counseling. A reduction in TUD-related encounters could potentially suggest a reduction in tobacco use or relapse. However, a reduction in these measures could also reflect other scenarios, such as a reduced willingness to seek help to quit smoking. Moreover, early separation of the curves suggests some of the observed differences might partially reflect systematic differences across groups prescribed these different medications rather than direct effects of the medications. Successful quitting without assistance is not captured. In addition, although the study population included patients with comorbid T2DM and TUD, we could not explicitly control the severity of TUD, though prior history of smoking cessation medication prescriptions and counseling

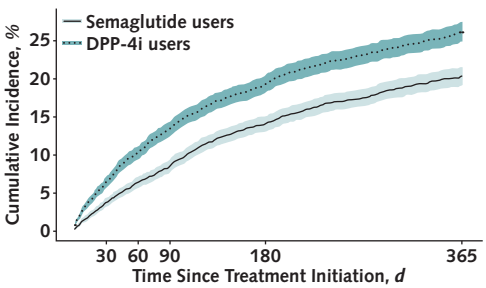
Figure 3. Cumulative incidences of medical encounters for TUD diagnosis for the 7 target trial emulations of users of semaglutide compared with antidiabetes medications during a 12-month follow-up.



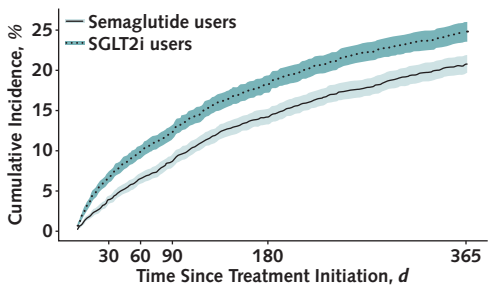
Users, *n*	30 d	60 d	90 d	180 d	365 d
Semaglutide	5627	5425	5269	4801	3740
Insulin	4904	4603	4392	3931	3293



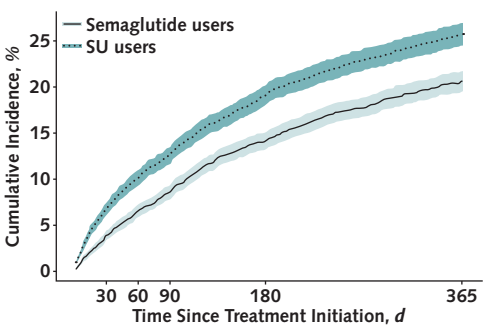
Users, *n*	30 d	60 d	90 d	180 d	365 d
Semaglutide	5627	5425	5269	4801	3738
Metformin	5902	5138	4950	4512	3871



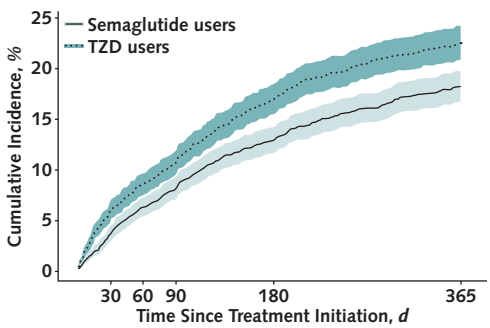
Users, *n*	30 d	60 d	90 d	180 d	365 d
Semaglutide	4565	4398	4270	3895	3021
DPP-4i	4330	4101	3916	3541	2984



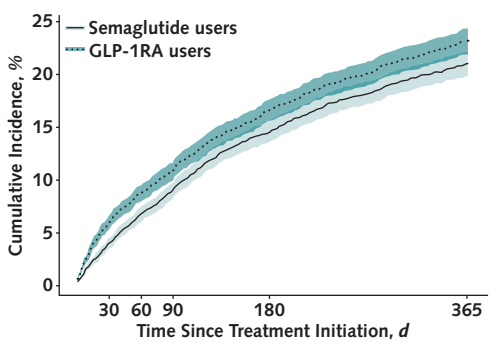
Users, *n*	30 d	60 d	90 d	180 d	365 d
Semaglutide	5029	4849	4705	4288	3324
SGLT2i	4784	4563	4395	3956	3207



Users, *n*	30 d	60 d	90 d	180 d	365 d
Semaglutide	5089	4907	4766	4342	3371
SU	4814	4588	4416	3960	3392



Users, *n*	30 d	60 d	90 d	180 d	365 d
Semaglutide	2509	2414	2346	2141	1671
TZD	2364	2265	2181	1932	1692



Users, *n*	30 d	60 d	90 d	180 d	365 d
Semaglutide	5037	4852	4704	4281	3310
GLP-1RA	4852	4657	4497	4090	3407

Continued on following page

Figure 3–Continued.

Each eligible patient in the matched groups was followed from the index event until the occurrence of the health care measure, death, loss to follow-up, or 12 months after the index event, whichever occurred first. DPP-4i = dipeptidyl-peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TZD = thiazolidinedione.

were controlled. In addition, those who quit smoking may gain weight, and this population of recent quitters may disproportionately comprise those on semaglutide.

Tobacco smoking is the leading cause of preventable morbidity and mortality including cardiovascular diseases, cancer types, and all-cause mortality (37). Smoking cessation reduces the risk for many adverse health effects; however, fewer than 1 in 10 adult cigarette smokers succeed in quitting each year. In 2022, only 9.6% of cigarette smokers aged 18 years and older successfully quit smoking in the past year (38). A recent report by the U.S. Preventive Services Task Force (USPSTF) reviewed the effectiveness of smoking cessation therapeutics, reporting the following risk ratios to quit smoking at 6 months or more compared with placebo or minimal support: varenicline, 2.24; bupropion, 1.64; NRT, 1.55; and behavioral interventions, 1.76 (39). Based on these results, the USPSTF concluded that the evidence showed with moderate to high certainty that U.S. Food and Drug Administration (FDA)–approved medications for smoking cessation and behavioral interventions significantly increased smoking cessation but commented that the findings have not changed much in 30 years. This could change if randomized clinical trials confirm the therapeutic benefits of semaglutide and other GLP-1RAs for treating TUD. The fact that semaglutide (and other GLP-1RAs) leads to weight loss becomes particularly relevant because smoking cessation is associated with weight gain, which contributes to relapse, particularly in women (40). Moreover, because smoking impairs glycemic control (41) and increases cardiovascular and cancer risks (42), the beneficial effects of semaglutide for glycemic control (43), and reduction in cardiovascular (44, 45) and cancer events (27), would offer additional benefits. Furthermore, semaglutide has a higher adherence rate than other medications (46), including other GLP-1RAs, in patients with T2DM (47).

In this study, we compared semaglutide to other antidiabetes medications in patients with comorbid T2DM and TUD who were matched for 20 clinical codes for obesity and BMI categories. In addition, separate analyses were performed in patients with and without a diagnosis of obesity. Risks for TUD-related measures were lower in patients with T2DM whether they had a diagnosis of obesity or not. However, we could not directly compare semaglutide to other antiobesity medications in patients with comorbid obesity and TUD due to sample size limitations centering on the size of comparison groups prescribed other drugs to treat obesity. In addition, the EHR data captures the presence or absence of diagnosis codes for obesity and BMI, but not the actual BMI data.

The mechanisms underlying the observed lower-risk associations of semaglutide with TUD-related measures are unclear, but preclinical studies suggest that they likely reflect the involvement of GLP-1 receptors in modulating the brain's reward and aversive systems (48). Specifically, the GLP-1RA exenatide in rodents attenuated nicotine-induced increases in dopamine release in the nucleus accumbens (NAc), a common mechanism underlying the rewarding effects of addictive drugs (6), and it enhanced the aversive effects of nicotine by activating the habenular circuit (33).

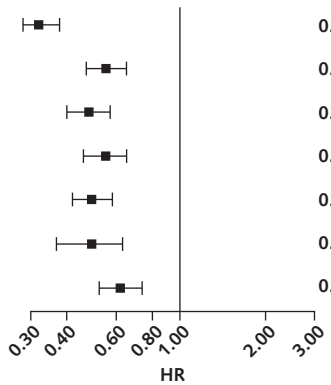
If GLP-1RAs have similar effects on humans as in rodents, reducing the rewarding effects of nicotine while increasing its aversive effects, this could have contributed to the finding of an association with a lower risk for TUD-related measures compared with non-GLP-RA antidiabetes medications, including the need for smoking cessation treatments. In addition, the reduction in body weight associated with GLP-1RA might have also contributed to the reduced risk for TUD-related measures because fear of weight gain on smoking cessation contributes to smoking and relapse (49). Interestingly, semaglutide was associated with a lower risk for TUD-related measures compared with other GLP-1RAs in patients without and with a diagnosis of obesity. This could reflect differences in brain bioavailability or adherence between semaglutide and the other GLP-1RA medications and merits further investigation.

This retrospective observational study of patient EHRs has inherent limitations including overdiagnosis, underdiagnosis, and misdiagnosis; unmeasured or uncontrolled confounders; and biases. As such, some of our results could reflect residual confounding by indications that were not captured by the propensity-score matching. In addition, patients in our study represented those who had medical encounters with health care systems contributing to the TriNetX platform. Results need to be validated in other EHR databases and analytics platforms. Another limitation is that the follow-up time was 12 months, and future studies should examine longer follow-ups. In addition, we could not compare semaglutide with other antiobesity medications in patients with comorbid obesity and TUD due to sample size limitations. The EHRs lack information related to the severity of TUD including the number of cigarettes smoked per day and the severity of craving and withdrawal. Instead, we used clinical

Figure 4. Comparison of risk and hazard rate of smoking cessation medication prescriptions in patients with T2DM and TUD between propensity-score matched semaglutide versus other antidiabetes medication groups.

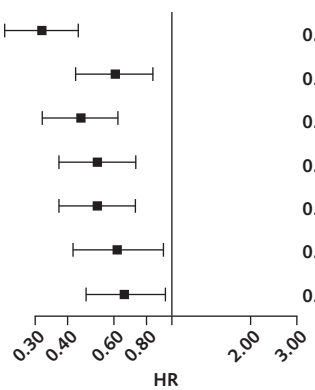
Smoking Cessation Medication Prescriptions in Patients With T2DM and TUD (Comparison Between Matched Semaglutide vs. Other Antidiabetes Medication Cohorts)

Size/Cohort, *n*	Exposure	Comparison	Cases, Overall Risk, *n* (%)		RD (95% CI), %	HR (95% CI)
			Exposure	Comparison		
5954	Semaglutide	Insulins	242 (4.1)	670 (11.3)	−7.2 (−8.1 to −6.2)	0.32 (0.28 to 0.38)
5955	Semaglutide	Metformin	244 (4.1)	428 (7.2)	−3.1 (−3.9 to −2.3)	0.55 (0.47 to 0.65)
4831	Semaglutide	DPP-4i	187 (3.9)	372 (7.7)	−3.8 (−4.8 to −2.9)	0.48 (0.40 to 0.57)
5325	Semaglutide	SGLT2i	211 (4.0)	369 (6.9)	−3.0 (−3.8 to −2.1)	0.55 (0.46 to 0.65)
5388	Semaglutide	SU	215 (4.0)	418 (7.8)	−3.8 (−4.7 to −2.9)	0.49 (0.42 to 0.58)
2659	Semaglutide	TZD	81 (3.0)	159 (6.0)	−2.9 (−4.0 to −1.8)	0.49 (0.37 to 0.63)
5337	Semaglutide	Other GLP-1RAs*	212 (4.0)	331 (6.2)	−2.2 (−3.1 to −1.4)	0.62 (0.52 to 0.74)



Smoking Cessation Medication Prescriptions in Patients With T2DM and TUD (Without Obesity) (Comparison Between Matched Semaglutide vs. Other Antidiabetes Medication Cohorts)

Size/Cohort, *n*	Exposure	Comparison	Cases, Overall Risk, *n* (%)		RD (95% CI), %	HR (95% CI)
			Exposure	Comparison		
1302	Semaglutide	Insulins	54 (4.1)	148 (11.4)	−7.2 (−9.3 to −5.2)	0.32 (0.23 to 0.44)
1305	Semaglutide	Metformin	54 (4.1)	85 (6.5)	−2.4 (−4.1 to −0.7)	0.61 (0.43 to 0.85)
1283	Semaglutide	DPP-4i	51 (4.0)	109 (8.5)	−4.5 (−6.4 to −2.7)	0.45 (0.32 to 0.62)
1293	Semaglutide	SGLT2i	54 (4.2)	98 (7.6)	−3.4 (−5.2 to −1.6)	0.52 (0.37 to 0.73)
1292	Semaglutide	SU	52 (4.0)	95 (7.4)	−3.3 (−5.1 to −1.5)	0.52 (0.37 to 0.73)
1033	Semaglutide	TZD	41 (4.0)	62 (6.0)	−2.0 (−3.0 to −0.2)	0.62 (0.42 to 0.93)
1268	Semaglutide	Other GLP-1RAs*	52 (4.1)	75 (5.9)	−1.8 (−3.5 to −0.1)	0.66 (0.47 to 0.95)



DPP-4i = dipeptidyl-peptidase-4 inhibitor; GLP-1RA = glucagon-like peptide-1 receptor agonist; HR = hazard ratio; RD = risk difference; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TUD = tobacco use disorder; TZD = thiazolidinedione. Results for (*top*) the whole cohort and (*bottom*) the cohort without a diagnosis of obesity. Each eligible patient in the matched groups was followed from the index event until the occurrence of the health care measure, death, loss to follow-up, or 12 months after the index event, whichever occurred first. Hazard rates were calculated using a Cox proportional hazards model with censoring applied.
* Other GLP-1RAs included albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.

codes for TUD-related measures including medical encounters for TUD, smoking cessation medication prescriptions and counseling. However, as discussed herein, these measures might reflect the willingness to seek help to quit smoking. Finally, EHRs do not capture medication adherence, though studies showed that semaglutide has a higher adherence rate than other obesity medications (46) including other GLP-1RAs in patients with T2DM (47). We could not explicitly control for variations in practice patterns among health care organizations, nor patient health care utilization, though both exposure and comparison cohorts were drawn from the same 64 health care organizations within the TriNetX network.

Although our results may be consistent with the hypothesis that semaglutide might be beneficial for smoking cessation, study limitations preclude firm conclusions (6) and should not be interpreted to justify clinicians' use of semaglutide off-label for smoking cessation. This will need to be examined in randomized clinical trials.

From Center for Science, Health, and Society, Case Western Reserve University School of Medicine, Cleveland, Ohio (W.W., N.A.B.); National Institute on Drug Abuse, National Institutes of Health, Bethesda, Maryland (N.D.V.); Center for Community Health Integration, Case Western Reserve University School of

Medicine, Cleveland, Ohio (P.B.D.); Center for Clinical Informatics Research and Education, The MetroHealth System, Cleveland, Ohio (D.C.K.); and Center for Artificial Intelligence in Drug Discovery, Case Western Reserve University School of Medicine, Cleveland, Ohio (R.X.).

Note: The authors confirm the originality of the content. Dr. Xu had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

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Disclosures: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M23-2718.

Reproducible Research Statement: *Study protocol:* Not available. *Statistical code:* All of the statistical analyses in this study including propensity-score matching and Cox proportional hazards used web-based built-in functions within the TriNetX Analytics platform that are implemented using Survival 3.2-3 in R 4.0.2 and libraries/utilities for data science and statistics in Python 3.7 and Java 11.0.16. Data and code to re-create figures in the study can be accessed at https://github.com/bill-pipi/semaglutide_TUD. *Data set:* This study used population-level aggregate and HIPAA-deidentified data collected by the TriNetX platform, available from TriNetX (https://trinetx.com), but third-party restrictions apply to the availability of these data. The data were used under license for this study with restrictions that do not allow for the data to be redistributed or made publicly available. To gain access to the data, a request can be made to TriNetX (join@trinetx.com), but costs may be incurred and a data-sharing agreement may be necessary. Data specific to this study including diagnosis codes and cohort characteristics in aggregated format are included in the manuscript as tables and figures and in the Supplement. Data through the TriNetX platform are queried in real time with results being returned typically in seconds to minutes. Data from the underlying EHRs of participating health care organizations are refreshed in the TriNetX platform from daily to every couple of months depending on the health care organization.

Corresponding Authors: Nora D. Volkow, MD, National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD 20852 (e-mail, nvolkow@nida.nih.gov); or Rong Xu, PhD, Center for Artificial Intelligence in Drug Discovery, 2103 Cornell Road, Cleveland, OH 44106 (e-mail, rxx@case.edu).

Author contributions are available at Annals.org.

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Analysis and interpretation of the data: W. Wang, N.D. Volkow, N.A. Berger, D.C. Kaelber, R. Xu.
Drafting of the article: W. Wang, N.D. Volkow, R. Xu.
Critical revision of the article for important intellectual content: N.D. Volkow, N.A. Berger, P.B. Davis, D.C. Kaelber, R. Xu.
Final approval of the article: W. Wang, N.D. Volkow, N.A. Berger, P.B. Davis, D.C. Kaelber, R. Xu.
Statistical expertise: W. Wang, R. Xu.
Obtaining of funding: N.A. Berger, P.B. Davis, D.C. Kaelber, R. Xu.
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Supplementary Material*

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Title Page

Association of semaglutide with tobacco use disorder in patients with type 2 diabetes: target trial emulation using real-world data

William Wang[1], Nora D. Volkow[2*], Nathan A. Berger[1], Pamela B Davis[3], David C. Kaelber[4], Rong Xu[5]

[1]Center for Science, Health, and Society, Case Western Reserve University School of Medicine, Cleveland, OH, USA
[2]National Institute on Drug Abuse, National Institutes of Health, Bethesda, MD, USA
[3]Center for Community Health Integration, Case Western Reserve University School of Medicine, Cleveland, OH, USA
[4]Center for Clinical Informatics Research and Education, The MetroHealth System, Cleveland, OH, USA
[5]Center for Artificial Intelligence in Drug Discovery, Case Western Reserve University School of Medicine, Cleveland, OH, USA

TriNetX Analytics Platform

The data used in this study were collected and analyzed on April 22, 2024 within the TriNetX Analytics platform based on the"Research US Collaborative Network". We used the TriNetX platform to access aggregated and de-identified electronic health records (EHRs) of 113 million patients from 64 healthcare organizations in the US across 50 states, covering diverse geographic regions, age, race/ethnic, income and insurance groups and clinical setting. TriNetX, LLC is compliant with the Health Insurance Portability and Accountability Act (HIPAA). Any data displayed on the TriNetX Platform in aggregate form, or any patient level data provided in a data set generated by the TriNetX Platform only contains de-identified data as per the de-identification standard defined in Section §164.514(a) of the HIPAA Privacy Rule. TriNetX built-in analytic functions (e.g., incidence, prevalence, outcomes analysis, survival analysis, propensity score matching) allow for patient-level analyses, while only reporting population level data. The MetroHealth System, Cleveland OH, IRB determined research using TriNetX, in the way described here, is not Human Subject Research and therefore IRB is not required.

TriNetX is a platform that de-identifies and aggregates electronic health record (EHR) data from contributing healthcare systems, most of which are large academic medical institutions with both inpatient and outpatient facilities at multiple locations, across all 50 states in the US. TriNetX Analytics provides web-based and secure access to patient EHR data from hospitals, primary care, and specialty treatment providers, covering diverse geographic locations, age groups, racial and ethnic groups, income levels and insurance types including various commercial insurances, governmental insurance (Medicare and Medicaid), self-pay/uninsured, worker compensation insurance, military/VA insurance among others.

Self-reported sex (female, male), race and ethnicity data in TriNetX comes from the underlying clinical EHR systems of the contributing healthcare systems. TriNetX maps race and ethnicity data from the contributing healthcare systems to the following categories: (1) Race: Asian, American Indian or Alaskan Native, Black or African American, Native Hawaiian or Other, White, Unknown race; and (2) Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Unknown Ethnicity.

TriNetX completes an intensive data preprocessing stage to minimize missing values. TriNetX maps the data to a consistent clinical data model with a consistent semantic meaning so that the data can be queried consistently regardless of the underlying data source. All covariates are either binary, categorical (which expands to a set of binary columns), or continuous but essentially guaranteed to exist. Age is guaranteed to exist. Missing sex values are represented using "Unknown Sex". The missing data for race and ethnicity are presented as "Unknown race" or "Unknown Ethnicity". For other variables including medical conditions, procedures, lab tests and socio-economic determinant health, the value is either present or absent so "missing" is not pertinent.

Supplement Table 1. Specification and emulation of pragmatic target trials
Comparing the new use of semaglutide with the new use of other anti-diabetes medications for risk of TUD-related outcomes in patients with comorbid T2DM and TUD using EHR data and analytics functions from the TriNetX Analytics Platform. Target trial specifications and emulations were similar unless otherwise stated.

Protocol	Specification of Target Trials	Emulation of Target Trials
Eligibility criteria	• Had medical encounters with healthcare organizations between December 1, 2017 and March 31, 2023 • Had a diagnosis of T2DM and a diagnosis of TUD • No prescription of anti-diabetes medications (semglutide, insulins, metformin, DPP-4i, SGLT2i, SU, TZD, other GLP-1RAs) within the past year • had at least one of the diseases based on the prescription guideline for semaglutide (obesity, hypertension, hypercholesterolemia, hyperlipidemia, heart diseases, or stroke). • No history of bariatric surgery • No contraindication, warning, and limited use where one drug would be preferred over the other (pancreatitis, type 1 diabetes, thyroid cancer, and gastroparesis)	Same as for the target trials
Treatment strategies	For the target trial comparing semaglutide vs insulins • Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. • Initiate use of insulins at index event and not initiate semaglutide For the target trial comparing semaglutide vs metaformin • Initiate use of semaglutide at index event and not initiate other anti-diabetes medications • Initiate use of metformin at index event and not initiate semaglutide. For the target trial comparing semaglutide vs DPP-4i • Initiate use of semaglutide at index event and not initiate other anti-diabetes medications.	Same as for the target trials. The date of medication initiation was defined as the date of a first medication prescription.

	• Initiate use of DPP-4i at index event and not initiate semaglutide. For the target trial comparing semaglutide vs SGLT2i • Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. • Initiate use of SGLT-2i at index event and not initiate semaglutide. For the target trial comparing semaglutide vs SU • Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. • Initiate use of SU at index event and not initiate semaglutide. For the target trial comparing semaglutide vs TZD • Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. • Initiate use of TZD at index event and not initiate semaglutide. For the target trial comparing semaglutide vs other GLP-1RAs (albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide) • Initiate use of semaglutide at index event and not initiate other anti-diabetes medications. • Initiate use of GLP-1RAs at index event and not semaglutide.	
Treatment assignment	Individuals are randomly assigned to a treatment strategy at baseline. Individuals will be aware of the assigned treatment strategies.	Individuals are assigned to the strategy compatible with their first prescription and assumed randomization by propensity-score matching for baseline covariates.
Outcomes	TUD-related outcomes: • Medical encounters for TUD diagnosis • Smoking cessation medication prescriptions • Smoking cessation counselling Outcomes for sensitivity analyses: • Overall medical encounters	Same as for the target trials

Follow-up	Follow-up for each individual will start at treatment assignment and end on day of outcome, death, loss to follow-up, or 12 month after baseline, whichever occurs first.	Same as for the target trials
Casual contrast of interest	Intention-to-treat	Observational analog to intention-to-treat
Statistical analysis	• Kaplan-Meier estimator to obtain cumulative incidences for each treatment strategy within 12 months of follow-up. Compare cumulative incidence between treatment strategies by risk differences. • Cox proportional hazards analyses to compare rates of time-to-events on daily basis during follow-up time since the baseline. • Models are adjusted for confounders at baseline	Same as for the target trial except observational analogs of intention-to-treat analyses required matching for confounding variables by propensity-score matching.

DPP-4i denotes dipeptidyl-peptidase-4 inhibitors; SGLT2i sodium-glucose cotransporter-2 inhibitors, SU for sulfonylureas, TZD for thiazolidinediones. Other GLP-1RAs include albiglutide, dulaglutide, exenatide, liraglutide, and lixisenatide.
ICD-10 International Classification of Diseases System, version 10,

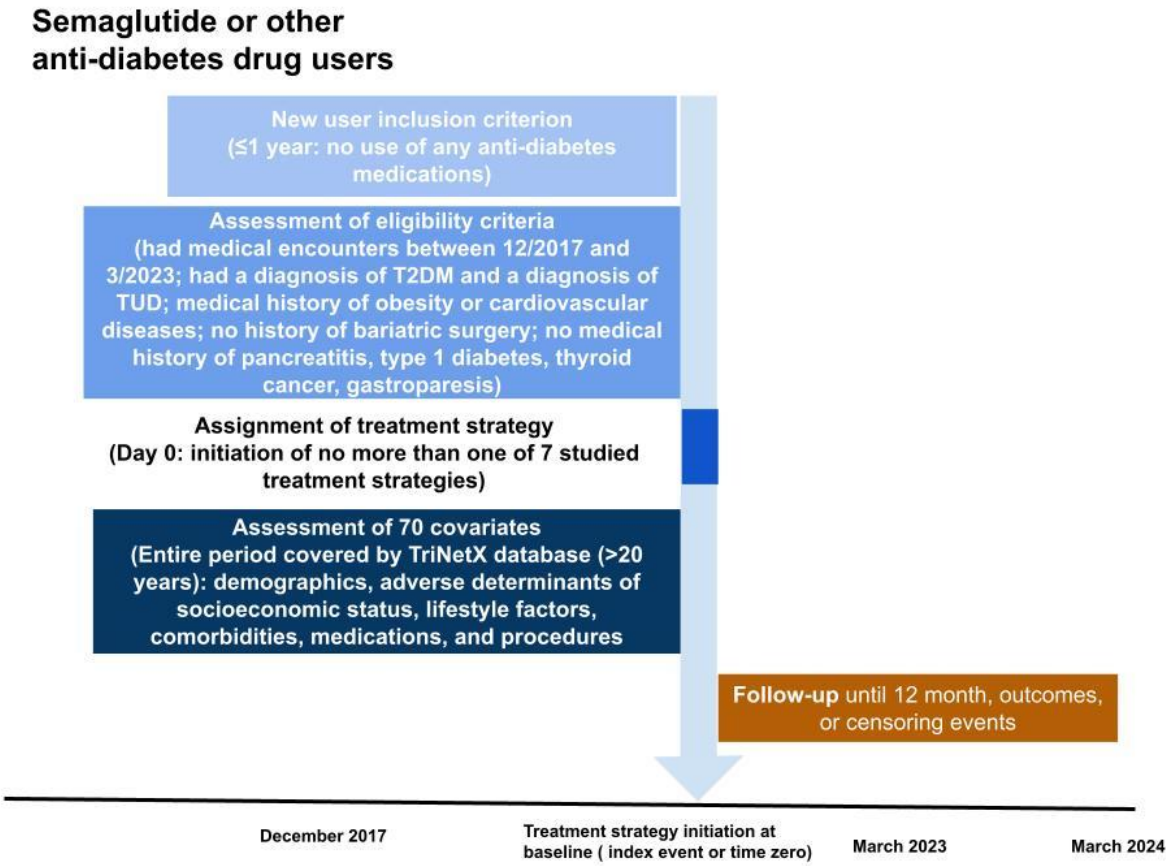
Supplement Table 2. Eligibility criteria and exposure definitions.

Eligibility criteria		
Variable	**Values**	**Name and Codes**
Diagnosis of T2DM	Binary: present/absent	Type 2 diabetes mellitus (ICD-10 code: E11)
Diagnosis of TUD	Binary: present/absent	Nicotine dependence (ICD-10 code: F17) Personal history of nicotine dependence (ICD-10 code: Z87.891)
No prescription for anti-diabetes medications (semaglutide, insulins, metformin, DPP-4i, SGLT2i, SU, TZD, other GLP-1RAs) within the past year	Binary: present/absent	Semaglutide (RxNorm code: 1991302) Insulins (ATC code: A10A) Metformin (ATC code: A10BA) Dipeptidyl peptidase 4 (DPP-4) inhibitors (ATC code: A10BH) Sodium-glucose co-transporter 2 (SGLT2) inhibitors (ATC code: A10BK)

		Sulfonylureas (ATC code: A10BB) Thiazolidinediones (ATC code: A10BF) Albiglutide: RxNorm code: 1534763 Exenatide: RxNorm code: 60548 Dulaglutide: RxNorm code:1551291 Liraglutide: RxNorm code: 475968 Lixisenatide: RxNorm code: 1440051
Had at least one of the diseases based on the prescription guideline for semaglutide (obesity, hypertension, hypercholesterolemia, hyperlipidemia, heart diseases, stroke).	Binary: present/absent	Hypertension (ICD-10: I10-I1A) Hypercholesterolemia (ICD-10 E78.0) Hyperlipidemia (ICD-10: E78.2, E78.4, E78.5) Heart diseases (ICD-10: I20-I25, I30-I5A) Stroke (ICD-10: I63, I60-I69) Obesity (E66.0, E66.2, E66.8, E66.9, Z68.30, Z68.31, Z68.32, Z68.33, Z68.34, Z68.35, Z68.36, Z68.37, Z68.38, Z68.39, Z68.30, Z68.30, Z68.39, Z68.41, Z68.42, Z68.43, Z68.44, Z68.45)
No history of bariatric surgery	Binary: present/absent	Gastrointestinal System / Bypass / Stomach (ICD-10 Procedure Coding System (PCS): 0D16) Bariatric surgery status (ICD-10: Z98.84)
No contraindication, warning, and limited use where one drug would be preferred over the other (pancreatitis, type 1 diabetes, thyroid cancer, and gastroparesis)	Binary: present/absent	Pancreatitis (ICD-10: K85, K86.0, K86.1) Type 1 diabetes (ICD-10: E10) Gastroparesis (ICD-10: K31.84) Thyroid cancer (ICD-10: C73, Z85.850, E31.2)
Exposure definitions		
Initiate use of semaglutide at baseline	Binary: present/absent	Semaglutide (RxNorm code: 1991302)

Initiate use of insulins at baseline	Binary: present/absent	Insulins (ATC code: A10A)
Initiate use of metformin at baseline	Binary: present/absent	Metformin (ATC code: A10BA)
Initiate use of DPP-4i at baseline	Binary: present/absent	Dipeptidyl peptidase 4 (DPP-4) inhibitors (ATC code: A10BH)
Initiate use of SGLT2i at baseline	Binary: present/absent	Sodium-glucose co-transporter 2 (SGLT2) inhibitors (ATC code: A10BK)
Initiate use of SU at baseline	Binary: present/absent	Sulfonylureas (ATC code: A10BB)
Initiate use of TZD at baseline	Binary: present/absent	Thiazolidinediones (ATC code: A10BF)
Initiate use of other GLP-1RA at baseline	Binary: present/absent	Albiglutide: RxNorm code: 1534763 Exenatide: RxNorm code: 60548 Dulaglutide: RxNorm code:1551291 Liraglutide: RxNorm code: 475968 Lixisenatide: RxNorm code: 1440051

Supplement Figure 1. Graphical illustration of the study design



See Supplement Table 2 for definitions of eligibility criteria, exposure, covariates, and outcomes. Follow-up for each individual started at treatment assignment and ended on the day of outcome, death, loss to follow-up, or 12 months after baseline, whichever occured first.

Supplement Table 3. Outcome definitions.

Eligibility criteria		
Variable	**Values**	**Name and Codes**
Primary outcomes		
Medical encounters for TUD diagnosis	Binary: present/absent	Nicotine dependence (ICD-10 code: F17)
Smoking cessation medication prescription	Binary: present/absent	Drugs used in nicotine dependence (ATC: N07BA)

		Bupropion (Brand: Zyban) (RxNorm: 42347)
Smoking cessation counselling	Binary: present/absent	Smoking and tobacco use cessation counseling visit (CPT:1018513) Tobacco abuse counseling (ICD-10: Z71.6)
Outcomes for sensitivity analysis		
Overall medical encounters	Binary: present/absent	Visit (TNX: Visit)

Supplement Table 4: Definitions of covariates.

Variable	**Value**	**Code**	**Coding terminology**
Age at Index	continuous	AI	Demographics
Divorced	Binary: present/absent	D	Demographics
Female	Binary: present/absent	F	Demographics
Black or African American	Binary: present/absent	2054-5	Demographics
Male	Binary: present/absent	M	Demographics
White	Binary: present/absent	2106-3	Demographics
Never Married	Binary: present/absent	S	Demographics
Unknown Race	Binary: present/absent	UNK	Demographics
Widowed	Binary: present/absent	W	Demographics
Unknown Gender	Binary: present/absent	UN	Demographics
Not Hispanic or Latino	Binary: present/absent	2186-5	Demographics
Hispanic or Latino	Binary: present/absent	2135-2	Demographics
Asian	Binary: present/absent	2028-9	Demographics
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Binary: present/absent	Z55-Z65	ICD-10
Problems related to lifestyle	Binary: present/absent	Z72	ICD-10
Schizophrenia, schizotypal, delusional, and other non-mood psychotic disorders	Binary: present/absent	F20-F29	ICD-10
Mood [affective] disorders	Binary: present/absent	F30-F39	ICD-10

Anxiety, dissociative, stress-related, somatoform and other nonpsychotic mental disorders	Binary: present/absent	F40-F48	ICD-10
Behavioral syndromes associated with physiological disturbances and physical factors	Binary: present/absent	F50-F59	ICD-10
Disorders of adult personality and behavior	Binary: present/absent	F60-F69	ICD-10
Cocaine related disorders	Binary: present/absent	F14	ICD-10
Other stimulant related disorders	Binary: present/absent	F15	ICD-10
Other psychoactive substance related disorders	Binary: present/absent	F19	ICD-10
Alcohol related disorders	Binary: present/absent	F10	ICD-10
Depressive episode	Binary: present/absent	F32	ICD-10
Major depressive disorder, recurrent	Binary: present/absent	F33	ICD-10
Chronic pain, not elsewhere classified	Binary: present/absent	G89.2	ICD-10
Conduct disorders	Binary: present/absent	F91	ICD-10
Symptoms and signs involving emotional state	Binary: present/absent	R45	ICD-10
Opioid related disorders	Binary: present/absent	F11	ICD-10
Cannabis related disorders	Binary: present/absent	F12	ICD-10
Neoplasms	Binary: present/absent	C00-D49	ICD-10
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	Binary: present/absent	F90-F98	ICD-10
Morbid (severe) obesity due to excess calories	Binary: present/absent	E66.01	ICD-10
Morbid (severe) obesity with alveolar hypoventilation	Binary: present/absent	E66.2	ICD-10
Obesity due to excess calories	Binary: present/absent	E66.0	ICD-10

Other obesity	Binary: present/absent	E66.8	ICD-10
Obesity, unspecified	Binary: present/absent	E66.9	ICD-10
Body mass index [BMI] 30.0-30.9, adult	Binary: present/absent	Z68.30	ICD-10
Body mass index [BMI] 31.0-31.9, adult	Binary: present/absent	Z68.31	ICD-10
Body mass index [BMI] 32.0-32.9, adult	Binary: present/absent	Z68.32	ICD-10
Body mass index [BMI] 33.0-33.9, adult	Binary: present/absent	Z68.33	ICD-10
Body mass index [BMI] 34.0-34.9, adult	Binary: present/absent	Z68.34	ICD-10
Body mass index [BMI] 35.0-35.9, adult	Binary: present/absent	Z68.35	ICD-10
Body mass index [BMI] 36.0-36.9, adult	Binary: present/absent	Z68.36	ICD-10
Body mass index [BMI] 37.0-37.9, adult	Binary: present/absent	Z68.37	ICD-10
Body mass index [BMI] 38.0-38.9, adult	Binary: present/absent	Z68.38	ICD-10
Body mass index [BMI] 39.0-39.9, adult	Binary: present/absent	Z68.39	ICD-10
Body mass index [BMI] 40.0-44.9, adult	Binary: present/absent	Z68.41	ICD-10
Body mass index [BMI] 45.0-49.9, adult	Binary: present/absent	Z68.42	ICD-10
Body mass index [BMI] 50.0-59.9, adult	Binary: present/absent	Z68.43	ICD-10
Body mass index [BMI] 60.0-69.9, adult	Binary: present/absent	Z68.44	ICD-10
Body mass index [BMI] 70 or greater, adult	Binary: present/absent	Z68.45	ICD-10
Hypertensive diseases	Binary: present/absent	I10-I1A	ICD-10
Pure hypercholesterolemia	Binary: present/absent	E78.0	ICD-10
Mixed hyperlipidemia	Binary: present/absent	E78.2	ICD-10
Other hyperlipidemia	Binary: present/absent	E78.4	ICD-10
Hyperlipidemia, unspecified	Binary: present/absent	E78.5	ICD-10
Ischemic heart diseases	Binary: present/absent	I20-I25	ICD-10
Other forms of heart disease	Binary: present/absent	I30-I5A	ICD-10
Cerebral infarction	Binary: present/absent	I63	ICD-10
Cerebrovascular diseases	Binary: present/absent	I60-I69	ICD-10

Disorders of lipoprotein metabolism and other lipidemias	Binary: present/absent	E78	ICD-10
Tobacco abuse counseling	Binary: present/absent	Z71.6	ICD-10
Smoking cessation education	Binary: present/absent	225323000	SNOMED
Smoking and tobacco use cessation counseling visit	Binary: present/absent	1018513	CPT
Hospital Inpatient and Observation Care Services	Binary: present/absent	1013659	CPT
nicotine	Binary: present/absent	7407	RxNorm
varenicline	Binary: present/absent	591622	RxNorm
Drugs used in nicotine dependence	Binary: present/absent	N07BA	ATC
bupropion	Binary: present/absent	42347	RxNorm
nortriptyline	Binary: present/absent	7531	RxNorm

ICD-10: International Classification of Diseases,Tenth Revision (ICD-10). RxNORM: medical prescription normalized Medical prescription. CPT: Current Procedural Terminology. ATC: Anatomical Therapeutic Chemical. SNOMED: Systematized Medical Nomenclature for Medicine

Supplement Table 5: Characteristics of before and after propensity-score matched semaglutide vs metformin cohorts for the study population of patients with comorbid T2DM and TUD.

	Before propensity-score matching			**After propensity-score matching**		
	semaglutide	**metformin**	**SMD**	**semaglutide**	**metformin**	**SMD**
Total number	5,967	112,318		5,955	5,955	
Age at index event (years, mean±SD)	58.5 ± 11.9	60.8 ± 12.8	0.18*	58.5 ± 11.9	58.7 ± 12.9	0.02
Sex (%)						
Female	50.4	39.6	0.22*	50.4	49.8	0.01
Male	41.5	55.6	0.29*	41.5	41.4	0.002
Unknown	8.1	4.9	0.13*	8.1	8.7	0.02
Ethnicity (%)						
Hispanic/Latinx	4.4	7.0	0.11*	4.4	4.2	0.006
Not Hispanic/Latinx	77.7	72.7	0.12*	77.7	77.0	0.02
Unknown	17.9	20.4	0.06	17.9	18.7	0.02
Race (%)						
Asian	3.5	3.3	0.01	3.5	3.5	<.001
Black	11.8	20.0	0.23*	11.8	11.0	0.02

White	69.1	61.7	0.16*	69.1	69.3	0.004
Unknown	11.9	10.6	0.04	12.0	12.4	0.01
Marital status (%)						
Never Married	11.7	15.4	0.11*	11.7	11.7	0.002
Divorced	7.9	7.0	0.04	7.9	7.9	0.001
Widowed	5.3	6.4	0.05	5.3	5.2	0.006
Adverse socioeconomic determinants of health (%)	6.4	5.8	0.02	6.4	6.7	0.01
Problems related to lifestyle (%)	21.9	19.7	0.06	21.9	21.6	0.008
Pre-existing diagnoses of medical conditions (%)						
Obesity diagnoses						
Morbid (severe) obesity due to excess calories	40.9	17.8	0.52*	40.8	39.8	0.02
Morbid (severe) obesity with alveolar hypoventilation	1.8	0.9	0.08	1.8	1.6	0.02
Obesity due to excess calories	45.2	20.4	0.55*	45.1	44.0	0.02
Other obesity	1.7	0.8	0.09	1.7	1.7	0.004
Obesity, unspecified	53.5	33.8	0.41*	53.4	53.2	0.004
BMI 30.0-30.9	6.6	4.6	0.09	6.6	6.6	0.001
BMI 31.0-31.9	7.0	4.6	0.11*	7.0	7.2	0.006
BMI 32.0-32.9	7.9	4.6	0.14*	7.9	7.9	0.001
BMI 33.0-33.9	8.7	4.6	0.17*	8.7	8.6	0.003
BMI 34.0-34.9	9.1	4.5	0.18*	9.0	8.9	0.004
BMI 35.0-35.9	9.9	4.7	0.20*	9.8	10.1	0.01
BMI 36.0-36.9	9.2	4.1	0.21*	9.2	9.4	0.009
BMI 37.0-37.9	8.9	3.8	0.21*	8.8	9.2	0.01
BMI 38.0-38.9	8.7	3.6	0.22*	8.6	9.0	0.01
BMI 39.0-39.9	8.3	3.0	0.23*	8.1	8.4	0.008
BMI 40.0-44.9	21.0	8.2	0.37*	20.9	20.9	0.002
BMI 45.0-49.9	12.9	4.2	0.31*	12.8	12.8	<.001
BMI 50.0-59.9	9.0	2.8	0.27*	9.0	8.4	0.02
BMI 60.0-69.9	2.7	0.7	0.16*	2.6	2.8	0.007
BMI ≥70	0.7	0.3	0.06	0.7	0.7	0.002
Mental/Behavioral health conditions						
Depression	35.0	26.1	0.19*	34.9	34.4	0.01
Major depression, recurrent	11.3	7.2	0.14*	11.2	11.1	0.005
Mood disorders	40.1	31.2	0.19*	40.0	39.5	0.01
Anxiety disorders	43.0	30.2	0.27*	42.9	43.1	0.005
Psychotic disorders	2.5	5.1	0.14*	2.5	2.5	0.002
Behavioral disorders	9.6	5.1	0.17*	9.6	9.3	0.01

Disorders of adult personality and behavior	1.8	2.1	0.02	1.8	1.8	0.001
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	4.3	2.3	0.11*	4.2	4.3	0.002
Conduct disorders	0.4	0.5	0.02	0.4	0.4	0.003
Symptoms and signs involving emotional state	6.5	6.7	0.01	6.5	7.0	0.02
Alcohol use disorder	5.5	9.4	0.15*	5.5	5.4	0.004
Opioid use disorder	3.4	3.8	0.02	3.4	3.4	<.001
Cannabis use disorder	2.8	4.4	0.09	2.8	2.8	0.003
Cocaine use disorder	1.4	3.3	0.13*	1.4	1.1	0.02
Other stimulant disorders	1.1	1.7	0.05	1.1	0.8	0.03
Other psychoactive substance related disorders	2.7	4.2	0.08	2.7	2.4	0.02
Cardiovascular and other risk/conditions						
Hypertension	84.1	82.2	0.05	84.1	84.2	0.003
Disorders of lipoprotein metabolism and other lipidemias	81.1	71.5	0.23*	81.1	81.3	0.006
Hyperlipidemia	67.7	59.9	0.16*	67.7	68.2	0.01
Hypercholesterolemia	30.0	23.3	0.15*	30.0	30.0	0.001
Ischemic heart diseases	31.1	29.7	0.03	31.1	30.7	0.009
Other forms of heart disease	41.4	37.3	0.08	41.4	41.0	0.007
Cerebral infarction	4.9	6.5	0.07	4.9	4.7	0.01
Cerebrovascular diseases	12.7	14.2	0.05	12.6	12.8	0.004
Cancer	44.7	34.3	0.21*	44.7	44.5	0.003
Chronic pain	36.0	25.4	0.23*	36.0	36.4	0.01
Pre-existing medical procedures and medication prescriptions (%)						
Hospitalizations	27.0	24.2	0.06	26.9	26.1	0.02
Tobacco abuse counseling	4.4	3.2	0.06	4.4	4.6	0.01
Smoking and tobacco use cessation counseling visit	5.4	4.8	0.03	5.4	5.3	0.007
Smoking cessation education	0.2	0.2	0.004	0.2	0.2	<.001
Drugs used in nicotine dependence	17.6	17.2	0.01	17.6	17.6	0.001
NRT	12.9	14.4	0.04	12.9	12.8	0.006
Varenicline	7.9	5.0	0.12*	7.8	7.7	0.004
Bupropion	15.9	8.5	0.23*	15.8	15.5	0.007

Nortriptyline	2.4	1.7	0.05	2.4	2.5	0.004

Supplement Table 6: Characteristics of before and after propensity-score matched semaglutide vs DPP-4i cohorts for the study population of patients with comorbid T2DM and TUD.

	Before propensity-score matching			**After propensity-score matching**		
	semaglutide	**DPP-4i**	**SMD**	**semaglutide**	**DPP-4i**	**SMD**
Total number	5,967	15,854		4,831	4,831	
Age at index event (years, mean±SD)	58.5 ± 11.9	65.7 ± 12.4	0.59*	60.1 ± 11.4	60.0 ± 12.7	0.008
Sex (%)						
Female	50.4	40.0	0.21*	48.0	47.5	0.01
Male	41.5	55.0	0.27*	44.6	45.3	0.01
Unknown	8.1	5.1	0.12*	7.4	7.2	0.008
Ethnicity (%)						
Hispanic/Latinx	4.4	6.9	0.11*	5.0	5.0	0.002
Not Hispanic/Latinx	77.7	71.2	0.15*	76.4	76.6	0.004
Unknown	17.9	21.9	0.11*	18.6	18.4	0.005
Race (%)						
Asian	3.5	4.9	0.07	3.7	3.3	0.02
Black	11.8	17.1	0.15*	12.7	12.4	0.01
White	69.1	62.9	0.13*	68.3	68.7	0.009
Unknown	11.9	10.5	0.05	11.6	11.7	0.005
Marital status (%)						
Never Married	11.7	12.0	0.01	11.8	11.9	0.003
Divorced	7.9	7.5	0.01	8.0	8.1	0.005
Widowed	5.3	9.7	0.17*	6.0	6.2	0.005
Adverse socioeconomic determinants of health (%)	6.4	4.2	0.10*	5.4	5.1	0.01
Problems related to lifestyle (%)	21.9	15.6	0.16*	19.8	20.0	0.005
Pre-existing diagnoses of medical conditions (%)						
Obesity diagnoses						
Morbid (severe) obesity due to excess calories	40.9	14.1	0.63*	32.2	32.5	0.006
Morbid (severe) obesity with alveolar hypoventilation	1.8	0.9	0.08	1.4	1.3	0.005
Obesity due to excess calories	45.2	16.0	0.67*	36.0	36.3	0.005
Other obesity	1.7	0.6	0.10*	1.3	1.4	0.007

Obesity, unspecified	53.5	30.4	0.48*	48.3	49.0	0.02
BMI 30.0-30.9	6.6	5.6	0.04	6.8	7.3	0.02
BMI 31.0-31.9	7.0	5.0	0.09	7.2	7.5	0.01
BMI 32.0-32.9	7.9	5.2	0.11*	8.0	7.9	0.002
BMI 33.0-33.9	8.7	4.9	0.15*	8.5	8.6	0.001
BMI 34.0-34.9	9.1	4.5	0.18*	8.5	8.4	0.005
BMI 35.0-35.9	9.9	4.6	0.21*	8.8	8.8	<.001
BMI 36.0-36.9	9.2	4.3	0.20*	8.1	8.0	0.001
BMI 37.0-37.9	8.9	3.7	0.22*	7.7	7.4	0.01
BMI 38.0-38.9	8.7	3.4	0.22*	7.2	7.4	0.01
BMI 39.0-39.9	8.3	2.6	0.25*	6.1	5.9	0.009
BMI 40.0-44.9	21.0	7.1	0.41*	16.1	16.0	0.005
BMI 45.0-49.9	12.9	3.3	0.36*	8.7	8.4	0.01
BMI 50.0-59.9	9.0	2.0	0.31*	5.3	5.3	0.001
BMI 60.0-69.9	2.7	0.5	0.18*	1.4	1.3	0.009
BMI ≥70	0.7	0.2	0.08	0.5	0.5	0.003
Mental/Behavioral health conditions						
Depression	35.0	23.6	0.25*	31.3	30.7	0.01
Major depression, recurrent	11.3	5.3	0.22*	9.1	8.6	0.02
Mood disorders	40.1	27.4	0.27*	36.2	35.5	0.01
Anxiety disorders	43.0	25.6	0.37*	37.7	37.6	0.002
Psychotic disorders	2.5	3.7	0.07	2.7	2.8	0.008
Behavioral disorders	9.6	3.8	0.24*	7.1	6.6	0.02
Disorders of adult personality and behavior	1.8	1.4	0.04	1.8	1.9	0.009
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	4.3	1.3	0.18*	3.0	2.7	0.02
Conduct disorders	0.4	0.3	0.01	0.4	0.4	0.003
Symptoms and signs involving emotional state	6.5	4.9	0.07	6.0	5.6	0.02
Alcohol use disorder	5.5	6.0	0.02	5.4	5.6	0.009
Opioid use disorder	3.4	2.6	0.05	3.2	3.2	0.002
Cannabis use disorder	2.8	2.4	0.02	2.7	2.6	0.009
Cocaine use disorder	1.4	1.8	0.04	1.4	1.6	0.02
Other stimulant disorders	1.1	0.9	0.03	1.0	1.1	0.006
Other psychoactive substance related disorders	2.7	2.5	0.01	2.6	2.7	0.004

Cardiovascular and other risk/conditions						
Hypertension	84.1	88.1	0.12*	85.4	85.1	0.007
Disorders of lipoprotein metabolism and other lipidemias	81.1	78.7	0.06	81.0	81.5	0.01
Hyperlipidemia	67.7	67.4	0.005	67.7	68.1	0.008
Hypercholesterolemia	30.0	26.3	0.08	29.5	29.5	0.001
Ischemic heart diseases	31.1	39.8	0.18*	32.9	33.2	0.005
Other forms of heart disease	41.4	45.8	0.09	42.0	42.4	0.008
Cerebral infarction	4.9	7.9	0.13*	5.5	5.1	0.02
Cerebrovascular diseases	12.7	18.5	0.16*	13.9	13.5	0.01
Cancer	44.7	34.7	0.21*	42.3	42.8	0.01
Chronic pain	36.0	20.9	0.34*	31.6	31.6	<.001
Pre-existing medical procedures and medication prescriptions (%)						
Hospitalizations	27.0	25.9	0.03	26.3	25.9	0.01
Tobacco abuse counseling	4.4	2.3	0.12*	3.5	3.9	0.02
Smoking and tobacco use cessation counseling visit	5.4	3.4	0.10*	4.4	4.7	0.02
Smoking cessation education	0.2	0.1	0.01	0.2	0.2	<.001
Drugs used in nicotine dependence	17.6	11.7	0.17*	15.6	15.4	0.004
NRT	12.9	10.0	0.09	12.1	12.2	0.002
Varenicline	7.9	3.2	0.21*	6.1	5.8	0.01
Bupropion	15.9	6.0	0.32*	11.6	11.2	0.01
Nortriptyline	2.4	1.2	0.09	1.9	1.8	0.006

Supplement Table 7: Characteristics of before and after propensity-score matched semaglutide vs SGLT2i cohorts for the study population of patients with comorbid T2DM and TUD.

	Before propensity-score matching			**After propensity-score matching**		
	semaglutide	**SGLT2i**	**SMD**	**semaglutide**	**SGLT2i**	**SMD**
Total number	5,967	18,264		5,325	5,325	
Age at index event (years, mean±SD)	58.5 ± 11.9	63.3 ± 11.8	0.40*	59.4 ± 11.7	59.4 ± 12.2	0.003
Sex (%)						
Female	50.4	31.3	0.40*	47.3	46.4	0.02

Male	41.5	63.2	0.45*	44.8	45.7	0.02
Unknown	8.1	5.5	0.10*	7.9	7.9	0.001
Ethnicity (%)						
Hispanic/Latinx	4.4	7.2	0.12*	4.8	4.8	<.001
Not Hispanic/Latinx	77.7	74.0	0.09	76.8	76.2	0.01
Unknown	17.9	18.8	0.02	18.4	19.0	0.02
Race (%)						
Asian	3.5	4.1	0.03	3.5	3.8	0.008
Black	11.8	16.1	0.13*	12.3	12.1	0.006
White	69.1	64.7	0.09	68.6	68.3	0.006
Unknown	11.9	10.6	0.04	11.9	12.3	0.01
Marital status (%)						
Never Married	11.7	12.0	0.01	11.7	11.5	0.008
Divorced	7.9	6.9	0.04	7.7	7.9	0.006
Widowed	5.3	6.2	0.04	5.6	5.6	0.001
Adverse socioeconomic determinants of health (%)	6.4	5.1	0.06	5.8	5.7	0.007
Problems related to lifestyle (%)	21.9	19.3	0.06	21.1	21.1	<.001
Pre-existing diagnoses of medical conditions (%)						
Obesity diagnoses						
Morbid (severe) obesity due to excess calories	40.9	19.4	0.48*	36.1	36.3	0.004
Morbid (severe) obesity with alveolar hypoventilation	1.8	1.4	0.03	1.7	1.9	0.01
Obesity due to excess calories	45.2	22.1	0.51*	40.4	40.5	0.002
Other obesity	1.7	1.1	0.05	1.6	1.6	0.003
Obesity, unspecified	53.5	37.2	0.33*	51.0	50.6	0.008
BMI 30.0-30.9	6.6	6.6	0.001	6.8	6.9	0.004
BMI 31.0-31.9	7.0	6.5	0.02	7.3	7.5	0.009
BMI 32.0-32.9	7.9	6.5	0.05	8.1	8.0	0.003
BMI 33.0-33.9	8.7	6.8	0.07	8.9	9.2	0.01
BMI 34.0-34.9	9.1	6.3	0.10*	9.0	8.7	0.009
BMI 35.0-35.9	9.9	6.5	0.13*	9.6	9.9	0.01
BMI 36.0-36.9	9.2	5.6	0.14*	8.9	8.9	0.001
BMI 37.0-37.9	8.9	5.2	0.15*	8.3	8.4	0.005
BMI 38.0-38.9	8.7	4.7	0.16*	8.0	8.4	0.01
BMI 39.0-39.9	8.3	3.9	0.18*	7.2	7.1	0.003
BMI 40.0-44.9	21.0	9.8	0.31*	18.3	18.3	<.001
BMI 45.0-49.9	12.9	4.5	0.30*	10.3	10.4	0.005
BMI 50.0-59.9	9.0	2.8	0.27*	6.7	6.7	0.002
BMI 60.0-69.9	2.7	0.6	0.17*	1.7	1.7	<.001
BMI ≥70	0.7	0.3	0.06	0.6	0.6	0.005

Mental/Behavioral health conditions						
Depression	35.0	24.1	0.24*	32.6	32.0	0.01
Major depression, recurrent	11.3	6.0	0.19*	10.0	9.9	0.001
Mood disorders	40.1	28.3	0.25*	37.6	37.1	0.01
Anxiety disorders	43.0	28.1	0.31*	40.1	39.5	0.01
Psychotic disorders	2.5	2.9	0.03	2.6	2.3	0.02
Behavioral disorders	9.6	4.7	0.19*	8.3	8.3	0.001
Disorders of adult personality and behavior	1.8	1.2	0.05	1.7	1.5	0.02
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	4.3	1.5	0.16*	3.3	3.3	0.001
Conduct disorders	0.4	0.2	0.04	0.3	0.4	0.02
Symptoms and signs involving emotional state	6.5	5.3	0.05	6.2	5.8	0.02
Alcohol use disorder	5.5	7.9	0.10*	5.8	5.8	<.001
Opioid use disorder	3.4	3.0	0.02	3.4	3.5	0.002
Cannabis use disorder	2.8	3.8	0.06	2.9	3.0	0.009
Cocaine use disorder	1.4	2.5	0.09	1.5	1.7	0.02
Other stimulant disorders	1.1	1.7	0.05	1.2	1.1	0.004
Other psychoactive substance related disorders	2.7	3.3	0.03	2.7	2.6	0.007
Cardiovascular and other risk/conditions						
Hypertension	84.1	89.0	0.15*	85.4	85.8	0.01
Disorders of lipoprotein metabolism and other lipidemias	81.1	81.6	0.01	81.4	81.9	0.02
Hyperlipidemia	67.7	70.9	0.07	68.1	67.9	0.004
Hypercholesterolemia	30.0	27.8	0.05	29.8	30.6	0.02
Ischemic heart diseases	31.1	50.8	0.41*	33.6	33.7	0.002
Other forms of heart disease	41.4	54.9	0.27*	43.2	42.7	0.01
Cerebral infarction	4.9	8.3	0.14*	5.3	5.5	0.01
Cerebrovascular diseases	12.7	19.1	0.18*	13.7	13.4	0.008
Cancer	44.7	35.6	0.19*	43.2	43.5	0.006
Chronic pain	36.0	25.0	0.24*	33.9	33.1	0.02
Pre-existing medical procedures and medication prescriptions (%)						
Hospitalizations	27.0	32.9	0.13*	27.8	26.7	0.02
Tobacco abuse counseling	4.4	3.2	0.06	4.0	3.9	0.004

Smoking and tobacco use cessation counseling visit	5.4	5.0	0.02	5.3	5.4	0.007
Smoking cessation education	0.2	0.3	0.02	0.2	0.2	<.001
Drugs used in nicotine dependence	17.6	15.0	0.07	16.8	16.7	0.003
NRT	12.9	12.5	0.01	12.8	12.7	0.002
Varenicline	7.9	4.4	0.14*	7.0	7.1	0.004
Bupropion	15.9	7.6	0.26*	13.6	13.0	0.02
Nortriptyline	2.4	1.7	0.05	2.3	2.3	0.003

Supplement Table 8: Characteristics of before and after propensity-score matched semaglutide vs SU cohorts for the study population of patients with comorbid T2DM and TUD.

	Before propensity-score matching			**After propensity-score matching**		
	semaglutide	**SU**	**SMD**	**semaglutide**	**SU**	**SMD**
Total number	5,967	30,318		5,388	5,388	
Age at index event (years, mean±SD)	58.5 ± 11.9	65.1 ± 12.6	0.54*	59.3 ± 11.7	59.0 ± 13.1	0.02
Sex (%)						
Female	50.4	36.3	0.29*	48.7	48.3	0.009
Male	41.5	59.5	0.37*	43.8	44.9	0.02
Unknown	8.1	4.2	0.16*	7.5	6.8	0.03
Ethnicity (%)						
Hispanic/Latinx	4.4	6.1	0.08	4.6	4.5	0.007
Not Hispanic/Latinx	77.7	73.2	0.11*	77.3	78.2	0.02
Unknown	17.9	20.7	0.07	18.1	17.4	0.02
Race (%)						
Asian	3.5	2.9	0.03	3.5	4.0	0.03
Black	11.8	18.0	0.18*	12.3	12.1	0.007
White	69.1	65.9	0.07	68.9	69.5	0.01
Unknown	11.9	9.3	0.09	11.6	10.9	0.02
Marital status (%)						
Never Married	11.7	13.1	0.04	11.9	12.4	0.02
Divorced	7.9	7.0	0.03	7.9	8.3	0.02
Widowed	5.3	9.1	0.15*	5.6	5.2	0.02
Adverse socioeconomic determinants of health (%)	6.4	4.1	0.10*	5.7	5.5	0.01
Problems related to lifestyle (%)	21.9	15.3	0.17*	20.5	20.0	0.01
Pre-existing diagnoses of medical conditions (%)						
Obesity diagnoses						

Morbid (severe) obesity due to excess calories	40.9	15.0	0.60*	36.7	36.4	0.008
Morbid (severe) obesity with alveolar hypoventilation	1.8	0.9	0.07	1.7	1.8	0.01
Obesity due to excess calories	45.2	16.7	0.65*	40.9	40.5	0.008
Other obesity	1.7	0.6	0.11*	1.5	1.5	0.005
Obesity, unspecified	53.5	29.9	0.49*	50.7	51.5	0.02
BMI 30.0-30.9	6.6	4.0	0.12*	6.3	6.4	0.002
BMI 31.0-31.9	7.0	4.2	0.13*	7.0	7.1	0.006
BMI 32.0-32.9	7.9	4.1	0.16*	7.6	7.6	0.002
BMI 33.0-33.9	8.7	4.0	0.20*	8.2	7.9	0.01
BMI 34.0-34.9	9.1	3.8	0.22*	8.4	7.9	0.02
BMI 35.0-35.9	9.9	4.0	0.23*	8.9	8.2	0.02
BMI 36.0-36.9	9.2	3.4	0.24*	8.2	7.7	0.02
BMI 37.0-37.9	8.9	3.0	0.26*	7.6	7.7	0.001
BMI 38.0-38.9	8.7	2.7	0.26*	7.2	7.2	<.001
BMI 39.0-39.9	8.3	2.4	0.26*	6.6	6.3	0.01
BMI 40.0-44.9	21.0	6.9	0.41*	18.2	17.9	0.008
BMI 45.0-49.9	12.9	3.4	0.35*	10.8	10.4	0.01
BMI 50.0-59.9	9.0	2.1	0.31*	7.1	6.5	0.02
BMI 60.0-69.9	2.7	0.5	0.17*	1.9	1.9	0.005
BMI ≥70	0.7	0.2	0.09	0.5	0.5	0.005
Mental/Behavioral health conditions						
Depression	35.0	21.8	0.30*	32.7	32.5	0.005
Major depression, recurrent	11.3	4.8	0.24*	9.7	9.4	0.01
Mood disorders	40.1	25.8	0.31*	37.7	37.3	0.008
Anxiety disorders	43.0	24.5	0.40*	39.9	39.8	0.003
Psychotic disorders	2.5	3.6	0.06	2.5	2.6	0.002
Behavioral disorders	9.6	3.7	0.24*	8.2	8.5	0.009
Disorders of adult personality and behavior	1.8	1.3	0.04	1.8	1.7	0.01
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	4.3	1.4	0.17*	3.6	3.3	0.02
Conduct disorders	0.4	0.3	0.005	0.4	0.5	0.01
Symptoms and signs involving emotional state	6.5	4.8	0.007	6.1	5.9	0.01
Alcohol use disorder	5.5	6.8	0.06	5.6	5.8	0.006
Opioid use disorder	3.4	2.4	0.06	3.3	3.4	0.007
Cannabis use disorder	2.8	2.9	0.005	2.7	2.5	0.02

Cocaine use disorder	1.4	2.1	0.06	1.4	1.3	0.01
Other stimulant disorders	1.1	0.9	0.02	1.0	1.0	0.002
Other psychoactive substance related disorders	2.7	2.7	0.001	2.7	2.9	0.02
Cardiovascular and other risk/conditions						
Hypertension	84.1	87.3	0.09	84.7	84.6	0.003
Disorders of lipoprotein metabolism and other lipidemias	81.1	75.4	0.14*	80.8	81.0	0.004
Hyperlipidemia	67.7	64.6	0.06	67.3	67.8	0.01
Hypercholesterolemia	30.0	24.0	0.13*	29.4	29.2	0.004
Ischemic heart diseases	31.1	37.5	0.14*	31.9	31.9	<.001
Other forms of heart disease	41.4	43.8	0.05	41.7	41.0	0.01
Cerebral infarction	4.9	7.6	0.11*	5.1	4.8	0.02
Cerebrovascular diseases	12.7	17.2	0.13*	13.1	12.4	0.02
Cancer	44.7	32.8	0.25*	43.2	42.9	0.006
Chronic pain	36.0	20.6	0.35*	33.5	33.8	0.007
Pre-existing medical procedures and medication prescriptions (%)						
Hospitalizations	27.0	25.3	0.04	26.8	26.7	0.002
Tobacco abuse counseling	4.4	2.3	0.12*	3.8	3.8	0.001
Smoking and tobacco use cessation counseling visit	5.4	3.6	0.09	5.2	4.8	0.02
Smoking cessation education	0.2	0.1	0.01	0.2	0.2	<.001
Drugs used in nicotine dependence	17.6	11.7	0.17*	16.8	16.7	0.002
NRT	12.9	9.8	0.10*	12.6	12.2	0.01
Varenicline	7.9	3.3	0.20*	7.0	7.4	0.02
Bupropion	15.9	5.8	0.33*	13.5	13.4	0.003
Nortriptyline	2.4	1.5	0.07	2.2	2.1	0.009

Supplement Table 9: Characteristics of before and after propensity-score matched semaglutide vs TZD cohorts for the study population of patients with comorbid T2DM and TUD.

	Before propensity-score matching			**After propensity-score matching**		
	semaglutide	**TZD**	**SMD**	**semaglutide**	**TZD**	**SMD**
Total number	5,967	4,231		2,659	2,659	
Age at index event (years, mean±SD)	58.5 ± 11.9	65.5 ± 11.9	0.59*	62.3 ± 11.2	62.6 ± 11.9	0.02
Sex (%)						

Female	50.4	33.9	0.34*	39.7	40.0	0.005
Male	41.5	63.1	0.44*	56.0	55.8	0.003
Unknown	8.1	3.0	0.22*	4.3	4.2	0.006
Ethnicity (%)						
Hispanic/Latinx	4.4	9.5	0.21*	6.8	6.1	0.03
Not Hispanic/Latinx	77.7	72.7	0.12*	75.6	76.7	0.03
Unknown	17.9	17.7	0.004	17.7	17.2	0.01
Race (%)						
Asian	3.5	4.2	0.04	4.4	4.3	0.004
Black	11.8	14.0	0.07	12.7	12.9	0.008
White	69.1	69.1	<.001	70.2	70.7	0.01
Unknown	11.9	8.1	0.13*	9.1	8.2	0.03
Marital status (%)						
Never Married	11.7	12.3	0.02	12.4	12.1	0.01
Divorced	7.9	6.7	0.04	7.6	7.9	0.01
Widowed	5.3	8.6	0.13*	6.5	7.0	0.02
Adverse socioeconomic determinants of health (%)	6.4	3.4	0.14*	3.7	3.4	0.01
Problems related to lifestyle (%)	21.9	14.1	0.20*	16.2	16.4	0.004
Pre-existing diagnoses of medical conditions (%)						
Obesity diagnoses						
Morbid (severe) obesity due to excess calories	40.9	15.5	0.59*	22.9	22.6	0.008
Morbid (severe) obesity with alveolar hypoventilation	1.8	0.6	0.11*	0.6	0.8	0.03
Obesity due to excess calories	45.2	17.4	0.63*	26.0	25.2	0.02
Other obesity	1.7	0.6	0.10*	1.0	0.9	0.008
Obesity, unspecified	53.5	30.3	0.48*	38.6	39.0	0.008
BMI 30.0-30.9	6.6	4.5	0.09	5.5	5.8	0.01
BMI 31.0-31.9	7.0	4.3	0.12*	5.9	5.8	0.005
BMI 32.0-32.9	7.9	4.4	0.15*	5.2	5.8	0.03
BMI 33.0-33.9	8.7	4.5	0.17*	5.9	6.2	0.01
BMI 34.0-34.9	9.1	4.1	0.20*	6.0	5.8	0.006
BMI 35.0-35.9	9.9	4.3	0.22*	6.2	6.3	0.003
BMI 36.0-36.9	9.2	3.9	0.21*	5.4	5.6	0.007
BMI 37.0-37.9	8.9	3.4	0.23*	5.2	4.8	0.02
BMI 38.0-38.9	8.7	2.8	0.25*	4.3	4.1	0.007
BMI 39.0-39.9	8.3	2.3	0.27*	3.7	3.5	0.01
BMI 40.0-44.9	21.0	7.6	0.39*	11.7	10.9	0.03
BMI 45.0-49.9	12.9	3.4	0.35*	5.1	5.3	0.008
BMI 50.0-59.9	9.0	2.2	0.30*	2.8	3.3	0.03
BMI 60.0-69.9	2.7	0.6	0.17*	0.8	0.9	0.02

BMI ≥70	0.7	0.2	0.07	0.4	0.4	<.001
Mental/Behavioral health conditions						
Depression	35.0	20.3	0.33*	24.7	23.8	0.02
Major depression, recurrent	11.3	4.3	0.26*	6.0	5.7	0.01
Mood disorders	40.1	24.3	0.34*	29.3	28.3	0.02
Anxiety disorders	43.0	22.9	0.44*	29.2	29.4	0.005
Psychotic disorders	2.5	2.8	0.02	2.5	2.6	0.005
Behavioral disorders	9.6	4.1	0.22*	4.7	5.4	0.03
Disorders of adult personality and behavior	1.8	1.3	0.04	1.5	1.3	0.02
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	4.3	1.3	0.18*	2.3	1.8	0.03
Conduct disorders	0.4	0.4	0.002	0.4	0.4	<.001
Symptoms and signs involving emotional state	6.5	3.9	0.02	4.6	4.4	0.009
Alcohol use disorder	5.5	5.5	0.001	5.2	5.0	0.009
Opioid use disorder	3.4	1.6	0.11*	2.3	2.1	0.01
Cannabis use disorder	2.8	2.0	0.05	2.4	2.1	0.02
Cocaine use disorder	1.4	1.2	0.01	1.1	1.2	0.01
Other stimulant disorders	1.1	0.8	0.04	0.8	1.0	0.02
Other psychoactive substance related disorders	2.7	1.6	0.08	1.9	1.7	0.01
Cardiovascular and other risk/conditions						
Hypertension	84.1	87.4	0.10*	86.6	86.2	0.01
Disorders of lipoprotein metabolism and other lipidemias	81.1	78.1	0.07	80.5	80.3	0.004
Hyperlipidemia	67.7	66.7	0.02	67.8	67.6	0.006
Hypercholesterolemia	30.0	25.8	0.09	27.7	27.9	0.004
Ischemic heart diseases	31.1	34.2	0.07	32.9	32.6	0.007
Other forms of heart disease	41.4	37.1	0.09	38.1	38.1	<.001
Cerebral infarction	4.9	7.5	0.11*	5.8	5.6	0.005
Cerebrovascular diseases	12.7	16.5	0.11*	14.3	14.1	0.005
Cancer	44.7	31.8	0.27*	35.8	36.4	0.01
Chronic pain	36.0	19.6	0.37*	24.5	24.9	0.009
Pre-existing medical procedures and medication prescriptions (%)						
Hospitalizations	27.0	22.2	0.11*	22.5	22.1	0.009
Tobacco abuse counseling	4.4	2.1	0.13*	2.6	2.4	0.01

Smoking and tobacco use cessation counseling visit	5.4	3.3	0.11*	3.9	3.8	0.008
Smoking cessation education	0.2	0.2	0.02	0.4	0.4	<.001
Drugs used in nicotine dependence	17.6	10.0	0.22*	13.0	12.1	0.03
NRT	12.9	7.7	0.17*	9.7	9.0	0.02
Varenicline	7.9	3.2	0.20*	5.0	4.6	0.02
Bupropion	15.9	4.9	0.37*	6.7	6.9	0.009
Nortriptyline	2.4	0.9	0.11*	1.4	1.2	0.01

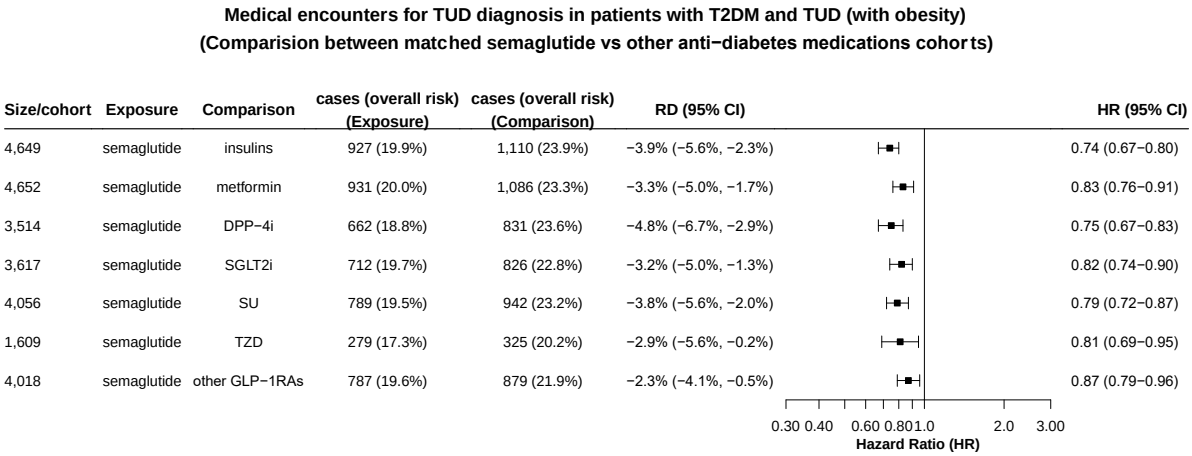
Supplement Table 10: Characteristics of before and after propensity-score matched semaglutide vs other GLP-1RAs cohorts for the study population of patients with comorbid T2DM and TUD.

	Before propensity-score matching			**After propensity-score matching**		
	semaglutide	**Other GLP-1RAs**	**SMD**	**semaglutide**	**Other GLP-1RAs**	**SMD**
Total number	5,967	10,037		5,337	5,337	
Age at index event (years, mean±SD)	58.5 ± 11.9	59.2 ± 12.0	0.06	58.8 ± 11.9	58.8± 12.2	0.001
Sex (%)						
Female	50.4	48.7	0.04	50.7	50.5	0.005
Male	41.5	47.3	0.12*	42.9	43.0	0.001
Unknown	8.1	4.0	0.17*	6.3	6.5	0.008
Ethnicity (%)						
Hispanic/Latinx	4.4	6.9	0.11*	4.8	5.0	0.01
Not Hispanic/Latinx	77.7	74.0	0.09	78.1	77.4	0.02
Unknown	17.9	19.2	0.03	17.1	17.6	0.01
Race (%)						
Asian	3.5	1.9	0.10*	3.0	3.0	0.004
Black	11.8	19.4	0.21*	12.9	12.8	0.005
White	69.1	64.0	0.11*	69.7	69.5	0.004
Unknown	11.9	10.2	0.06	10.5	11.0	0.02
Marital status (%)						
Never Married	11.7	13.8	0.06	12.0	12.4	0.01
Divorced	7.9	7.4	0.02	7.9	7.6	0.01
Widowed	5.3	5.4	0.003	5.5	5.4	0.007
Adverse socioeconomic determinants of health (%)	6.4	5.3	0.05	6.0	6.0	0.003
Problems related to lifestyle (%)	21.9	19.1	0.07	21.1	20.5	0.02
Pre-existing diagnoses of medical conditions (%)						
Obesity diagnoses						

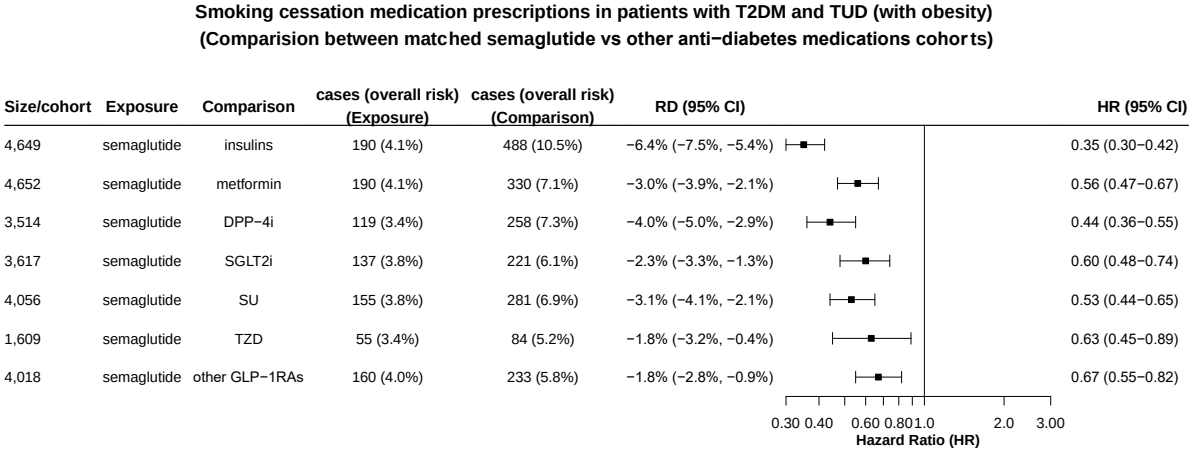
Morbid (severe) obesity due to excess calories	40.9	29.4	0.24*	38.0	37.6	0.009
Morbid (severe) obesity with alveolar hypoventilation	1.8	1.7	0.007	1.8	1.9	0.006
Obesity due to excess calories	45.2	32.0	0.27*	42.0	41.4	0.01
Other obesity	1.7	1.2	0.04	1.6	1.5	0.01
Obesity, unspecified	53.5	44.7	0.18*	51.4	51.5	0.003
BMI 30.0-30.9	6.6	5.1	0.06	6.3	6.4	0.006
BMI 31.0-31.9	7.0	5.2	0.08	6.4	6.7	0.01
BMI 32.0-32.9	7.9	5.4	0.10*	7.1	7.1	0.002
BMI 33.0-33.9	8.7	5.9	0.11*	7.7	7.8	0.003
BMI 34.0-34.9	9.1	5.7	0.13*	7.7	8.1	0.01
BMI 35.0-35.9	9.9	6.9	0.11*	8.8	8.9	0.002
BMI 36.0-36.9	9.2	5.6	0.14*	7.8	7.7	0.003
BMI 37.0-37.9	8.9	5.7	0.13*	7.7	8.0	0.008
BMI 38.0-38.9	8.7	5.7	0.12*	7.9	8.0	0.003
BMI 39.0-39.9	8.3	4.8	0.14*	7.0	6.5	0.02
BMI 40.0-44.9	21.0	13.8	0.19*	18.8	18.3	0.01
BMI 45.0-49.9	12.9	7.8	0.17*	11.1	11.4	0.01
BMI 50.0-59.9	9.0	5.3	0.14*	7.7	7.8	0.004
BMI 60.0-69.9	2.7	1.4	0.09	2.2	2.2	0.001
BMI ≥70	0.7	0.5	0.02	0.6	0.6	<.001
Mental/Behavioral health conditions						
Depression	35.0	31.5	0.07	34.2	33.7	0.01
Major depression, recurrent	11.3	8.6	0.09	10.5	10.3	0.005
Mood disorders	40.1	36.7	0.07	39.3	38.8	0.01
Anxiety disorders	43.0	33.3	0.20*	40.7	40.9	0.006
Psychotic disorders	2.5	3.5	0.06	2.6	2.8	0.01
Behavioral disorders	9.6	6.4	0.12*	8.8	8.6	0.007
Disorders of adult personality and behavior	1.8	2.1	0.02	1.9	1.9	0.001
Behavioral and emotional disorders with onset usually occurring in childhood and adolescence	4.3	2.7	0.08	3.7	3.6	0.005
Conduct disorders	0.4	0.4	0.003	0.3	0.3	0.007
Symptoms and signs involving emotional state	6.5	6.1	0.02	6.3	6.1	0.007
Alcohol use disorder	5.5	6.3	0.03	5.5	5.6	0.006
Opioid use disorder	3.4	3.9	0.03	3.4	3.7	0.01
Cannabis use disorder	2.8	3.5	0.04	2.9	2.8	0.007

Cocaine use disorder	1.4	2.4	0.08	1.5	1.6	0.01
Other stimulant disorders	1.1	1.1	0.001	1.1	1.1	0.004
Other psychoactive substance related disorders	2.7	3.1	0.02	2.7	2.8	0.007
Cardiovascular and other risk/conditions						
Hypertension	84.1	85.2	0.03	84.5	84.1	0.009
Disorders of lipoprotein metabolism and other lipidemias	81.1	76.9	0.10*	80.1	79.8	0.006
Hyperlipidemia	67.7	65.3	0.05	66.8	66.6	0.006
Hypercholesterolemia	30.0	24.5	0.12*	28.3	28.6	0.005
Ischemic heart diseases	31.1	33.1	0.04	31.6	31.2	0.008
Other forms of heart disease	41.4	39.5	0.04	41.2	41.1	0.003
Cerebral infarction	4.9	6.2	0.06	5.1	5.0	0.004
Cerebrovascular diseases	12.7	13.9	0.04	13.1	12.6	0.02
Cancer	44.7	34.0	0.22*	41.9	43.0	0.02
Chronic pain	36.0	28.7	0.16*	34.1	34.0	0.002
Pre-existing medical procedures and medication prescriptions (%)						
Hospitalizations	27.0	25.9	0.02	27.0	26.9	<.001
Tobacco abuse counseling	4.4	2.9	0.08	3.8	3.7	0.002
Smoking and tobacco use cessation counseling visit	5.4	4.5	0.04	5.1	5.0	0.003
Smoking cessation education	0.2	0.1	0.02	0.2	0.2	<.001
Drugs used in nicotine dependence	17.6	16.3	0.04	17.1	16.9	0.006
NRT	12.9	13.2	0.008	13.1	12.7	0.01
Varenicline	7.9	5.4	0.10*	7.1	7.1	0.001
Bupropion	15.9	10.8	0.15*	14.2	14.4	0.004
Nortriptyline	2.4	2.0	0.03	2.3	2.3	0.004

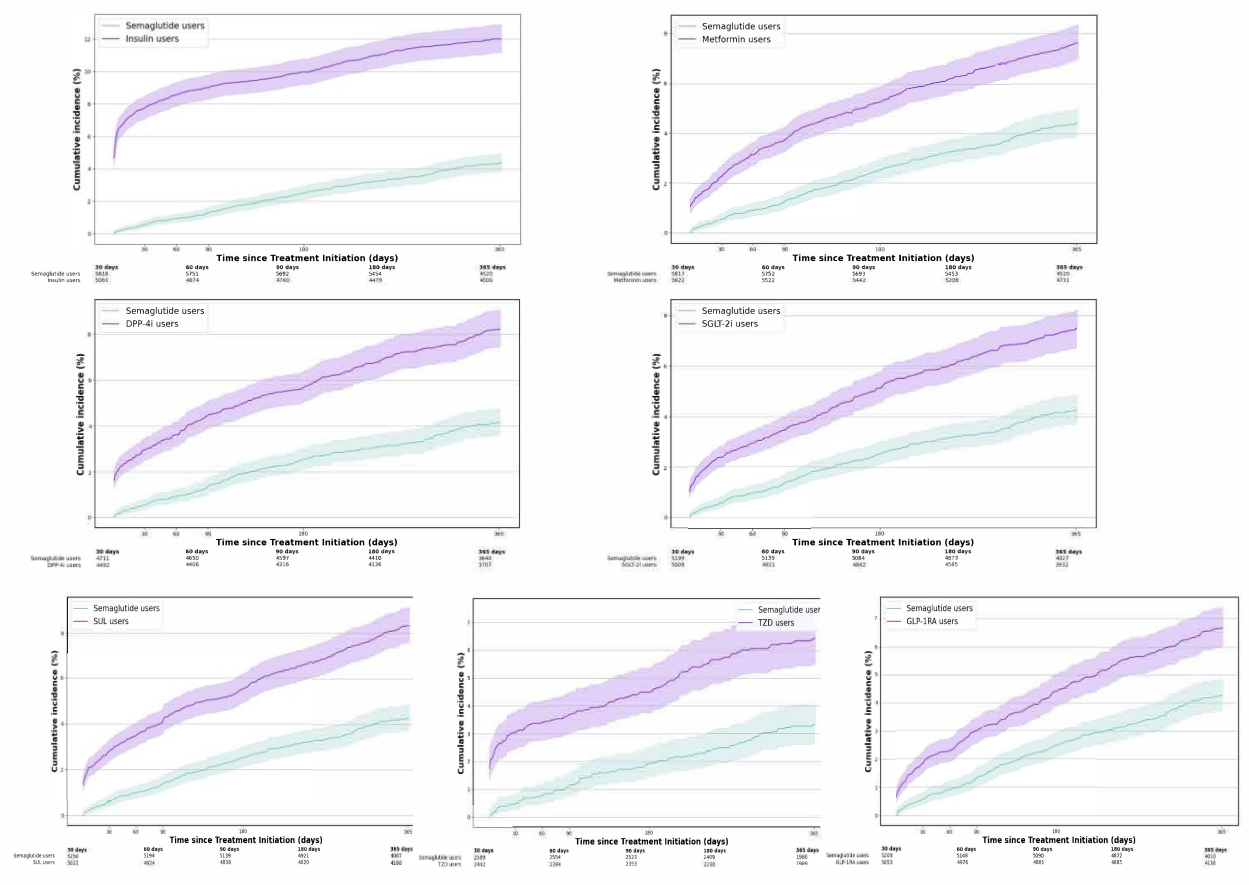
Supplement Figure 2. Risks and hazard rate of medical encounters for TUD diagnosis in patients with T2DM and TUD who had a diagnosis of obesity.



Supplement Figure 3. Risks and hazard rate of smoking cessation medication prescriptions in patients with T2DM and TUD who had a history of obesity.



Supplement Figure 4. Cumulative incidences of smoking cessation medication prescriptions for the seven target trial emulations of users of semaglutide compared with anti-diabetes medications during a 12-month follow-up.

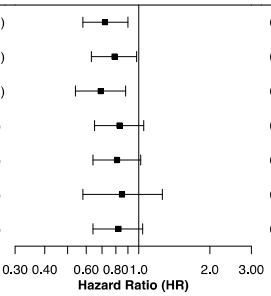


Supplement Figure 5. Risks and hazard rate of smoking cessation counseling in patients with T2DM and TUD, with and without a diagnosis of obesity.

A

Smoking cessation counseling in patients with T2DM and TUD
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

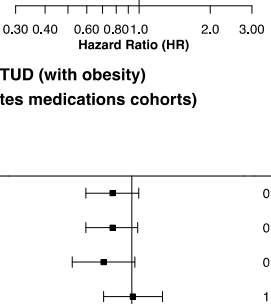
Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
5,954	semaglutide	insulins	140 (2.4%)	178 (3.0%)	−0.6% (−1.2%, −0.1%)	0.72 (0.58–0.90)
5,955	semaglutide	metformin	140 (2.4%)	176 (3.0%)	−0.6% (−1.2%, −0.0%)	0.79 (0.63–0.98)
4,831	semaglutide	DPP–4i	109 (2.3%)	154 (3.2%)	−0.9% (−1.6%, −0.3%)	0.69 (0.54–0.88)
5,325	semaglutide	SGLT2i	122 (2.3%)	143 (2.7%)	−0.4% (−1.0%, 0.2%)	0.83 (0.65–1.05)
5,388	semaglutide	SU	127 (2.4%)	153 (2.8%)	−0.5% (−1.1%, 0.1%)	0.81 (0.64–1.02)
2,659	semaglutide	TZD	47 (1.8%)	53 (2.0%)	−0.2% (−1.0%, 0.5%)	0.85 (0.58–1.26)
5,337	semaglutide	other GLP–1RAs	124 (2.3%)	149 (2.8%)	−0.5% (−1.1%, 0.1%)	0.82 (0.64–1.04)



B

Smoking cessation counseling in patients with T2DM and TUD (without obesity)
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

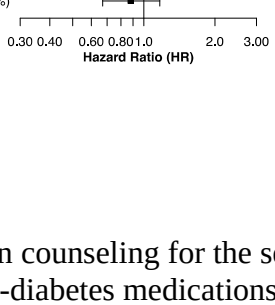
Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
1,302	semaglutide	insulins	28 (2.1%)	26 (2.0%)	0.2% (−0.9%, 1.2%)	0.95 (0.56–1.62)
1,305	semaglutide	metformin	29 (2.2%)	48 (3.7%)	−1.5% (−2.8%, −0.2%)	0.58 (0.37–0.82)
1,283	semaglutide	DPP–4i	27 (2.1%)	38 (3.0%)	−0.9% (−2.1%, 0.4%)	0.69 (0.42–1.13)
1,293	semaglutide	SGLT2i	29 (2.2%)	31 (2.4%)	−0.2% (−1.3%, 1.0%)	0.90 (0.54–1.49)
1,292	semaglutide	SU	27 (2.1%)	50 (3.9%)	−1.8% (−3.1%, −0.5%)	0.52 (0.32–0.83)
1,033	semaglutide	TZD	21 (2.0%)	27 (2.6%)	−0.6% (−1.9%, 0.7%)	0.73 (0.41–1.29)
1,268	semaglutide	other GLP–1RAs	26 (2.1%)	39 (3.1%)	−1.0% (−2.3%, 0.2%)	0.64 (0.39–1.05)



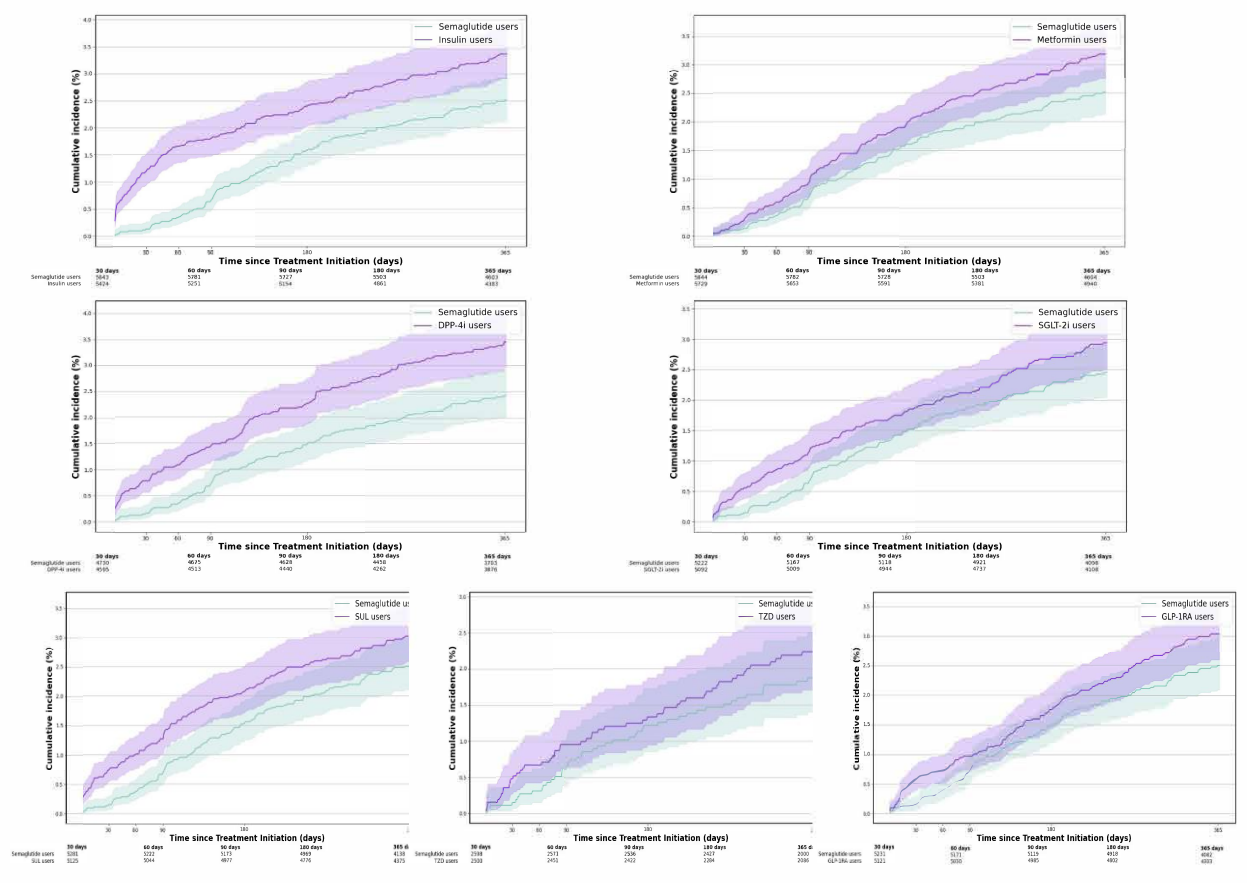
C

Smoking cessation counseling in patients with T2DM and TUD (with obesity)
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
4,649	semaglutide	insulins	110 (2.4%)	123 (2.6%)	−0.3% (−0.9%, 0.4%)	0.83 (0.64–1.07)
4,652	semaglutide	metformin	112 (2.4%)	135 (2.9%)	−0.5% (−1.1%, 0.2%)	0.83 (0.64–1.06)
3,514	semaglutide	DPP–4i	74 (2.1%)	95 (2.7%)	−0.6% (−1.3%, 0.1%)	0.76 (0.56–1.03)
3,617	semaglutide	SGLT2i	93 (2.6%)	90 (2.5%)	0.1% (−0.6%, 0.8%)	1.01 (0.76–1.35)
4,056	semaglutide	SU	88 (2.2%)	105 (2.6%)	−0.4% (−1.1%, 0.2%)	0.82 (0.62–1.09)
1,609	semaglutide	TZD	32 (2.0%)	29 (1.8%)	0.2% (−0.8%, 1.1%)	1.07 (0.65–1.77)
4,018	semaglutide	other GLP–1RAs	92 (2.3%)	103 (2.6%)	−0.3% (−0.9%, 0.4%)	0.88 (0.67–1.17)



Supplement Figure 6. Cumulative incidences of smoking cessation counseling for the seven target trial emulations of users of semaglutide compared with anti-diabetes medications during a 12-month follow-up.

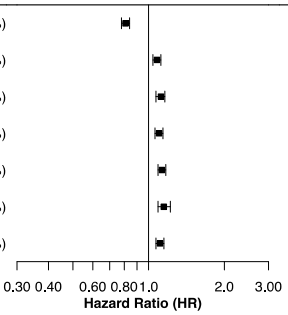

Semaglutide users
Insulin users
Cumulative incidence (%)
Time since Treatment Initiation (days)
Semaglutide users
Metformin users
Cumulative incidence (%)
Time since Treatment Initiation (days)
Semaglutide users
DPP-4i users
Cumulative incidence (%)
Time since Treatment Initiation (days)
Semaglutide users
SGLT-2i users
Cumulative incidence (%)
Time since Treatment Initiation (days)
Semaglutide users
SUL users
Cumulative incidence (%)
Time since Treatment Initiation (days)
Semaglutide users
TZD users
Cumulative incidence (%)
Time since Treatment Initiation (days)
Semaglutide users
GLP-1RA users
Cumulative incidence (%)
Time since Treatment Initiation (days)

Supplement Figure 7. Risks and hazard rate of overall medical encounters in patients with T2DM and TUD, with and without a diagnosis of obesity.

A

Overall medical encounters in patients with T2DM and TUD
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

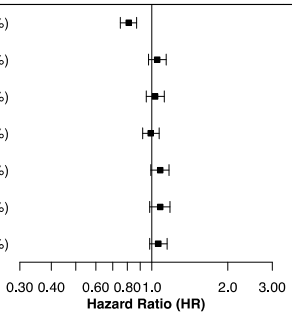
Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
5,954	semaglutide	insulins	5,869 (98.6%)	5,654 (95.0%)	3.6% (3.0%, 4.2%)	0.81 (0.78–0.84)
5,955	semaglutide	metformin	5,870 (98.6%)	5,773 (96.9%)	1.6% (1.1%, 2.2%)	1.08 (1.04–1.12)
4,831	semaglutide	DPP–4i	4,755 (98.4%)	4,636 (96.0%)	2.5% (1.8%, 3.1%)	1.12 (1.07–1.16)
5,325	semaglutide	SGLT2i	5,244 (98.5%)	5,152 (96.8%)	1.7% (1.1%, 2.3%)	1.10 (1.06–1.14)
5,388	semaglutide	SU	5,309 (98.5%)	5,152 (95.6%)	2.9% (2.3%, 3.5%)	1.13 (1.09–1.17)
2,659	semaglutide	TZD	2,603 (97.9%)	2,495 (93.8%)	4.1% (3.0%, 5.1%)	1.15 (1.09–1.22)
5,337	semaglutide	other GLP–1RAs	5,258 (98.5%)	5,124 (96.1%)	2.5% (1.9%, 3.1%)	1.11 (1.07–1.15)



B

Overall medical encounters in patients with T2DM and TUD (without obesity)
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
1,302	semaglutide	insulins	1,267 (97.3%)	1,201 (92.2%)	5.1% (3.4%, 6.8%)	0.81 (0.75–0.87)
1,305	semaglutide	metformin	1,269 (97.2%)	1,226 (93.9%)	3.3% (1.7%, 4.9%)	1.05 (0.97–1.14)
1,283	semaglutide	DPP–4i	1,248 (97.3%)	1,213 (94.5%)	2.7% (1.2%, 4.3%)	1.03 (0.95–1.12)
1,293	semaglutide	SGLT2i	1,257 (97.3%)	1,229 (95.1%)	2.2% (0.7%, 3.6%)	0.99 (0.92–1.07)
1,292	semaglutide	SU	1,256 (97.2%)	1,210 (93.7%)	3.6% (2.0%, 5.2%)	1.08 (0.99–1.17)
1,033	semaglutide	TZD	1,000 (96.8%)	957 (92.6%)	4.2% (2.2%, 6.1%)	1.08 (0.98–1.18)
1,268	semaglutide	other GLP–1RAs	1,233 (97.2%)	1,187 (93.6%)	3.6% (2.0%, 5.2%)	1.06 (0.98–1.15)



C

Overall medical encounters in patients with T2DM and TUD (with obesity)
(Comparision between matched semaglutide vs other anti–diabetes medications cohorts)

Size/cohort	Exposure	Comparison	cases (overall risk) (Exposure)	cases (overall risk) (Comparison)	RD (95% CI)	HR (95% CI)
4,649	semaglutide	insulins	4,600 (98.9%)	4,431 (95.3%)	3.6% (3.0%, 4.3%)	0.81 (0.77–0.84)
4,652	semaglutide	metformin	4,603 (98.9%)	4,528 (97.3%)	1.6% (1.1%, 2.2%)	1.14 (1.09–1.18)
3,514	semaglutide	DPP–4i	3,472 (98.8%)	3,399 (96.7%)	2.1% (1.4%, 2.8%)	1.10 (1.05–1.16)
3,617	semaglutide	SGLT2i	3,574 (98.8%)	3,516 (97.2%)	1.6% (1.0%, 2.2%)	1.16 (1.10–1.21)
4,056	semaglutide	SU	4,010 (98.9%)	3,886 (95.8%)	3.1% (2.4%, 3.8%)	1.15 (1.10–1.20)
1,609	semaglutide	TZD	1,583 (98.4%)	1,537 (95.5%)	2.9% (1.7%, 4.0%)	1.16 (1.08–1.24)
4,018	semaglutide	other GLP–1RAs	3,973 (98.9%)	3,883 (96.6%)	2.2% (1.6%, 2.9%)	1.15 (1.10–1.20)