Supplementary Materials for GLP-1RA and Risks of Substance Use Disorders Among US Veterans with Type 2 Diabetes: A Cohort Study

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Supplementary Methods

Baseline covariates

We prespecified a set of baseline covariates for each of the eight emulated trials based on prior knowledge and guided by a causal framework and directed acyclic graphs (DAG) (Supplementary Figure S1 for Protocol 1 and Supplementary Figure S2 for Protocol 2). For readability, the DAGs group covariates into domains (Supplementary Figure S1 for Protocol 1 and Supplementary Figure S2 for Protocol 2); we provide the full list of covariates below; the weighting models included each listed covariate as a separate term (i.e., no domain-level summaries were used for adjustment).

Socio-demographic variables included age, sex, race (American Indian or Alaska Native, Asian, Black, Native Hawaiian or Pacific Islander, Other, White), ethnicity (Hispanic or non-Hispanic), rurality (highly rural, insular island, rural, and urban), calendar week of treatment initiation, and area deprivation index—a composite measure of income, education, employment, and housing used as a summary measure of contextual disadvantage at the participants' residential locations[1]. Health behavior factors included smoking status (current, former, and never smoker)[2]. Laboratory or physiological measurements included albuminuria, average HbA1c within 1 year, body mass index (BMI), diastolic blood pressure, estimated glomerular filtration rate (eGFR), low-density lipoprotein (LDL), and systolic blood pressure[3-5]. Health care utilisation included long-term care use, number of HbA1c measurements, number of outpatient encounters and hospitalizations from Medicare, number of blood panel tests, number of hospitalizations, number of outpatient encounters, and number of prescriptions[6-8].

We also adjusted for diabetes medication use[3-5] including use of metformin, thiazolidinediones, DPP-4 inhibitors (DPP-4i), sulfonylureas, and insulin, as well as the duration of use of metformin, thiazolidinediones, DPP-4i, sulfonylureas, and insulin within 5 years before T_0, each as a separate variable. The duration of medication use was calculated as the cumulative sum of days' supply from all filled prescriptions for each medication class (metformin, thiazolidinediones, DPP-4i, sulfonylureas, and insulin) in the 5 years before T_0.

We also adjusted for comorbidities and medications that may influence the likelihood of GLP-1RA initiation and risks of SUD outcomes[9-11]. We adjusted for cardiometabolic conditions or medications including angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACE/ARB) use, acute coronary disease, acute kidney injury defined based on serum creatinine–based Kidney Disease Improving Global Outcomes guidelines, atrial fibrillation, beta-blockers, calcium channel blockers, diuretics, heart failure, ischemic cardiomyopathy, myocardial infarction, non-ischemic cardiomyopathy, statin use, stroke, and transient ischemic attack.

We also adjusted for gastrointestinal conditions including abdominal pain, constipation, diarrhea, diverticulosis and diverticulitis, dyspepsia, gastroesophageal reflux disease (GERD), gastritis, intestinal obstruction and ileus, nausea, non-alcoholic fatty liver disease, and ulcerative colitis.

We also adjusted for mental health conditions or medications[12 13] including acute stress, adjustment disorders, benzodiazepines, buprenorphine, bupropion, generalized anxiety disorder, major depressive disorder recurrent, methadone, mixed anxiety disorder, mood disorder, naltrexone, panic disorder, post-traumatic stress disorder, psychotic disorder, serotonin-Norepinephrine reuptake inhibitors, selective serotonin reuptake inhibitors, sleep aid medications, sleep disorder, suicidal ideation, and tricyclic antidepressants.

Covariates also included bariatric surgery, cancer, HIV, hyperlipidemia, nutritional deficiencies, orlistat, phentermine, thyroid disorders, topiramate, and urinary tract infection[14].

Trial-specific adjustment for SUDs was a critical application of this framework. Our predefined list included specific SUD diagnoses (alcohol, cannabis, cocaine, nicotine, opioid, other) and their related medications (e.g., disulfiram, varenicline, nicotine replacement therapy). For Protocol 1 (Incident SUDs): Since participants with a prior history of the outcome of interest were excluded by design, we adjusted for all other SUD and related medications. For instance, the alcohol use disorder trial adjusted for all SUD covariates except alcohol use disorder and disulfiram. The primary trial included no SUD covariates, as all participants with any prior SUD were excluded. For Protocol 2 (Pre-existing SUDs): This trial adjusted for the entire list of SUD diagnoses and related medications.

Time-varying covariates

We included time-varying social stressors because social or economic adversity is associated with medication continuity and may increase the likelihood of discontinuing GLP-1RA use[15-17]. The specified social stressors (10 variables) were defined using diagnosis codes and included discord with neighbors, lodgers, or landlord, extreme poverty, homelessness, inadequate housing, lack of adequate food, living in a residential institution, low income, other housing or economic problems, insufficient social insurance or welfare support, and unspecified housing or economic circumstances.

VA appointment status reflects whether a scheduled clinical encounter was completed, cancelled, or missed[18]. We included these variables because patterns of missed or cancelled visits may signal reduced engagement with the VA health system and predict subsequent discontinuation of GLP-1RA use. The specific visit-level VA appointment status (5 covariates) included appointment cancelled by the clinic, appointment cancelled by the patient, checked-out (completed) appointment, inpatient appointment, and no-show.

Time-varying outpatient care engagement included changes in outpatient care utilisation —for example decreased routine care or increased acute or specialty visits — may indicate shifts in underlying health status or care engagement that could influence the likelihood of discontinuing GLP-1RA[10]. Time-varying outpatient care engagement was captured using VA stop codes (28 separate variables): allergy, cardiology, community care consult, dental care, dermatology, emergency department, endocrinology, gastroenterology, hematology, hepatology, imaging, infectious disease, laboratory, mental health, nephrology, neurology, oncology, optometry, pain clinic, pharmacy, podiatry, primary care, pulmonary, physical therapy/occupational therapy, rheumatology, sleep clinic, surgery, and urology[19].

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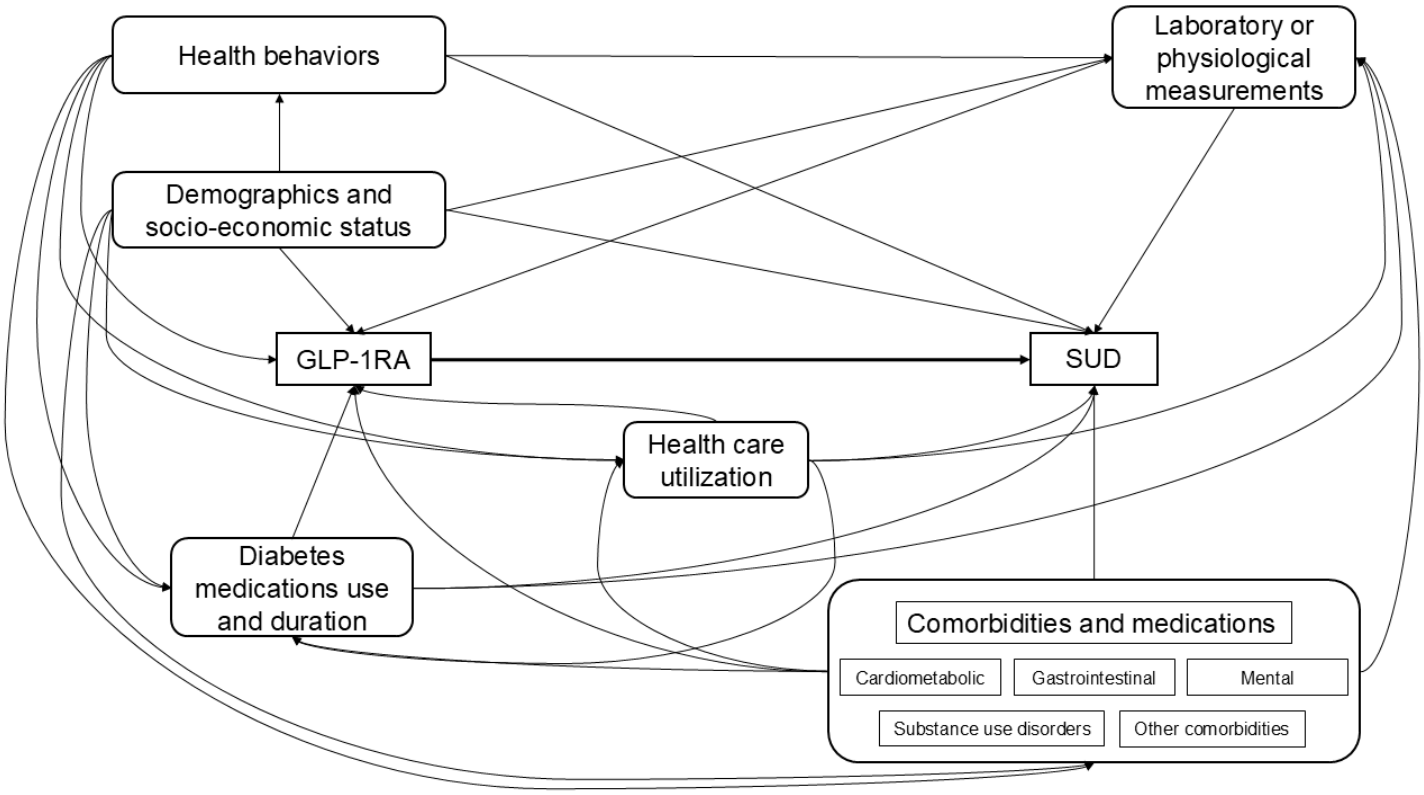
Supplementary Figure S1 Directed acyclic graph for baseline covariate selection in Protocol 1.

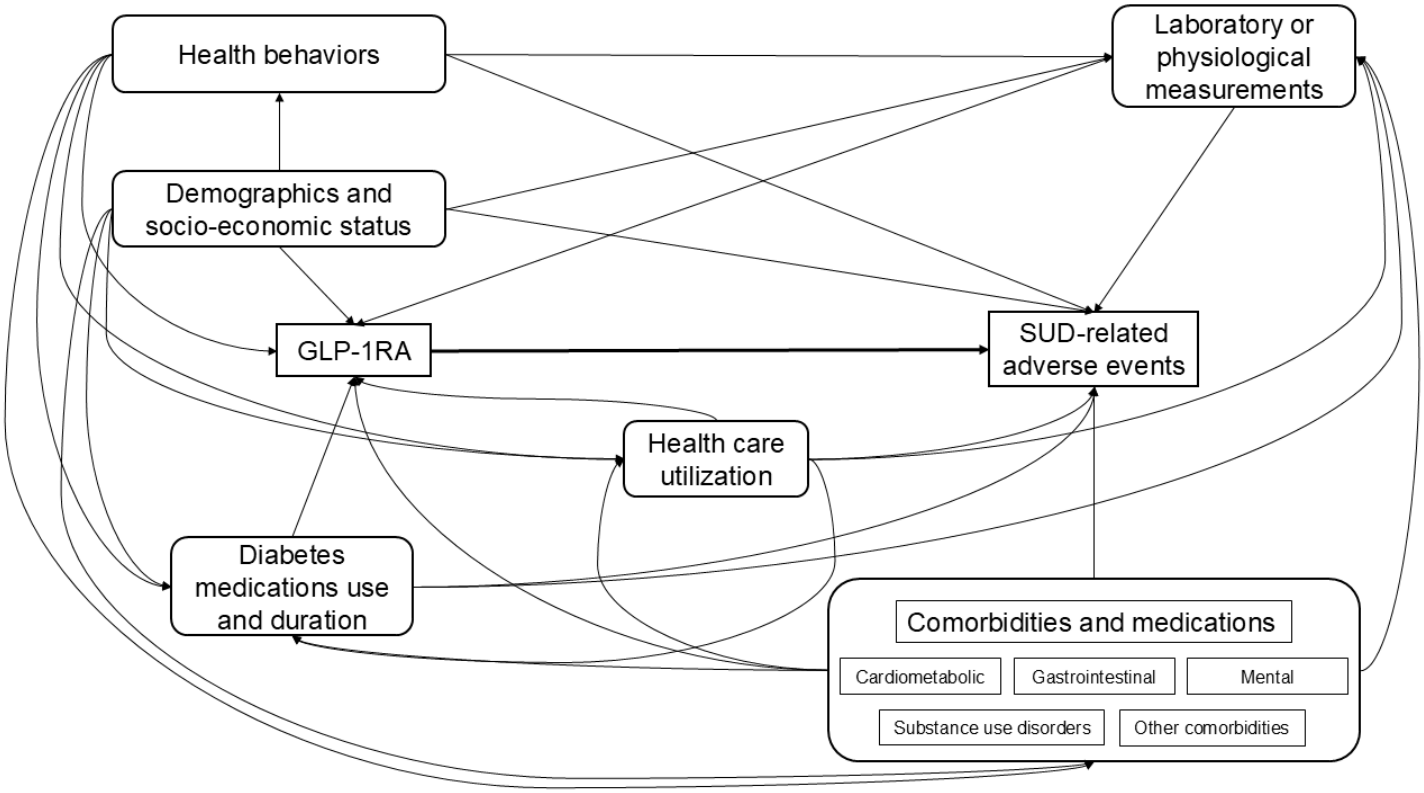


GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; SUD, substance use disorder.

For readability, the DAG groups covariates into domains. The full list of covariates is provided in supplementary methods. The weighting models included each listed covariate as a separate term (i.e., no domain-level summaries were used for adjustment).

Protocol 1 comprises seven parallel trials, each excluding participants with a pre-existing SUD: any SUD (trial 1, the primary trial), alcohol (trial 2), cannabis (trial 3), cocaine (trial 4), nicotine (trial 5), opioid (trial 6), and other SUD (hallucinogen-, inhalant-, psychoactive-, sedative/hypnotic-, and stimulant-related disorders) (trial 7). The objective was to evaluate whether initiating a GLP-1RA versus an SGLT2i reduces the incident risk of a specific SUD. For each trial, the analytic cohort was restricted to individuals without a prior diagnosis of that specific SUD at baseline. This design resulted in seven partially overlapping but distinct analytic cohorts, aligning the at-risk population with the specific outcome for each trial.

Supplementary Figure S2 Directed acyclic graph for baseline covariate selection in Protocol 2.

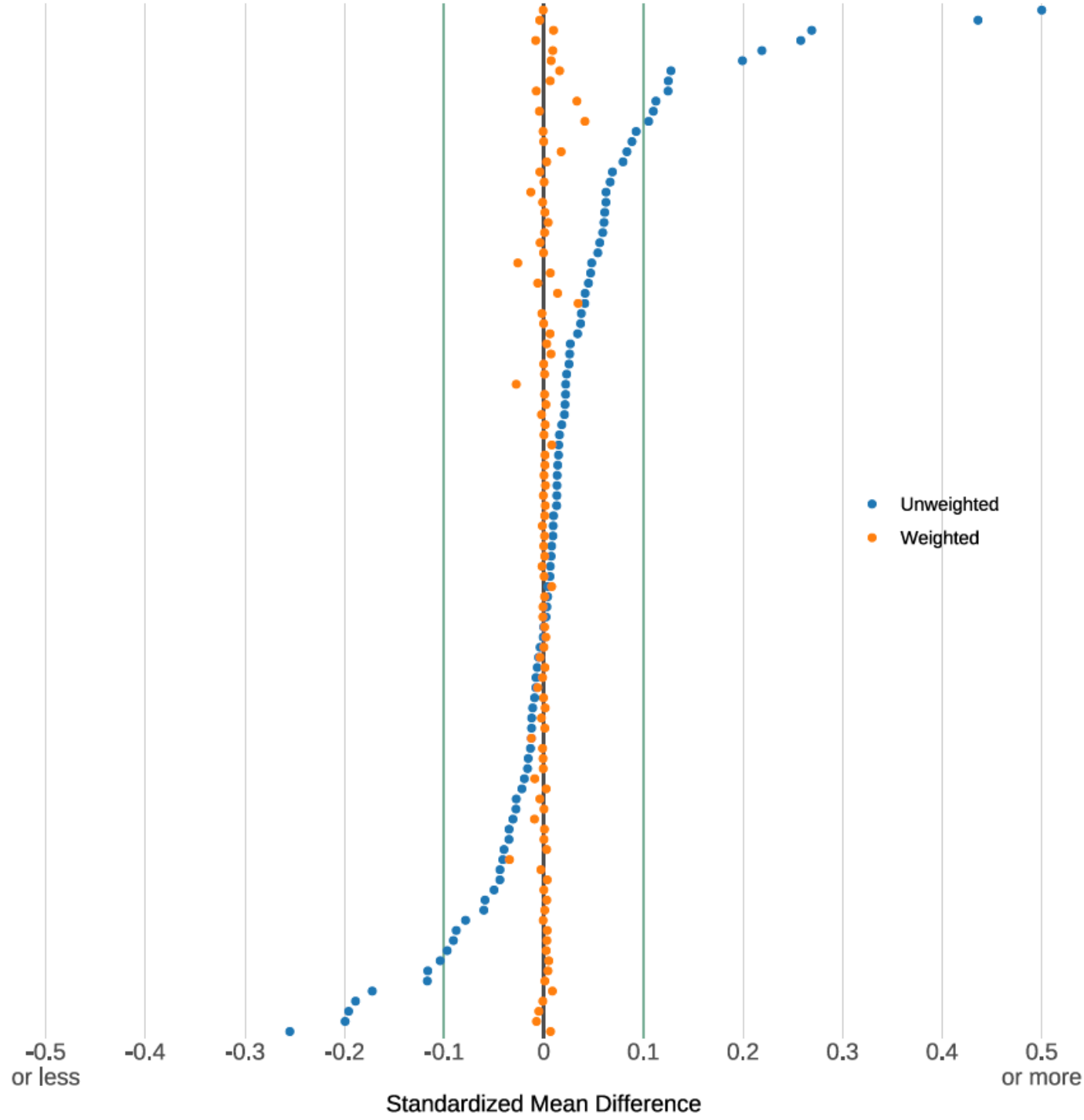


GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; SUD, substance use disorder.

For readability, the DAG groups covariates into domains. The full list of covariates is provided in supplementary methods. The weighting models included each listed covariate as a separate term (i.e., no domain-level summaries were used for adjustment).

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

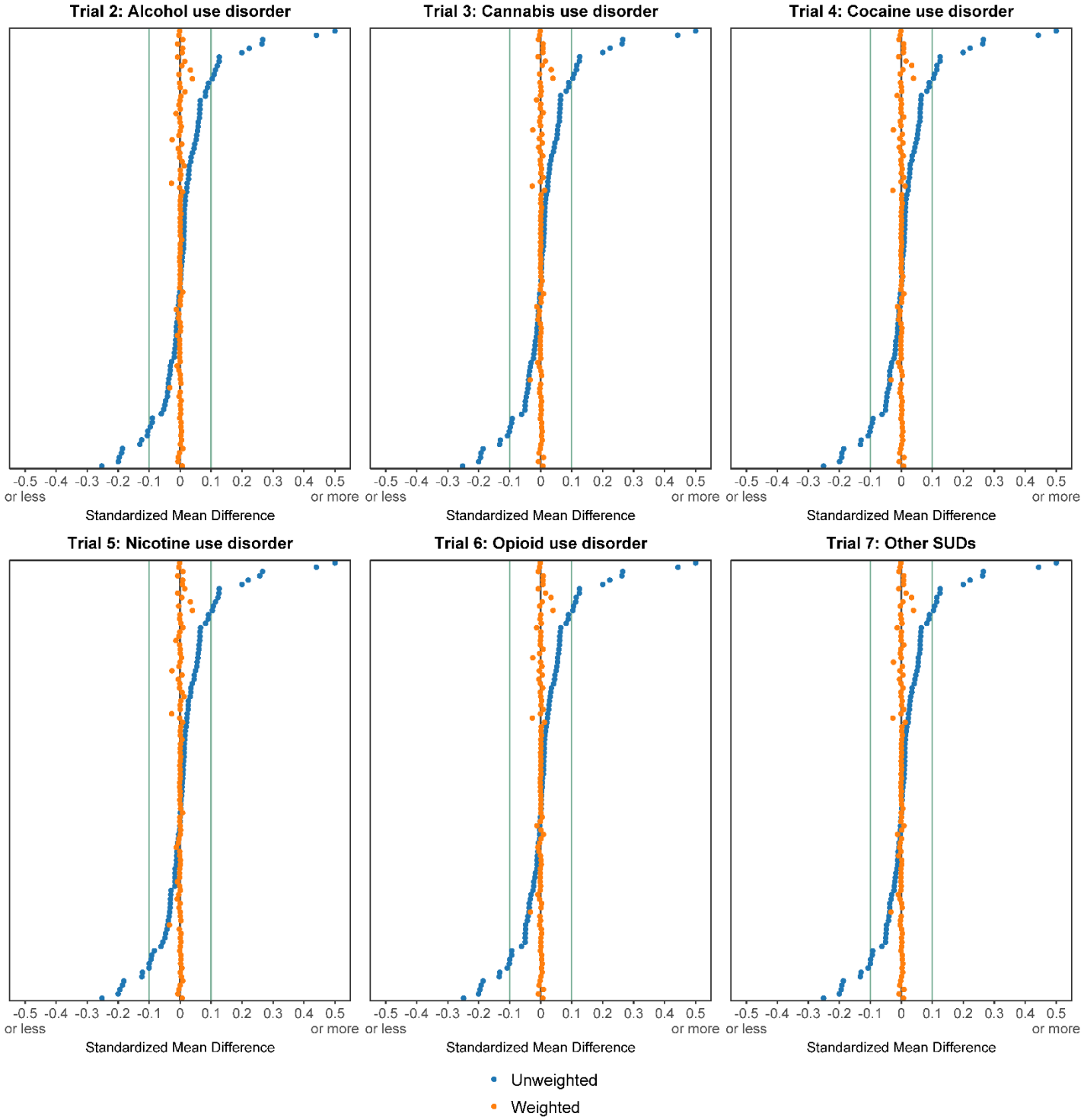
Supplementary Figure S3 Standardized mean differences for covariates before and after weighting: Protocol 1, Trial 1 (primary trial).



GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors.

Protocol 1 includes seven parallel trials. Trial 1 (the primary trial) excluded participants with any prior SUD and evaluated the composite endpoint of all SUDs. The absolute values of standardized mean differences after weighting <0.1 indicate good covariate balance.

Supplementary Figure S4 Standardized mean differences for covariates before and after weighting: Protocol 1, Trials 2–7.



Protocol 1 comprises seven parallel trials, each excluding participants with a pre-existing SUD: any SUD (trial 1, the primary trial), alcohol (trial 2), cannabis (trial 3), cocaine (trial 4), nicotine (trial 5), opioid (trial 6), and other SUD (hallucinogen-, inhalant-, psychoactive-, sedative/hypnotic-, and stimulant-related disorders) (trial 7). The objective was to evaluate whether initiating a GLP-1RA versus an SGLT2i reduces the incident risk of a specific SUD. For each trial, the analytic cohort was restricted to individuals without a prior diagnosis of that specific SUD at baseline. The absolute values of standardized mean differences after weighting <0.1 indicate good covariate balance.

Supplementary Figure S5 Cumulative risk of incident substance use disorder (composite) in Protocol 1, estimated using (A) cause-specific hazards, (B) Fine–Gray subdistribution hazards, and (C) cause-specific hazards with time-varying inverse probability-of-death censoring weights.

Hazard ratio	NRD per 1000 persons	Net 3-year risk per 1000 persons in GLP-1RA	Net 3-year risk per 1000 persons in SGLT2i
0.86 (0.83 to 0.88)	-6.61 (-7.95 to -5.26)	40.12 (38.96 to 41.29)	46.73 (46.04 to 47.42)

Hazard ratio	3-year risk difference per 1000 persons	3-year risk per 1000 persons in GLP-1RA	3-year risk per 1000 persons in SGLT2i
0.86 (0.83 to 0.89)	-6.48 (-7.98 to -4.95)	40.15 (39.09 to 41.26)	46.69 (45.56 to 47.64)

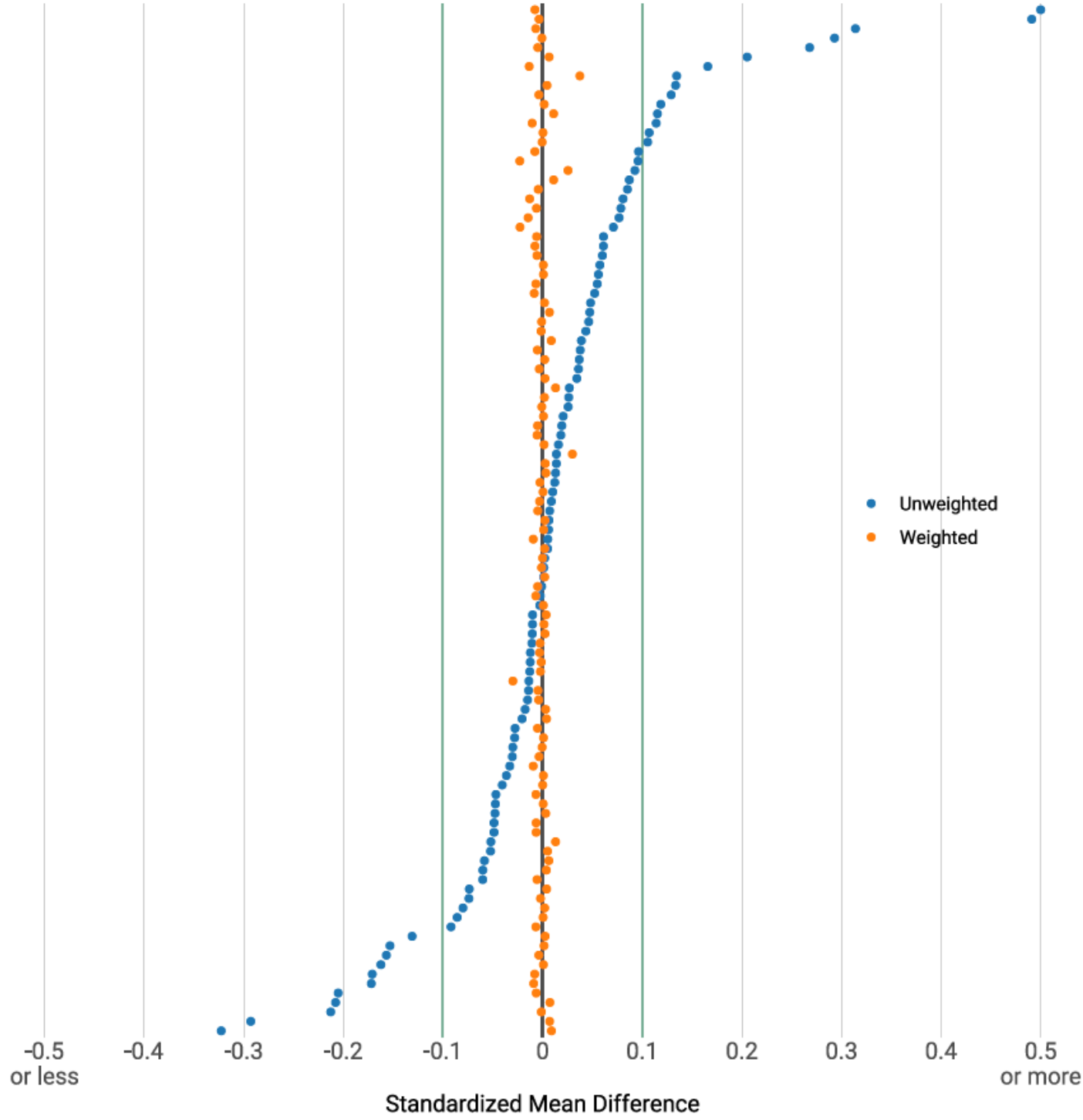
Risk ratio	3-year risk difference per 1000 persons	3-year risk per 1000 persons in GLP-1RA	3-year risk per 1000 persons in SGLT2i
0.85 (0.80 to 0.89)	-6.40 (-8.44 to -4.38)	35.65 (34.29 to 37.10)	42.06 (40.68 to 43.40)

GLP-1RA, glucagon-like peptide-1 receptor agonist; NRD: Net 3-year risk difference; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors.

The cause-specific hazard model with time-varying inverse-probability-of-censoring-weights was estimated using a marginal structural model accounting for both baseline covariates and time-varying covariates at 90-day intervals (12 intervals) during 3 years of follow-up.

Protocol 1 includes seven parallel trials, each excluding participants with a pre-existing SUD. Trial 1 (the primary trial) presented here excluded participants with any prior SUD and evaluated the composite endpoint of all SUDs.

Supplementary Figure S6 Standardized mean differences for covariates before and after weighting: Protocol 2.



GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

Supplementary Figure S7 Cumulative risk of the three-component composite outcome in Protocol 2 (emergency department visit for SUD, hospitalization for SUD, SUD-associated mortality), estimated using (A) cause-specific hazards, (B) Fine–Gray subdistribution hazards, and (C) cause-specific hazards with time-varying inverse probability-of-death censoring weights.

Hazard ratio	NRD per 1000 persons	Net 3-year risk per 1000 persons in GLP-1RA	Net 3-year risk per 1000 persons in SGLT2i
0.71 (0.65 to 0.79)	-11.79 (-14.98 to -8.60)	30.03 (27.27 to 32.78)	41.82 (40.19 to 43.45)

Hazard ratio	3-year risk difference per 1000 persons	3-year risk per 1000 persons in GLP-1RA	3-year risk per 1000 persons in SGLT2i
0.73 (0.66 to 0.82)	-11.21 (-14.47 to -7.13)	29.70 (27.09 to 32.69)	40.85 (38.14 to 43.38)

Risk ratio	3-year risk difference per 1000 persons	3-year risk per 1000 persons in GLP-1RA	3-year risk per 1000 persons in SGLT2i
0.69 (0.58 to 0.83)	-10.88 (-16.06 to -6.00)	24.85 (21.82 to 28.58)	35.81 (32.30 to 39.73)

GLP-1RA, glucagon-like peptide-1 receptor agonist; NRD: Net 3-year risk difference; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors.

The cause-specific hazard model with time-varying inverse-probability-of-censoring-weights was estimated using a marginal structural model accounting for both baseline covariates and time-varying covariates at 90-day intervals (12 intervals) during 3 years of follow-up.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

Supplementary Table S1 Specification and emulation of seven target trials: Protocol 1.

Protocol Components	Target Trial Protocol	Emulation
Research question	Among US veterans aged ≥18 years with type 2 diabetes who are eligible for both GLP-1 receptor agonists (GLP-1RA, intervention) and SGLT2 inhibitors (SGLT2i, active comparator), and who have no prior history of the specific substance use disorder (SUD) at baseline, what is the effect of initiating GLP-1RA versus initiating SGLT2i on the incident SUD of interest? This question applies to seven parallel trials, each focused on a specific SUD (alcohol, cannabis, cocaine, nicotine, opioid, other, and a composite SUD) such that each analytical cohort includes only individuals at risk for that specific SUD (participants who have no prior history of the specific SUD at baseline).	Same as protocol
Enrollment period	The enrollment period is from January 1, 2017 to December 31, 2024.	Same as protocol
Eligibility criteria	Inclusion: US veterans who • Aged ≥18 years on the date of enrollment, • Had type 2 diabetes, • Were VA health care system users (defined as having ≥2 encounters and ≥1 pharmacy utilisation in the year before the enrollment date). Exclusion: • Had contraindication for GLP-1RA or SGLT2i (diabetic ketoacidosis, gastroparesis, malignant neoplasm of thyroid gland, multiple endocrine neoplasia type II, pancreatitis, severe hypoglycemia [hypoglycemia with coma or requiring hospitalization], or severe renal impairment [eGFR <30 mL/min/1.73 m², dialysis, or kidney transplant]) in the year before the enrollment date), • Had prior use of GLP-1RA in the year before the enrollment date, • Had prior use of SGLT2i in the year before the enrollment date, • Had a prior diagnosis of the specific SUD of interest in the year before the enrollment date. This outcome-specific exclusion created seven parallel analytic cohorts, each restricted to participants at risk for	Same as protocol

	the corresponding SUD by removing individuals with a prior history of that specific SUD: (1) Trial 1 (the primary trial): no history of the composite end point of all SUDs. (2) Trial 2: no history of alcohol use disorder, (3) Trial 3: no history of cannabis use disorder, (4) Trial 4: no history of cocaine use disorder, (5) Trial 5: no history of nicotine use disorder, (6) Trial 6: no history of opioid use disorder, (7) Trial 7: no history of other SUD (hallucinogen-related disorder, inhalant-related disorder, psychoactive-related disorder, sedative/hypnotic-related disorder, stimulant-related disorder).	
Treatment assignment	Eligible participants would be individually randomised to initiate either a GLP-1RA (intervention) or an SGLT2i (active comparator). Participants and clinicians would be aware of the assigned treatment strategy.	Because treatment intention is not observed in electronic health record data, we defined baseline exposure using observed initiation of GLP-1RA or SGLT2i on the index dispensing date, and used SMR weighting to standardize the comparator group to the covariate distribution of GLP-1RA initiators (ATT). Propensity scores were estimated using six prespecified domains of baseline covariates as detailed in the Methods: (1) socio-demographic status, (2) health behavior, (3) laboratory or physiological measurements, (4) health care utilisation, (5) diabetes medication use, and (6) comorbidities and medications including a) cardiometabolic conditions or medications, b) gastrointestinal conditions, c) mental health conditions or medications, d) diagnoses of specific SUDs or their related medications (trial-specific covariates for SUD), and e) others.

		Trial-specific covariate adjustment was applied for SUD: each trial adjusted for all other SUD diagnoses and related medications, excluding the SUD that defined the outcome in that specific trial. For example, trial 2 for alcohol use disorder adjusted for cannabis, cocaine, nicotine, opioid, and other SUD, as well as varenicline and nicotine replacement therapy, but did not adjust for alcohol use disorder or disulfiram. Trial 1 the primary trial for composite SUD outcome included no SUD covariates, as all participants with any prior SUD were excluded. We assessed covariate balance after weighting using absolute standardized mean differences (SMDs); achieving small residual imbalance (e.g., absolute SMD <0.10) was used as a diagnostic of adequate baseline covariate balance between groups.
Treatment initiation	Participants initiated either (1) GLP-1RA (intervention) or (2) SGLT2i (comparator) on the date of randomization. The calendar date of the index dispensing is T_0.	Treatment initiation was ascertained based on outpatient pharmacy records of release (fill) of the medication.
Treatment strategy	Participants initiate the strategy to which they are assigned: (1) Intervention: GLP-1RA. (2) Comparator: SGLT2i. Treatment is open-label and participants would be aware of their assigned strategy.	Strategies were operationalized as initiation of GLP-1RA vs initiation of SGLT2i at baseline (T0).
Outcomes	Incident outcomes include (1) Trial 1 (the primary trial): a composite end point of all SUDs, (2) Trial 2: alcohol use disorder, (3) Trial 3: cannabis use disorder, (4) Trial 4: cocaine use disorder, (5) Trial 5: nicotine use disorder, (6) Trial 6: opioid use disorder, (7) Trial 7: other SUD composited from hallucinogen-related disorder, inhalant-related disorder, psychoactive-related disorder, sedative/hypnotic-related disorder, stimulant-related disorder.	Same as protocol.

Follow-up	Follow-up starts at treatment initiation (T_0). Participants would be followed until the earliest occurrence of outcome, death, administrative censoring on October 06, 2025, or at 3 years after T_0.	Same as protocol.
Causal contrasts of interest	We prespecified two causal contrasts: (1) Treatment initiation (as-initiated) effect: the effect of initiating a GLP-1RA versus initiating an SGLT2i among GLP-1RA initiators, regardless of subsequent treatment changes during follow-up. This analysis estimated the average treatment effect among treated (ATT) with treated defined as those who were initiated on GLP-1RA. (2) Treatment adherence effect: the effect of sustained adherence to GLP-1RA during the 3-year follow-up period versus SGLT2i.	Same as protocol.
Analysis plan to estimate causal contrasts of interest	(1) Treatment initiation (as-initiated) analysis The treatment initiation effect for the outcomes would be estimated using cause-specific hazard models, which quantify the effect of GLP-1RA initiation on the instantaneous rate of developing SUD among participants who remain alive and free of the event. Relative effects will be reported as hazard ratios, and absolute effects as net 3-year risk differences (NRDs) per 1,000 persons. (2) Treatment adherence analysis The treatment adherence effect would be estimated by comparing the risk of the composite SUD outcome under sustained adherence to the initiated treatment strategy for the 3-year follow-up. Participants who deviated from their initiated strategy would be censored on the date of protocol violation. Marginal structural models (MSMs) would be applied to estimate the treatment adherence effect of the initiated treatment during follow-up. Inverse-probability-of-censoring weights (IPCW) would be constructed at 90-day intervals (12 intervals in total) to appropriately account for potential informative censoring due to protocol violation considering the	Same as protocol.

	complex, time-dependent relationship between treatment status and time-varying confounders. Both baseline and time-varying covariates would be used to model the probability of remaining adherent at each interval. Weighted discrete-time survival analysis would be used to estimate the effect estimates. Relative effects will be reported as risk ratios at 3 years, and absolute effects as 3-year absolute risk difference per 1,000 persons.	
Causal estimand	Among US Veterans aged ≥18 years with type 2 diabetes who are eligible for both GLP-1RA and SGLT2i, and who have no prior history of the specific substance use disorder (SUD) at baseline, we estimate the treatment initiation effect (initiating a GLP-1RA versus initiating an SGLT2i) and treatment adherence effect (sustained adherence to GLP-1RA during the 3-year follow-up period versus an SGLT2i) on the 3-year risk of incident substance use disorder. The estimands are summarized on the relative scale (cause-specific hazard ratio for treatment initiation effect and risk ratio for treatment adherence effect) and on the absolute scale (NRD per 1,000 persons for treatment initiation analysis and risk difference per 1,000 persons for treatment adherence analysis).	Same as protocol
Subgroup analyses	Subgroups by age groups (≤65 and >65 years), sex (male and female), race groups (White, Black, and other), BMI categories (≤30, 30-35, and >35 kg/m²), HbA1c levels (≤6.5, 6.5-8, and >8%), and GLP-1RA agents (Semaglutide, Liraglutide, and Dulaglutide).	Same as protocol

Supplementary Table S2 Specification and emulation of the target trial: Protocol 2.

Protocol Components	Target Trial Protocol	Emulation
Research question	Among US veterans aged ≥18 years with type 2 diabetes who are eligible for both GLP-1 receptor agonists (GLP-1RA, intervention) and SGLT2 inhibitors (SGLT2i, active comparator), and who have a pre-existing substance use disorder (SUD) at baseline, what is the effect of initiating GLP-1RA versus initiating SGLT2i on SUD-associated downstream adverse clinical outcomes?	Same as protocol
Enrollment period	The enrollment period is from January 1, 2017 to December 31, 2024.	Same as protocol
Eligibility criteria	Inclusion: US veterans who • Aged ≥18 years on the date of enrollment, • Had type 2 diabetes, • Were VA health care system users (defined as having ≥2 encounters and ≥1 pharmacy utilisation in the year before the enrollment date), • Had a diagnosis of substance use disorder in the year prior to enrollment. Exclusion: • Had contraindication for GLP-1RA or SGLT2i (diabetic ketoacidosis, gastroparesis, malignant neoplasm of thyroid gland, multiple endocrine neoplasia type II, pancreatitis, severe hypoglycemia [hypoglycemia with coma or requiring hospitalization], or severe renal impairment [eGFR <30 mL/min/1.73 m², dialysis, or kidney transplant]) in the year before the enrollment date), • Had prior use of GLP-1RA in the year before the enrollment date, • Had prior use of SGLT2i in the year before the enrollment date.	Same as protocol
Treatment assignment	Eligible participants would be individually randomised at baseline to initiate either a GLP-1RA (intervention) or an SGLT2i (active comparator). Participants and clinicians would be aware of the assigned treatment strategy.	Because treatment intention is not observed in electronic health record data, we defined baseline exposure using observed initiation of GLP-1RA or SGLT2i on the index dispensing date, and used SMR weighting to standardize the comparator group to the covariate distribution of GLP-1RA initiators (ATT).

		Propensity scores were estimated using six prespecified domains of baseline covariates as detailed in the Methods: (1) socio-demographic status, (2) health behavior, (3) laboratory or physiological measurements, (4) health care utilization, (5) diabetes medication use, and (6) comorbidities and medications including: a) cardiometabolic conditions or medications, b) gastrointestinal conditions, c) mental health conditions or medications, d) diagnoses of specific SUDs or their related medications, and e) others. We assessed covariate balance after weighting using absolute standardized mean differences (SMDs); achieving small residual imbalance (e.g., absolute SMD <0.10) was used as a diagnostic of adequate baseline covariate balance between groups.
Treatment initiation	Participants initiated either (1) GLP-1RA (intervention) or (2) SGLT2i (comparator) on the date of randomization. The calendar date of the index dispensing is T_0.	Treatment initiation was ascertained based on outpatient pharmacy records of release (fill) of the medication.
Treatment strategy	Participants initiate the strategy to which they are assigned: (1) Intervention: GLP-1RA. (2) Comparator: SGLT2i. The trial would be open label; participants and clinicians would be aware of the assigned strategy.	Strategies were operationalized as initiation of GLP-1RA vs initiation of SGLT2i at baseline (T0).
Outcomes	**Primary outcomes** (1) emergency department visit for SUD, (2) hospitalization for SUD, (3) SUD-associated mortality, and (4) a composite outcome of these 3 outcomes.	Same as protocol.

	Secondary outcomes (1) drug overdose and (2) suicidal attempt or ideation.	
Follow-up	Follow-up starts at treatment initiation (T_0). Participants would be followed until the earliest occurrence of outcome, death, administrative censoring on October 06, 2025, or at 3 years after T_0.	Same as protocol.
Causal contrasts of interest	We prespecified two causal contrasts: (1) Treatment initiation (as-initiated) effect: the effect of initiating a GLP-1RA versus initiating an SGLT2i among GLP-1RA initiators, regardless of subsequent treatment changes during follow-up. This analysis estimated the average treatment effect among the treated (ATT) with treated defined as those who were initiated on GLP-1RA. (2) Treatment adherence effect: the effect of sustained adherence to GLP-1RA during the 3-year follow-up period versus SGLT2i.	Same as protocol.
Analysis plan to estimate causal contrasts of interest	(1) Treatment initiation (as-initiated) analysis The treatment initiation effect for non-death outcomes would be estimated using cause-specific hazard models, which quantify the effect of GLP-1RA initiation on the instantaneous rate of developing SUD among participants who remain alive and free of the event. The treatment initiation effect for SUD-associated mortality would be estimated using Cox proportional hazard models. Relative effects will be reported as hazard ratios, and absolute effects as net 3-year risk differences (NRDs) per 1,000 persons. (2) Treatment adherence analysis The treatment adherence effect would be estimated by comparing the risk of the composite SUD outcome under sustained adherence to the initiated treatment strategy for the 3-year follow-up. Participants who deviated from their initiated strategy would be censored on the date of protocol violation.	Same as protocol.

	Marginal structural models (MSMs) would be applied to estimate the treatment adherence effect of the initiated treatment during follow-up. Inverse-probability-of-censoring weights (IPCW) would be constructed at 90-day intervals (12 intervals in total) to appropriately account for potential informative censoring due to protocol violation considering the complex, time-dependent relationship between treatment status and time-varying confounders. Both baseline and time-varying covariates would be used to model the probability of remaining adherent at each interval. Weighted discrete-time survival analysis would be used to estimate the effect estimates. Relative effects will be reported as risk ratios at 3 years, and absolute effects as 3-year absolute risk difference per 1,000 persons.	
Causal estimand	Among US Veterans aged ≥18 years with type 2 diabetes who are eligible for both GLP-1RA and SGLT2i, and who have a pre-existing SUD at baseline, we estimate the treatment initiation effect (initiating a GLP-1RA versus initiating an SGLT2i) and treatment adherence effect (sustained adherence to GLP-1RA during the 3-year follow-up period versus an SGLT2i) on the 3-year risk of SUD-associated downstream adverse clinical outcomes. The estimands are summarized on the relative scale (cause-specific hazard ratio for treatment initiation analysis and risk ratio for treatment adherence analysis) and on the absolute scale (NRD per 1,000 persons for treatment initiation analysis and risk difference per 1,000 persons for treatment adherence analysis).	Same as protocol
Subgroup analyses	Subgroup analyses on the three-point composite outcome of emergency department visit for SUD, hospitalization for SUD, and SUD-associated mortality among participants with each specific pre-existing SUD (alcohol use disorder, cocaine use disorder, opioid use disorder, and other substance use disorder).	Same as protocol

Supplementary Table S3 Definitions of pre-existing substance use disorders for Protocols 1 and 2.

Substance use disorder	ICD-10 diagnosis code
Alcohol use disorder	F10
Cannabis use disorder	F12
Cocaine use disorder	F14
Nicotine use disorder	F17
Opioid use disorder	F11
Other SUD (composite of hallucinogen related disorder, inhalant related disorder, psychoactive substance disorder, sedative/hypnotics use disorder, and stimulant related disorder)	• Hallucinogen-related disorder: F16 • Inhalant related disorder: F18 • Psychoactive substance disorder: F19 • Sedative/hypnotics use disorder: F13 • Stimulant related disorder: F15
Composite endpoint of all SUDs	F11, F12, F13, F14, F15, F16, F17, F18, F19

ICD-10: the International Classification of Diseases, 10th Revision; SUD, substance use disorder.

Supplementary Table S4 Outcome definitions for Protocols 1 and 2.

Cohorts	Outcome definitions
Protocol 1	**1. Alcohol use disorder:** any outpatient or inpatient diagnosis for alcohol use disorder, excluding remission codes. ICD-10 codes included: F10.10, F10.12, F10.13, F10.14, F10.15, F10.18, F10.19, F10.20, F10.22, F10.23, F10.24, F10.25, F10.26, F10.27, F10.28, F10.29, F10.90, F10.92, F10.93, F10.94, F10.95, F10.96, F10.97, F10.98, F10.99. **2. Cannabis use disorder:** any outpatient or inpatient diagnosis for cannabis use disorder, excluding remission codes. ICD-10 codes included: F12.10, F12.12, F12.13, F12.15, F12.18, F12.19, F12.20, F12.22, F12.23, F12.25, F12.28, F12.29, F12.90, F12.92, F12.93, F12.95, F12.98, F12.99. **3. Cocaine use disorder:** any outpatient or inpatient diagnosis for cocaine use disorder, excluding remission codes. ICD-10 codes included: F14.10, F14.12, F14.13, F14.14, F14.15, F14.18, F14.19, F14.20, F14.22, F14.23, F14.24, F14.25, F14.28, F14.29, F14.90, F14.92, F14.93, F14.94, F14.95, F14.98, F14.99. **4. Nicotine use disorder:** defined using a high-specificity composite requiring either of the following a) Smoking-cessation counseling documented by billing codes for tobacco-cessation counseling (CPT 99406: intermediate, 3–10 minutes; CPT 99407: intensive, >10 minutes), or b) Engagement with specialty smoking-cessation care, defined as both • an outpatient visit to a substance use disorder clinic (individual visit: VA stop code 513; group visit: VA stop code 560), and • receipt of a nicotine-replacement therapy medication (chewing gum, lozenges, transdermal patch, oral inhaler, or nasal spray). **5. Opioid use disorder:** defined using a high-specificity composite requiring both of the following a) Receipt of a medication for opioid use disorder, including buprenorphine, methadone, naloxone, or naltrexone, and b) Engagement with specialty substance use disorder (SUD) care, defined as outpatient encounters coded as visits to SUD clinics—individual visits (VA stop code 513) or group visits (VA stop code 560). These stop codes are assigned only to encounters delivered in designated SUD treatment settings (e.g., opioid substitution therapy, relapse-prevention counseling, or addiction specialty follow-up). **6. Other SUD**: any outpatient or inpatient diagnosis of the following five less prevalent SUDs, excluding remission codes: a) Hallucinogen-related disorder. ICD-10 code: F16.10, F16.12, F16.14, F16.15, F16.18, F16.19, F16.20, F16.22, F16.24, F16.25, F16.28, F16.29, F16.90, F16.92, F16.94, F16.95, F16.98, F16.99. b) Inhalant-related disorder. ICD-10 code: F18.10, F18.12, F18.14, F18.15, F18.17, F18.18, F18.19, F18.20, F18.22, F18.24, F18.25, F18.27, F18.28, F18.29, F18.90, F18.92, F18.94, F18.95, F18.97, F18.98, F18.99. c) Psychoactive-related disorder. ICD-10 code: F19.10, F19.12, F19.13, F19.14, F19.15, F19.16, F19.17, F19.18, F19.19, F19.20, F19.22, F19.23, F19.24, F19.25, F19.26, F19.27, F19.28, F19.29, F19.90, F19.92, F19.93, F19.94, F19.95, F19.96, F19.97, F19.98, F19.99. d) Sedative/hypnotic-related disorder. ICD-10 code: F13.10, F13.12, F13.13, F13.14, F13.15, F13.18, F13.19, F13.20, F13.22, F13.23, F13.24, F13.25, F13.26, F13.27, F13.28, F13.29, F13.90, F13.92, F13.93, F13.94, F13.95, F13.96, F13.97, F13.98, F13.99.

	e) Stimulant-related disorder. ICD-10 code: F15.10, F15.12, F15.13, F15.14, F15.15, F15.18, F15.19, F15.20, F15.22, F15.23, F15.24, F15.25, F15.28, F15.29, F15.90, F15.92, F15.93, F15.94, F15.95, F15.98, F15.99. **7. Composite end point of all SUDs**, defined as the earliest occurrence of any of the above 6 outcomes.
Protocol 2	**Primary outcomes** (1) Emergency department visit for SUD is defined as an emergency department or urgent care visit with a primary diagnosis of SUD (2) Hospitalization for SUD is defined as an inpatient admission with the primary diagnosis code for SUD (admission diagnosis text or the principal discharge ICD-10 diagnosis code). (3) SUD-associated mortality is defined as death within 30 days after a diagnosis code for SUD within the preceding 30 days. (4) composite outcome, defined as the earliest occurrence of any of the above 3 outcomes. **Secondary outcomes** (1) Drug overdose is defined as an emergency department visit, urgent care encounter, or hospital admission with a co-existing diagnosis of drug overdose (ICD-10 code: T39, T40, T41, T42, T43). (2) Suicidal attempt or ideation is defined as an emergency department visit, urgent care encounter, or hospital admission with a co-existing diagnosis of suicidal attempt (ICD-10 code: R45.851) or suicidal ideation (ICD-10 code: T14.91).

CPT: Current Procedural Terminology; ICD-10: the International Classification of Diseases, 10th Revision; SUD, substance use disorder.

Supplementary Table S5 Baseline characteristics of participants in the GLP-1RA and SGLT2i groups before weighting in the primary trial (trial 1) of Protocol 1.

Baseline characteristics	GLP-1RA N=124,001	SGLT2i N=400,816	SMD
Socio-demographic status			
Age in years, Mean (SD)	65.84 (10.96)	68.59 (10.67)	-0.255
Sex, N (%)			
Female	12187 (9.83)	18756 (4.68)	0.199
Male	111814 (90.17)	382060 (95.32)	-0.199
Race, N (%) [a]			
American Indian or Alaska Native	1264 (1.02)	3724 (0.93)	0.009
Asian	1135 (0.92)	5359 (1.34)	-0.040
Black	23046 (18.59)	76399 (19.06)	-0.012
Native Hawaiian or Pacific Islander	1524 (1.23)	4789 (1.19)	0.003
Other	6640 (5.35)	22482 (5.61)	-0.011
White	90392 (72.9)	288063 (71.87)	0.023
Ethnicity, N (%) [a]			
Hispanic, N (%)	7768 (6.26)	29256 (7.3)	-0.041
Non-Hispanic, N (%)	116233 (93.74)	371560 (92.7)	0.041
Rurality			
Highly rural	1573 (1.27)	5651 (1.41)	-0.012
Insular island	146 (0.12)	474 (0.12)	0.000
Rural	44468 (35.86)	144985 (36.17)	-0.006
Urban	77814 (62.75)	249706 (62.3)	0.009
Area deprivation index, mean (SD)	57.01 (18.57)	57.58 (18.64)	-0.031
Health behavior factors			
Smoking status			
Current smoker	15657 (12.63)	54385 (13.57)	-0.028
Former smoker	54080 (43.61)	181768 (45.35)	-0.035
Never smoker	54264 (43.76)	164663 (41.08)	0.054
Laboratory or physiological measurements			
Albuminuria, N (%)	38728 (31.23)	122453 (30.55)	0.015
Average HbA1c within one year, mean (SD)	8.52 (1.65)	8.11 (1.53)	0.258
BMI, mean (SD)	35.8 (7.02)	32.9 (6.31)	0.436
Diastolic blood pressure, mmHg, mean (SD)	75.88 (9.81)	75.96 (9.88)	-0.008
Estimated glomerular filtration rate, mL/min/1.73 m^2, mean (SD)	74.32 (22.15)	73.85 (20.33)	0.022
Low-density lipoprotein, mg/dL, mean (SD)	83.14 (35.47)	82.63 (35.61)	0.014
Systolic blood pressure, mmHg, mean (SD)	133.01 (16.58)	133.75 (17.31)	-0.044
Health care utilisation			
Long-term care facility use, N (%)	1012 (0.82)	2805 (0.7)	0.013
Number of HbA1c measurements, mean (SD)	2.42 (1.27)	2.16 (1.1)	0.219
Number of Medicare hospitalizations, mean (SD)	0.08 (0.43)	0.07 (0.35)	0.047
Number of Medicare outpatient encounters, mean (SD)	0.37 (1.03)	0.33 (0.94)	0.037
Number of blood panel tests, mean (SD)	3.3 (3.52)	3.21 (3.65)	0.026

Number of hospitalizations, mean (SD)	0.04 (0.32)	0.05 (0.35)	-0.022
Number of outpatient encounters, mean (SD)	4.32 (1.41)	4.14 (1.37)	0.125
Number of prescriptions, mean (SD)	14.55 (8.23)	12.46 (7.36)	0.269
Diabetes medications			
DPP-4i, N (%)	25719 (20.74)	75452 (18.82)	0.048
Duration of DPP-4i use in days, Mean (SD)	453.05 (509.68)	552.18 (540.19)	-0.189
Duration of Insulin use in days, Mean (SD)	956.3 (660.71)	946.34 (677.86)	0.015
Duration of metformin use in days, Mean (SD)	785.38 (667.61)	824.54 (667.16)	-0.059
Duration of sulfonylureas use in days, Mean (SD)	718.22 (658.72)	786.76 (660.72)	-0.104
Duration of thiazolidinediones use in days, Mean (SD)	454.03 (550.07)	566.26 (593.57)	-0.196
Insulin, N (%)	73392 (59.19)	129605 (32.34)	0.560
Metformin, N (%)	81958 (66.09)	267287 (66.69)	-0.013
Sulfonylureas, N (%)	40877 (32.97)	135824 (33.89)	-0.020
Thiazolidinediones, N (%)	8012 (6.46)	20073 (5.01)	0.063
Cardiometabolic conditions/medications			
ACE/ARB, N (%)	76840 (61.97)	256907 (64.1)	-0.044
Acute coronary disease, N (%)	2827 (2.28)	17529 (4.37)	-0.117
Acute kidney injury, N (%)	9487 (7.65)	26390 (6.58)	0.041
Atrial fibrillation, N (%)	7790 (6.28)	34415 (8.59)	-0.088
Beta blockers, N (%)	53140 (42.85)	189853 (47.37)	-0.091
Calcium channel blockers, N (%)	37780 (30.47)	128596 (32.08)	-0.035
Diuretics, N (%)	53720 (43.32)	172848 (43.12)	0.004
Heart failure, N (%)	10612 (8.56)	56056 (13.99)	-0.172
Ischemic cardiomyopathy, N (%)	1574 (1.27)	10441 (2.6)	-0.097
Myocardial infarction, N (%)	1270 (1.02)	7931 (1.98)	-0.079
Non-ischemic cardiomyopathy, N (%)	2681 (2.16)	16847 (4.2)	-0.116
Statins, N (%)	98260 (79.24)	327182 (81.63)	-0.060
Stroke, N (%)	3449 (2.78)	13045 (3.25)	-0.028
Transient ischemic attack, N (%)	1380 (1.11)	4857 (1.21)	-0.009
Gastrointestinal conditions			
Abdominal pain, N (%)	5732 (4.62)	16776 (4.19)	0.021
Constipation, N (%)	5111 (4.12)	15289 (3.81)	0.016
Diarrhea, N (%)	4050 (3.27)	12814 (3.2)	0.004
Diverticulosis and diverticulitis, N (%)	3694 (2.98)	13030 (3.25)	-0.016
Dyspepsia, N (%)	454 (0.37)	1809 (0.45)	-0.013
GERD, N (%)	27232 (21.96)	88883 (22.18)	-0.005
Gastritis, N (%)	1487 (1.2)	4708 (1.17)	0.002
Intestinal obstruction and ileus, N (%)	521 (0.42)	1702 (0.42)	-0.001
Nausea, N (%)	2123 (1.71)	5770 (1.44)	0.022
Non-alcoholic fatty liver disease, N (%)	5846 (4.71)	15267 (3.81)	0.045
Ulcerative colitis, N (%)	879 (0.71)	3416 (0.85)	-0.016
Mental health conditions/medications			
Acute stress, N (%)	181 (0.15)	445 (0.11)	0.010
Adjustment disorders, N (%)	5457 (4.4)	14670 (3.66)	0.038
Benzodiazepines, N (%)	7483 (6.03)	18734 (4.67)	0.060

Buprenorphine, N (%)	283 (0.23)	800 (0.2)	0.006
Bupropion, N (%)	8902 (7.18)	20276 (5.06)	0.089
Generalized anxiety disorder, N (%)	13901 (11.21)	38070 (9.5)	0.056
Major depressive disorder recurrent, N (%)	14703 (11.86)	38965 (9.72)	0.069
Methadone, N (%)	189 (0.15)	421 (0.11)	0.013
Mixed anxiety disorder, N (%)	1034 (0.83)	2716 (0.68)	0.018
Mood disorder, N (%)	6222 (5.02)	14673 (3.66)	0.067
Naltrexone, N (%)	804 (0.65)	519 (0.13)	0.083
Panic disorder, N (%)	1136 (0.92)	2922 (0.73)	0.021
Post-traumatic stress disorder, N (%)	22633 (18.25)	63749 (15.9)	0.062
Psychotic disorder, N (%)	1829 (1.47)	5304 (1.32)	0.013
SNRI, N (%)	15830 (12.77)	37370 (9.32)	0.110
SSRI, N (%)	31013 (25.01)	84608 (21.11)	0.093
Sleep aid medications, N (%)	25049 (20.2)	71657 (17.88)	0.059
Sleep disorder, N (%)	54741 (44.15)	152388 (38.02)	0.125
Suicidal ideation, N (%)	760 (0.61)	2064 (0.51)	0.013
TCA, N (%)	1108 (0.89)	2686 (0.67)	0.025
Other covariates			
Bariatric surgery, N (%)	188 (0.15)	181 (0.05)	0.034
Cancer, N (%)	5591 (4.51)	22457 (5.6)	-0.050
HIV, N (%)	505 (0.41)	1472 (0.37)	0.006
Hyperlipidemia, N (%)	52308 (42.18)	157037 (39.18)	0.061
Nutritional deficiencies, N (%)	19974 (16.11)	63485 (15.84)	0.007
Orlistat, N (%)	1137 (0.92)	451 (0.11)	0.113
Phentermine, N (%)	913 (0.74)	281 (0.07)	0.105
Thyroid disorders, N (%)	15897 (12.82)	47871 (11.94)	0.027
Topiramate, N (%)	3037 (2.45)	5460 (1.36)	0.080
Urinary tract infection, N (%)	5460 (4.4)	8566 (2.14)	0.128

[a]. Self-reported race and ethnicity information was collected from electronic health records and used in the study in accordance with the requirement by the funding agency (US Department of Veterans Affairs) and the Office of Management and Budget which defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies.

[b]. Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.

[c]. Duration of continued medication use in days based on pharmacy records within 5 years before T_0 within those with a history of medication use.

Abbreviations: ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; SD, standard deviation; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SMD, standardized mean difference; SNRI, serotonin-Norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

Supplementary Table S6 Association of GLP-1RA initiation with incident substance use disorders at 3 years: Protocol 1.

Outcome	HR	NRD per 1000 persons	Net 3-year risk in GLP-1RA per 1000 persons	Net 3-year risk in SGLT2i per 1000 persons
Alcohol use disorder	0.82 (0.78 to 0.85)	-5.57 (-6.61 to -4.53)	25.25 (24.35 to 26.14)	30.82 (30.28 to 31.36)
Cannabis use disorder	0.86 (0.81 to 0.90)	-2.25 (-3.00 to -1.50)	13.53 (12.88 to 14.18)	15.79 (15.40 to 16.17)
Cocaine use disorder	0.80 (0.72 to 0.88)	-0.97 (-1.37 to -0.57)	3.83 (3.49 to 4.18)	4.80 (4.59 to 5.02)
Nicotine use disorder	0.80 (0.74 to 0.87)	-1.64 (-2.19 to -1.09)	6.58 (6.10 to 7.05)	8.22 (7.93 to 8.51)
Opioid use disorder	0.75 (0.67 to 0.85)	-0.86 (-1.19 to -0.52)	2.59 (2.31 to 2.87)	3.45 (3.27 to 3.63)
Other SUD[a]	0.87 (0.81 to 0.94)	-1.12 (-1.68 to -0.55)	7.81 (7.32 to 8.30)	8.93 (8.64 to 9.21)
Composite endpoint of all SUDs[b]	0.86 (0.83 to 0.88)	-6.61 (-7.95 to -5.26)	40.12 (38.96 to 41.29)	46.73 (46.04 to 47.42)

[a]. Other SUD is composite of hallucinogen related disorder, inhalant related disorder, psychoactive substance disorder, sedative/hypnotics use disorder, and stimulant related disorder.
[b]. Composite endpoint of all SUDs is composite of alcohol use disorder, cannabis use disorder, cocaine use disorder, nicotine use disorder, opioid use disorder, and other SUD.

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; HR, hazard ratio; NRD: net 3-year risk difference; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SUD, substance use disorder; CI, Confidence Intervals.

Protocol 1 comprises seven parallel trials, each excluding participants with a pre-existing SUD: any SUD (trial 1, the primary trial), alcohol (trial 2), cannabis (trial 3), cocaine (trial 4), nicotine (trial 5), opioid (trial 6), and other SUD (hallucinogen-, inhalant-, psychoactive-, sedative/hypnotic-, and stimulant-related disorders) (trial 7). The objective was to evaluate whether initiating a GLP-1RA versus an SGLT2i reduces the incident risk of a specific SUD. For each trial, the analytic cohort was restricted to individuals without a prior diagnosis of that specific SUD at baseline. The absolute values of standardized mean differences after weighting <0.1 indicate good covariate balance.

Supplementary Table S7 Cumulative adherence to treatment strategies over follow-up: Protocol 1.

Follow-up	Percent of adherence (number of adherence/number at risk)	
	GLP-1RA	SGLT2i
At the end of year 1	69.3% (84,512/122,032)	68.1% (267,913/393,157)
At the end of year 2	57.9% (69,906/120,698)	58.1% (225,424/387,810)
At the end of year 3	51.2% (61,238/119,657)	53.6% (205,973/384,489)

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors.

Protocol 1 includes seven parallel trials, each excluding participants with a pre-existing SUD. Trial 1 (the primary trial) presented here excluded participants with any prior SUD and evaluated the composite endpoint of all SUDs.

Supplementary Table S8 Association of sustained adherence to GLP-1RA vs SGLT2i with incident substance use disorders over follow-up: Protocol 1.

Follow-up	Risk ratio	Risk difference per 1000 persons	3-year risk per 1000 persons	
			GLP-1RA	SGLT2i
At the end of year 1	0.78 (0.73 to 0.83)	-4.12 (-5.13 to -3.15)	14.56 (13.85 to 15.31)	18.67 (18.10 to 19.35)
At the end of year 2	0.76 (0.72 to 0.80)	-7.97 (-9.43 to -6.59)	25.37 (24.34 to 26.47)	33.38 (32.52 to 34.24)
At the end of year 3	0.76 (0.73 to 0.80)	-10.79 (-12.70 to -8.84)	34.99 (33.57 to 36.50)	45.78 (44.62 to 46.92)

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SUD, substance use disorder; CI, Confidence Intervals.

The outcome evaluated here is a composite of alcohol use disorder, cannabis use disorder, nicotine use disorder, opioid use disorder, and other SUD.

Protocol 1 includes seven parallel trials, each excluding participants with a pre-existing SUD. Trial 1 (the primary trial) presented here excluded participants with any prior SUD and evaluated the composite endpoint of all SUDs.

Supplementary Table S9 Subgroup analyses of GLP-1RA initiation and incident substance use disorders by demographic and clinical characteristics: Protocol 1.

Category	Subgroup	Sample Size		Hazard ratio	NRD per 1000 persons	Net 3-year risk per 1000 persons	
		GLP-1RA	SGLT2i			GLP-1RA	SGLT2i
Age	≤65	50,289	127,961	0.87 (0.81 to 0.93)	-8.31 (-12.56 to -4.06)	58.33 (56.15 to 60.52)	66.64 (62.97 to 70.30)
	>65	73,712	272,855	0.85 (0.77 to 0.94)	-4.74 (-7.66 to -1.82)	27.57 (26.30 to 28.84)	32.31 (29.67 to 34.94)
Sex	Male	111,814	382,060	0.86 (0.81 to 0.91)	-6.53 (-9.25 to -3.81)	40.42 (39.18 to 41.65)	46.95 (44.51 to 49.38)
	Female	12,187	18,756	0.85 (0.73 to 0.98)	-6.74 (-12.76 to -0.72)	37.63 (33.96 to 41.28)	44.37 (39.52 to 49.18)
Race	White	90,392	288,063	0.88 (0.82 to 0.94)	-4.95 (-7.74 to -2.16)	36.71 (35.39 to 38.02)	41.66 (39.19 to 44.13)
	Black	23,046	76,399	0.83 (0.74 to 0.93)	-10.92 (-17.87 to -3.97)	55.08 (51.89 to 58.26)	66.00 (59.77 to 72.19)
	Other	10,563	36,354	0.82 (0.67 to 1.01)	-8.09 (-16.85 to 0.68)	37.71 (33.81 to 41.59)	45.79 (37.88 to 53.64)
BMI	<30	25,271	140,402	0.83 (0.71 to 0.96)	-8.59 (-15.88 to -1.29)	41.65 (39.00 to 44.29)	50.24 (43.40 to 57.03)
	30-35	36,738	130,539	0.86 (0.77 to 0.96)	-6.25 (-11.04 to -1.46)	39.96 (37.82 to 42.09)	46.21 (41.91 to 50.50)
	>35	61,992	129,875	0.87 (0.81 to 0.93)	-5.87 (-8.88 to -2.87)	39.66 (38.01 to 41.31)	45.54 (43.01 to 48.06)
HbA1c	≤6.5	12,969	51,771	0.77 (0.64 to 0.92)	-14.11 (-24.66 to -3.57)	47.63 (43.32 to 51.92)	61.75 (51.91 to 71.48)
	6.5-8	37,551	164,798	0.83 (0.73 to 0.94)	-7.29 (-12.35 to -2.23)	36.31 (34.25 to 38.36)	43.60 (38.94 to 48.23)
	>8	73,481	184,247	0.88 (0.82 to 0.94)	-5.32 (-8.25 to -2.38)	40.81 (39.30 to 42.31)	46.13 (43.60 to 48.65)
GLP-1RA agent	Semaglutide	70,124	400,816	0.86 (0.83 to 0.90)	-6.61 (-8.42 to -4.80)	43.38 (41.72 to 45.04)	49.99 (49.24 to 50.75)
	Liraglutide	28,007	400,816	0.88 (0.82 to 0.94)	-4.98 (-7.32 to -2.64)	36.99 (34.73 to 39.24)	41.97 (41.34 to 42.60)
	Dulaglutide	20,776	400,816	0.84 (0.77 to 0.90)	-6.67 (-9.30 to -4.04)	34.61 (32.06 to 37.16)	41.28 (40.65 to 41.91)

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; NRD: net 3-year risk difference; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors.

Protocol 1 includes seven parallel trials, each excluding participants with a pre-existing SUD. Trial 1 (the primary trial) presented here excluded participants with any prior SUD and evaluated the composite endpoint of all SUDs.

Supplementary Table S10 Baseline characteristics of participants in the GLP-1RA and SGLT2i groups before weighting in Protocol 2.

Baseline characteristics	GLP-1RA N = 16,768	SGLT2i N = 64,849	SMD
Socio-demographic status			
Age in years, Mean (SD)	61.64 (10.42)	64.65 (10.12)	-0.293
Sex, N (%)			
Female	1572 (9.38)	2745 (4.23)	0.205
Male	15196 (90.63)	62104 (95.77)	-0.205
Race, N (%) [a]			
American Indian or Alaska Native	190 (1.13)	692 (1.07)	0.006
Asian	98 (0.58)	471 (0.73)	-0.018
Black	3743 (22.32)	16512 (25.46)	-0.074
Native Hawaiian or Pacific Islander	185 (1.1)	707 (1.09)	0.001
Other	775 (4.62)	3285 (5.07)	-0.021
White	11777 (70.23)	43182 (66.59)	0.079
Ethnicity, N (%) [a]			
Hispanic, N (%)	1089 (6.49)	4435 (6.84)	-0.014
Non-Hispanic, N (%)	15679 (93.51)	60414 (93.16)	0.014
Rurality			
Highly rural	175 (1.04)	745 (1.15)	-0.010
Insular island	27 (0.16)	87 (0.13)	0.007
Rural	5539 (33.03)	21052 (32.46)	0.012
Urban	11027 (65.76)	42965 (66.25)	-0.010
Area deprivation index, mean (SD) [b]	56.57 (18.68)	57.18 (18.7)	-0.033
Health behavior factors			
Smoking status			
Current smoker	8576 (51.15)	34860 (53.76)	-0.052
Former smoker	5102 (30.43)	18972 (29.26)	0.026
Never smoker	3090 (18.43)	11017 (16.99)	0.038
Laboratory or physiological measurements			
Albuminuria, N (%)	5305 (31.64)	20888 (32.21)	-0.012
Average HbA1c within one year, mean (SD)	8.63 (1.78)	8.09 (1.68)	0.314
BMI, mean (SD)	35.47 (7.04)	32.16 (6.44)	0.491
Diastolic blood pressure, mmHg, mean (SD)	76.94 (10.06)	76.91 (10.2)	0.002
Estimated glomerular filtration rate, mL/min/1.73 m^2, mean (SD)	80.06 (21.84)	78.55 (20.68)	0.071
Low-density lipoprotein, mg/dL, mean (SD)	86.07 (37.16)	85.57 (37.44)	0.013
Systolic blood pressure, mmHg, mean (SD)	131.76 (16.5)	132.28 (17.61)	-0.030
Health care utilisation			
Long-term care facility use, N (%)	424 (2.53)	1482 (2.29)	0.016
Number of HbA1c measurements, mean (SD)	2.61 (1.28)	2.29 (1.13)	0.268
Number of Medicare hospitalizations, mean (SD)	0.08 (0.46)	0.06 (0.4)	0.036
Number of Medicare outpatient encounters, mean (SD)	0.24 (0.82)	0.19 (0.7)	0.061
Number of blood panel tests, mean (SD)	4.74 (5.89)	5.21 (6.73)	-0.074

Number of hospitalizations, mean (SD)	0.18 (0.74)	0.26 (0.94)	-0.092
Number of outpatient encounters, mean (SD)	5.08 (1.38)	4.9 (1.39)	0.129
Number of prescriptions, mean (SD)	18.36 (9.54)	15.67 (8.84)	0.293
Diabetes medications			
DPP-4i, N (%)	3300 (19.68)	10387 (16.02)	0.096
Duration of DPP-4i use in days, Mean (SD) [c]	403.83 (476.71)	487.7 (505.54)	-0.171
Duration of Insulin use in days, Mean (SD) [c]	844.41 (644.82)	787.59 (657.46)	0.087
Duration of metformin use in days, Mean (SD) [c]	712.21 (639.73)	712.96 (637.89)	-0.001
Duration of sulfonylureas use in days, Mean (SD) [c]	619.91 (623.14)	670.05 (629.3)	-0.080
Duration of thiazolidinediones use in days, Mean (SD) [c]	409.34 (498.93)	499.54 (551.46)	-0.172
Insulin, N (%)	9793 (58.4)	20441 (31.52)	0.561
Metformin, N (%)	11926 (71.12)	43710 (67.4)	0.081
Sulfonylureas, N (%)	5496 (32.78)	19419 (29.94)	0.061
Thiazolidinediones, N (%)	978 (5.83)	2699 (4.16)	0.077
Cardiometabolic conditions/medications			
ACE/ARB, N (%)	10457 (62.36)	43103 (66.47)	-0.086
Acute coronary disease, N (%)	668 (3.98)	5993 (9.24)	-0.213
Acute kidney injury, N (%)	2298 (13.7)	10230 (15.78)	-0.058
Atrial fibrillation, N (%)	1085 (6.47)	6532 (10.07)	-0.131
Beta blockers, N (%)	7454 (44.45)	33779 (52.09)	-0.153
Calcium channel blockers, N (%)	5301 (31.61)	21958 (33.86)	-0.048
Diuretics, N (%)	7301 (43.54)	29912 (46.13)	-0.052
Heart failure, N (%)	1886 (11.25)	15102 (23.29)	-0.323
Ischemic cardiomyopathy, N (%)	312 (1.86)	3084 (4.76)	-0.162
Myocardial infarction, N (%)	380 (2.27)	3397 (5.24)	-0.157
Non-ischemic cardiomyopathy, N (%)	580 (3.46)	5400 (8.33)	-0.208
Statins, N (%)	13928 (83.06)	55287 (85.25)	-0.060
Stroke, N (%)	633 (3.78)	3247 (5.01)	-0.060
Transient ischemic attack, N (%)	261 (1.56)	1126 (1.74)	-0.014
Gastrointestinal conditions			
Abdominal pain, N (%)	1276 (7.61)	4785 (7.38)	0.009
Constipation, N (%)	1228 (7.32)	4799 (7.4)	-0.003
Diarrhea, N (%)	868 (5.18)	3342 (5.15)	0.001
Diverticulosis and diverticulitis, N (%)	702 (4.19)	3124 (4.82)	-0.030
Dyspepsia, N (%)	95 (0.57)	567 (0.87)	-0.036
GERD, N (%)	4855 (28.95)	18845 (29.06)	-0.002
Gastritis, N (%)	360 (2.15)	1538 (2.37)	-0.015
Intestinal obstruction and ileus, N (%)	130 (0.78)	579 (0.89)	-0.013
Nausea, N (%)	483 (2.88)	2180 (3.36)	-0.028
Non-alcoholic fatty liver disease, N (%)	1228 (7.32)	3864 (5.96)	0.055
Ulcerative colitis, N (%)	146 (0.87)	534 (0.82)	0.005
Mental health conditions/medications			
Acute stress, N (%)	56 (0.33)	168 (0.26)	0.014

Adjustment disorders, N (%)	1338 (7.98)	4724 (7.28)	0.026
Benzodiazepines, N (%)	1878 (11.2)	6576 (10.14)	0.034
Buprenorphine, N (%)	385 (2.3)	1432 (2.21)	0.006
Bupropion, N (%)	2521 (15.03)	6863 (10.58)	0.134
Generalized anxiety disorder, N (%)	3804 (22.69)	13115 (20.22)	0.060
Major depressive disorder recurrent, N (%)	4154 (24.77)	14788 (22.8)	0.046
Methadone, N (%)	118 (0.7)	322 (0.5)	0.027
Mixed anxiety disorder, N (%)	329 (1.96)	1105 (1.7)	0.019
Mood disorder, N (%)	2311 (13.78)	7121 (10.98)	0.085
Naltrexone, N (%)	605 (3.61)	1843 (2.84)	0.043
Panic disorder, N (%)	412 (2.46)	1152 (1.78)	0.047
Post-traumatic stress disorder, N (%)	5818 (34.7)	19310 (29.78)	0.105
Psychotic disorder, N (%)	876 (5.22)	3129 (4.83)	0.018
SNRI, N (%)	3446 (20.55)	10360 (15.98)	0.119
SSRI, N (%)	6767 (40.36)	22596 (34.84)	0.114
Sleep aid medications, N (%)	4932 (29.41)	17550 (27.06)	0.052
Sleep disorder, N (%)	9420 (56.18)	31080 (47.93)	0.166
Suicidal ideation, N (%)	702 (4.19)	2585 (3.99)	0.010
TCA, N (%)	327 (1.95)	868 (1.34)	0.048
Substance use disorder/medications			
Alcohol use disorder, N (%)	6192 (36.93)	25484 (39.3)	-0.049
Cannabis use disorder, N (%)	1635 (9.75)	7255 (11.19)	-0.047
Cocaine use disorder, N (%)	1257 (7.5)	5577 (8.6)	-0.041
Disulfiram, N (%)	41 (0.24)	99 (0.15)	0.021
Nicotine replacement therapy, N (%)	3655 (21.8)	14408 (22.22)	-0.010
Nicotine use disorder, N (%)	10096 (60.21)	39935 (61.58)	-0.028
Opioid use disorder, N (%)	1402 (8.36)	4435 (6.84)	0.057
Other SUD, N (%) [d]	1257 (7.5)	5047 (7.78)	-0.011
Varenicline, N (%)	865 (5.16)	2587 (3.99)	0.056
Other covariates			
Bariatric surgery, N (%)	29 (0.17)	29 (0.04)	0.039
Cancer, N (%)	775 (4.62)	3677 (5.67)	-0.047
HIV, N (%)	149 (0.89)	546 (0.84)	0.005
Hyperlipidemia, N (%)	7968 (47.52)	27713 (42.73)	0.096
Nutritional deficiencies, N (%)	3556 (21.21)	14084 (21.72)	-0.012
Orlistat, N (%)	213 (1.27)	94 (0.14)	0.135
Phentermine, N (%)	104 (0.62)	49 (0.08)	0.093
Thyroid disorders, N (%)	2020 (12.05)	7054 (10.88)	0.037
Topiramate, N (%)	720 (4.29)	1541 (2.38)	0.107
Urinary tract infection, N (%)	977 (5.83)	2212 (3.41)	0.115

[a]. Self-reported race and ethnicity information was collected from electronic health records and used in the study in accordance with the requirement by the funding agency (US Department of Veterans Affairs) and the Office of Management and Budget which defines minimum standards for maintaining, collecting and presenting data on race and ethnicity for all Federal reporting agencies.

[b]. Area Deprivation Index is a measure of socioeconomic disadvantage, with a range from low to high disadvantage of 0 to 100.
[c]. Duration of continued medication use in days based on pharmacy records within 5 years before T_0 within those with a history of medication use.
[d] Other SUD comprising 5 less prevalent SUDs: hallucinogen-, inhalant-, psychoactive-, sedative/hypnotic-, and stimulant-related disorders.

Abbreviations: ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin-receptor blockers; BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GERD, gastroesophageal reflux disease; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HIV, human immunodeficiency virus; SD, standard deviation; SGLT2i, sodium-glucose co-transporter-2 inhibitor; SMD, standardized mean difference; SNRI, serotonin-Norepinephrine reuptake inhibitors; SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

Supplementary Table S11 Association of GLP-1RA initiation with adverse clinical outcomes at 3 years: Protocol 2.

Outcome	HR	NRD per 1000 persons	Net 3-year risk in GLP-1RA per 1000 persons	Net 3-year risk in SGLT2i per 1000 persons
Primary outcomes				
Emergency department visit for SUD	0.69 (0.61 to 0.78)	-8.92 (-11.59 to -6.25)	20.56 (18.26 to 22.86)	29.48 (28.10 to 30.86)
Hospitalization for SUD	0.74 (0.65 to 0.85)	-6.23 (-8.73 to -3.74)	18.20 (16.03 to 20.36)	24.43 (23.17 to 25.69)
SUD-associated mortality	0.50 (0.32 to 0.79)	-1.52 (-2.32 to -0.72)	1.53 (0.88 to 2.19)	3.05 (2.59 to 3.52)
Composite outcome of ED visit for SUD, hospitalization for SUD, and SUD-associated mortality	0.71 (0.65 to 0.79)	-11.79 (-14.98 to -8.60)	30.03 (27.27 to 32.78)	41.82 (40.19 to 43.45)
Secondary outcomes				
Drug overdose	0.61 (0.42 to 0.88)	-1.49 (-2.43 to -0.55)	2.32 (1.53 to 3.12)	3.81 (3.30 to 4.32)
Suicidal ideation or attempt	0.75 (0.67 to 0.83)	-9.95 (-13.14 to -6.77)	29.93 (27.16 to 32.70)	39.89 (38.29 to 41.49)

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; HR: hazard ratio; NRD: net 3-year risk difference; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SUD, substance use disorder; ED, emergency department; CI, Confidence Intervals.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

Supplementary Table S12 Cumulative adherence to treatment strategies over follow-up: Protocol 2.

Follow-up	Percent of adherence (number of adherence/number at risk)	
	GLP-1RA	SGLT2i
At the end of year 1	66.4% (10,969/16,532)	65.0% (41,233/63,430)
At the end of year 2	54.0% (8,864/16,400)	54.5% (34,259/62,810)
At the end of year 3	47.8% (7,809/16,325)	50.2% (31,341/62,463)

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

Supplementary Table S13 Association of sustained adherence to GLP-1RA vs SGLT2i with adverse clinical outcomes over follow-up: Protocol 2.

Follow-up	Risk ratio (95% CI)	Risk difference per 1000 persons	3-year risk per 1000 persons	
			GLP-1RA	SGLT2i
At the end of year 1	0.55 (0.46 to 0.66)	-9.28 (-12.07 to -6.71)	11.37 (9.75 to 13.28)	20.68 (19.06 to 22.70)
At the end of year 2	0.57 (0.48 to 0.66)	-14.17 (-17.86 to -10.57)	18.50 (16.05 to 21.39)	32.78 (30.45 to 35.16)
At the end of year 3	0.54 (0.46 to 0.64)	-19.25 (-23.91 to -14.51)	22.78 (19.69 to 26.60)	42.04 (39.09 to 45.17)

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; HR: hazard ratio; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; CI, Confidence Intervals.

The outcome evaluated here is a three-point composite outcome of emergency department visit for SUD, hospitalization for SUD, and SUD-associated mortality.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

Supplementary Table S14 Association of GLP-1RA initiation with the three-point composite adverse clinical outcome among participants with pre-existing substance use disorders at 3 years: Protocol 2.

Pre-existing SUD	N in GLP-1RA	N in SGLT2i	HR [b]	NRD per 1,000 persons [b]	Net 3-year risk per 1000 persons in GLP-1RA[b]	Net 3-year risk per 1000 persons in SGLT2i [b]
Alcohol use disorder	6,192	25,484	0.72 (0.64 to 0.81)	-22.49 (-29.75 to -15.23)	60.04 (53.68 to 66.36)	82.53 (78.93 to 86.11)
Cocaine use disorder	1,257	5,577	0.78 (0.67 to 0.92)	-40.70 (-65.01 to -16.39)	165.97 (143.99 to 187.38)	206.67 (195.36 to 217.82)
Opioid use disorder	1,402	4,435	0.70 (0.56 to 0.87)	-30.57 (-47.96 to -13.17)	75.41 (60.69 to 89.91)	105.98 (96.35 to 115.51)
Other SUD[a]	1,257	5,047	0.74 (0.62 to 0.87)	-47.08 (-70.52 to -23.63)	145.58 (124.76 to 165.90)	192.65 (181.06 to 204.08)

a. Other SUD is composite of hallucinogen related disorder, inhalant related disorder, psychoactive substance disorder, sedative/hypnotics use disorder, and stimulant related disorder.

[b] The outcome investigated here is a three-point composite outcome including emergency department visit for substance use disorder (SUD), hospitalization for SUD, and SUD-associated mortality.

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; HR: hazard ratio; NRD: net 3-year risk difference; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SUD, substance use disorder; CI, Confidence Intervals.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

Supplementary Table S15 Sensitivity analyses for composite outcomes.

Models	HR	
	Protocol 1 the primary trial	**Protocol 2**
Main model	0.86 (0.83 to 0.88)	0.71 (0.65 to 0.79)
1. Doubly robust	0.86 (0.83 to 0.90)	0.71 (0.63 to 0.81)
2. Overlap weighting	0.85 (0.81 to 0.90)	0.71 (0.61 to 0.83)
3. Additional adjustment for high-dimensional covariates		
Additional 100 high-dimensional covariates	0.86 (0.83 to 0.89)	0.71 (0.64 to 0.79)
Additional 200 high-dimensional covariates	0.86 (0.83 to 0.89)	0.72 (0.65 to 0.80)
Additional 300 high-dimensional covariates	0.85 (0.82 to 0.88)	0.73 (0.65 to 0.81)
4. Different target population		
Overall (average treatment effect)	0.84 (0.81 to 0.87)	0.69 (0.62 to 0.77)
Control (average treatment effect on the control)	0.83 (0.81 to 0.85)	0.69 (0.64 to 0.73)
5. Different truncation percentiles		
No truncation	0.85 (0.81 to 0.88)	0.72 (0.64 to 0.81)
0.1th and 99.9th	0.86 (0.82 to 0.89)	0.71 (0.63 to 0.80)
0.5th and 99.5th	0.86 (0.82 to 0.89)	0.71 (0.63 to 0.81)
1.5th and 98.5th	0.85 (0.82 to 0.89)	0.71 (0.63 to 0.81)
6. Different trimming percentiles		
0.1th and 99.9th	0.85 (0.82 to 0.89)	0.72 (0.64 to 0.81)
0.5th and 99.5th	0.86 (0.82 to 0.89)	0.71 (0.63 to 0.80)
1.5th and 98.5th	0.85 (0.81 to 0.88)	0.72 (0.63 to 0.82)
7. Remove participants with prior use of GLP-1RA or SGLT2i before T_0		
Remove prior use in 2 years [a]	0.85 (0.83 to 0.88)	0.71 (0.64 to 0.78)
Remove prior use in 3 years [b]	0.85 (0.83 to 0.88)	0.71 (0.64 to 0.78)
Remove all prior use [c]	0.85 (0.83 to 0.88)	0.72 (0.64 to 0.79)
8. Analysis based on data with complete covariates [d]	0.86 (0.83 to 0.90)	0.69 (0.62 to 0.77)
9. Different control: sulphonylureas [e]	0.88 (0.85 to 0.91)	0.64 (0.58 to 0.70)

[a]. This removes 0.11% of the sample from participants without pre-existing SUD and 0.08% of the sample from participants with pre-existing SUD.
[b]. This removes 0.21% of the sample from participants without pre-existing SUD and 0.13% of the sample from participants with pre-existing SUD.
[c]. This removes 0.64% of the sample from participants without pre-existing SUD and 0.52% of the sample from participants with pre-existing SUD.
[d]. This includes 87.3% of the entire sample from participants without pre-existing SUD and 91.9% of the sample from participants with pre-existing SUD.
[e]. N=159,308 for GLP-1RA and N=217,138 for the control among participants without pre-existing SUD; N=22,336 for GLP-1RA, N=35,391 for the control among participants with pre-existing SUD.

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; HR, hazard ratio; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SUD, substance use disorder.

Protocol 1 includes seven parallel trials, each excluding participants with a pre-existing SUD. Trial 1 (the primary trial) presented here excluded participants with any prior SUD.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.

Supplementary Table S16 Negative outcome control analyses.

Outcomes	HR	NRD per 1,000 persons	Net 3-year risk per 1000 persons in GLP-1RA	Net 3-year risk per 1000 persons in SGLT2i
Protocol 1 the primary trial				
Benign prostatic hyperplasia	1.00 (0.98 to 1.02)	0.00 (-2.32 to 2.32)	137.23 (135.18 to 139.27)	137.23 (136.10 to 138.35)
Emergency department visit for superficial injury of neck/trunk	1.03 (0.95 to 1.12)	0.21 (-0.36 to 0.78)	7.21 (6.70 to 7.71)	6.99 (6.72 to 7.27)
Headache	1.03 (1.00 to 1.05)	1.69 (0.00 to 3.38)	66.61 (65.12 to 68.10)	64.92 (64.12 to 65.73)
Uptake of respiratory syncytial virus vaccine	1.01 (0.99 to 1.04)	1.08 (-0.91 to 3.07)	91.65 (89.90 to 93.40)	90.58 (89.62 to 91.53)
Protocol 2				
Benign prostatic hyperplasia	0.99 (0.94 to 1.04)	-1.14 (-7.24 to 4.97)	127.91 (122.42 to 133.36)	129.04 (126.27 to 131.80)
Emergency department visit for superficial injury of neck/trunk	0.92 (0.77 to 1.09)	-0.96 (-2.85 to 0.94)	10.63 (8.95 to 12.32)	11.59 (10.70 to 12.47)
Headache	0.97 (0.91 to 1.03)	-2.35 (-7.55 to 2.85)	88.08 (83.42 to 92.73)	90.44 (88.07 to 92.80)
Uptake of respiratory syncytial virus vaccine	1.02 (0.96 to 1.09)	1.84 (-3.30 to 6.98)	82.73 (78.10 to 87.35)	80.89 (78.60 to 83.17)

GLP-1RA, Glucagon-Like Peptide-1 Receptor Agonists; HR: hazard ratio; NRD: net 3-year risk difference; SGLT2i, Sodium-Glucose Cotransporter 2 Inhibitors; SUD, substance use disorder.

Protocol 1 includes seven parallel trials, each excluding participants with a pre-existing SUD. Trial 1 (the primary trial) presented here excluded participants with any prior SUD.

Protocol 2 is a single trial that enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1RA versus an SGLT2i on the risk of SUD-associated adverse clinical outcomes.