Glucagon-like peptide-1 receptor agonists and risk of substance use disorders among US veterans with type 2 diabetes: cohort study

Miao Cai,[1,2] Taeyoung Choi,[1,2,3] Yan Xie,[1,2,3,4] Ziyad Al-Aly[1,2,5,6,7]

For numbered affiliations see end of the article

Correspondence to: Z Al-Aly VA Saint Louis Health Care System, Saint Louis, MO 63106, USA
zalaly@gmail.com
(or @zalaly on X;
ORCID 0000-0002-2600-0434)

Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2026;392:e086886
http://dx.doi.org/10.1136/bmj-2025-086886

Accepted: 26 January 2026

ABSTRACT

OBJECTIVES

To investigate whether initiation of glucagon-like peptide-1 (GLP-1) receptor agonists is associated with both reduced risks of incident alcohol, cannabis, cocaine, nicotine, opioid, and other substance use disorders (SUDs) in people with no history of SUDs (protocol 1) and with reduced risk of SUD related adverse clinical outcomes among people with a pre-existing SUD (protocol 2).

DESIGN

Emulation of eight parallel, new user, active comparator target trials using electronic health records: seven trials for each incident SUD outcome (protocol 1) and one trial for adverse outcomes in people with pre-existing SUD (protocol 2).

SETTING

US Department of Veterans Affairs.

PARTICIPANTS

From a base population of 606 434 US veterans with type 2 diabetes, participants were assigned to one of the two protocols and followed for up to three years. Trial 1 (primary trial) of protocol 1 included 524 817 initiators of GLP-1 receptor agonists (n=124 001) or sodium-glucose cotransporter-2 (SGLT-2) inhibitors (n=400 816). Protocol 2 included 81 617 initiators of GLP-1 receptor agonists (n=16 768) and SGLT-2 inhibitors (n=64 849).

MAIN OUTCOME MEASURES

Incident outcomes were alcohol, cannabis, cocaine, nicotine, opioid, other SUDs, and a composite of these outcomes. Adverse outcomes among participants with pre-existing SUDs included SUD related emergency department visits, SUD related hospital admissions, and SUD related mortality, and drug overdose and suicidal ideation or attempt. Hazard ratios and net three year risk difference (NRD) per 1000 people were reported based on inverse probability weighted (standardised mortality ratio weighted) cause specific Cox survival models.

RESULTS

Compared with initiation of SGLT-2 inhibitors, initiation of GLP-1 receptor agonists was associated with reduced risk of disorders related to alcohol use (hazard ratio 0.82 (95% confidence interval (CI) 0.78 to 0.85); NRD per 1000 people −5.57 (−6.61 to −4.53)), cannabis use (0.86 (0.81 to 0.90), NRD −2.25 (−3.00 to −1.50)), cocaine use (0.80 (0.72 to 0.88), NRD −0.97 (−1.37 to −0.57)), nicotine use (0.80 (0.74 to 0.87), NRD −1.64 (−2.19 to −1.09)), and opioid use (0.75 (0.67 to 0.85), NRD −0.86 (−1.19 to −0.52)), and other SUDs (0.87 (0.81 to 0.94), NRD −1.12 (−1.68 to −0.55)) and composite outcome of all incident SUDs (0.86 (0.83 to 0.88), NRD −6.61 (−7.95 to −5.26)). Among people with pre-existing SUDs, initiation of GLP-1 receptor agonists was associated with reduced risk of SUD related emergency department visits (0.69 (0.61 to 0.78), NRD −8.92 (−11.59 to −6.25)), SUD related hospital admissions (0.74 (0.65 to 0.85), NRD −6.23 (−8.73 to −3.74)), and SUD related mortality (0.50 (0.32 to 0.79), NRD −1.52 (−2.32 to −0.72)), and drug overdose (0.61 (0.42 to 0.88), NRD −1.49 (−2.43 to −0.55)) and suicidal ideation or attempt (0.75 (0.67 to 0.83), NRD −9.95 (−13.14 to −6.77)). Analyses of treatment adherence showed directionally consistent results with analyses of treatment initiation for both incident SUDs and adverse outcomes among participants with pre-existing SUDs.

CONCLUSIONS

Use of GLP-1 receptor agonists was consistently associated with reduced risks of developing various incident SUDs, suggesting a broad preventive effect across multiple substance types. Use was also associated with reduced risks of adverse clinical outcomes in people with pre-existing SUDs. These observational data suggest a potential role for GLP-1 receptor agonists in both the prevention and the treatment of various SUDs, warranting further evaluation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Preclinical studies suggest glucagon-like peptide-1 (GLP-1) receptor agonists act on the mesolimbic reward pathways and reduce drug reinforcement in animal models of alcohol, nicotine, cocaine, and opioid use disorders

Observational studies in humans link GLP-1 receptor agonist use to lower risk of incident and recurrent alcohol, tobacco, and cannabis use disorders, but evidence for other substances is lacking

Large studies evaluating GLP-1 receptor agonists for preventing substance use disorders (SUDs) or improving hard clinical outcomes in people with established SUDs are lacking

WHAT THIS STUDY ADDS

GLP-1 receptor agonists were associated with lower risks of incident alcohol, cannabis, cocaine, nicotine, opioid, and other SUDs, suggesting potential preventive effects across a broad range of substances

In participants with pre-existing SUDs, GLP-1 receptor agonists were associated with reduced risks of SUD related emergency department visits, hospital admissions, and mortality, and drug overdoses and suicidal behaviours

Introduction

Evidence from observational studies shows that use of glucagon-like peptide-1 (GLP-1) receptor agonists is associated with various health benefits,[1] including

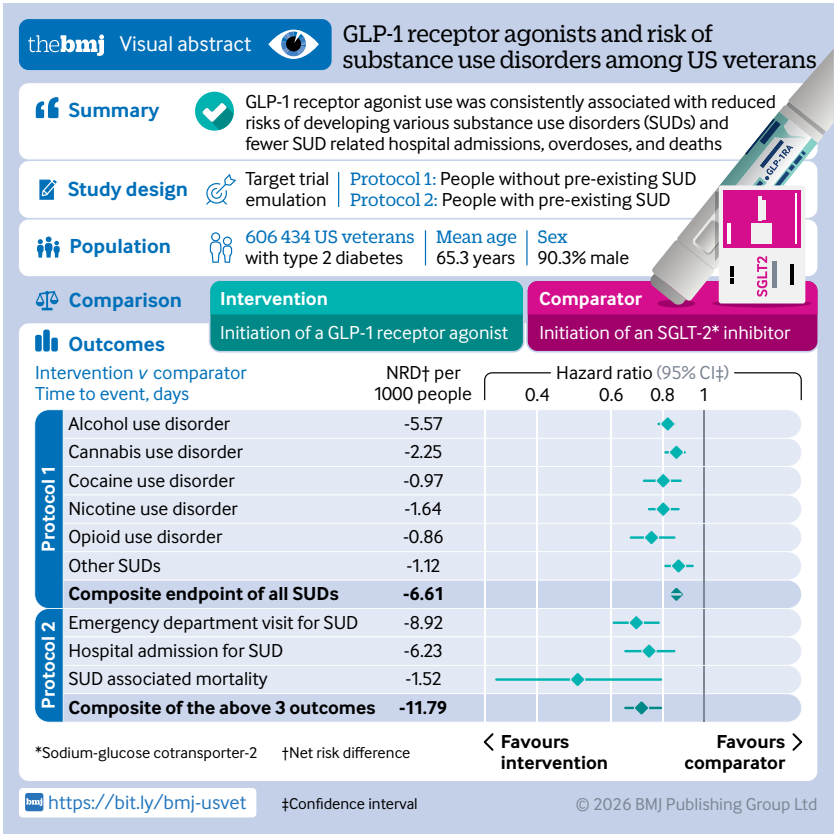
reduced risks of incident alcohol use disorder[2 3] and incident cannabis use disorder[4] and reduced frequency of healthcare encounters for tobacco use disorder.[5] However, much less is known about the association between GLP-1 receptor agonists and risks of developing other substance use disorders (SUDs), such as opioid use disorder and stimulant use disorder.[6]

Observational studies within populations with a pre-existing SUD have also emerged suggesting that use of GLP-1 receptor agonists is associated with reduced risks of adverse events such as opioid overdose,[7 8] alcohol intoxication,[7] and risk of hospital admission for alcohol use disorder.[9] While the evidence base is growing, it does not comprehensively include all common SUDs.

Evidence from randomised clinical trials also remains preliminary, with small trials showing promising but mixed results[10 11] and some showing reduced alcohol craving and consumption outcomes in people with alcohol use disorder[12] and reduced alcohol intake in smokers.[13] One randomised controlled trial showed no statistically significant reduction in heavy drinking except in people with a body mass index (BMI) >30.[14] Small randomised controlled trials evaluating the effect of GLP-1 receptor agonists on promoting abstinence during smoking cessation also suggest mixed results, with one study showing no effect on abstinence rates[15] and another showing improved cigarette abstinence.[16]

Although the growing popularity of GLP-1 receptor agonists[17] and the intense interest in their neuropsychiatric effects[18] have resulted in a surge of studies investigating the potential connections between these drugs and SUDs, important knowledge gaps persist.[18-21] Existing observational and randomised studies have largely focused on the risk of developing one SUD or at most two specific SUDs. Consequently, a comprehensive understanding of the effects of GLP-1 receptor agonists on risk of developing all common SUDs remains elusive. Notably, studies that simultaneously assess the risk of incident SUDs across a range of substances and the potential for adverse clinical consequences in individuals with pre-existing SUDs are absent. Analyses of electronic health records, providing a comprehensive assessment of the full spectrum of SUD risks associated with use of GLP-1 receptor agonists, including nuanced insights into differential risks across various substances and the impact on clinically relevant outcomes in populations with established SUDs, would considerably enhance the existing knowledge base.

We used the healthcare databases of the US Department of Veterans Affairs to emulate eight new user, active comparator target trials under two main protocols, both comparing the treatment strategies of initiating a GLP-1 receptor agonist versus a sodium-glucose cotransporter-2 (SGLT-2) inhibitor. Protocol 1 comprised seven distinct trials (investigating seven separate SUDs), each in a target population of veterans with type 2 diabetes without a history of a specific SUD, assessing the outcome of that specific incident SUD. Protocol 2 was a single trial in a target population of patients with a pre-existing SUD, assessing the outcome of adverse SUD related clinical events. For all eight trials, we estimated the causal contrast (average treatment effect among treated) as the net three year risk difference (NRD) and hazard ratio over a three year follow-up period.



Methods

Target trial emulation

We conducted an observational study emulating a set of eight parallel, pragmatic, active comparator, new user target trials using US Department of Veterans Affairs electronic health records. These emulated trials followed two distinct protocols, with detailed design features (see supplementary tables S1 and S2). Protocol 1 evaluated incident SUDs in those without a history of an SUD; protocol 2 evaluated subsequent adverse outcomes in those with pre-existing SUDs.

Protocol 1

Protocol 1 comprised seven parallel trials, one for each SUD outcome of interest, including alcohol, cannabis, cocaine, nicotine, opioid, other SUD (disorders related to hallucinogens, inhalants, psychoactive drugs, sedatives or hypnotics, and stimulants), and a composite of all these SUDs. The objective was to evaluate whether initiating a GLP-1 receptor agonist versus an SGLT-2 inhibitor reduces the incident risk of a specific SUD. For each trial, the analytical cohort was restricted to individuals without a previous diagnosis of that specific SUD at baseline. This design resulted

in seven partially overlapping but distinct analytical cohorts (trial 1 (the primary trial) for the composite SUD, and trials 2-7 for alcohol, cannabis, cocaine, nicotine, opioid, and other SUD), aligning the at risk population with the outcome for each trial.

Protocol 2

In protocol 2, the single trial enrolled participants with a pre-existing SUD to evaluate the effectiveness of initiating a GLP-1 receptor agonist versus an SGLT-2 inhibitor on the risk of SUD associated adverse clinical outcomes.

Supplementary tables S1 and S2 provide the detailed design features of the seven target trials in protocol 1 and the single target trial in protocol 2 and their emulations.

Setting

The study was conducted using electronic health records from the US Department of Veterans Affairs, the largest integrated healthcare system in the US, consisting of 170 medical centres and 1193 outpatient clinics.[22-25] All enrolled veterans received a comprehensive package of medical benefits, including prescription coverage for GLP-1 receptor agonists.

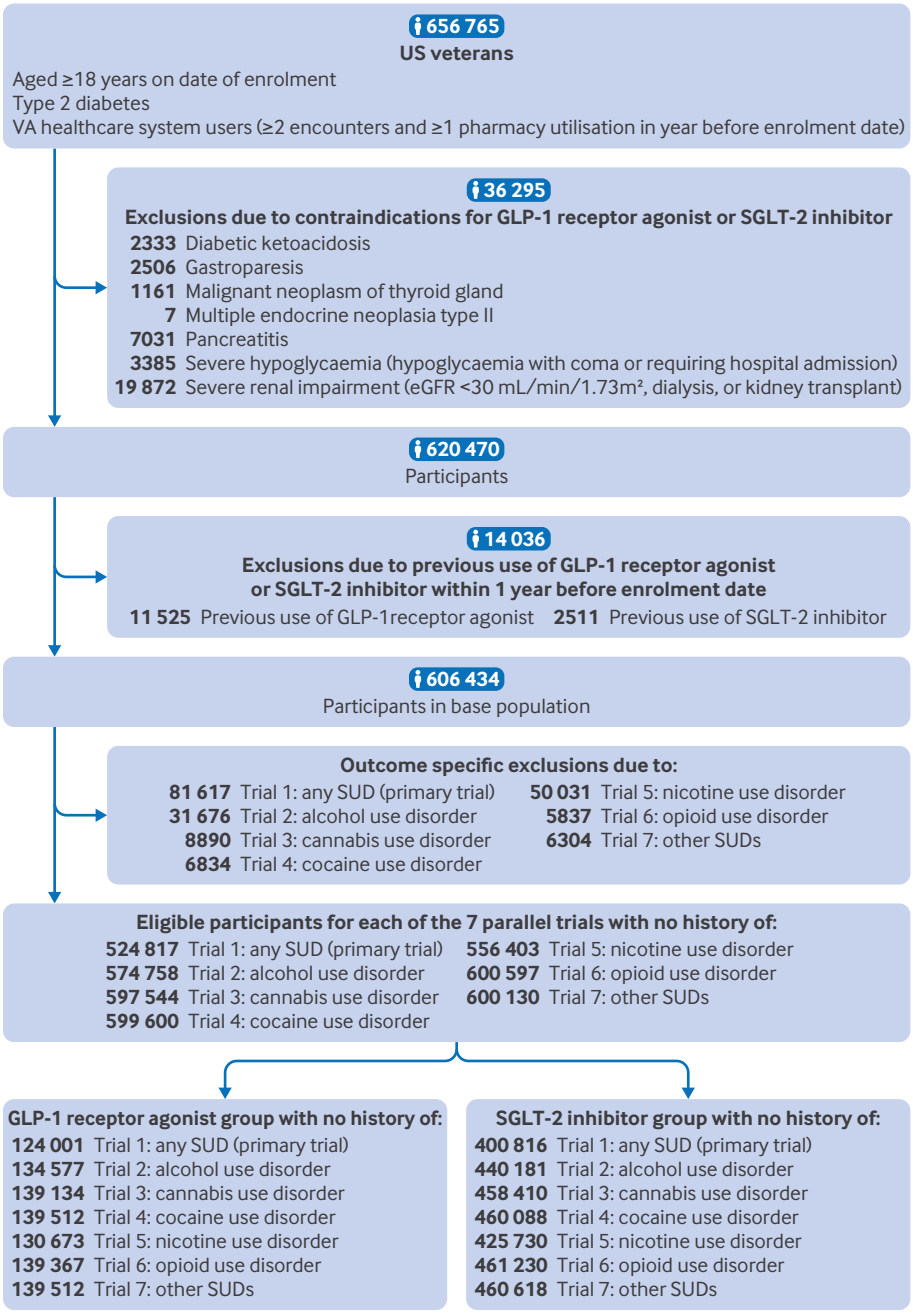


Fig 1 | Flowchart showing selection of study participants in protocol 1 across seven outcome specific trials. eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2; SUD=substance use disorder; VA=Veterans Affairs

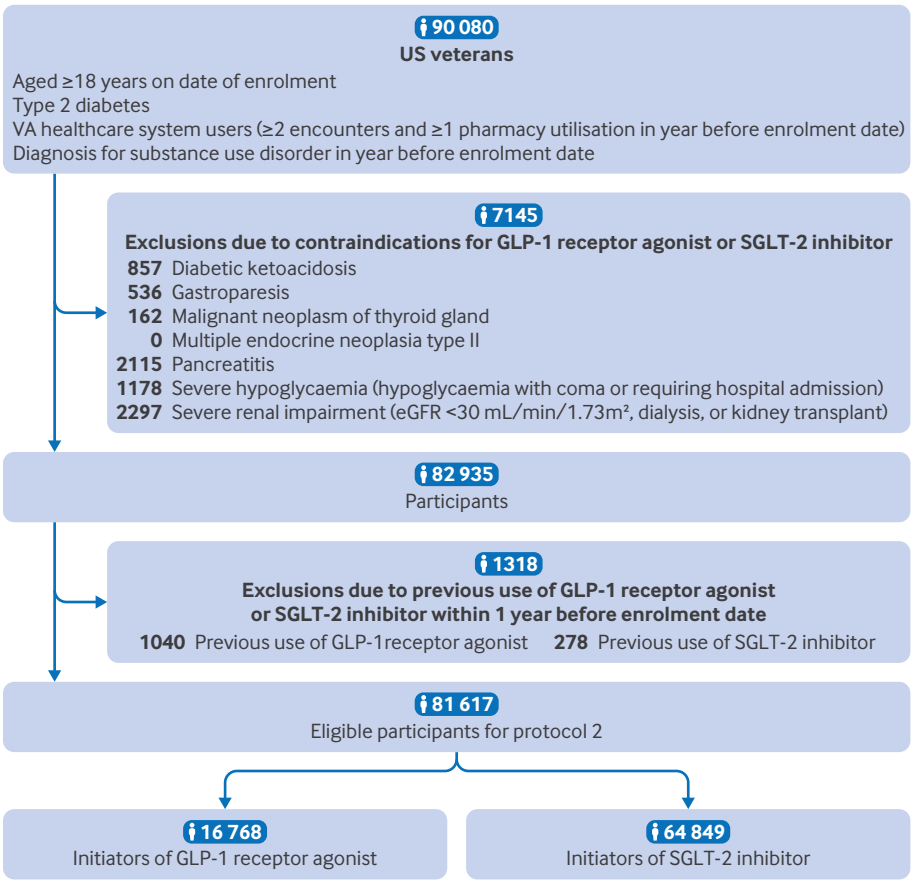


Fig 2 | Flowchart showing selection of study participants in protocol 2. eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2; SUD=substance use disorder; VA=Veterans Affairs

Data sources

The study was based on multiple datasets in the VA (Veterans Affairs) Corporate Data Warehouse (CDW). Data were drawn from multiple domains, including Outpatient Encounters and Inpatient Encounters, Outpatient Pharmacy, Laboratory Results, Vital Signs, Patient domain, VA Vital Status, and health factors.[26-28] Additionally, Medicare data from VA Information Resource Center were used to capture healthcare utilisation outside of the Veterans Affairs system.[29] The area deprivation index, derived from participants' residential addresses, was also included to represent neighbourhood level socioeconomic status.

Cohort construction

Protocol 1

Veterans who were eligible for inclusion in the first protocol were aged 18 years or older, had a diagnosis of type 2 diabetes, and were active users of the Veterans Affairs healthcare system (defined as having ≥2 encounters and ≥1 pharmacy utilisation in the year before the enrolment date) (n=656 765). We first excluded 36 295 people with recorded contraindications for either drug class in the previous year, including diabetic ketoacidosis, gastroparesis, malignant neoplasm of the thyroid gland, multiple endocrine neoplasia type II, pancreatitis, severe hypoglycaemia, or severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73m^2, dialysis, or kidney transplant), yielding 620 470 participants. We then excluded 14 036 people who had any previous use of either a GLP-1 receptor agonist or an SGLT-2 inhibitor in the year before the enrolment date, yielding 606 434 participants.

This final cohort of 606 434 new users served as the base population for seven distinct trials, one for each of the prespecified SUD outcomes. To create an analytical cohort for each trial, we applied an outcome specific exclusion: individuals with a previous diagnosis of the SUD being evaluated were removed from the base population. For example, trial 2 examining incident alcohol use disorder excluded all participants with a history of alcohol use disorder. This yielded seven analytical trials (one for each SUD outcome). These cohorts were largely overlapping, differing only by the outcome specific exclusion (fig 1). Supplementary table S3 shows the definitions of pre-existing SUDs.

Protocol 2

Veterans who were eligible for inclusion in protocol 2 were aged 18 years or older, had a diagnosis of type 2 diabetes, were active users of the Veterans Affairs

healthcare system (as defined in protocol 1), and had a diagnosis for SUD in the year before enrolment date (n=90 080). We first excluded 7145 people with recorded contraindications for either drug class (the same definition as for protocol 1) in the previous year, yielding 82 935 participants. We then excluded 1318 people who had any previous use of either a GLP-1 receptor agonist or an SGLT-2 inhibitor in the year before the enrolment date, yielding 81 617 eligible users with 16 768 in the GLP-1 receptor agonist arm and 64 849 in the SGLT-2 inhibitor arm (fig 2).

Treatment groups

Drug use was defined based on filled outpatient pharmacy records, as initiators of GLP-1 receptor agonists and initiators of SGLT-2 inhibitors. GLP-1 receptor agonist class (n=140 769) comprised albiglutide (n=2155, 1.53%), dulaglutide (n=23 385, 16.61%), exenatide (n=2146, 1.52%), liraglutide (n=31 619, 22.46%), lixisenatide (n=12, 0.01%), semaglutide (n=80 007, 56.84%), and tirzepatide (n=1445, 1.03%), and the SGLT-2 inhibitor class (n=465 665) included empagliflozin (n=465 019, 99.86%) and bexagliflozin, canagliflozin, dapagliflozin, ertugliflozin, and sotagliflozin (n=646, together accounted for 0.14%). The beginning of follow-up and censoring began on the date of the first filled prescription for either drug class.

Outcomes

To characterise the association between GLP-1 receptor agonists and the risk of incident SUDs, we evaluated seven incident SUD outcomes identified from ICD-10 (international classification of diseases, 10th revision) diagnosis codes in inpatient or outpatient diagnosis domains,[30 31] counselling services documented through Current Procedural Terminology codes,[5] outpatient encounters for specialty care,[32] and pharmacotherapy prescriptions,[33] as appropriate for each outcome. These outcomes included disorders related to use of alcohol, cannabis, cocaine, nicotine, and opioids, as well as a composite other SUD outcome comprising five less prevalent but clinically meaningful SUDs in the cohort to ensure adequate representation of less common disorders: disorders related to hallucinogens, inhalants, psychoactive drugs, sedatives or hypnotics, and stimulants.[34 35] We additionally constructed a composite SUD outcome that included all the six outcomes. For each outcome, we assessed the risk of incident SUD among participants with no history of that specific disorder in the one year before the date of the first filled prescription.

To investigate the relation between GLP-1 receptor agonists and risk of subsequent adverse clinical events among individuals with pre-existing SUDs,[36-38] we specified a list of primary outcomes, including SUD related emergency department visits, SUD related hospital admissions, and SUD related mortality. Emergency department visits for SUD were defined as encounters with the principal ICD-10 diagnosis code indicating SUD. Hospital admission for SUDs was defined by the presence of SUD terms in the admission diagnosis text or the principal discharge ICD-10 diagnosis code corresponding to a SUD. A composite outcome encompassing the three SUD related primary outcomes (emergency department visits, hospital admissions, and mortality) was also specified. Secondary outcomes included drug overdose and suicidal ideation or attempt, which were identified based on ICD-10 diagnosis codes from outpatient or inpatient diagnosis domains. Supplementary table S4 provides details of the outcome definitions.

Covariates

This study captured two sets of covariates: baseline and time varying.

We prespecified a set of baseline covariates for each of the eight emulated trials based on previous knowledge and guided by a causal framework and directed acyclic graphs (see supplementary figure S1 for protocol 1 and supplementary figure S2 for protocol 2).[39-47] For readability, the directed acyclic graphs in supplementary figures S1 and S2 depict covariates grouped into conceptual domains; however, covariates were operationalised and entered as individual variables in the propensity score models, and (for the adherence analyses) in the time varying censoring models, as detailed in the full list of covariates provided in the supplementary methods. Covariate selection was optimised for each trial's specific drug use-outcome pair. The comprehensive pool of potential baseline confounders we drew from for these models consisted of six categories: sociodemographic status, health behaviour, laboratory or physiological measurements, healthcare utilisation, antidiabetic drug use, and comorbidities. Covariates were measured within one year before the date of first filled prescription for either drug class unless specified otherwise. For variables with repeated measurement, we selected the measurement before and closest to the date of first filled prescription for either drug class. The supplementary methods provide details of baseline covariates.

To estimate the treatment adherence effect for the composite endpoints during follow-up, we constructed marginal structural models accounting for both baseline and time varying covariates through inverse probability of censoring weights. The time varying covariates were selected based on their association with treatment discontinuation and were collected from the beginning of follow-up (the date of the first filled prescription for either drug class) until the end of each 90 day time interval: days 1 to 90, days 91 to 180, and so on up to days 991 to 1080, for a total of 12 time varying intervals during three years of follow-up. We updated the values of baseline covariates at each 90 day interval during follow-up and complemented them with 43 additional covariates relevant in the time varying context. These additional time varying variables included three categories associated with non-adherence to GLP-1 receptor agonists during follow-up[48-50]: social stressors (10 covariates),

veterans affairs appointment status (five covariates), and outpatient care engagement (28 covariates). The supplementary methods provide details of time varying covariates.

Missing values occurred in several baseline covariates in the overall cohort (n=606 434): 23 084 (3.81%) BMI, 790 (0.13%) diastolic and systolic blood pressure, 4037 (0.67%) estimated glomerular filtration rate, 22 622 (3.73%) glycated haemoglobin (HbA_{1c}), 4499 (0.74%) low density lipoprotein cholesterol measurements, and 26 408 (4.35%) smoking status. We applied multiple imputation using fully conditional specification with chained equations to create 10 imputed datasets, where missing values for each variable were imputed using predictive mean matching method conditional on the covariates.[51] Estimates from the 10 imputed datasets were pooled using Rubin's rules. Continuous variables, including area deprivation index, age, BMI, diastolic and systolic blood pressure, estimated glomerular filtration rate, HbA_{1c}, high density lipoprotein cholesterol, and low density lipoprotein cholesterol were adjusted in the form of restricted cubic splines in propensity score models, with knots at 5th, 35th, 65th, and 95th centiles.[52]

Statistical analysis

Baseline characteristics for GLP-1 receptor agonist and SGLT-2 inhibitor groups are presented as means and standard deviations, and frequencies and proportions as appropriate in protocol 1 and protocol 2. Balance between the two groups was assessed using standardised mean differences, with absolute values below 0.1 indicating good balance of covariates.[53]

The primary treatment initiation (as initiated) analysis estimated the effect of initiating GLP-1 receptor agonists versus initiating SGLT-2 inhibitors among initiators of GLP-1 receptor agonists; this analysis estimated the average treatment effect among those treated, with treated defined as those who had initiated GLP-1 receptor agonists. Standardised mortality ratio weighting was used to balance baseline characteristics between groups in the trials of participants in protocol 1 and in protocol 2. The probability of a participant initiating GLP-1 receptor agonists was estimated as the propensity score using logistic regression based on the prespecified covariates. We then constructed standardised mortality ratio weights to estimate the average treatment effect on those treated, with weights defined as 1 for participants in the GLP-1 receptor agonist group and as propensity score / (1−propensity score) for those in the SGLT-2 inhibitor group. The weights were then applied to Cox survival models to estimate the adjusted hazard ratio, net three year risk per 1000 people, and NRD per 1000 people. Because we aimed to estimate the causal effect of initiating GLP-1 receptor agonists on SUD outcomes, we used cause specific hazard models for all non-death outcomes.[54] In this framework, deaths remove individuals from the risk set and were therefore treated as censoring events. This approach aligns with the causal question of interest—whether initiating GLP-1 receptor agonists versus SGLT-2 inhibitors changes the hazard of SUD conditional on being alive. In contrast, SUD associated mortality was modelled using a standard Cox proportional hazard models because death is the event of interest. To complement the primary cause specific hazard models, we also evaluated the risks of the composite endpoints using the Fine and Gray model and separately a cause specific hazard model with time varying inverse probability of death censoring weights in both protocol 1 and protocol 2.

We conducted a complementary analysis to estimate the effect of treatment adherence on the composite outcomes under sustained adherence to the initiated treatment strategy during the three year follow-up in both protocol 1 and protocol 2. Participants who deviated from their initiated strategy were censored on the date of non-adherence. To account for potential informative censoring due to non-adherence to the initiated treatment, we applied marginal structural models with inverse probability of censoring weights.[55] These weights were constructed at each 90 day interval (12 intervals in total) to model the probability of not being censored at each interval using both baseline and time varying covariates. Each participant's overall weight was computed as the cumulative product of these inverse probabilities and was stabilised by the marginal probability of not being censored. Weighted discrete time survival models were then fit using generalised estimating equations with a logit link and binomial distribution to estimate the per protocol risk ratio, risk difference, and risk in each treatment group per 1000 people. The associated 95% confidence intervals (CIs) were estimated using parametric bootstrapping with 1000 simulations on the basis of the covariance matrix generated from the generalised estimating equations based models.[55]

We evaluated the association between initiation of a GLP-1 receptor agonist and the risk of composite SUD outcome in protocol 1 in subgroups across age (≤65 and >65 years), sex (male and female), race (white, black, and other), BMI categories (≤30, 30-35, and >35), HbA_{1c} levels (≤6.5, 6.5-8, and >8%), and types of GLP-1 receptor agonists (semaglutide, liraglutide, and dulaglutide).

To further evaluate the association between initiation of a GLP-1 receptor agonist and the composite outcome of SUD related emergency department visits, SUD related hospital admission, and SUD related mortality in people with specific SUDs, we applied the same inverse probability weighting approach within multiple subcohorts in protocol 2, each comprising participants with a specific pre-existing SUD: alcohol use disorder, cocaine use disorder, opioid use disorder, or other SUD. We then applied a weighted cause specific hazard model to evaluate the association within each specific pre-existing SUD cohort.

Sensitivity analyses and negative outcome controls

We conducted several sensitivity analyses to test the robustness of the results. Firstly, instead of the primary

approach in which the covariates were applied only in models for drug usage, we constructed doubly robust adjustment models. Secondly, we used the overlap weighting approach to balance covariates (instead of standardised mortality ratio weights used in the primary approach). Thirdly, we augmented our list of prespecified covariates with an algorithmically selected list of 100, 200, and 300 covariates from

Table 1 | Baseline sociodemographic and health related characteristics of participants in the GLP-1 receptor agonist and SGLT-2 inhibitor groups after weighting in the primary trial (trial 1) of protocol 1. Values are number (percentage) unless stated otherwise

Characteristics	GLP-1 receptor agonists (n=124 001)	SGLT-2 inhibitors (n=400 816)	SMD
Sociodemographic characteristics			
Mean (SD) age (years)	65.84 (10.96)	65.76 (10.78)	0.007
Sex:			
Female	12 187 (9.83)	38 524 (9.61)	0.007
Male	111 814 (90.17)	362 292 (90.39)	−0.007
Race*:			
American Indian or Alaska Native	1264 (1.02)	4054 (1.01)	0.001
Asian	1135 (0.92)	3561 (0.89)	0.003
Black	23 046 (18.59)	74 864 (18.68)	−0.002
Native Hawaiian or Pacific Islander	1524 (1.23)	4962 (1.24)	−0.001
Other	6640 (5.35)	21 337 (5.32)	0.001
White	90 392 (72.9)	292 038 (72.86)	0.001
Ethnicity*:			
Hispanic	7768 (6.26)	28 559 (7.13)	−0.03
Non-Hispanic	116 233 (93.74)	372 257 (92.87)	0.03
Rurality:			
Highly rural	1573 (1.27)	5037 (1.26)	0.001
Insular island	146 (0.12)	461 (0.11)	0.001
Rural	44 468 (35.86)	143 514 (35.81)	0.001
Urban	77 814 (62.75)	251 804 (62.82)	−0.001
Mean (SD) area deprivation index†	57.01 (18.57)	57.18 (18.26)	−0.009
Health behaviour factors			
Smoking status:			
Current smoker	15 657 (12.63)	50 579 (12.62)	0.000
Former smoker	54 080 (43.61)	174 773 (43.6)	0.000
Never smoker	54 264 (43.76)	175 463 (43.78)	0.000
Laboratory or physiological measurements			
Albuminuria	38 728 (31.23)	124 955 (31.18)	0.001
Mean (SD) average HbA_{1c} within one year	8.52 (1.65)	8.53 (1.56)	−0.008
Mean (SD) body mass index	35.8 (7.02)	35.83 (7.1)	−0.004
Mean (SD) diastolic blood pressure (mm Hg)	75.88 (9.81)	75.94 (9.81)	−0.006
Mean (SD) eGFR ($mL/min/1.73m^2$)	74.32 (22.15)	74.92 (20.7)	−0.028
Mean (SD) low density lipoprotein cholesterol (mg/dL)	83.14 (35.47)	83.09 (35.49)	0.001
Mean (SD) systolic blood pressure (mm Hg)	133.01 (16.58)	133.06 (16.59)	−0.003
Healthcare utilisation			
Long term care facility use	1012 (0.82)	3261 (0.81)	0.000
Mean (SD) No of HbA_{1c} measurements	2.42 (1.27)	2.41 (1.22)	0.009
Mean (SD) No of Medicare hospital admissions	0.08 (0.43)	0.08 (0.42)	0.007
Mean (SD) No of Medicare outpatient encounters	0.37 (1.03)	0.37 (1.04)	0.000
Mean (SD) No of blood panel tests	3.3 (3.52)	3.28 (3.13)	0.007
Mean (SD) No of hospital admissions	0.04 (0.32)	0.04 (0.3)	0.002
Mean (SD) No of outpatient encounters	4.32 (1.41)	4.31 (1.39)	0.006
Other covariates			
Bariatric surgery	188 (0.15)	513 (0.13)	0.006
Cancer	5591 (4.51)	18 066 (4.51)	0.000
HIV	505 (0.41)	1677 (0.42)	−0.002
Hyperlipidaemia	52 308 (42.18)	168 846 (42.13)	0.001
Nutritional deficiencies	19 974 (16.11)	64 433 (16.08)	0.001
Orlistat	1137 (0.92)	2510 (0.63)	0.033
Phentermine	913 (0.74)	1696 (0.42)	0.041
Thyroid disorders	15 897 (12.82)	51 000 (12.72)	0.003
Topiramate	3037 (2.45)	9640 (2.41)	0.003
Urinary tract infection	5460 (4.4)	16 364 (4.08)	0.016

SMD larger than −0.1 and less than 0.1 was considered evidence of good balance.
eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; HbA_{1c}=haemoglobin A_{1c}; HIV=human immunodeficiency virus; SD=standard deviation; SGLT-2=sodium-glucose co-transporter-2; SMD=standardised mean difference.
*Self-reported race 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. The "Other" race category included those whose race was not declared through self-reports or was missing.
†Measure of socioeconomic disadvantage, range 0-100, with 0 representing low disadvantage and 100 representing high disadvantage.

Table 2 | Baseline drug and health related characteristics of participants in the GLP-1 receptor agonist and SGLT-2 inhibitor groups after weighting in the primary trial (trial 1) of protocol 1. Values are number (percentage) unless stated otherwise

Characteristics	GLP-1 receptor agonists (n=124 001)	SGLT-2 inhibitors (n=400 816)	SMD
Antidiabetic drugs			
DPP-4 inhibitors	25 719 (20.74)	87 414 (21.81)	−0.026
Mean (SD) duration of DPP-4 inhibitor use (days)*	453.05 (509.68)	453.34 (487.46)	−0.001
Mean (SD) duration of insulin use (days)*	956.3 (660.71)	951.18 (668.87)	0.008
Mean (SD) duration of metformin use (days)*	785.38 (667.61)	783.49 (665.57)	0.003
Mean (SD) duration of sulfonylureas use (days)*	718.22 (658.72)	714.75 (655.81)	0.005
Mean (SD) duration of thiazolidinediones use (days)*	454.03 (550.07)	456.66 (540.93)	−0.005
Insulin	73 392 (59.19)	237 360 (59.22)	−0.001
Metformin	81 958 (66.09)	267 273 (66.68)	−0.012
Sulfonylureas	40 877 (32.97)	133 843 (33.39)	−0.009
Thiazolidinediones	8012 (6.46)	27 199 (6.79)	−0.013
Cardiometabolic conditions/drugs			
ACE/ARB	76 840 (61.97)	247 705 (61.8)	0.003
Acute coronary disease	2827 (2.28)	9072 (2.26)	0.001
Acute kidney injury	9487 (7.65)	29 205 (7.29)	0.014
Atrial fibrillation	7790 (6.28)	24 848 (6.2)	0.003
Beta blockers	53 140 (42.85)	171 156 (42.7)	0.003
Calcium channel blockers	37 780 (30.47)	121 999 (30.44)	0.001
Diuretics	53 720 (43.32)	172 057 (42.93)	0.008
Heart failure	10 612 (8.56)	33 339 (8.32)	0.009
Ischaemic cardiomyopathy	1574 (1.27)	4976 (1.24)	0.003
Myocardial infarction	1270 (1.02)	4131 (1.03)	−0.001
Non-ischaemic cardiomyopathy	2681 (2.16)	8423 (2.1)	0.004
Statins	98 260 (79.24)	317 449 (79.2)	0.001
Stroke	3449 (2.78)	11 409 (2.85)	−0.004
Transient ischaemic attack	1380 (1.11)	4473 (1.12)	0.000
Gastrointestinal conditions			
Abdominal pain	5732 (4.62)	18347 (4.58)	0.002
Constipation	5111 (4.12)	16 502 (4.12)	0.000
Diarrhoea	4050 (3.27)	13 033 (3.25)	0.001
Diverticulosis and diverticulitis	3694 (2.98)	11 992 (2.99)	−0.001
Dyspepsia	454 (0.37)	1498 (0.37)	−0.001
GERD	27 232 (21.96)	88 638 (22.11)	−0.004
Gastritis	1487 (1.2)	4848 (1.21)	−0.001
Intestinal obstruction and ileus	521 (0.42)	1632 (0.41)	0.002
Nausea	2123 (1.71)	6821 (1.7)	0.001
Non-alcoholic fatty liver disease	5846 (4.71)	19 414 (4.84)	−0.006
Ulcerative colitis	879 (0.71)	2861 (0.71)	−0.001
Mental health conditions/drugs			
Acute stress	181 (0.15)	571 (0.14)	0.001
Adjustment disorders	5457 (4.4)	17 796 (4.44)	−0.002
Benzodiazepines	7483 (6.03)	23 771 (5.93)	0.004
Buprenorphine	283 (0.23)	908 (0.23)	0.000
Bupropion	8902 (7.18)	28 786 (7.18)	0.000
Generalised anxiety disorder	13 901 (11.21)	45 400 (11.33)	−0.004
Major depressive disorder recurrent	14 703 (11.86)	48 037 (11.98)	−0.004
Methadone	189 (0.15)	585 (0.15)	0.002
Mixed anxiety disorder	1034 (0.83)	3291 (0.82)	0.001
Mood disorder	6222 (5.02)	20 082 (5.01)	0.000
Naltrexone	804 (0.65)	2067 (0.52)	0.017
Panic disorder	1136 (0.92)	3761 (0.94)	−0.002
Post-traumatic stress disorder	22 633 (18.25)	73 335 (18.3)	−0.001
Psychotic disorder	1829 (1.47)	5837 (1.46)	0.002
SNRIs	15 830 (12.77)	51 768 (12.92)	−0.004
SSRIs	31 013 (25.01)	100 371 (25.04)	−0.001
Sleep aid drugs	25 049 (20.2)	80 834 (20.17)	0.001
Sleep disorder	54 741 (44.15)	178 433 (44.52)	−0.007
Suicidal ideation	760 (0.61)	2471 (0.62)	0.000
Tricyclic antidepressants	1108 (0.89)	3585 (0.89)	0.000

ACE/ARB=angiotensin converting enzyme inhibitors/angiotensin receptor blockers; DPP-4=dipeptidyl peptidase-4; GERD=gastroesophageal reflux disease; GLP-1=glucagon-like peptide-1; SD=standard deviation; SGLT-2=sodium-glucose cotransporter-2; SMD=standardised mean difference; SNRIs=serotonin-norepinephrine reuptake inhibitor; SSRIs=selective serotonin reuptake inhibitor.
*Duration of continued drug treatment in days based on pharmacy records within five years before date of first filled prescription for GLP-1 receptor agonist or SGLT-2 inhibitor in those with a history of drug treatment.

high dimensional data domains of Veterans Affairs electronic health records. Fourthly, instead of the target estimand of the average treatment effect among those treated in the primary approach, we estimated both the average treatment effect and the average treatment effect on the control. Fifthly, we applied a range of upper (and corresponding lower) truncation cut-off thresholds (no truncation, 0.1 and 99.9; 0.5 and 99.5; and 1.5 and 98.5 centiles) for propensity score weights instead of truncation at 1 and 99 centiles in the primary analyses. Sixthly, we applied propensity score weight trimming and varied their cut-off thresholds (0.1 and 99.9; 0.5 and 99.5; and 1.5 and 98.5 centiles) instead of truncation, which was used in the primary analyses. Seventhly, instead of the one year look-back period to define initiators of GLP-1 receptor agonists or SGLT-2 inhibitors, we varied different look-back periods (two years, three years, and any history). Eighthly, instead of the multiple imputation approach to handle missing data in the primary analyses, we conducted analyses on complete data. Finally, we used initiators of sulfonylureas instead of initiators of SGLT-2 inhibitors as the control.

We specified several negative outcome controls that lack mechanistic support for or clinical evidence of a causal relation with GLP-1 receptor agonists, including benign prostatic hyperplasia, emergency department visit for superficial injury of neck or trunk, headache, and uptake of respiratory syncytial virus vaccine.

Analyses were conducted using Statistical Analysis System (SAS) enterprise guide 8.3 and data visualisations were produced by R 4.3.3.

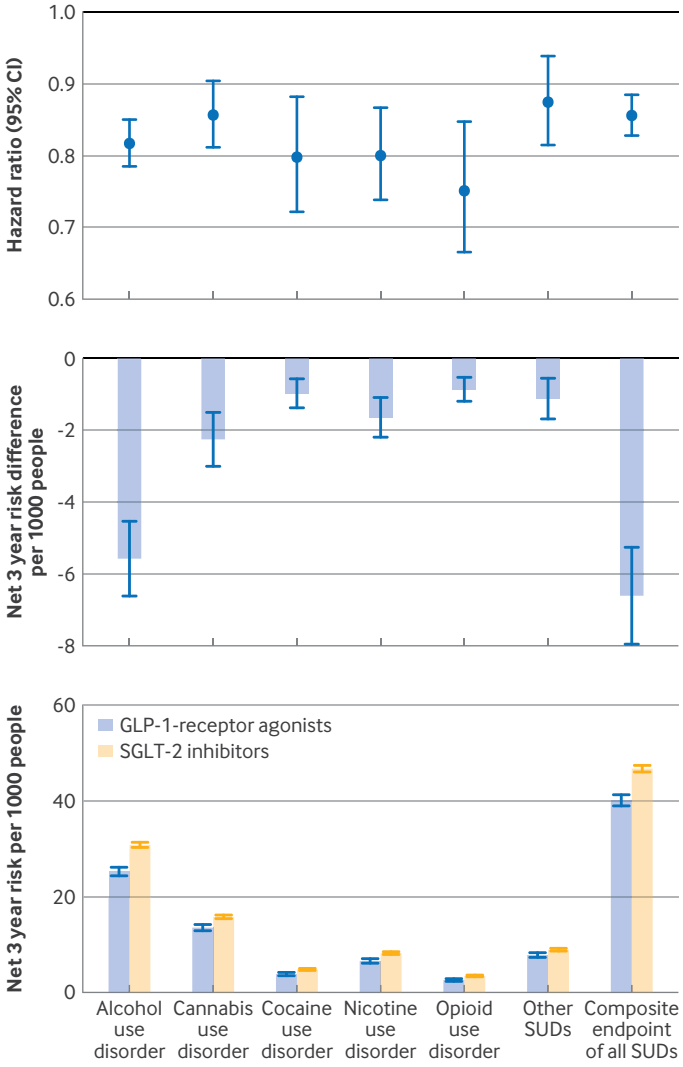


Fig 3 | Associations between initiation of glucagon-like peptide-1 receptor agonists and risk of incident SUD at three years' follow-up in protocol 1. Hazard ratios <1 indicate lower risk among GLP-1 receptor agonist initiators compared with SGLT-2 inhibitor initiators. Negative net three year risk differences indicate lower risk among initiators of GLP-1 receptor agonists compared with initiators of SGLT-2 inhibitors. All estimates were derived at three years' follow-up using fully weighted models accounting for predefined covariates. Other SUDs include substance use disorder related to hallucinogens, inhalants, psychoactive drugs, sedatives or hypnotics, and stimulants. The 95% CIs (whiskers) should be interpreted in the context of the adjusted covariates and potential residual confounding. CI=confidence interval; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2; SUD=substance use disorder

Patient and public involvement

No patients or members of the public participated in developing the hypothesis, specific aims, or research questions owing to a limited timeline for this project, neither were they involved in designing or implementing the study. Additionally, patients were not involved in interpreting the findings or preparing the manuscript.

Results

From a base population of 606 434 US veterans with type 2 diabetes, protocol 1 included seven parallel target trial emulations, each evaluating a different SUD (fig 1). In trial 1 (the primary trial) after exclusion of participants with any previous SUD, 524 817 participants remained (124 001 in the GLP-1 receptor agonist group and 400 816 in the SGLT-2 inhibitor group). Cohort participants were followed for a median of 3.00 (interquartile range 2.26-3.00) years, totalling 1 353 787.16 person years of follow up. Table 1, table 2, and supplementary table S5 provide demographic and health characteristics before and after application of weighting for trial 1. Examination of absolute standardised mean differences for all the seven trials after weighting showed that all absolute values of standardised mean differences were below 0.1 suggesting good balance between the GLP-1 receptor agonist and the SGLT-2 inhibitor groups (see supplementary figure S3 for trial 1 and supplementary figure S4 for trials 2-7).

Risks of incident SUDs

In the primary (treatment initiation; as initiated) analyses, initiation of a GLP-1 receptor agonist was associated with a reduced risk of several incident SUDs (fig 3, fig 4, and supplementary table S6), including disorders related to alcohol use (hazard ratio 0.82 (95% CI 0.78 to 0.85), NRD per 1000 people −5.57 (−6.61 to −4.53)), cannabis use (0.86 (0.81 to 0.90), NRD −2.25 (−3.00 to −1.50)), cocaine use (0.80 (0.72 to 0.88), NRD −0.97 (−1.37 to −0.57)), nicotine use

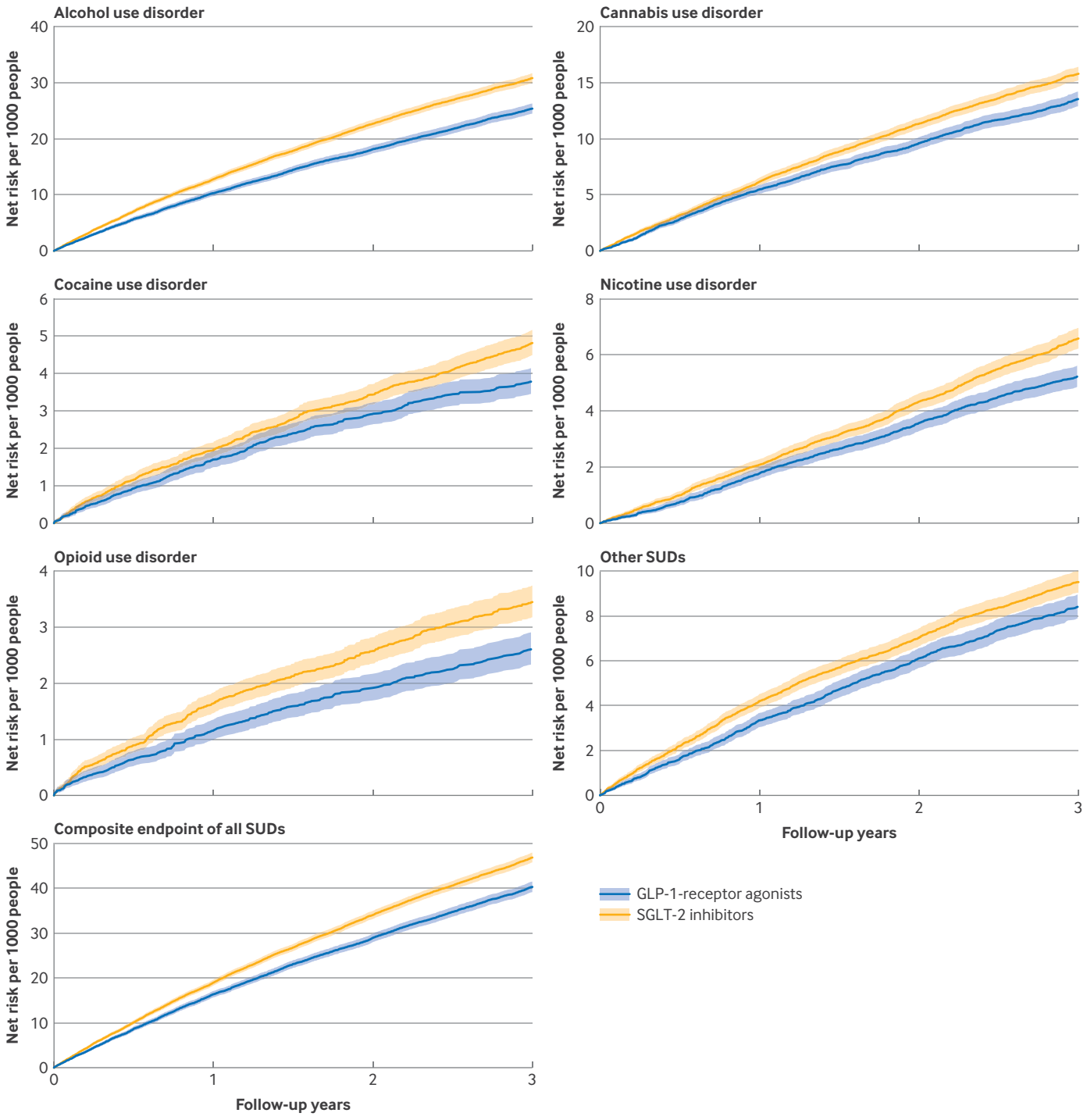


Fig 4 | Cumulative net risks of SUDs in treatment groups. All estimates were derived at three years' follow-up using fully weighted models accounting for predefined covariates. Other SUDs include substance use disorder related to hallucinogens, inhalants, psychoactive drugs, sedatives or hypnotics, and stimulants. GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2; SUD=substance use disorder

(0.80 (0.74 to 0.87), NRD −1.64 (−2.19 to −1.09)), and opioids use (0.75 (0.67 to 0.85), NRD −0.86 (−1.19 to −0.52)), and other SUDs (0.87 (0.81 to 0.94), NRD −1.12 (−1.68 to −0.55)).

Initiation of a GLP-1 receptor agonist was associated with reduced risk of composite endpoint of all SUDs (hazard ratio 0.86 (0.83 to 0.88), NRD −6.61 (−7.95 to −5.26)) (fig 3, fig 4 and supplementary table S6). To complement the primary analyses which used a cause specific hazard model, we evaluated the risk of composite endpoint using a Fine and Gray model and separately constructed a cause specific hazard model with time varying inverse probability-of-death censoring weights; these complementary analyses yielded consistent results (see supplementary figure S5).

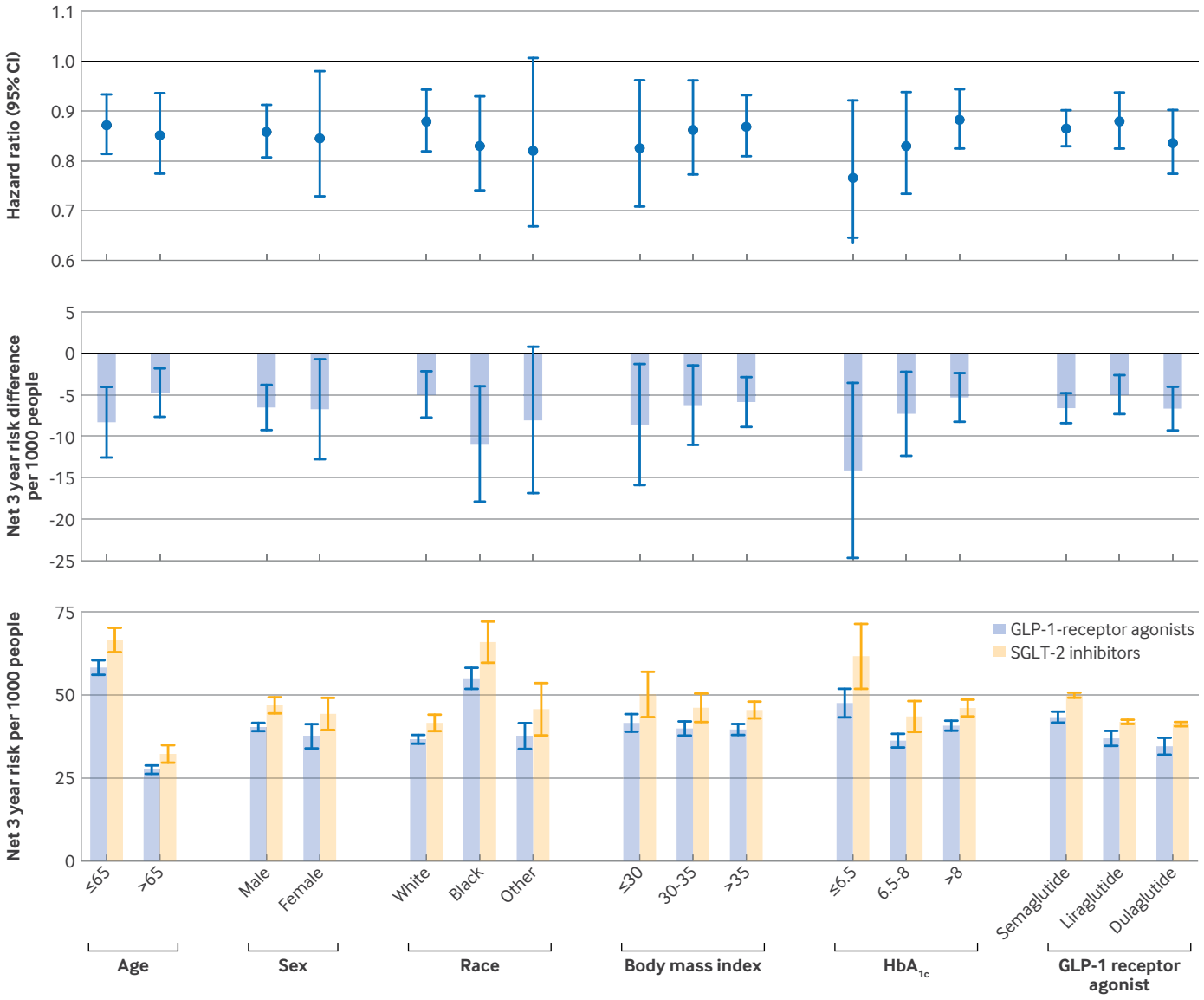


Fig 5 | Stratified subgroup analyses for initiation of GLP-1 receptor agonists and risk of composite endpoint of all SUDs in protocol 1. Hazard ratios <1 indicate lower risk among initiators of GLP-1 receptor agonists compared with initiators of SGLT-2 inhibitors. Negative net three year risk differences indicate lower risk among initiators of GLP-1 receptor agonists compared with initiators of SGLT-2 inhibitors. All estimates were derived at three years' follow-up using fully weighted models accounting for predefined covariates. The 95% CIs should be interpreted in the context of the adjusted covariates and potential residual confounding. CI=confidence interval; GLP-1=glucagon-like peptide-1; HbA_{1c}=haemoglobin A_{1c}; SGLT-2=sodium-glucose cotransporter-2; SUD=substance use disorder

We additionally estimated the treatment adherence effect using marginal structural models incorporating time varying covariates on the composite endpoint. Cumulative adherence at three years was 51.2% (61 238/119 657) and 53.6% (205 973/384 489) for the GLP-1 receptor agonist and SGLT-2 inhibitor groups, respectively (see supplementary table S7). Analyses of treatment adherence effect showed near constant results for adherent users (risk ratio ≈0.76) at one, two, and three years; this translated into a steadily increasing absolute risk difference over time, from −4.12 per 1000 people at one year to −10.79 per 1000 people at three years (see supplementary table S8).

We evaluated initiation of a GLP-1 receptor agonist and the risk of the composite endpoint of all SUDs by subgroups defined according to age, sex, race, BMI categories, HbA_{1c} levels, and type of GLP-1 receptor agonist. Compared with initiation of an SGLT-2 inhibitor, initiation of a GLP-1 receptor agonist was associated with lower risk of SUDs across subgroups defined by age (≤65 and >65 years), sex, race (white and black), BMI categories (≤30, 30-35, and >35), HbA_{1c} levels (≤6.5, 6.5-8, and >8%), and GLP-1 receptor agonist agents (semaglutide, liraglutide, and dulaglutide) (fig 5 and supplementary table S9).

Table 3 | Baseline sociodemographic and health related characteristics of participants in the GLP-1 receptor agonist and SGLT-2 inhibitor groups after weighting in protocol 2. Values are number (percentage) unless stated otherwise

Characteristics	GLP-1 receptor agonists (n=16 768)	SGLT-2 inhibitors (n=64 849)	SMD
Sociodemographic characteristics			
Mean (SD) age (years)	61.64 (10.42)	61.56 (10.35)	0.007
Sex:			
Female	1572 (9.38)	5957 (9.19)	0.006
Male	15 196 (90.63)	58 892 (90.81)	−0.006
Race*:			
American Indian or Alaska Native	190 (1.13)	720 (1.11)	0.002
Asian	98 (0.58)	364 (0.56)	0.003
Black	3743 (22.32)	14 367 (22.15)	0.004
Native Hawaiian or Pacific Islander	185 (1.1)	723 (1.11)	−0.001
Other	775 (4.62)	2944 (4.54)	0.004
White	11 777 (70.23)	45 731 (70.52)	−0.006
Ethnicity*:			
Hispanic	1089 (6.49)	4702 (7.25)	−0.030
Non-Hispanic	15 679 (93.51)	60 147 (92.75)	0.030
Rurality:			
Highly rural	175 (1.04)	654 (1.01)	0.004
Insular island	27 (0.16)	118 (0.18)	−0.005
Rural	5539 (33.03)	21 503 (33.16)	−0.003
Urban	11 027 (65.76)	42 575 (65.65)	0.002
Mean (SD) area deprivation index†	56.57 (18.68)	56.74 (18.55)	−0.009
Health behaviour factors			
Smoking status:			
Current smoker	8576 (51.15)	33 007 (50.9)	0.005
Former smoker	5102 (30.43)	19 758 (30.47)	−0.001
Never smoker	3090 (18.43)	12 084 (18.63)	−0.005
Laboratory or physiological measurements			
Albuminuria	5305 (31.64)	20 608 (31.78)	−0.003
Mean (SD) average HbA_{1c} within one year	8.63 (1.78)	8.64 (1.66)	−0.007
Mean (SD) body mass index	35.47 (7.04)	35.5 (7.15)	−0.004
Mean (SD) diastolic blood pressure (mm Hg)	76.94 (10.06)	76.94 (10.03)	0.000
Mean (SD) eGFR (mL/min/1.73m^2)	80.06 (21.84)	80.55 (20.78)	−0.023
Mean (SD) low density lipoprotein cholesterol (mg/dL)	86.07 (37.16)	85.95 (36.91)	0.003
Mean (SD) systolic blood pressure (mm Hg)	131.76 (16.5)	131.77 (16.48)	−0.001
Healthcare utilisation			
Long term care facility use	424 (2.53)	1625 (2.51)	0.001
Mean (SD) No of HbA_{1c} measurements	2.61 (1.28)	2.62 (1.24)	−0.005
Mean (SD) No of Medicare hospital admissions	0.08 (0.46)	0.08 (0.47)	−0.003
Mean (SD) No of Medicare outpatient encounters	0.24 (0.82)	0.24 (0.84)	−0.008
Mean (SD) No of blood panel tests	4.74 (5.89)	4.75 (5.35)	−0.002
Mean (SD) No of hospital admissions	0.18 (0.74)	0.19 (0.74)	−0.007
Mean (SD) No of outpatient encounters	5.08 (1.38)	5.08 (1.37)	−0.004
Other covariates			
Bariatric surgery	29 (0.17)	90 (0.14)	0.009
Cancer	775 (4.62)	2990 (4.61)	0.001
HIV	149 (0.89)	565 (0.87)	0.002
Hyperlipidaemia	7968 (47.52)	31 069 (47.91)	−0.008
Nutritional deficiencies	3556 (21.21)	13791 (21.27)	−0.001
Orlistat	213 (1.27)	574 (0.88)	0.037
Phentermine	104 (0.62)	282 (0.44)	0.025
Thyroid disorders	2020 (12.05)	7769 (11.98)	0.002
Topiramate	720 (4.29)	2780 (4.29)	0.000
Urinary tract infection	977 (5.83)	3613 (5.57)	0.011

SMD larger than −0.1 and less than 0.1 was considered evidence of good balance.
eGFR=estimated glomerular filtration rate; GLP-1=glucagon-like peptide-1; HbA_{1c}=haemoglobin A_{1c}; HIV=human immunodeficiency virus; SD=standard deviation; SGLT-2=sodium-glucose co-transporter-2; SMD=standardised mean difference.
*Self-reported race 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. The "Other" race category included those whose race was not declared through self-reports or was missing.
†Measure of socioeconomic disadvantage, range 0-100, with 0 representing low disadvantage and 100 representing high disadvantage.

Risks of adverse outcomes among people with pre-existing SUDs

We then evaluated people with pre-existing SUDs; we aimed to determine whether initiation of a GLP-1 receptor agonist in this patient population was associated with reduced risk of SUD related emergency department visits, hospital admissions, and mortality. In protocol 2 there were 81 617 participants (16 768

Table 4 | Baseline drug and health related characteristics of participants in the GLP-1 receptor agonist and SGLT-2 inhibitor groups after weighting in protocol 2. Values are number (percentage) unless stated otherwise

Characteristics	GLP-1 receptor agonists (n=16 768)	SGLT-2 inhibitors (n=64 849)	SMD
Antidiabetic drugs			
DPP-4 inhibitors	3300 (19.68)	13 359 (20.6)	−0.023
Mean (SD) duration of drug use (days)*:			
DPP-4 inhibitors	403.83 (476.71)	407.4 (452.62)	−0.008
Insulin	844.41 (644.82)	837.6 (651.77)	0.011
Metformin	712.21 (639.73)	715.42 (637.55)	−0.005
Sulfonylureas	619.91 (623.14)	618.53 (617.54)	0.002
Thiazolidinediones	409.34 (498.93)	413.61 (503.66)	−0.009
Insulin	9793 (58.4)	38 121 (58.78)	−0.008
Metformin	11 926 (71.12)	46 505 (71.71)	−0.013
Sulfonylureas	5496 (32.78)	21 438 (33.06)	−0.006
Thiazolidinediones	978 (5.83)	4007 (6.18)	−0.015
Cardiometabolic conditions/drugs			
ACEs/ARBs	10 457 (62.36)	40 428 (62.34)	0.000
Acute coronary disease	668 (3.98)	2600 (4.01)	−0.001
Acute kidney injury	2298 (13.7)	8750 (13.49)	0.006
Atrial fibrillation	1085 (6.47)	4157 (6.41)	0.002
Beta blockers	7454 (44.45)	28 781 (44.38)	0.001
Calcium channel blockers	5301 (31.61)	20 410 (31.47)	0.003
Diuretics	7301 (43.54)	27 819 (42.9)	0.013
Heart failure	1886 (11.25)	7115 (10.97)	0.009
Ischaemic cardiomyopathy	312 (1.86)	1200 (1.85)	0.001
Myocardial infarction	380 (2.27)	1507 (2.32)	−0.004
Non-ischaemic cardiomyopathy	580 (3.46)	2158 (3.33)	0.007
Statins	13 928 (83.06)	53 776 (82.92)	0.004
Stroke	633 (3.78)	2519 (3.88)	−0.006
Transient ischaemic attack	261 (1.56)	1048 (1.62)	−0.005
Gastrointestinal conditions			
Abdominal pain	1276 (7.61)	4988 (7.69)	−0.003
Constipation	1228 (7.32)	4737 (7.31)	0.001
Diarrhoea	868 (5.18)	3328 (5.13)	0.002
Diverticulosis and diverticulitis	702 (4.19)	2762 (4.26)	−0.004
Dyspepsia	95 (0.57)	364 (0.56)	0.001
GERD	4855 (28.95)	18 979 (29.27)	−0.007
Gastritis	360 (2.15)	1430 (2.21)	−0.004
Intestinal obstruction and ileus	130 (0.78)	516 (0.79)	−0.002
Nausea	483 (2.88)	1924 (2.97)	−0.005
Non-alcoholic fatty liver disease	1228 (7.32)	4865 (7.5)	−0.007
Ulcerative colitis	146 (0.87)	623 (0.96)	−0.009
Mental health conditions/drugs			
Acute stress	56 (0.33)	207 (0.32)	0.003
Adjustment disorders	1338 (7.98)	5143 (7.93)	0.002
Benzodiazepines	1878 (11.2)	7216 (11.13)	0.002
Buprenorphine	385 (2.3)	1479 (2.28)	0.001
Bupropion	2521 (15.03)	9649 (14.88)	0.004
Generalised anxiety disorder	3804 (22.69)	14 869 (22.93)	−0.006
Major depressive disorder recurrent	4154 (24.77)	16 094 (24.82)	−0.001
Methadone	118 (0.7)	389 (0.6)	0.013
Mixed anxiety disorder	329 (1.96)	1318 (2.03)	−0.005
Mood disorder	2311 (13.78)	9037 (13.94)	−0.004
Naltrexone	605 (3.61)	2358 (3.64)	−0.002
Panic disorder	412 (2.46)	1526 (2.35)	0.007
Post-traumatic stress disorder	5818 (34.7)	22 518 (34.72)	−0.001
Psychotic disorder	876 (5.22)	3469 (5.35)	−0.006
SNRIs	3446 (20.55)	13 286 (20.49)	0.002
SSRIs	6767 (40.36)	26 507 (40.87)	−0.011
Sleep aid drugs	4932 (29.41)	19325 (29.8)	−0.008
Sleep disorder	9420 (56.18)	36 866 (56.85)	−0.014
Suicidal ideation	702 (4.19)	2710 (4.18)	0.000
Tricyclic antidepressants	327 (1.95)	1248 (1.92)	0.002
Substance use disorder/drugs			
Alcohol use disorder	6192 (36.93)	24 152 (37.24)	−0.007
Cannabis use disorder	1635 (9.75)	6454 (9.95)	−0.007
Cocaine use disorder	1257 (7.5)	4860 (7.49)	0.000
Disulfiram	41 (0.24)	156 (0.24)	0.001

(Continued)

Table 4 | (Continued)

Characteristics	GLP-1 receptor agonists (n=16 768)	SGLT-2 inhibitors (n=64 849)	SMD
Nicotine replacement therapy	3655 (21.8)	14 098 (21.74)	0.001
Nicotine use disorder	10 096 (60.21)	39 018 (60.17)	0.001
Opioid use disorder	1402 (8.36)	5410 (8.34)	0.001
Other SUD†	1257 (7.5)	4905 (7.56)	−0.003
Varenicline	865 (5.16)	3334 (5.14)	0.001

ACEs/ARBs=angiotensin converting enzyme inhibitors/angiotensin receptor blockers; DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular filtration rate; GERD=gastroesophageal reflux disease; GLP-1=glucagon-like peptide-1; SD=standard deviation; SGLT-2=sodium-glucose cotransporter-2; SMD=standardised mean difference; SNRIs=serotonin-norepinephrine reuptake inhibitor; SSRIs=selective serotonin reuptake inhibitor; SUD=substance use disorder.
*Duration of continued drug treatment in days based on pharmacy records within five years before date of first filled prescription for GLP-1 receptor agonist or SGLT-2 inhibitor in those with a history of drug treatment.
†Comprising five less prevalent SUDs: disorders related to hallucinogens, inhalants, psychoactive drugs, sedatives or hypnotics, and stimulants.

in the GLP-1 receptor agonist group and 64 849 in the SGLT-2 inhibitor group) (table 3, table 4, and supplementary table S10), totalling 205 451 person years of follow-up. Supplementary figure S6 shows the standardised mean differences before and after weighting.

Within participants with pre-existing SUDs, initiation of a GLP-1 receptor agonist was associated with reduced risk of SUD related emergency department visits (hazard ratio 0.69 (95% CI 0.61 to 0.78), NRD −8.92 (95% CI −11.59 to −6.25)), SUD related hospital admission (0.74 (0.65 to 0.85), NRD −6.23 (−8.73 to −3.74)), and SUD related mortality (0.50 (0.32 to 0.79), NRD −1.52 (−2.32 to −0.72)), and associated with reduced risk of the composite endpoint of the three outcomes (0.71 (0.65 to 0.79), NRD −11.79 (−14.98 to −8.60)) (fig 6 and supplementary table S11). Complementary analyses using a Fine and Gray model and separate application of a cause specific hazard model with time varying inverse probability-of-death censoring weights yielded consistent results (supplementary figure S7).

We then estimated the treatment adherence effect using marginal structural models incorporating time varying covariates on the composite endpoint. Cumulative adherence at three years was 47.8% (7809/16 325) and 50.2% (31 341/62 463) for the GLP-1 receptor agonist and SGLT-2 inhibitor groups, respectively (supplementary table S12). Analyses of treatment adherence effect showed a near constant effect for adherent users (risk ratio ≈0.55) at one, two, and three years; this translated into a steadily increasing absolute risk difference over time, from −9.28 per 1000 people at one year to −19.25 per 1000 people at three years (supplementary table S13).

We then investigated the association between initiation of a GLP-1 receptor agonist and the composite outcome in patients with specific categories of pre-existing SUDs, including disorders related to alcohol, cocaine, and opioids, and other SUD, given their strong relevance to clinically significant SUD associated adverse outcomes. The results showed that initiation of a GLP-1 receptor agonist was associated with reduced risk of the composite outcome in participants with pre-existing disorders related to alcohol use (hazard ratio 0.72 (95% CI 0.64 to 0.81), NRD −22.49 (95% CI −29.75 to −15.23)), cocaine use (0.78 (0.67 to 0.92), NRD −40.70 (−65.01 to −16.39)), and opioids use (0.70 (0.56 to 0.87), NRD −30.57 (−47.96 to −13.17)), and other SUDs (0.74 (0.62 to 0.87), NRD −47.08 (−70.52 to −23.63)) (fig 7 and supplementary table S14).

We also examined the association between initiation of GLP-1 receptor agonists and secondary outcomes, including drug overdose and separately suicidal ideation or attempt. Initiation of a GLP-1 receptor agonist was associated with reduced risk of drug overdose (0.61 (0.42 to 0.88), NRD −1.49 (−2.43 to −0.55)) and suicidal ideation or attempt (0.75 (0.67 to 0.83), NRD −9.95 (−13.14 to −6.77)) (fig 6 and supplementary table S11).

Sensitivity analyses and negative outcome controls

We tested the robustness of our results in multiple sensitivity analyses, which yielded results consistent (in direction and magnitude) with those of the primary approach (supplementary table S15). Testing of several negative outcome controls yielded null results consistent with a priori expectations (supplementary table S16).

Discussion

In this study of 606 434 people (protocol 1 and protocol 2 combined) evaluating both treatment initiation and treatment adherence effects over a median of three years—totalling 1 559 238 person years, GLP-1 receptor agonist use (versus SGLT-2 inhibitor use) was consistently associated with a reduced risk of developing various SUDs, including disorders related to alcohol use, cannabis use, cocaine use, nicotine use, and opioids use, and other SUDs. In analyses of people with pre-existing SUDs, GLP-1 receptor agonist use (versus SGLT-2 inhibitor use) was associated with a reduced risk of subsequent adverse clinical events, including SUD related emergency department visits, hospital admissions, and mortality, drug overdose, and suicidal ideation or attempt. These results suggest two key potential anti-addictive properties of GLP-1 receptor agonists: prevention of SUDs as evidenced by the consistent effect in reducing the incidence of new SUD across a broad range of substances, and treatment of SUD as evidenced by GLP-1 receptor agonist's role in harm reduction by reducing the risk of SUD related adverse events among people with established SUDs.

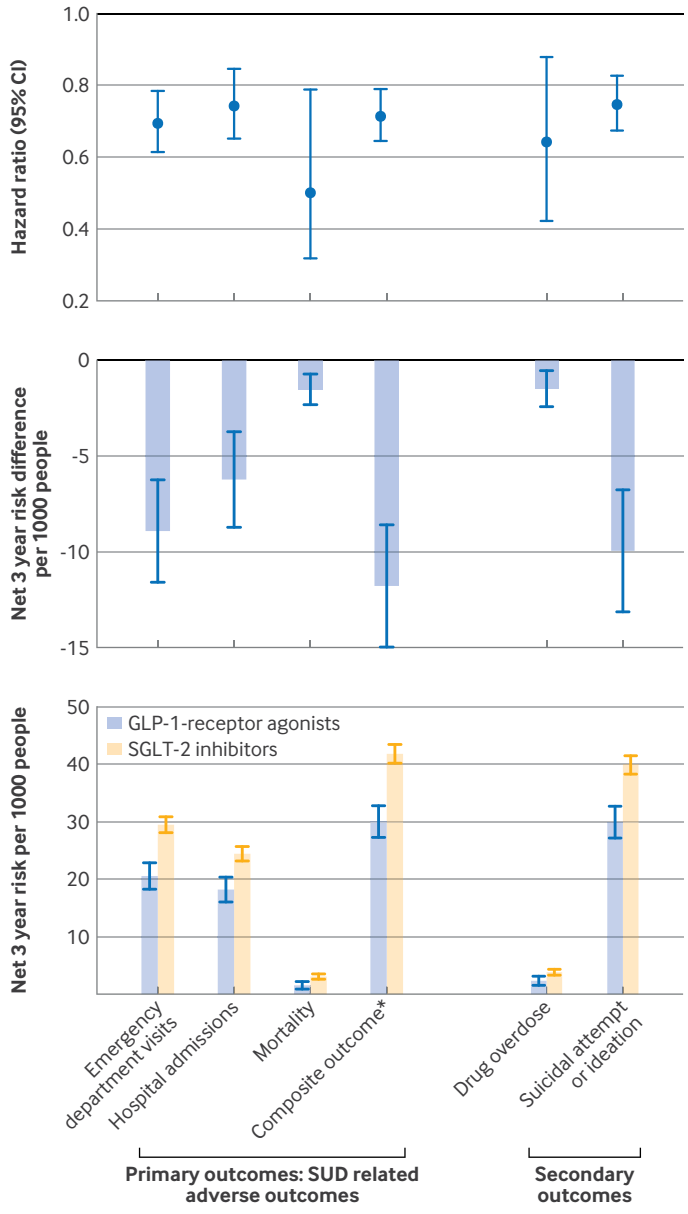


Fig 6 | Associations between initiation of GLP-1 receptor agonists and risks of adverse outcomes at three years' follow-up in protocol 2 (primary outcome is SUD related emergency department visits, SUD related hospital admission, and SUD related mortality, and a composite of these three outcomes, and secondary outcome is suicidal attempt or ideation. Comparisons are between GLP-1 receptor agonist and SGLT-2 inhibitor groups. Hazard ratios <1 and negative net three year risk differences indicate lower risk among initiators of GLP-1 receptor agonists compared with initiators of SGLT-2 inhibitors. All estimates were derived at three years' follow-up using fully weighted models accounting for predefined covariates. The 95% CIs (whiskers) should be interpreted in the context of the adjusted covariates and potential residual confounding. CI=confidence interval; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2; SUD=substance use disorder

Our findings expand the rapidly growing body of clinical research evaluating the role of GLP-1 receptor agonists in SUDs.[2 5 6 17 18 56] Consistent with mechanistic evidence, our results show that GLP-1 receptor agonist related agonism may prevent addiction phenotypes across all major drug classes (reduced incident SUD across alcohol, cannabis, nicotine, cocaine, and opioids) and provide clinically meaningful harm reduction among people with an established SUD (fewer SUD related deaths and other adverse events). Our results are generally consistent in direction and magnitude with the existing clinical research, including trials showing reduced heavy alcohol consumption among those with obesity,[14] reduced drinking in an experimental bar setting,[12] and pharmacoepidemiological analyses showing that GLP-1 receptor agonists are associated with lower incidence and recurrence of alcohol use disorder,[2] reduced need for tobacco use related care,[5] lower incidence and relapse of cannabis use disorder,[4] and reduced risk of opioid overdose in patients with opioid use disorders.[8]

Our results show that among people with a pre-existing SUD, GLP-1 receptor agonist use was associated with a reduced risk of several adverse clinical outcomes (SUD related emergency department visits, hospital admission, and mortality, drug overdose, and suicidal attempt or ideation). The finding on suicidal ideation is noteworthy, as this was previously a concern following reports of possible cases of self-injury and suicidal thoughts among Icelandic people using GLP-1 receptor agonists.[57] These reports resulted in a 2023 European Medicines Agency review, which found no evidence of a causal link. Several other subsequent studies have since suggested that GLP-1 receptor agonist use may actually reduce the risk of suicidal ideation.[1 58-60] Our findings corroborate these subsequent studies, especially showing that in people with SUDs, who are generally at higher risk of suicidal ideation, GLP-1 receptor agonists were associated with reduced risk of suicidal ideation.

We used SGLT-2 inhibitors as active comparators. The substantial overlap in the indication to initiate GLP-1 receptor agonist and SGLT-2 inhibitor in people with diabetes enhances exchangeability and success of trial emulation.[61 62] Notwithstanding the similarities in their antihyperglycaemic properties, SGLT-2 inhibitors and GLP-1 receptor agonists do not share a similar neuropsychiatric profile. SGLT-2 inhibitors act primarily in the renal proximal tubule and have no established direct actions on mesolimbic reward circuits in the brain.[63] On the contrary, neurotropism is a distinct property of GLP-1 receptor agonists.[62] GLP-1 is produced in the brain, GLP-1 receptors are present in areas of the brain involved in impulse control and reward signalling, and a pharmacologically administered exogenous GLP-1 receptor agonist crosses the blood-brain barrier and enters the brain within minutes, strengthening the inference that the observed GLP-1 receptor agonist anti-addictive properties are likely specific and biologically plausible drug effect of GLP-1 receptor agonism, distinct from the general benefits of treating diabetes that would be expected with both SGLT-2 inhibitors and GLP-1 receptor agonists.[64 65]

These observational findings do not by themselves justify the prescribing of GLP-1 receptor agonists specifically to prevent or treat SUDs. The findings do, however, yield actionable signals that can guide research priorities and inform the design of research

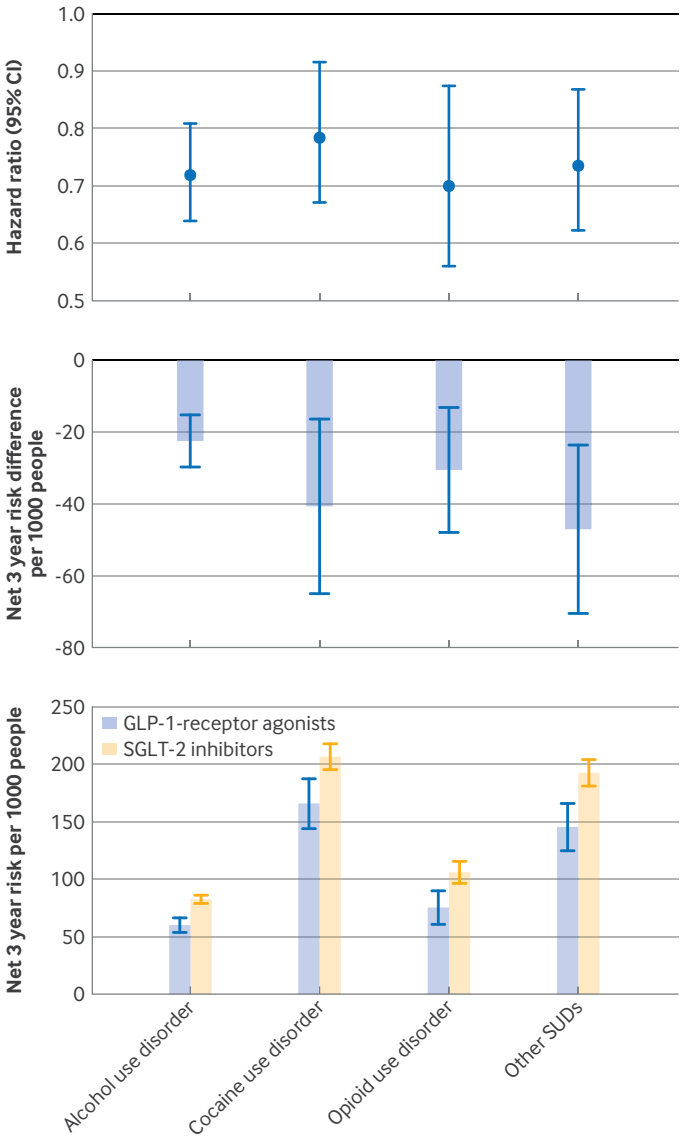


Fig 7 | Associations between initiation of GLP-1 receptor agonists and risk of the composite outcome of SUD related emergency department visits, SUD related hospital admissions, and SUD related mortality among four categories of participants with specific pre-existing SUDs in protocol 2. Comparisons are between GLP-1 receptor agonist and SGLT-2 inhibitor groups. Hazard ratios <1 and negative net three year risk differences indicate lower risk among initiators of GLP-1 receptor agonists compared with initiators of SGLT-2 inhibitors. All estimates were derived at three years' follow-up using fully weighted models accounting for predefined covariates. Other SUDs include substance use disorders related to hallucinogens, inhalants, psychoactive drugs, sedatives or hypnotics, and stimulants. The 95% CIs (whiskers) should be interpreted in the context of the adjusted covariates and potential residual confounding. CI=confidence interval; GLP-1=glucagon-like peptide-1; SGLT-2=sodium-glucose cotransporter-2; SUD=substance use disorder

studies, including randomised trials. Clinically, the associations may also inform drug choice for patients who already have guideline supported indications for use of a GLP-1 receptor agonist (eg, type 2 diabetes) and who are at high risk for, or currently living with, an SUD; in such cases, selecting a GLP-1 receptor agonist over another antihyperglycaemic drug could plausibly confer ancillary benefit. Any potential advantage must be weighed against the well characterised adverse event profile of GLP-1 receptor agonists—including gastrointestinal intolerance, gallbladder disease, acute pancreatitis, and other adverse events—within a shared, patient centred decision making process that balances individual risk against potential additive gains.[1]

The observed epidemiological patterns in our study are highly consistent with the known pharmacology and neurobiological mechanisms of GLP-1 receptor agonists. The early separation of the cumulative incidence functions reflects the drug's rapid mechanism of action, a finding supported by preclinical studies (in rodents and vervet monkeys) and human data showing immediate changes in craving and substance use after administration of a GLP-1 receptor agonist.[3 11 66 67] Our treatment adherence analyses are consistent with this, showing a constant relative effect that is established early and sustained during adherence (eg, risk ratio ≈0.76 for protocol 1 at the end of year 1, 2, and 3). This stability in risk ratios translates into a steadily growing absolute risk difference from one to three years. This rapid and sustained effect is biologically plausible, as GLP-1 receptors are expressed in key central nervous system areas implicated in reward, motivation, stress, and addiction.[20] At clinically therapeutic doses, GLP-1 receptor agonists cross the blood-brain barrier and are thought to modulate dopamine neurotransmission in the mesolimbic system, reducing the rewarding properties of addictive drugs.[3 14 20 21 68-71] Other potential mechanisms include the potentiation of inhibitory γ-aminobutyric acid-ergic tone,[72] modulation of the hypothalamic-pituitary-axis, serotonin, and glutamate systems,[18-21] and indirect neuroprotective and anti-inflammatory effects that could mitigate the chronic neurobiological consequences of SUDs.[62]

Limitations and strengths of this study

This study has several limitations. Firstly, it was conducted within the Veterans Affairs healthcare system, which serves a population that is predominantly older, male, and white, potentially limiting the generalisability of our findings. However, the large size of our cohort (n=606 434) provided substantial representation of various demographic groups, including 35 260 (5.81%) women, 119 700 (19.74%) people of black race, and 44 436 (7.33%) people aged <50 years, which enhances the applicability of our results. Secondly, we implemented several design features to mitigate biases: we defined a causal framework, used direct acyclic graphs to guide the selection of confounders, specified new user, active comparator target trials, and used inverse probability weighting to adjust for a comprehensive set of covariates from multiple data domains. However, we cannot completely rule out residual confounding; unmeasured or imperfectly measured variables not captured in the electronic health record—such as socioeconomic status or specific lifestyle interventions (eg, diet, exercise)—could still bias the results if they were associated with both treatment initiation and the outcomes. Thirdly, our study relied on electronic health

record data, which is subject to misclassification. This is particularly relevant for our outcomes, as SUDs are often underdiagnosed in clinical practice. However, this underdiagnosis is unlikely to be differential (ie, it should be similar between the GLP-1 receptor agonist and SGLT-2 inhibitor arms); it may lower the absolute rates (to the same extent in the two groups) but is unlikely to bias the rates on the relative scale. Fourthly, our active comparator design estimates the relative effect of GLP-1 receptor agonist versus SGLT-2 inhibitor, not the effect versus no treatment. Although SGLT-2 inhibitors have not been noticeably associated with SUD outcomes, the observed effect represents the causal contrast between these two specific drug classes, which may differ from the contrast with another comparator or placebo. Fifthly, for some of the less common SUD subtypes, the event counts were small. This may have limited our statistical power to detect smaller effects, increasing the risk of type II error in those specific subanalyses. Finally, our primary analyses reported net risks (eg, NRD) derived from cause specific hazard models. This causal estimand represents the risk in a hypothetical scenario where the competing risk of death is eliminated, and it may differ from prognostic estimates. We confirmed the robustness of our findings for the composite outcomes, as complementary analyses using both a Fine-Gray model and a cause specific hazard model with time varying inverse probability-of-death censoring weights yielded consistent results on both relative and absolute scales (supplementary figures S5 and S7). While our primary findings are robust to the choice of competing risk model, the net risk estimand should be interpreted in the context of the cause specific hazard model assumptions.

This study has several strengths. We specified and emulated eight target trials to address the aims of this study; the trial emulation framework helps align determination of eligibility, treatment assignment, and the beginning of follow-up, reducing important sources of bias—including immortal time bias (which arises when treatment strategies are defined after the start of follow-up) and selection bias (which arises when follow-up starts after treatment assignment).[73] We used data from the US Department of Veterans Affairs which integrates information from multiple data streams including healthcare encounters (both inpatient and outpatient), diagnostic codes, laboratory test results, vital signs, medication use, sociodemographic data, and data on use of supportive and rehabilitation services. The US Department of Veterans Affairs offers comprehensive medical coverage, including prescription drug benefits to all US veterans; this reduces the likelihood that the choice of antihyperglycaemic drug (GLP-1 receptor agonist versus SGLT-2 inhibitor) was influenced by the financial status of the patient. We used an incident user, active comparator design, and leveraged advanced methodologies in pharmacoepidemiology to evaluate the potential role of GLP-1 receptor agonists in both the prevention and the treatment of SUDs. We reported risk estimates on both the relative scale and the absolute scale; the latter complements the proportional change to provide a more easily interpretable and clinically relevant measure of the association between GLP-1 receptor agonists and SUDs. We challenged the robustness of our findings in multiple sensitivity analyses, which yielded consistent results. We tested several negative outcome controls, the results of which were consistent with pre-test expectations.

Conclusions

Use of GLP-1 receptor agonists was associated with reduced risk of a broad array of incident SUDs, suggesting potential preventive effects across a range of substances; GLP-1 receptor agonists were also associated with reduced risk of SUD related adverse clinical outcomes in people with pre-existing SUDs, suggesting potential utility of GLP-1 receptor agonists in the treatment of SUDs.

AUTHOR AFFILIATIONS

[1]Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA

[2]Veterans Research and Education Foundation of Saint Louis, Saint Louis, MO, USA

[3]Division of Pharmacoepidemiology, Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA

[4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, Saint Louis, MO, USA

[5]Department of Medicine, Washington University School of Medicine, Saint Louis, MO, USA

[6]Nephrology Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, MO, USA

[7]Institute for Public Health, Washington University in Saint Louis, Saint Louis, MO, USA

Contributors: ZAA conceived the research question. MC, YX, and ZAA designed the study. MC, YX, TC, and ZAA acquired the data. MC, TC, YX, and ZAA analysed and interpreted the data. MC and ZAA performed statistical analyses. MC, YX, and ZAA drafted and critically revised the manuscript. ZAA provided administrative and technical support and obtained funding. ZAA provided supervision and mentorship. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. ZAA is the guarantor and takes responsibility for this study being reported honestly, accurately, and transparently; that no important aspects of the study have been omitted, and that any discrepancies from the study as planned have been explained.

Funding: This research was funded by the US Department of Veterans Affairs (grant No VA-HSR-IIR 20-042 for ZAA). The funders of this study had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. The contents of this paper do not represent the views of the US Department of Veterans Affairs or the US government.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare. YX reports consulting (uncompensated) for Pfizer; ZAA reports funding from the US Department of Veterans Affairs; no financial relationships with any organisations that may have a financial interest in the submitted work in the previous three years; and no relationships or activities that could have influenced the submitted work.

Transparency: The lead author (ZAA) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: No plans are currently in place to disseminate the

results to study participants. Once the manuscript is published, the authors will issue a press release and work with their public affairs team to promote visibility of this study in traditional and social media outlets. They will also present the findings at scientific meetings and conferences.

Provenance and peer review: Not commissioned; externally peer reviewed.

Ethical approval: This study was approved by the institutional review board of the VA St Louis Health Care System, which granted a waiver of informed consent (protocol No 1606333).

Data sharing: Data are available through the US Department of Veterans Affairs. SAS analytical code used for statistical analyses are publicly available and can be found at: https://github.com/caimiao0714/GLP-SUD.

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Supplementary information: Supplementary methods, figures S1-S7, and tables S1-S16