nature medicine

Article

https://doi.org/10.1038/s41591-024-03412-w

Mapping the effectiveness and risks of GLP-1 receptor agonists

Received: 14 June 2024

Accepted: 12 November 2024

Published online: 20 January 2025

Check for updates

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

Glucagon-like peptide 1 receptor agonists (GLP-1RAs) are increasingly being used to treat diabetes and obesity. However, their effectiveness and risks have not yet been systematically evaluated in a comprehensive set of possible health outcomes. Here, we used the US Department of Veterans Affairs databases to build a cohort of people with diabetes who initiated GLP-1RA (n = 215,970) and compared them to those who initiated sulfonylureas (n = 159,465), dipeptidyl peptidase 4 (DPP4) inhibitors (n = 117,989) or sodium–glucose cotransporter-2 (SGLT2) inhibitors (n = 258,614), a control group composed of an equal proportion of individuals initiating sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors (n = 536,068), and a control group of 1,203,097 individuals who continued use of non-GLP-1RA antihyperglycemics (usual care). We used a discovery approach to systematically map an atlas of the associations of GLP-1RA use versus each comparator with 175 health outcomes. Compared to usual care, GLP-1RA use was associated with a reduced risk of substance use and psychotic disorders, seizures, neurocognitive disorders (including Alzheimer's disease and dementia), coagulation disorders, cardiometabolic disorders, infectious illnesses and several respiratory conditions. There was an increased risk of gastrointestinal disorders, hypotension, syncope, arthritic disorders, nephrolithiasis, interstitial nephritis and drug-induced pancreatitis associated with GLP-1RA use compared to usual care. The results provide insights into the benefits and risks of GLP-1RAs and may be useful for informing clinical care and guiding research agendas.

Glucagon-like peptide 1 receptor agonists (GLP-1RAs), a new class of antihyperglycemic agents, have gained substantial popularity in the past decade owing to their protective cardiovascular and renal properties and profound effects on weight loss[1–20]. Along with the increased utilization of these drugs, reports from observational studies and randomized controlled trials are also emerging that suggest increased risks of several gastrointestinal side effects[21,22] and decreased risks of substance use disorders and possibly Alzheimer's disease and Parkinson's disease[23–27].

However, despite the seemingly wide pleiotropic effects of GLP-1RAs[28,29], their effectiveness and risks have not yet been systematically evaluated in a comprehensive set of possible outcomes. A systematic approach to evaluate the effectiveness and risks of GLP-1RAs in a comprehensive set of outcomes may generate previously unreported associations with health outcomes (both harmful and protective), which will inform clinical practice and guide future mechanistic and clinical research, including the design of trials to further evaluate these signals.

[1]Clinical Epidemiology Center, Research and Development Service, VA St. Louis Health Care System, St. Louis, MO, USA. [2]Veterans Research and Education Foundation of St. Louis, St. Louis, MO, USA. [3]Division of Pharmacoepidemiology, Clinical Epidemiology Center, Research and Development Service, VA St. Louis Health Care System, St. Louis, MO, USA. [4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA. [5]Department of Medicine, Washington University School of Medicine, St. Louis, MO, USA. [6]Nephrology Section, Medicine Service, VA St. Louis Health Care System, St. Louis, MO, USA. [7]Institute for Public Health, Washington University in St. Louis, St. Louis, MO, USA. e-mail: zalaly@gmail.com

https://doi.org/10.1038/s41591-024-03412-w

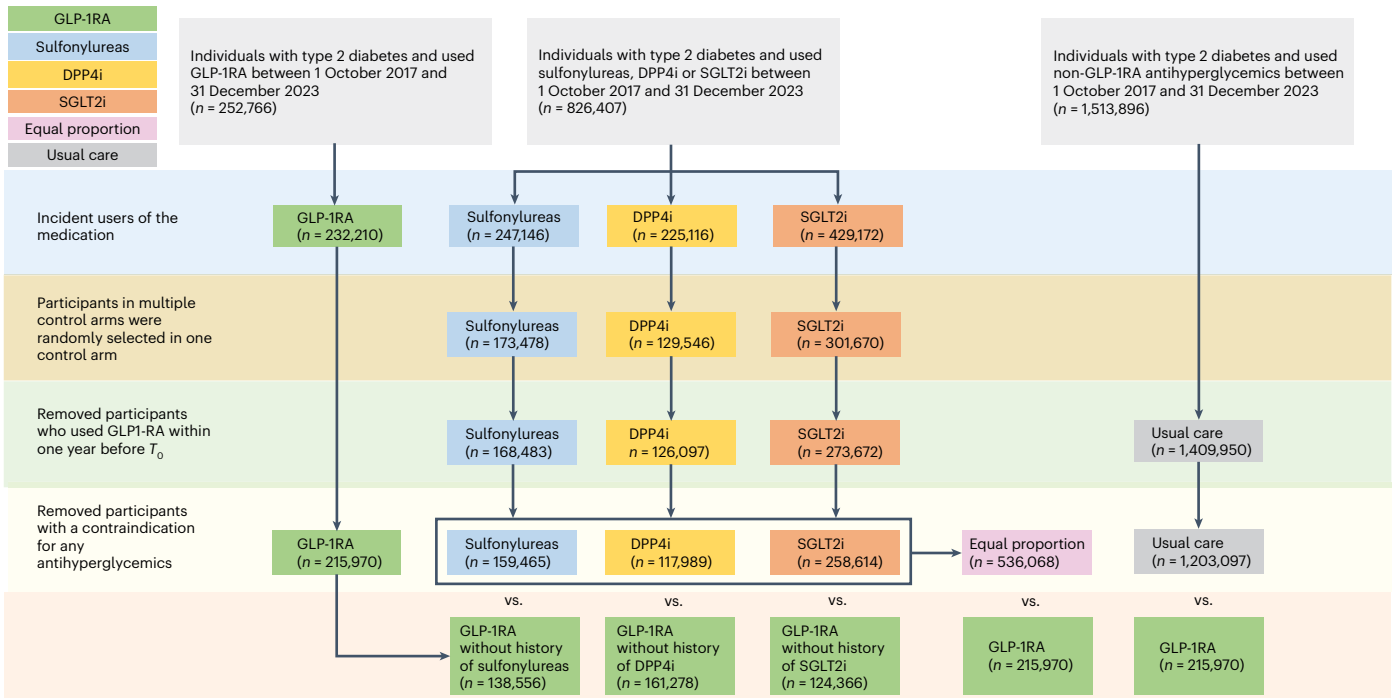


Fig. 1 | Cohort construction flow chart. The equal-proportion control group was composed of an equal proportion of incident users of sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors. The usual care control group represents individuals who continued the use of non-GLP-1RA antihyperglycemics. GLP-1RA, glucagon-like peptide-1 receptor agonists; DPP4i, dipeptidyl peptidase 4 inhibitors; SGLT2i, sodium–glucose cotransporter-2 inhibitors.

In this study, we used a discovery approach[30] to systematically evaluate the effectiveness and risks of incident GLP-1RA use on a comprehensive set of 175 health outcomes. We compared GLP-1RA use to incident use of each of three commonly used antihyperglycemics (sulfonylureas, dipeptidyl peptidase 4 (DPP4) inhibitors and sodium–glucose cotransporter-2 (SGLT2) inhibitors), a composite control group that included an equal proportion of individuals with incident use of these three antihyperglycemics, as well as a control group of individuals who continued their prior non-GLP-1RA antihyperglycemic regimen without additional new therapy (usual care).

Results

We used the US Department of Veterans Affairs healthcare databases to identify individuals with diabetes who were incident users of GLP-1RAs (n = 215,970), sulfonylureas (n = 159,465), DPP4 inhibitors (n = 117,989), SGLT2 inhibitors (n = 258,614) or a composite of the latter three antihyperglycemics (n = 536,068) and 1,203,097 individuals who continued usual care (Fig. 1). Participants were enrolled between 1 October 2017 and 31 December 2023.

Individuals were followed for a median of 3.68 (interquartile range (IQR) 2.05–5.37) years, resulting in 7,239,854 person-years of follow-up. The baseline characteristics of GLP-1RA users and each of the comparator groups before and after inverse probability weighting are presented in Supplementary Tables 1–4 and Extended Data Fig. 1. Standardized mean differences for all covariates between the GLP-1RA group and each of the control groups were less than 0.1 after weighting, suggesting that a good balance was achieved.

We then investigated the association between incident GLP-1RA use and the risk of 175 outcomes. Benjamini–Hochberg correction was applied to account for multiple comparisons.

Atlas of GLP-1RA effectiveness and risks

To understand the performance of GLP-1RAs relative to a specific antihyperglycemic drug class, we used our discovery approach to systematically evaluate the effectiveness and risks of GLP-1RAs versus each of the three commonly used antihyperglycemic drug classes with respect to 175 outcomes. An atlas mapping the associations for each pair (GLP-1RAs versus an antihyperglycemic class) and all 175 outcomes is provided in Figs. 2 and 3 and Supplementary Tables 5 and 6.

The results varied according to the comparator group, but consistently showed effectiveness and risks that extended beyond those currently recognized. Below, we report the proportion of outcomes with decreased and increased risk and the top five outcomes with the strongest associations (quantified based on P value) for each comparison. Compared to use of sulfonylureas, GLP-1RA use was associated with a decreased risk of 23 (13.14%) outcomes, including pneumonia, bronchitis, chronic obstructive pulmonary disease (COPD), suicidal ideation, and coagulopathy and clotting disorders, and an increased risk of 14 (8.00%) outcomes, including nausea and vomiting, gastroesophageal reflux disease (GERD), sleep disturbances, bone pain and abdominal pain. Compared to DPP4 inhibitor use, GLP-1RA use was associated with a decreased risk of 30 (17.14%) outcomes, including respiratory failure, post-thrombotic sequelae, pneumonia, anemia and bacterial infections, and an increased risk of 13 (7.43%) outcomes, including nausea and vomiting, sleep disturbances, hypotension, headaches and nephrolithiasis. Compared to SGLT2 inhibitor use, GLP-1RA use was associated with a decreased risk of 20 (11.43%) outcomes, including inflammatory conditions of male genital organs, alcohol use disorders, inflammatory diseases of female pelvic organs, fungal infections and deep vein thrombosis, and an increased risk of 29 (16.57%) outcomes, including anemia, nausea and vomiting, nephrolithiasis, GERD and abdominal pain.

We also present the results of GLP-1RA versus a composite control that included an equal distribution of the three classes of antihyperglycemics. Compared to the composite control, GLP-1RA use was associated with a decreased risk of 34 (19.43%) outcomes, including pneumonia, alcohol use disorders, respiratory failure, COPD and suicidal ideation, and an increased risk of 17 (9.71%) outcomes, including nausea and vomiting, GERD, abdominal pain, nephrolithiasis and sleep disturbances.

https://doi.org/10.1038/s41591-024-03412-w

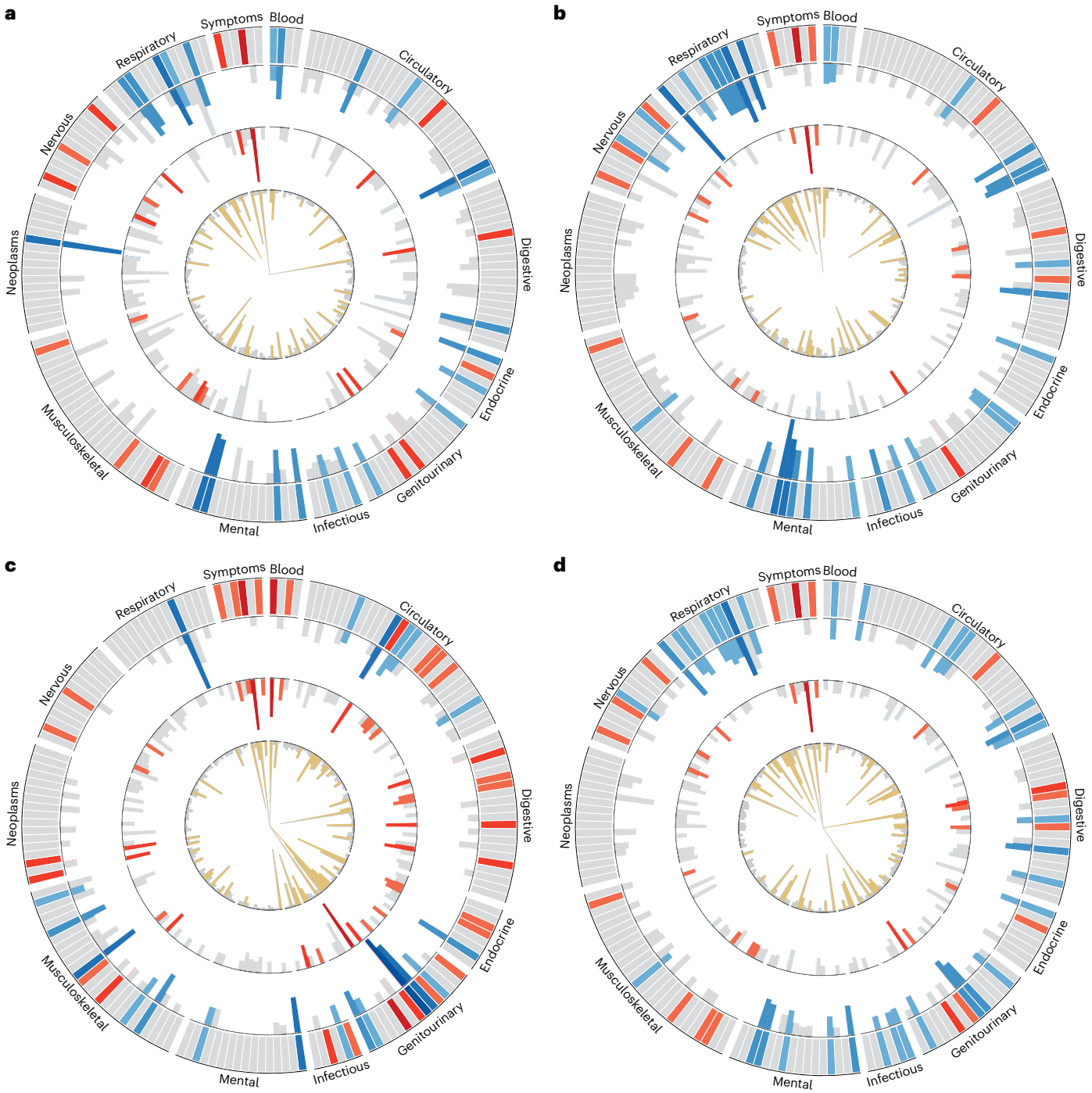


Fig. 2 | Systematic evaluation of the effectiveness and risks of incident use of GLP-1RAs compared to incident use of sulfonylureas, DPP4 inhibitors SGLT2 inhibitors and a control group composed of equal proportions of sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors. a–d, Comparisons between GLP-1RAs (n = 215,970) and sulfonylureas (**a**, n = 159,465), DPP4 inhibitors (**b**, n = 117,989), SGLT2 inhibitors (**c**, n = 258,614) and an equal proportion of the three antihyperglycemics (**d**, n = 536,068). The outermost ring represents the 12 diagnostic categories of health outcomes that could be affected by exposure to GLP-1RAs in the adult population. The second ring from the outermost ring, consisting of shaded blocks, represents a heatmap displaying HRs for the 175 outcomes. Red, significant HRs >1 (increased risk); blue, significant HRs <1 (reduced risk); gray, nonsignificant HRs. The intensity of color shading represents the magnitude of the HR. The third ring from the outermost ring represents a histogram of HRs that are <1. The height of each bar corresponds to the inverse magnitude of HR: blue, statistically significant; gray, nonsignificant. The intensity of color shading corresponds to the magnitude of the HR. The fourth ring from the outermost ring represents a histogram of HRs >1. The height of each bar corresponds to the HR magnitude: red, statistically significant; gray, nonsignificant. The intensity of color shading corresponds to the magnitude of the HR. The innermost ring represents a histogram of the negative log-transformed P values for the HRs, where the height represents the magnitude of the negative log-transformed P value: yellow, significant P values; gray, nonsignificant P values. All HRs were fully weighted for predefined and high-dimensional variables selected algorithmically. P values were based on two-sided Wald chi-squared tests. Benjamini–Hochberg correction for multiple tests was applied.

https://doi.org/10.1038/s41591-024-03412-w

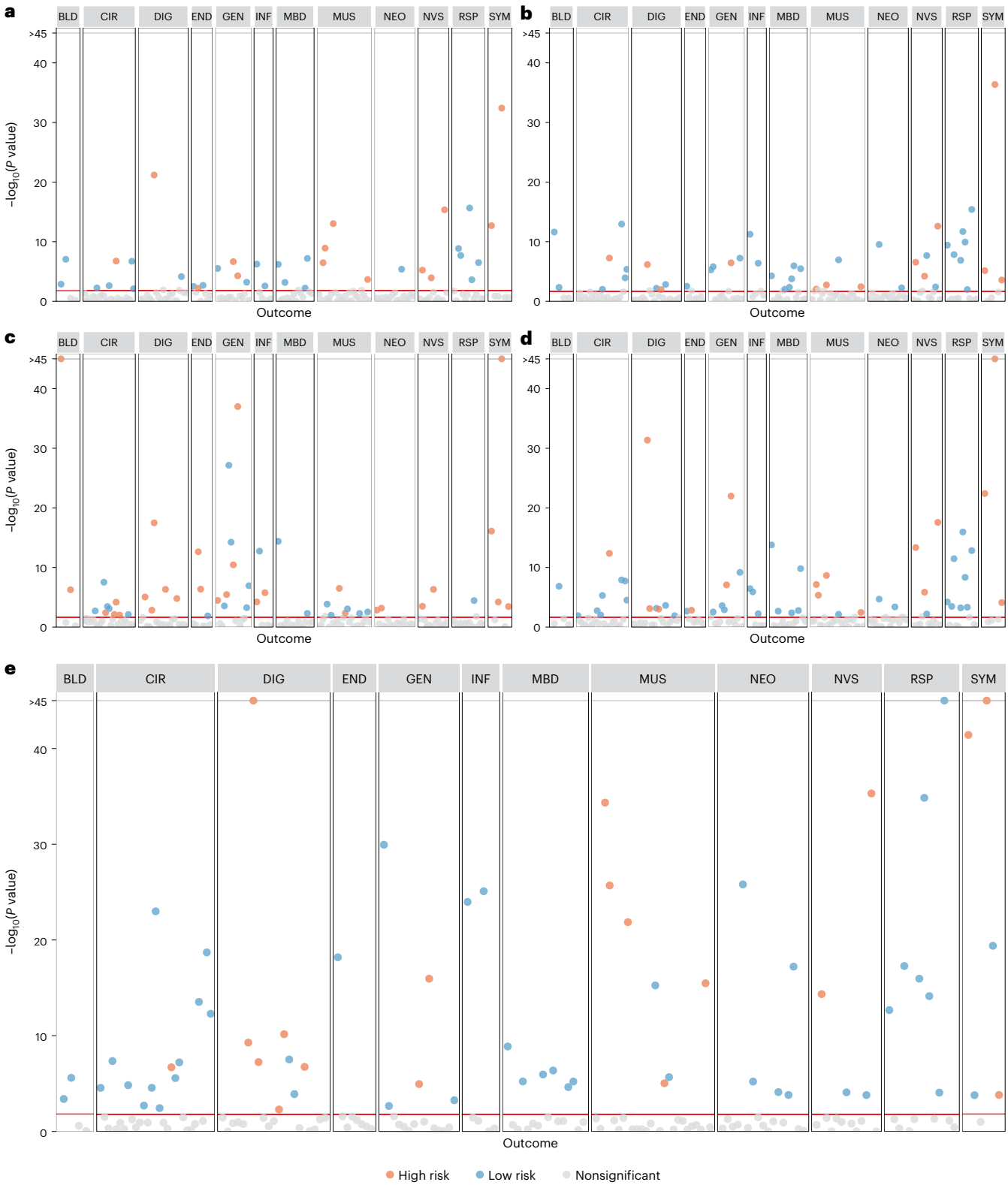


Fig. 3 | Manhattan plot for systematic evaluation of the effectiveness and risks of incident GLP-1RA use. a–e, Comparisons between the GLP-1RA group (n = 215,970) and the sulfonylurea group (**a**, n = 159,465), the DPP4 inhibitor group (**b**, n = 117,989), the SGLT2 inhibitor group (**c**, n = 258,614), the group with an equal proportion of sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors (**d**, n = 536,068) and the usual care control group who continued use of non-GLP-1RA antihyperglycemics (**e**, n = 1,203,097). The negative log-transformed P value was plotted for 175 outcomes. Orange dots, outcomes with higher risk that reached statistical significance; blue dots, outcomes with reduced risks that reached statistical significance. P values were based on two-sided Wald chi-squared tests. Benjamini–Hochberg correction for multiple tests was applied. The threshold of statistical significance after Benjamini-Hochberg correction is indicated by the horizonal red line. BLD, blood and blood-forming organs; CIR, circulatory system; DIG, digestive system; END, endocrine, nutritional and metabolic; GEN, genitourinary system; INF, infectious and parasitic diseases; MBD, mental; MUS, musculoskeletal system; NEO, neoplasms; NVS, nervous system; RSP, respiratory system; SYM, symptoms.

GLP-1RA versus usual care

We then compared GLP-1RA use to usual care (control group, representing standard care). This approach evaluated the effects of adding GLP-1RA to a treatment plan versus continuation of an existing treatment plan without the addition of GLP-1RA. Compared to usual care, GLP-1RA addition was associated with a decreased risk of 42 (24.00%) outcomes and an increased risk of 19 (10.86%) outcomes, while no statistically significant association was found for 114 (65.14%) outcomes. The numbers of statistically significant associations representing increased or decreased risk according to diagnostic category are provided in Figs. 3–5 and Supplementary Tables 7 and 8.

Effectiveness of GLP-1RAs by outcome. Our approach revealed evidence of the effectiveness of GLP-1RA on the nervous system. GLP-1RA use was associated with a reduced risk of several substance-related disorders, including alcohol use disorders (hazard ratio (HR) 0.89, 95% confidence interval (CI) (0.86–0.92)), cannabis use disorders (0.88 (0.83–0.93)), stimulant use disorders (0.84 (0.78–0.91)) and opioid use disorders (0.87 (0.82–0.92)). GLP-1RA use was associated with a reduced risk of suicidal ideation, attempt or intentional self-harm (0.90 (0.86–0.94)), bulimia (0.81 (0.77–0.84)) and schizophrenia and other psychotic disorders (0.82 (0.76–0.89)). GLP-1RA use was associated with a reduced risk of seizures (0.90 (0.85–0.95)) and neurocognitive disorders (0.95 (0.93–0.97))—the latter is driven by a decreased risk of dementia (0.92 (0.88–0.97)) and Alzheimer's disease (0.88 (0.78–0.99)) (Fig. 6 and Supplementary Table 9).

GLP-1RAs exhibited a decreased risk of coagulopathy and clotting disorders (0.92 (0.89–0.95)), thromboembolic disorders (0.86 (0.82–0.89)), acute pulmonary embolism (0.88 (0.83–0.94)), deep vein thrombosis (0.92 (0.87–0.97)), chronic phlebitis (0.86 (0.81–0.92)) and post-thrombotic sequelae (0.89 (0.87–0.92)), including pulmonary hypertension (0.82 (0.78–0.85)).

GLP-1RA use was associated with a reduced risk of myocardial infarction (0.91 (0.87–0.94)), cardiac arrest (0.78 (0.71–0.85)), incident heart failure (0.89 (0.87–0.91)), ischemic stroke (0.93 (0.90–0.96)) and hemorrhagic stroke (0.86 (0.78–0.95)). We also observed a reduced risk of acute kidney injury (0.88 (0.86–0.90)) and chronic kidney disease (0.97 (0.96–0.99)).

GLP-1RA use was associated with a reduced risk of infections, including bacterial infections (0.88 (0.86–0.90))—primarily driven by a reduced risk of bacterial pneumonia (0.89 (0.85–0.93)). There was also a reduced risk of septicemia (0.83 (0.80–0.86)), pneumonia (0.84 (0.82–0.86)), pneumonitis (0.89 (0.86–0.92)), aspiration pneumonitis (0.75 (0.69–0.81)), postprocedural respiratory complications (0.82 (0.74–0.91)), pleural effusion (0.86 (0.83–0.89)), COPD (0.9 (0.87–0.92)) and respiratory failure (0.77 (0.75–0.79)).

Our results also showed a reduced risk of anemia (0.97 (0.95–0.99)) and muscle pain (0.92 (0.90–0.94)). We also observed a reduced risk of hepatic failure (0.76 (0.69–0.84)), inflammatory bowel disease (0.88 (0.82–0.94)) and liver cancer (0.82 (0.75–0.89)) (Fig. 6 and Supplementary Table 9).

Risks of GLP-1RA by outcome. GLP-1RA use was associated with an increased risk of abdominal pain (1.12 (1.10,–1.13)), nausea and vomiting (1.30 (1.26–1.33)), GERD (1.14 (1.12–1.16)) and gastritis (1.10 (1.06–1.14)). GLP-1RA use was also associated with an increased risk of noninfectious gastroenteritis (1.12 (1.08–1.18)), gastroparesis (1.07 (1.02–1.13)) and diverticulosis and diverticulitis (1.08 (1.06–1.11)) (Fig. 6 and Supplementary Table 9).

There was also an increased risk of hypotension (1.06 (1.04–1.09)), syncope (1.06 (1.03–1.1)), sleep disturbances (1.12 (1.10–1.14)), headaches (1.10 (1.08–1.13)), arthritis (1.11 (1.09–1.13)), arthralgia (1.11 (1.09–1.13)), tendinitis and synovitis (1.10 (1.07–1.12)), interstitial nephritis (1.06 (1.03–1.09)) and nephrolithiasis (1.15 (1.12–1.19)). A targeted analysis of pancreatic disorders revealed an increased risk of drug-induced acute pancreatitis (2.46 (2.05–2.96)) (Fig. 6 and Supplementary Table 9).

Additional analyses

We further evaluated the signals detected in the main analyses (both increased risk and reduced risk) in a per-protocol analysis in which the treatment protocol required continued use of GLP-1RA throughout the follow-up period. The direction and magnitude of the associations were consistent with the main analysis; 56 of 61 (91.80%) significant associations in the main analyses were also statistically significant and in the same direction of risk in the per-protocol analyses. (Supplementary Table 10).

Sensitivity analyses

We conducted several sensitivity analyses. We restricted cohort enrollment to a subgroup of individuals who initiated GLP-1RA (and other antihyperglycemics) between 1 October 2017 and 2 June 2021 (the day before the US Food and Drug Administration granted approval for use of the GLP-1RA semaglutide for weight loss). We also conducted analyses to estimate the risk using cumulative incidence function and restricted mean survival time models. The results were consistent with the main findings (Supplementary Tables 11–13).

Positive and negative outcome controls

Positive and negative outcome controls were used to assess the presence of potential spurious biases from study design, variable specifications, covariate selection and adjustment approaches, and statistical analyses. We examined the association between GLP-1RA use and the positive outcome of control of weight loss, including a body mass index (BMI) decrease of 5 kg m^{-2} to 10 kg m^{-2}, and 10–30% weight loss from baseline, major adverse cardiovascular events (MACE) and major adverse kidney events (MAKE). Consistent with pretest expectations, GLP-1RAs were associated with decreased BMI and reduced risk of MACE and MAKE. We then examined the association between GLP-1RA use and the negative outcome control of accidental traffic injury. No associations were found between GLP-1RA use and the negative outcome control (Supplementary Table 14).

Discussion

In this study, we followed 1,955,135 individuals for a median of 3.68 (2.05–5.37) years—altogether corresponding to 7,239,854 person-years—to systematically map an atlas of the associations between GLP-1RA use and 175 health outcomes. We showed that, compared to several controls, GLP-1RA use was associated with broad pleiotropic effects, encompassing effectiveness and risks that extend beyond those currently recognized. Compared to the main control of usual care, GLP-1RA use was associated with a reduced risk of several substance use disorders, seizures, neurocognitive disorders (including Alzheimer's disease and dementia), coagulation and clotting disorders, cardiorenal and metabolic disorders, infectious illnesses, several respiratory conditions (for example, COPD), hepatic failure and inflammatory bowel disease. There was an increased risk of several gastrointestinal disorders, hypotension, syncope, arthritic disorders, nephrolithiasis, interstitial nephritis and drug-induced pancreatitis. Altogether, the data revealed broad pleiotropic effects, which may help guide clinical practice and inform future clinical and mechanistic research directions.

The findings showed that GLP-1RA use was associated with significant effects across a broad range of neuropsychiatric outcomes, including reduced risk of several substance use disorders (alcohol, cannabis, opioid and stimulant use disorders). Our results supplement previous evidence showing that GLP-1RA use is associated with a reduced risk of alcohol use disorders[26] and tobacco use disorders[27], as well as animal studies showing that GLP-1RAs may reduce the rewarding properties of alcohol and other addictive drugs[24,31–35]. The reduction in the risk of schizophrenia and other psychotic disorders complements

https://doi.org/10.1038/s41591-024-03412-w

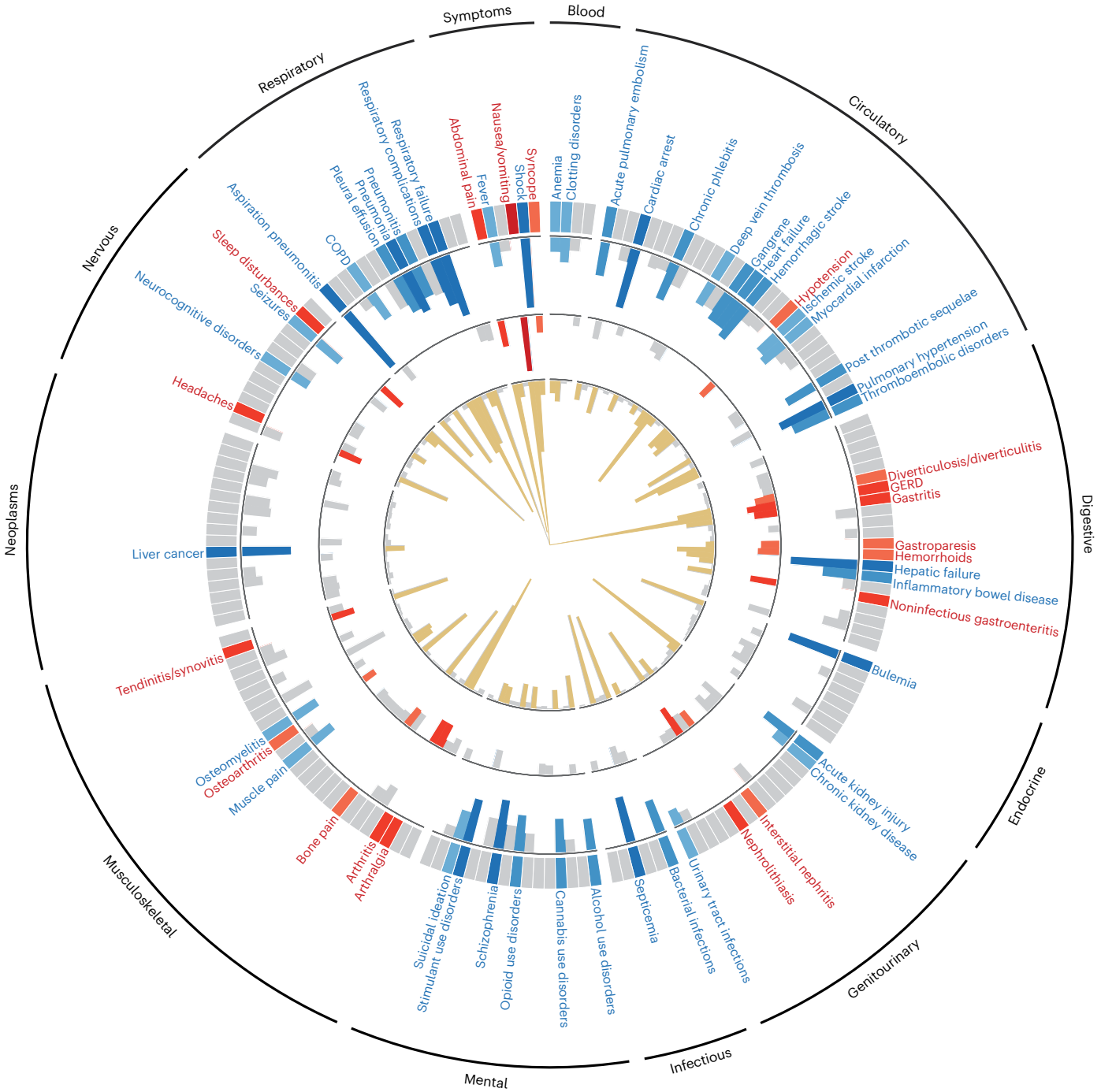


Fig. 4 | Systematic evaluation of the effectiveness and risks of incident GLP-1RA use compared to usual care. Comparisons between the GLP-1RA use group (n = 215,970) and the usual care control group of individuals with continued use of non-GLP-1RA antihyperglycemics (n = 1,203,097). The outermost ring represents the 12 diagnostic categories of outcomes that could be affected by GLP-1RA exposure in the adult population. The second ring from the outermost ring displays specific outcome names. Outcomes with increased risk (significant HR >1) are represented in red text, while outcomes with reduced risk (significant HR <1) are represented in blue text. The third ring from the outermost ring consisting of shaded blocks represents a heatmap displaying the HRs of the 175 outcomes. Outcomes with increased risk (significant HR >1) are shown in red, while those with reduced risk (significant HR <1) are shown in blue; gray, outcomes with a nonsignificant HR. The intensity of color shading represents the magnitude of the HR. The fourth ring from the outermost ring represents a histogram of HRs <1. The height of each bar corresponds to the inverse magnitude of the HR. Statistically significant HRs are shown as blue bars and the intensity of color shading corresponds to the magnitude of the HR; gray bars, nonsignificant HRs. The fifth ring from the outermost ring is a histogram of HRs >1. The height of each bar corresponds to the magnitude of the HR. Statistical significant HRs are shown as red bars and the intensity of color shading corresponds to the magnitude of the HR; gray bars, nonsignificant HRs. The innermost ring represents a histogram of the negative log-transformed P values for the HRs, where height represents the magnitude of the negative log-transformed P value: yellow bars, significant P values; gray bars, nonsignificant P values. All HRs were fully weighted for predefined and high-dimensional variables selected algorithmically. P values were based on two-sided Wald chi-squared tests. Benjamini–Hochberg correction for multiple tests was applied. COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; Postop, postprocedural; Schizophrenia, schizophrenia/other-psychotic-disorders; Suicidal ideation, suicidal ideation, attempt or intentional self-harm.

https://doi.org/10.1038/s41591-024-03412-w

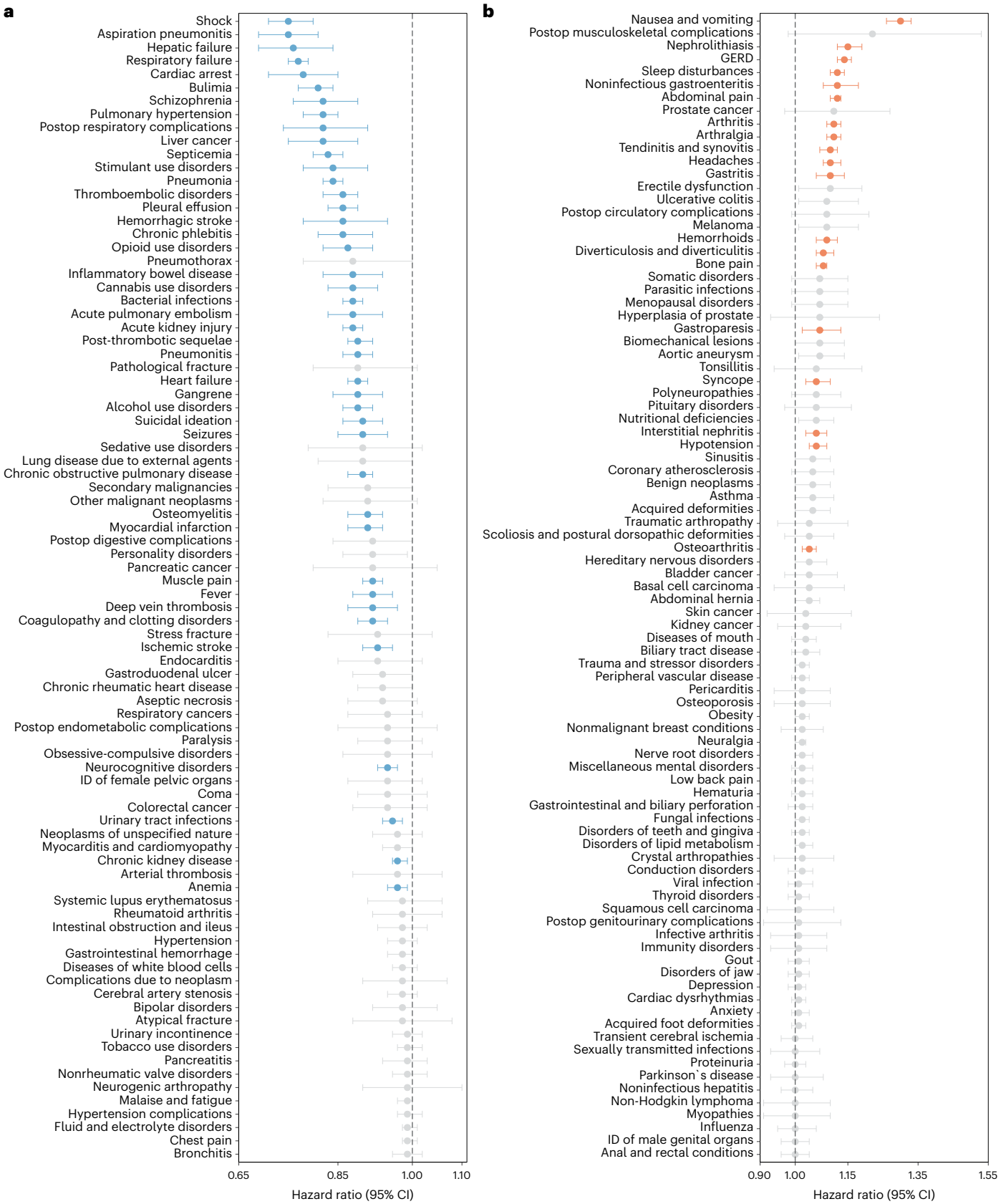


Fig. 5 | Forest plots for systematic evaluation of the effectiveness and risks of incident GLP-1RA use compared to usual care. a,**b**, Comparisons between the GLP-1RA use group (n = 215,970) and the usual care group who continued use of non-GLP-1RA antihyperglycemics (n = 1,203,097). **a**, Outcomes with HR <1 ranked by HR from low to high. **b**, Outcomes with HR ≥1 ranked by HR from high to low. Dots, HRs; 95% CIs of the HRs. Outcomes with statistically significant associations are shown in blue (reduced risk) or red (increased risk). P values were based on two-sided Wald chi-squared tests. Benjamini–Hochberg correction for multiple tests was applied. ID, inflammatory disease; Postop, postprocedural; schizophrenia, schizophrenia and other psychotic disorders; suicidal ideation, suicidal ideation, attempt or intentional self-harm.

https://doi.org/10.1038/s41591-024-03412-w

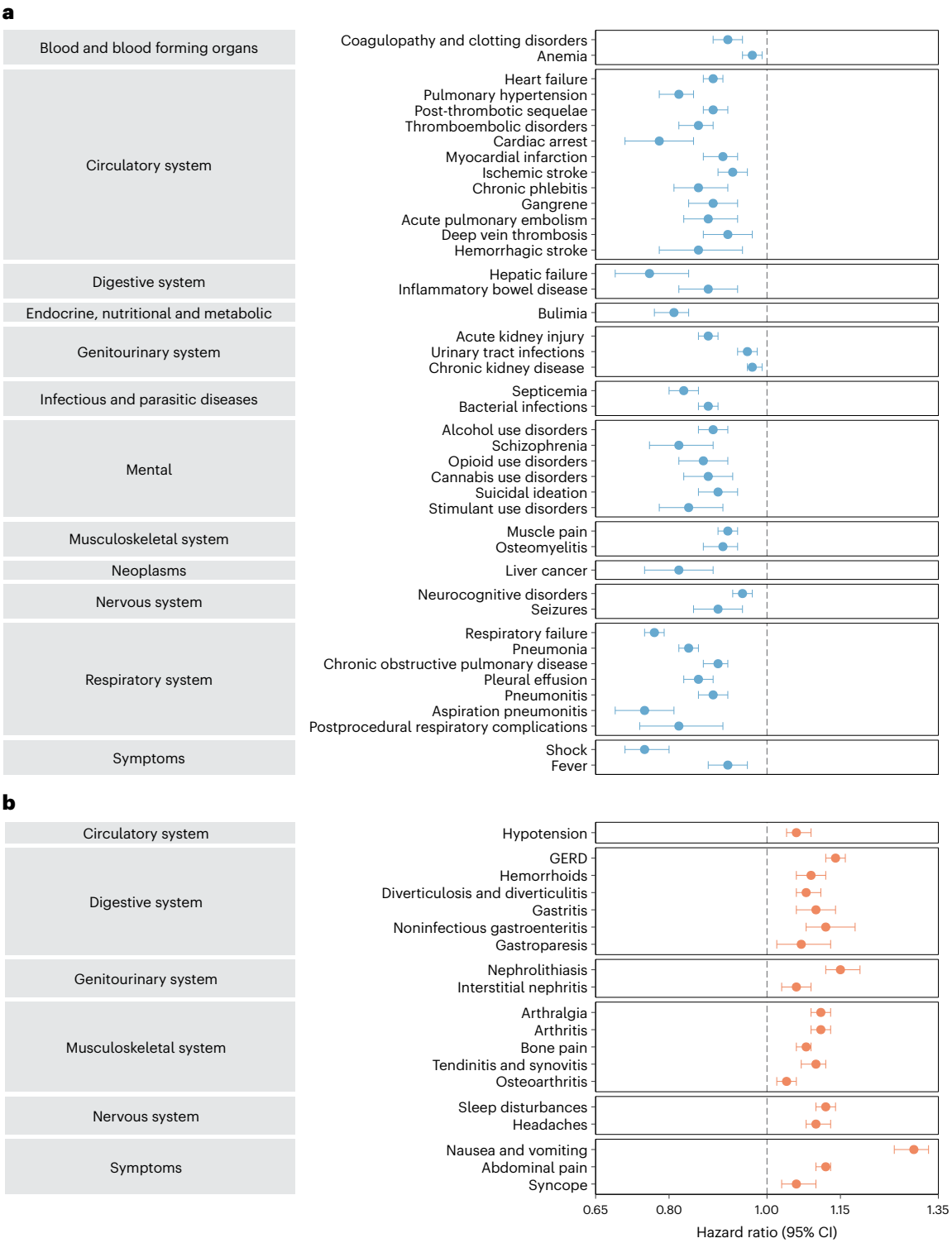


Fig. 6 | Outcomes with reduced or increased risks with incident GLP-1RA use compared to usual care. a,**b**, Comparisons between the GLP-1RA use group (n = 215,970) and the usual care group who continued use of non-GLP-1RA antihyperglycemics (n = 1,203,097). Shown are outcomes with reduced risk (**a**) and increased risk (**b**). Outcomes within each diagnostic category are ordered based on P value from lowest to highest. P values were based on two-sided Wald chi-squared tests. Benjamini–Hochberg correction for multiple tests was applied. Dots, HRs; 95% CIs of the HRs. COPD, chronic obstructive pulmonary disease; Schizophrenia, schizophrenia/other psychotic disorders; Suicidal ideation, suicidal ideation, attempt or intentional self-harm.

experimental data showing antipsychotic[36] effects in a mouse model of psychosis[37–39]. Our findings showed that GLP-1RA use reduced the risk of suicidal ideation, attempt or intentional self-harm. Initial reports raised concerns about suicidal thoughts and self-injury among GLP-1RA users, which prompted a 2023 review of GLP-1RA use by the European Medicines Agency; however, the review ultimately found no evidence of a causal link[40]. Our results are aligned with the European Medicines Agency's conclusions and are also consistent with studies by Wang and colleagues[23] supporting potentially reduced risk of suicidal ideation and potential antidepressive properties among GLP-1RA users.

Overall, our results extended the body of evidence on the potential utility of GLP-1RAs in neuropsychiatric disorders and suggest the need to further evaluate the biology and effectiveness of GLP-1RAs as either a primary or adjuvant therapeutic for use in the management of various substance use disorders, psychotic disorders and depressive disorders.

The results revealed evidence of the effectiveness of GLP-1RAs in neurocognitive disorders, including a reduced risk of dementia and Alzheimer's disease. GLP-1RA use was shown to reduce neuroinflammation, oxidative stress, amyloid β deposition and tau hyperphosphorylation in animal models of Alzheimer's disease[41–44]. Analyses of data from three randomized trials of GLP-1RA use in patients with type 2 diabetes and a nationwide Danish registry showed that the risk of dementia was lower in patients treated with GLP-1RAs[45]. The reduced risk of dementia was also evident in a recent analysis of health records that assessed several neuropsychiatric outcomes 12 months after use of GLP-1RA[46]. The neuroprotective effects of GLP-1RA are currently being evaluated in multiple randomized trials including evoke and evoke+, and the results are expected in 2025 (refs. 25,47).

The results also showed a reduced risk of seizures; these findings add to an emerging body of knowledge, both mechanistic and early clinical data, indicative of the anticonvulsant properties of GLP-1RA use[48]. GLP-1RAs should be further evaluated in future studies as potential adjuvant therapeutics for epilepsy and its associated comorbidities[49–51].

Consistent with evidence from randomized controlled trials, our results showed that GLP-1RAs reduced the risk of cardiovascular and renal outcomes, including heart failure[10], stroke[3,7], acute kidney injury[52], chronic kidney disease[8,52] and the composite outcomes of MACE[2–4,6–8,52] and MAKE[8,52]. The findings also revealed consistent associations between GLP-1RAs and the coagulation system, with a reduced risk of deep vein thrombosis, pulmonary embolism and post-thrombotic sequelae, including pulmonary hypertension. This is likely due to the effects of GLP-1RAs on endothelial function, platelet aggregation and thrombus formation demonstrated in vitro, ex vivo and in mouse models, as well as self-controlled clinical studies[53–58]. Because obesity is a major risk factor for thromboembolic disease, the anti-thromboembolic effect of GLP-1RA may also be partially (or wholly) mediated by their effect on weight[59].

However, our results also showed a hemodynamic effect of GLP-1RAs with an increased risk of hypotension and syncope. These results extend recent findings on the effectiveness of GLP-1RAs in reducing ambulatory blood pressure[60] and suggest that careful monitoring of blood pressure (and adjustment of antihypertensive medications) in individuals on GLP-1RA may be needed to avoid hypotension, which may be responsible for the increased risk of syncopal episodes[60–63].

There was also a reduced risk of sepsis, extending experimental evidence in mice of reduced oxidative stress, endotoxemia-induced microvascular thrombosis and reduced intravascular coagulation with GLP-1RAs[64–66]. These data also complement the analysis of the SELECT trial (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity), which showed that the GLP-1RA semaglutide reduced the risk of death due to infection and resulted in fewer COVID-19-related deaths than placebo[67].

Our results also revealed a reduced risk of hepatic failure, inflammatory bowel disease and diverticulitis associated with GLP-1RAs. This finding is likely attributable to the metabolic and anti-inflammatory properties of GLP-1RAs and the reduced risk of obesity-related cancers, including liver malignancies[68].

The results showed that GLP-1RAs were associated with a reduced risk of several respiratory illnesses, including pneumonia, COPD and respiratory failure. A previous meta-analysis of 28 randomized trials showed that GLP-1RA use was associated with a lower risk of respiratory diseases[69]. Emerging evidence also suggests a decreased risk of COPD with GLP-1RA use[70–72]. Furthermore, contrary to an earlier report suggesting an increased risk of postprocedural (endoscopy) aspiration pneumonia[73], our study and other reported data[74] do not corroborate this finding—the risk of postprocedural respiratory complications was 0.82 (0.74–0.91). The effects of GLP-1RAs on the respiratory system may be driven by reduced airway inflammation and oxidative stress and improved immunity and protease and antiprotease balance[75]; some of the effect may also be related to improved metabolic health and weight loss[69].

We reported that GLP-1RA use was associated with several adverse events, including in the gastrointestinal system[21], hypotension and syncopal episodes (discussed earlier in the context of hemodynamic effects of GLP-1RAs), sleep disturbances, headaches, joint pain and arthritic disorders, nephrolithiasis, interstitial nephritis and drug-induced pancreatitis. These adverse events should be further evaluated in future pharmacovigilance studies and should be monitored among patients taking GLP-1RAs.

Future investigations should leverage the pleiotropy of GLP-1RAs to evaluate their effectiveness in treating multimorbidities, rather than focusing on a single health condition, particularly where obesity or other mechanistic pathways affected by GLP-1RAs are leading drivers[76]. Furthermore, because of the substantial overlap between the biologic pathways activated by SARS-CoV-2 infection (leading to acute and postacute sequelae) and those influenced by GLP-1RAs, studies should also examine whether and to what extent GLP-1RAs may be useful in the prevention and treatment of sequelae (for example, cardiovascular and neurological) triggered by SARS-CoV-2 infection[77–84].

This study has several strengths. 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 the use of supportive and rehabilitative services. The US Department of Veterans Affairs offers comprehensive medical coverage, including prescription drug benefits, to all US veterans, so this approach reduced the likelihood that the choice of antihyperglycemic medication was influenced by the financial status of the patient. We conducted a systematic evaluation of the effectiveness and risks of GLP-1RA use in 175 health outcomes that could be plausibly impacted by GLP-1RA use in adults. We used an incident-user design and provide an atlas of head-to-head pairwise comparisons of GLP-1RAs versus three commonly used active comparators, a control composite of the three active comparators and a control representing usual care. We tested both positive and negative outcome controls to assess the presence of potential spurious biases.

Limitations of this study included using US veterans who are older, mostly white males, which may not represent the general population and could limit the generalizability of the results. This may be particularly true because the health effects of GLP-1RA use may vary across age, race, ethnicity and sex. However, due to the large size of our cohort, the study included 1,032,192 (5.28%) women; 30,846 (1.58%), 135,090 (6.91%) and 419,728 (21.47%) people aged less than 40, 50 and 60 years, respectively; and 357,228 (18.46%) and 201,123 (10.40%) individuals who identified as being of Black race or a race other than Black or white, respectively.

Although we used an active comparator design (to lessen differences between exposure and control groups) and adjusted using inverse weighting for a comprehensive set of covariates, including prespecified and algorithmically selected variables from multiple data domains, we cannot completely rule out the possibility of residual confounding or misclassification bias. We examined effect sizes by drug class; we did not examine within-class effects (that is, whether different GLP-1RAs have different effects). Our discovery approach tested 175 outcomes and we used Benjamini–Hochberg correction to correct for multiple testing. As a result, our approach will necessarily miss weaker signals that may not achieve statistical significance after correction. These signals might be detected in studies with a similar sample size but focus on a single outcome or a few prespecified outcomes where correction for multiple testing is not needed. In several

analyses, we evaluated the effects of GLP-1RAs compared to other active agents; the risk difference between GLP-1RAs and active agents may arise not only from the effects of GLP-1RAs but also from those of the active comparator.

Altogether, our discovery approach confirms previous studies and clinical trials and also uncovers previously unreported benefits and risks of GLP-1RAs. The results may be useful for informing clinical care, enhancing pharmacovigilance and guiding the development of mechanistic and clinical research to evaluate the broad pleiotropic effects of GLP-1RAs.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-024-03412-w.

References

1. Pfeffer, M. A. et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N. Engl. J. Med.* **373**, 2247–2257 (2015).
2. Marso, S. P. et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **375**, 311–322 (2016).
3. Marso, S. P. et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* **375**, 1834–1844 (2016).
4. Husain, M. et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* **381**, 841–851 (2019).
5. Holman, R. R. et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **377**, 1228–1239 (2017).
6. Hernandez, A. F. et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* **392**, 1519–1529 (2018).
7. Gerstein, H. C. et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* **394**, 121–130 (2019).
8. Gerstein, H. C. et al. Cardiovascular and renal outcomes with efpeglenatide in type 2 diabetes. *N. Engl. J. Med.* **385**, 896–907 (2021).
9. Perkovic, V. et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. *N. Engl. J. Med.* **391**, 109–121 (2024).
10. Kosiborod, M. N. et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* **389**, 1069–1084 (2023).
11. Gerstein, H. C. et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. *Lancet* **394**, 131–138 (2019).
12. Mann, J. F. E. et al. Liraglutide and renal outcomes in type 2 diabetes. *N. Engl. J. Med.* **377**, 839–848 (2017).
13. Muskiet, M. H. A. et al. Lixisenatide and renal outcomes in patients with type 2 diabetes and acute coronary syndrome: an exploratory analysis of the ELIXA randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol.* **6**, 859–869 (2018).
14. Tuttle, K. R. et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. *Lancet Diabetes Endocrinol.* **6**, 605–617 (2018).
15. Wilding, J. P. H. et al. Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* **384**, 989–1002 (2021).
16. Jastreboff, A. M. et al. Tirzepatide once weekly for the treatment of obesity. *N. Engl. J. Med.* **387**, 205–216 (2022).
17. Kelly, A. S. et al. A randomized, controlled trial of liraglutide for adolescents with obesity. *N. Engl. J. Med.* **382**, 2117–2128 (2020).
18. Wharton, S. et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. *N. Engl. J. Med.* **389**, 877–888 (2023).
19. Watanabe, J. H., Kwon, J., Nan, B. & Reikes, A. Trends in glucagon-like peptide 1 receptor agonist use, 2014 to 2022. *J. Am. Pharm. Assoc.* **64**, 133–138 (2024).
20. Hegland, T.A., Fang, Z. & Bucher, K. GLP-1 medication use for type 2 diabetes has soared.*JAMA* **332**, 952–953 (2024).
21. Sodhi, M., Rezaeianzadeh, R., Kezouh, A. & Etminan, M. Risk of gastrointestinal adverse events associated with glucagon-like peptide-1 receptor agonists for weight loss. *JAMA* **330**, 1795–1797 (2023).
22. Vidal, J., Flores, L., Jiménez, A., Pané, A. & de Hollanda, A. What is the evidence regarding the safety of new obesity pharmacotherapies. *Int. J. Obes.* https://doi.org/10.1038/s41366-024-01488-5 (2024).
23. Wang, W. et al. Association of semaglutide with risk of suicidal ideation in a real-world cohort. *Nat. Med.* **30**, 168–176 (2024).
24. Laurindo, L. F. et al. GLP-1a: going beyond traditional use. *Int. J. Mol. Sci.* **23**, 739 (2022).
25. Rubin, R. Could GLP-1 receptor agonists like semaglutide treat addiction, Alzheimer disease, and other conditions? *JAMA* **331**, 1519–1521 (2024).
26. Wang, W. et al. Associations of semaglutide with incidence and recurrence of alcohol use disorder in real-world population. *Nat. Commun.* **15**, 4548 (2024).
27. Wang, W. et al. Association of semaglutide with tobacco use disorder in patients with type 2 diabetes: target trial emulation using real-world data. *Ann. Intern. Med.* **177**, 1016–1027 (2024).
28. Drucker, D. J. The benefits of GLP-1 drugs beyond obesity. *Science* **385**, 258–260 (2024).
29. Lenharo, M. Why do obesity drugs seem to treat so many other ailments? *Nature* **633**, 758–760 (2024).
30. Al-Aly, Z., Xie, Y. & Bowe, B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* **594**, 259–264 (2021).
31. Leggio, L. et al. GLP-1 receptor agonists are promising but unproven treatments for alcohol and substance use disorders. *Nat. Med.* **29**, 2993–2995 (2023).
32. Wium-Andersen, I. K. et al. Use of GLP-1 receptor agonists and subsequent risk of alcohol-related events. A nationwide register-based cohort and self-controlled case series study. *Basic Clin. Pharmacol. Toxicol.* **131**, 372–379 (2022).
33. Klausen, M. K. et al. Exenatide once weekly for alcohol use disorder investigated in a randomized, placebo-controlled clinical trial. *JCI Insight* **7**, e159863 (2022).
34. Yammine, L., Balderas, J. C., Weaver, M. F. & Schmitz, J. M. Feasibility of exenatide, a GLP-1R agonist, for treating cocaine use disorder: a case series study. *J. Addict. Med.* **17**, 481–484 (2023).
35. Angarita, G. A. et al. Testing the effects of the GLP-1 receptor agonist exenatide on cocaine self-administration and subjective responses in humans with cocaine use disorder. *Drug Alcohol Depend.* **221**, 108614 (2021).
36. Dixit, T. S., Sharma, A. N., Lucot, J. B. & Elased, K. M. Antipsychotic-like effect of GLP-1 agonist liraglutide but not DPP-IV inhibitor sitagliptin in mouse model for psychosis. *Physiol. Behav.* **114–115**, 38–41 (2013).
37. Gunturu, S. The potential role of GLP-1 agonists in psychiatric disorders: a paradigm shift in mental health treatment. *Indian J. Psychol. Med.* **46**, 193–195 (2024).
38. López-Ojeda, W. & Hurley, R. A. Glucagon-like peptide 1: an introduction and possible implications for neuropsychiatry. *J. Neuropsychiatry Clin. Neurosci.* **36**, A4–A86 (2024).

39. Flintoff, J., Kesby, J. P., Siskind, D. & Burne, T. H. J. Treating cognitive impairment in schizophrenia with GLP-1RAs: an overview of their therapeutic potential. *Expert Opin. Investig. Drugs* **30**, 877–891 (2021).
40. European Medicines Agency. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8–11 April 2024. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-8-11-april-2024 (12 April 2024).
41. Du, H., Meng, X., Yao, Y. & Xu, J. The mechanism and efficacy of GLP-1 receptor agonists in the treatment of Alzheimer's disease. *Front. Endocrinol.* **13**, 1033479 (2022).
42. Mehan, S. et al. Potential roles of glucagon-like peptide-1 and its analogues in dementia targeting impaired insulin secretion and neurodegeneration. *Degener. Neurol. Neuromuscul. Dis.* **12**, 31–59 (2022).
43. Colin, I. M., Szczepanski, L. W., Gérard, A. C. & Elosegi, J. A. Emerging evidence for the use of antidiabetic drugs, glucagon-like peptide 1 receptor agonists, for the treatment of Alzheimer's disease. *touchREV. Endocrinol.* **19**, 16–24 (2023).
44. Lenharo, M. Obesity drugs have another superpower: taming inflammation. *Nature* **626**, 246 (2024).
45. Nørgaard, C. H. et al. Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. *Alzheimer's Dement.* **8**, e12268 (2022).
46. De Giorgi, R. et al. 12-month neurological and psychiatric outcomes of semaglutide use for type 2 diabetes: a propensity-score matched cohort study. *eClinicalMedicine* **74**, 102726 (2024).
47. Atri, A. et al. evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating the neuroprotective effects of semaglutide in early Alzheimer's disease. *Alzheimer's Dement.* **18**, e062415 (2022).
48. Manavi, M. A. Neuroprotective effects of glucagon-like peptide-1 (GLP-1) analogues in epilepsy and associated comorbidities. *Neuropeptides* **94**, 102250 (2022).
49. Wang, L. et al. Semaglutide attenuates seizure severity and ameliorates cognitive dysfunction by blocking the NLR family pyrin domain containing 3 inflammasome in pentylenetetrazole-kindled mice. *Int. J. Mol. Med.* **48**, 219 (2021).
50. Hussein, A. M. et al. Effects of GLP-1 receptor activation on a pentylenetetrazole–kindling rat model. *Brain Sci.* **9**, 108 (2019).
51. Liu, S. et al. The glucagon-like peptide-1 analogue liraglutide reduces seizures susceptibility, cognition dysfunction and neuronal apoptosis in a mouse model of Dravet syndrome. *Front. Pharmacol.* **11**, 136 (2020).
52. Sattar, N. et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.* **9**, 653–662 (2021).
53. Jia, G., Aroor, A. R. & Sowers, J. R. Glucagon-like peptide 1 receptor activation and platelet function: beyond glycemic control. *Diabetes* **65**, 1487–1489 (2016).
54. Drucker, D. J. The cardiovascular biology of glucagon-like peptide-1. *Cell Metab.* **24**, 15–30 (2016).
55. Sternkopf, M. et al. Native, intact glucagon-like peptide 1 is a natural suppressor of thrombus growth under physiological flow conditions. *Arter. Thromb. Vasc. Biol.* **40**, e65–e77 (2020).
56. Steven, S. et al. Glucagon-like peptide-1 receptor signalling reduces microvascular thrombosis, nitro-oxidative stress and platelet activation in endotoxaemic mice. *Br. J. Pharmacol.* **174**, 1620–1632 (2017).
57. Cameron-Vendrig, A. et al. Glucagon-like peptide 1 receptor activation attenuates platelet aggregation and thrombosis. *Diabetes* **65**, 1714–1723 (2016).
58. Zhang, Y., Chen, R., Jia, Y., Chen, M. & Shuai, Z. Effects of exenatide on coagulation and platelet aggregation in patients with type 2 diabetes. *Drug Des. Devel. Ther.* **15**, 3027–3040 (2021).
59. Horvei, L. D., Brækkan, S. K. & Hansen, J. B. Weight change and risk of venous thromboembolism: the Tromsø study. *PLoS ONE* **11**, e0168878 (2016).
60. de Lemos, J. A. et al. Tirzepatide reduces 24-hour ambulatory blood pressure in adults with body mass index ≥27 kg/m^2: SURMOUNT-1 Ambulatory Blood Pressure Monitoring Substudy. *Hypertension* **81**, e41–e43 (2024).
61. Goodwill, A. G. et al. Cardiovascular and hemodynamic effects of glucagon-like peptide-1. *Rev. Endocr. Metab. Disord.* **15**, 209–217 (2014).
62. Ribeiro-Silva, J. C., Tavares, C. A. M. & Girardi, A. C. C. The blood pressure lowering effects of glucagon-like peptide-1 receptor agonists: a mini-review of the potential mechanisms. *Curr. Opin. Pharmacol.* **69**, 102355 (2023).
63. Goud, A., Zhong, J., Peters, M., Brook, R. D. & Rajagopalan, S. GLP-1 agonists and blood pressure: a review of the evidence. *Curr. Hypertens. Rep.* **18**, 16 (2016).
64. Yang, F. et al. GLP-1 receptor: a new target for sepsis. *Front. Pharmacol.* **12**, 706908 (2021).
65. Helmstädter, J. et al. GLP-1 analog liraglutide improves vascular function in polymicrobial sepsis by reduction of oxidative stress and inflammation. *Antioxidants* **10**, 1175 (2021).
66. Yi, H. et al. Activation of glucagon-like peptide-1 receptor in microglia exerts protective effects against sepsis-induced encephalopathy via attenuating endoplasmic reticulum stress-associated inflammation and apoptosis in a mouse model of sepsis. *Exp. Neurol.* **363**, 114348 (2023).
67. Scirica, B. et al. The effect of semaglutide on mortality and COVID-19–related deaths.*JACC* **84**, 1632–1642 (2024).
68. Wang, L., Xu, R., Kaelber, D. C. & Berger, N. A. Glucagon-like peptide 1 receptor agonists and 13 obesity-associated cancers in patients with type 2 diabetes. *JAMA Netw. Open* **7**, e2421305 (2024).
69. Yu, M. et al. The relationship between the use of GLP-1 receptor agonists and the incidence of respiratory illness: a meta-analysis of randomized controlled trials. *Diabetol. Metab. Syndr.* **15**, 164 (2023).
70. Altintas Dogan, A. D. et al. Respiratory effects of treatment with a glucagon-like peptide-1 receptor agonist in patients suffering from obesity and chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* **17**, 405–414 (2022).
71. Foer, D. et al. Association of GLP-1 receptor agonists with chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes. *Am. J. Respir. Crit. Care Med.* **208**, 1088–1100 (2023).
72. Pradhan, R. et al. Novel antihyperglycaemic drugs and prevention of chronic obstructive pulmonary disease exacerbations among patients with type 2 diabetes: population based cohort study. *BMJ* **379**, e071380 (2022).
73. Yeo, Y.H. et al. Increased risk of aspiration pneumonia associated with endoscopic procedures among patients with glucagon-like peptide 1 receptor agonist use.*Gastroenterology* **167**, 402–404 (2024).
74. Dixit, A. A., Bateman, B. T., Hawn, M. T., Odden, M. C. & Sun, E. C. Preoperative GLP-1 receptor agonist use and risk of postoperative respiratory complications. *JAMA* **331**, 1672–1673 (2024).
75. Wang, W. et al. The role of glucagon-like peptide-1 receptor agonists in chronic obstructive pulmonary disease. *Int. J. Chron. Obstruct. Pulmon. Dis.* **18**, 129–137 (2023).
76. Langenberg, C., Hingorani, A. D. & Whitty, C. J. M. Biological and functional multimorbidity—from mechanisms to management. *Nat. Med.* **29**, 1649–1657 (2023).

77. Xie, Y., Choi, T. & Al-Aly, Z. Postacute sequelae of SARS-CoV-2 infection in the pre-Delta, Delta, and Omicron eras. *N. Engl. J. Med.* **391**, 515–525 (2024).
78. Cai, M., Xie, Y., Topol, E. J. & Al-Aly, Z. Three-year outcomes of post-acute sequelae of COVID-19. *Nat. Med.* **30**, 1564–1573 (2024).
79. Bowe, B., Xie, Y. & Al-Aly, Z. Postacute sequelae of COVID-19 at 2 years. *Nat. Med.* **29**, 2347–2357 (2023).
80. Xu, E., Xie, Y. & Al-Aly, Z. Long-term gastrointestinal outcomes of COVID-19. *Nat. Commun.* **14**, 983 (2023).
81. Xu, E., Xie, Y. & Al-Aly, Z. Risks and burdens of incident dyslipidaemia in long COVID: a cohort study. *Lancet Diabetes Endocrinol.* **11**, 120–128 (2023).
82. Xie, Y., Choi, T. & Al-Aly, Z. Long-term outcomes following hospital admission for COVID-19 versus seasonal influenza: a cohort study. *Lancet Infect. Dis.* **24**, 239–255 (2024).
83. Al-Aly, Z. & Topol, E. Solving the puzzle of long Covid. *Science* **383**, 830–832 (2024).
84. Al-Aly, Z. et al. Long COVID science, research and policy. *Nat. Med.* **30**, 2148–2164 (2024).

Methods

Ethics statement

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 number 1606333).

Setting

We used the US Department of Veterans Affairs databases, which maintain the electronic health records of all enrollees in the system since 1 October 1999 (refs. 85–88). The VA operates an integrated healthcare system comprising 143 hospitals and 1,241 outpatient clinics. All veterans enrolled in the system have access to a comprehensive package of medical benefits, including inpatient and outpatient services, preventative and primary care, specialty care, geriatric care, mental care, home care, extended care and rehabilitation services, prescription medication coverage and medical equipment and prosthetics coverage.

Data sources

The study was conducted using data from electronic health records stored in the VA Corporate Data Warehouse. Data domains included the Outpatient Encounters domain and Inpatient Encounters domain, Outpatient Pharmacy domain, Laboratory Results domain, Vital Signs domain, Patient domain, and VA Vital Status and Health Factors domain[89]. Medicare data from the VA Information Resource Center were used to collect information on care that occurred outside the VA health system[90]. The Area Deprivation Index based on individuals' residential location was also collected.

Cohort construction

The cohort flow is presented in Fig. 1. We first identified 252,766 individuals with type 2 diabetes who used a GLP-1RA between 1 October 2017 and 31 December 2023. During this time there were 232,210 incident GLP-1RA users. We then removed individuals with contraindications for any of the antihyperglycemics, including those with a history of medullary thyroid carcinoma, multiple endocrine neoplasia type II, gastroparesis, estimated glomerular filtration rate (eGFR) < 30 ml min^{-1} 1.73 m^{-2}, dialysis or kidney transplant, hypoglycemia with coma and hypoglycemia requiring hospitalization, resulting in 215,970 individuals in the GLP-1RA group.

We then constructed the control groups of sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors from the 826,407 individuals with type 2 diabetes who used sulfonylureas, DPP4 inhibitors or SGLT2 inhibitors between 1 October 2017 and 31 December 2023. Within this group, there were 247,146 incident sulfonylurea users, 225,116 incident DPP4 inhibitor users and 429,172 incident SGLT2 inhibitor users. T_0 for each participant was defined as the date of their incident prescription. Individuals who were in more than one of the three control groups were randomly selected into one of the control groups based on randomly generated numbers from uniform distributions. The random selection process resulted in 173,478 individuals in the sulfonylureas control group, 129,546 individuals in the DPP4 inhibitors control group and 301,670 individuals in the SGLT2 inhibitors control group. To remove the potential lag effect from historical use of GLP-1RA in the sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors control groups, we then removed those who had used a GLP-1RA within 1 year before T_0, resulting in 168,483 individuals in the sulfonylureas control group, 126,097 individuals in the DPP4 inhibitors control group and 273,672 individuals in the SGLT2 inhibitors control group. After removing individuals with contraindications, a total of 159,465 were included in the sulfonylureas control group, 117,989 were included in the DPP4 inhibitors control group and 258,614 were included in the SGLT2 inhibitors control group. We also combined the sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors control groups (n = 536,068) and applied inverse weighting based on the proportion of each medication class in the combined group to construct a control group with equal proportions of incident sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors use.

Separately, we also constructed a usual care control group of those who continued their prior non-GLP-1RA antihyperglycemic regimen without additional new antihyperglycemic therapy, which included 1,513,896 individuals with a refill prescription of any non-GLP-1RA antihyperglycemics between 1 October 2017 and 31 December 2023. T_0 for each individual was randomly selected from one of the qualified dates of refills during the enrollment period. Removing individuals who had used GLP-1RA within 1 year before T_0 resulted in 1,409,950 individuals remaining in the usual care control group. We then removed individuals with contraindications, resulting in 1,203,097 individuals in the usual care control group. Individuals from all groups were followed until death or 31 July 2024, whichever came first.

Exposures

Exposures for the study, including incident use of GLP-1RAs, sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors, were defined based on outpatient pharmacy records. The GLP-1RA class included liraglutide, exenatide, semaglutide, dulaglutide, tirzepatide and albiglutide; the sulfonylurea class included glyburide, glipizide and glimepiride; the DPP4 inhibitor class included alogliptin, saxagliptin, sitagliptin and linagliptin; and the SGLT2 inhibitor class included canagliflozin, dapagliflozin, empagliflozin and ertugliflozin (Supplementary Table 15). Historical use of medication was defined as the use of any medication within the medication class within 1 year before T_0. Comparisons between GLP-1RA and active exposure controls were conducted separately in populations without a history of GLP-1RA use and the control medications. For example, the GLP-1RA arm used in the comparison between GLP-1RAs and sulfonylureas was a subset of incident GLP-1RA users without a history of sulfonylurea use. The control group consisting of an equal distribution of sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors, was also constructed by combining the three groups and assigning inverse weighting based on the proportion of each antihyperglycemic class in the combined group to form an equal distribution of the three medications. Usual care was defined as a continued prior non-GLP-1RA antihyperglycemic regimen without additional new therapy at the time of cohort enrollment.

Outcomes

We evaluated health outcomes in 12 diagnostic categories that could be affected by exposure in the adult population. The outcome definitions were adapted from the Clinical Classifications Software Refined classification version 2024.1 (https://hcup-us.ahrq.gov/toolssoftware/ccsr/ccs_refined.jsp). Outcome categories included blood and blood-forming organs, circulatory system, digestive system, endocrine, nutritional and metabolic system, genitourinary system, infectious and parasitic diseases, mental health, musculoskeletal system, neoplasms, nervous system, respiratory system and symptoms. We did not examine outcomes with an event number less than 250 during follow-up (equivalent to an event rate less than 0.08 per 100 person-years) in any arm. The final set included 175 outcomes. In the analyses for each outcome, we examined the risk of an incident outcome in individuals without a history of that outcome within 2 years before T_0.

Covariates

We prespecified a set of covariates based on prior knowledge[91–95]; we also used a set of algorithmically selected covariates[96–99]. The covariates were measured within 2 years before T_0, unless otherwise specified. For variables with repeated measurements, the measurements before and closest to T_0 were selected.

The prespecified covariates included sociodemographic variables, including age, race (white, Black and other), sex and Area Deprivation Index; vital measurements, including blood pressure and BMI;

laboratory measurements, including glycated hemoglobin (HbA1c) at baseline, average HbA1c within 1 year and separately within 5 years before T_0, eGFR, albuminuria and low-density lipoprotein; and comorbidities, including duration of diabetes from October 1999 until T_0, acute kidney injury, cancer, HIV, hyperlipidemia, urinary tract infections, nonalcoholic fatty liver disease, thyroid disorders, nutritional deficiencies, bulimia, fluid and electrolyte disorders, pituitary disorders, postprocedural endometabolic complications, chronic rheumatic heart disease, nonrheumatic valve disorders, endocarditis, myocarditis and cardiomyopathy, pericarditis, myocardial infarction, coronary atherosclerosis, chest pain, acute pulmonary embolism, pulmonary hypertension, conduction disorders, cardiac dysrhythmias, cardiac arrest, heart failure, hemorrhagic stroke, cerebral artery stenosis, ischemic stroke, peripheral vascular disease, gangrene, aortic aneurysm, arterial thrombosis, hypotension, thromboembolic disorders, chronic phlebitis, deep vein thrombosis, post-thrombotic sequelae, postprocedural circulatory complications, gastroparesis, disorders of teeth and gingiva, diseases of the mouth, GERD, abdominal hernia, ulcerative colitis, intestinal obstruction and ileus, diverticulosis and diverticulitis, hemorrhoids, anal and rectal conditions, peritonitis and intra-abdominal abscess, biliary tract disease, hepatic failure, gastrointestinal hemorrhage, noninfectious gastroenteritis, noninfectious hepatitis and postprocedural digestive system complications.

We also adjusted for health behavior, including smoking status, influenza vaccination status, colonoscopy and esophagoscopy, and history of medication use, including history of use of statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (ACE/ARB), β-blockers, diuretics, calcium channel blockers, proton pump inhibitors, H_2 blockers, bupropion, naltrexone, orlistat, phentermine, topiramate, metformin, sulfonylureas, thiazolidinediones, DPP4 inhibitors, SGLT2 inhibitors and insulin. We also adjusted for the duration of metformin, sulfonylureas, thiazolidinediones, DPP4 inhibitors, SGLT2 inhibitors, and insulin use within 5 years before T_0. We also adjusted for healthcare utilization, including the number of outpatient encounters, number of hospitalizations, number of prescriptions, number of blood panel tests, number of HbA1c measurements and number of outpatient encounters and hospitalizations using Medicare. We additionally adjusted for the calendar week of treatment assignment and the health system where the incident prescription was issued to account for temporal and geographical variations in medication preferences and treatment guidelines. Covariates were also collected and accounted for during follow-up for the per-protocol analysis. Values were missing for HbA1c in 2.78%, eGFR in 4.94%, low-density lipoprotein in 4.39%, blood pressure in 1.90% and BMI data in 6.90% of individuals. We applied multivariate imputation using chained equations to assign values based on the predictive mean matching method[100]. Continuous variables were adjusted in the form of restricted cubic splines with knots at the 5th, 35th, 65th and 95th percentiles[101].

In addition to prespecified covariates, we used a high-dimensional variable selection approach to algorithmically select potential confounders or proxies of unmeasured confounders[102,103]. Variables were algorithmically selected from the data domains, including diagnostic codes, medication records, and laboratory test results and were assessed 1 year before T_0. The 100 variables with the strongest univariate bias scores in the relationship between exposure and outcome were selected[102,103]. The selection process was conducted independently for each control arm and for each outcome. Algorithmically selected variables were used along with prespecified variables in logistic regression.

Statistical analyses

Baseline characteristics for the GLP-1RA group, the sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors control groups, the equal-proportion control group and the usual care control group were presented as means and standard deviations or frequencies and proportions as appropriate. Balances between the GLP-1RA group and each of the control groups were evaluated through absolute standardized differences, where a value less than 0.1 was considered evidence of good balance[104].

Inverse probability weighting was used to balance baseline characteristics between the GLP-1RA arm and each of the control arms independently. For each of the two-arm active exposure comparisons, we first selected a subset of individuals in the GLP-1RA arm without a history of use of the control medication, along with the control medication arm, to build the analytic cohort. We then estimated the probability of individuals being assigned to the GLP-1RA arm (the propensity score) given covariates based on logistic regression. The individuals with limited overlap in covariate distribution determined by a propensity score of less than 0.1 or larger than 0.9, were removed[105]. The propensity score was then recomputed in a separate logistic regression for the remaining individuals. Inverse probability weights were constructed as the propensity score/(1−propensity score) for the control arm and 1 for the GLP-1RA arm. The weights were then applied to the Cox survival model to estimate the adjusted HR. Death was considered a competing risk and individuals were censored at the time of death.

To provide a more comprehensive evaluation of the health effects of GLP-1RAs, we conducted head-to-head analyses to compare the risks of GLP-1RAs versus each of the three antihyperglycemics independently. We also compared GLP-1RAs with a control comprising an equal distribution of the sulfonylureas, DPP4 inhibitors and SGLT2 inhibitors control groups and also compared the GLP-1RA group with the usual care control group.

We further examined the per-protocol effect on outcomes that displayed significant associations with GLP-1RA use in the main analyses. The treatment protocol was defined as continued use of GLP-1RA during follow-up. Time-updated inverse probability of treatment weights was applied when individuals in the GLP-1RA group did not refill their GLP-1RA prescription more than 90 days after the last date of supply. Time-updated inverse probability of censoring weights was applied to both the GLP-1RA and control groups when death occurred[106].

We conducted several sensitivity analyses. We restricted cohort enrollment to a subgroup of individuals who initiated GLP-1RAs (and other antihyperglycemics) between 1 October 2017 and 2 June 2021 (the day before the US FDA granted approval for use of the GLP-1RA semaglutide for weight loss), compared to the main analyses, which enrolled individuals between 1 October 2017 and 31 December 2023; we also conducted analyses to estimate risk based on cumulative incidence function and restricted mean survival time models compared to the main analyses, which were based on Cox survival models[107,108].

We tested positive and negative outcome controls to assess the presence of potential spurious biases from study design, variable specification, cohort construction, covariate adjustment and statistical analyses[92–95]. Because of the well-established association between GLP-1RAs and weight loss, we examined the association between GLP-1RA use and BMI decreases of 5 to 10 kg m^{-2}, 10–30% weight loss from baseline as a positive outcome control. We also examined the association between GLP-1RA use and MACE—a composite of myocardial infarction, stroke and all-cause mortality, and MAKE—a composite of incident macroalbuminuria, doubling of serum creatinine, >50% decline in eGFR, end-stage kidney disease and all-cause mortality, as positive outcome controls. Because of the lack of prior evidence or biological mechanism of a plausible association between GLP-1RA use and accidental traffic injury, we examined the risk of accidental traffic injury as a negative outcome control.

We reported point estimates and 95% CIs for estimated results. Benjamini–Hochberg correction for multiple tests was applied when

systematic examinations were conducted for each exposure–control pair comparison[109]. Analyses were conducted using the Statistical Analysis System enterprise guide 8.3, and data visualizations were produced using R v4.3.3.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The data that support the findings of this study are available from the US Department of Veterans Affairs. VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center (VIReC) at VIReC@va.gov.

Code availability

The analytic code is available at https://github.com/yxie618/GLP1.

References

85. Xie, Y. et al. Proton pump inhibitors and risk of incident CKD and progression to ESRD. *J. Am. Soc. Nephrol.* **27**, 3153–3163 (2016).
86. Xie, Y. et al. Risk of death among users of proton pump inhibitors: a longitudinal observational cohort study of United States veterans. *BMJ Open* **7**, e015735 (2017).
87. Xie, Y. et al. Long-term kidney outcomes among users of proton pump inhibitors without intervening acute kidney injury. *Kidney Int.* **91**, 1482–1494 (2017).
88. Xie, Y. et al. Higher blood urea nitrogen is associated with increased risk of incident diabetes mellitus. *Kidney Int.* **93**, 741–752 (2018).
89. Maynard, C. Ascertaining veterans' vital status: VA data sources for mortality ascertainment and cause of death. https://www.hsrd.research.va.gov/for_researchers/cyber_seminars/archives/3783-notes.pdf (2017).
90. Cai, M. et al. Temporal trends in incidence rates of lower extremity amputation and associated risk factors among patients using Veterans Health Administration services from 2008 to 2018. *JAMA Netw. Open* **4**, e2033953 (2021).
91. Xie, Y. et al. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of major adverse cardiovascular events: emulation of a randomised target trial using electronic health records. *Lancet Diabetes Endocrinol.* **11**, 644–656 (2023).
92. Xie, Y. et al. Clinical implications of estimated glomerular filtration rate dip following sodium–glucose cotransporter-2 inhibitor initiation on cardiovascular and kidney outcomes. *J. Am. Heart Assoc.* **10**, e020237 (2021).
93. Xie, Y. et al. Comparative effectiveness of sodium–glucose cotransporter 2 inhibitors vs sulfonylureas in patients with type 2 diabetes. *JAMA Intern. Med.* **181**, 1043–1053 (2021).
94. Xie, Y. et al. Comparative effectiveness of SGLT2 inhibitors, GLP-1 receptor agonists, DPP-4 inhibitors, and sulfonylureas on risk of kidney outcomes: emulation of a target trial using health care databases. *Diabetes Care* **43**, 2859–2869 (2020).
95. Xie, Y. et al. Comparative effectiveness of the sodium–glucose cotransporter 2 inhibitor empagliflozin versus other antihyperglycemics on risk of major adverse kidney events. *Diabetes Care* **43**, 2785–2795 (2020).
96. Xie, Y., Choi, T. & Al-Aly, Z. Nirmatrelvir and the risk of post-acute sequelae of COVID-19.*JAMA Intern. Med.* **183**, 554–564 (2023).
97. Xie, Y., Bowe, B. & Al-Aly, Z. Nirmatrelvir and risk of hospital admission or death in adults with Covid-19: emulation of a randomized target trial using electronic health records. *BMJ* **381**, e073312 (2023).
98. Xie, Y., Bowe, B. & Al-Aly, Z. Molnupiravir and risk of hospital admission or death in adults with Covid-19: emulation of a randomized target trial using electronic health records. *BMJ* **380**, e072705 (2023).
99. Xie, Y., Choi, T. & Al-Aly, Z. Molnupiravir and risk of post-acute sequelae of Covid-19: cohort study. *BMJ* **381**, e074572 (2023).
100. van Buuren, S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat. Methods Med. Res.* **16**, 219–242 (2007).
101. Harrell, F. E. *Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis* (Springer, 2015).
102. Schneeweiss, S. Automated data-adaptive analytics for electronic healthcare data to study causal treatment effects. *Clin. Epidemiol.* **10**, 771–788 (2018).
103. Schneeweiss, S. et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* **20**, 512–522 (2009).
104. Austin, P. C. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat. Med.* **28**, 3083–3107 (2009).
105. Crump, R. K., Hotz, V. J., Imbens, G. W. & Mitnik, O. A. Dealing with limited overlap in estimation of average treatment effects. *Biometrika* **96**, 187–199 (2009).
106. Hernan, M. A. & Robins, J. M. *Causal Inference: What If* (CRC Press, 2010).
107. Uno, H. et al. Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. *J. Clin. Oncol.* **32**, 2380–2385 (2014).
108. Andersen, P. K., Hansen, M. G. & Klein, J. P. Regression analysis of restricted mean survival time based on pseudo-observations. *Lifetime Data Anal.* **10**, 335–350 (2004).
109. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J. R. Stat. Soc. B* **57**, 289–300 (1995).

Acknowledgements

Support for VA and Centers for Medicare and Medicaid Services data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (Project Number/Data Use Agreement ID Al-Aly-01-A-1). This research was funded by the US Department of Veterans Affairs (to Z.A.A.). The funder of this study had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The contents do not represent the views of the US Department of Veterans Affairs or the US government.

Author contributions

Research area and study design: Y.X., Z.A.A.; data acquisition: Y.X., T.Y., Z.A.A.; data analysis and interpretation: Y.X., T.Y., Z.A.A.; statistical analysis: Y.X., T.Y., Z.A.A.; drafting the manuscript Y.X., Z.A.A.; critical revision of the manuscript Y.X., T.Y., Z.A.A.; administrative, technical, or material support: Z.A.A.; supervision and mentorship: Z.A.A. 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. Z.A.A. takes responsibility that this study has been 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. Y.X. and Z.A.A. had full access to all data and Y.X. and Z.A.A. verified the accuracy of the underlying data.

Competing interests
Y.X. and Z.A.A. are uncompensated consultants for Pfizer. No other potential competing interests relevant to this article are reported.

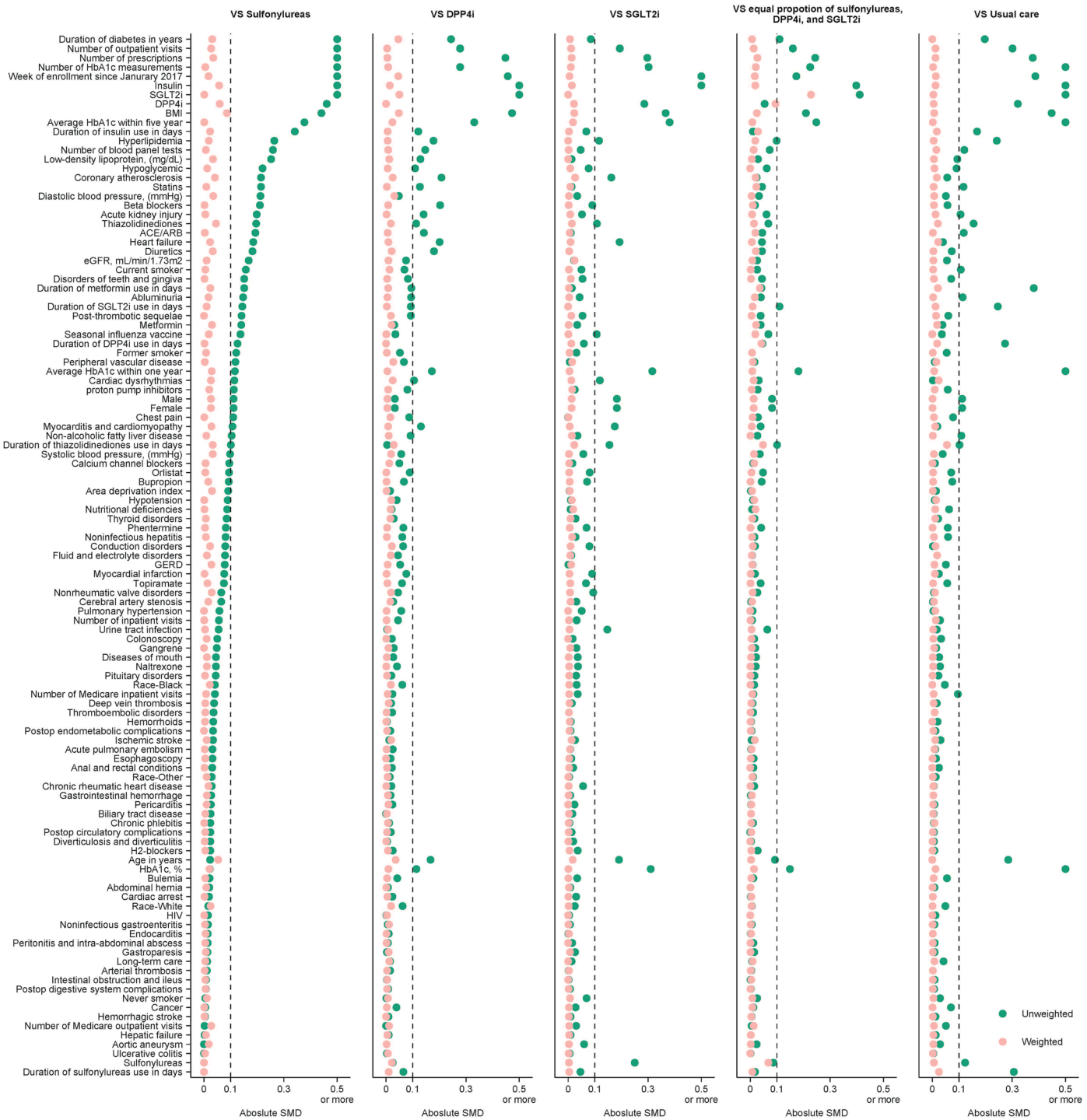
Additional information
Extended data is available for this paper at https://doi.org/10.1038/s41591-024-03412-w.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-024-03412-w.

Correspondence and requests for materials should be addressed to Ziyad Al-Aly.

Peer review information *Nature Medicine* thanks the anonymous reviewers for their contribution to the peer review of this work. Primary Handling Editor: Ming Yang, in collaboration with the *Nature Medicine* team.

https://doi.org/10.1038/s41591-024-03412-w



Extended Data Fig. 1 | Standardized mean differences of covariates in incident GLP-1RA compared to sulfonylureas, DPP4i, SGLT2i, a control composited of equal proportion of incident sulfonylureas, DPP4i, SGLT2i use and a control of participants who received usual care before and after weighting. X-axis: absolute standardized mean difference from 0 to 0.5 where a value larger than 0.5 was plotted as 0.5. A value of less than 0.1 indicates balance was achieved. eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; ACE/ARB, angiotensin converting enzyme inhibitors/angiotensin-receptor blockers Postop, Postprocedural; GLP-1RA, glucagon-like peptide-1 receptor agonist; DPP4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

nature portfolio

Corresponding author(s): Ziyad Al-Aly

Last updated by author(s): Oct 25, 2024

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☒	☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	SAS Enterprise Guide version 8.3 was used to collect data for the study.
Data analysis	Analyses were conducted using Statistical Analysis System (SAS) enterprise guide 8.3 and data visualizations were produced by R 4.3.3. Analytic codes are available at https://github.com/yxie618/GLP1

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The data that support the findings of this study are available from the US Department of Veterans Affairs. VA data are made freely available to researchers behind the VA firewall with an approved VA study protocol. For more information, please visit https://www.virec.research.va.gov or contact the VA Information Resource Center (VIReC) at VIReC@va.gov

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Information on sex was collected based on patient-self reported sex in the electronic health record. In the study cohort, 94.72% of the participants were male. Sex was balanced between groups during analyses. No sex based analyses were undertaken.
Reporting on race, ethnicity, or other socially relevant groupings	Information on race was collected based on patient-self reported race in the electronic health record. In the study cohort, 71.19% of the participants were White, 18.43% were Black, and 10.39% were of other race. Race was balanced between groups during analyses. No race based analyses were undertaken.
Population characteristics	The study included participants with a mean age 68.26 years; 71.19% were of white race, 18.43% were of black race and 94.72% were males.
Recruitment	Participants were identified based on criteria for cohort enrollment as specified in the methods section -- including incident users of GLP-1RA, sulfonylureas, DPP4i, SGLT2i and those received usual care between October 01, 2017 and December 31, 2023.
Ethics oversight	This study was approved by the institutional review board of the VA St. Louis Health Care System (protocol number 1606333).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	We enrolled 215,970 participants in the GLP-1RA arm, 159,465 in the sulfonylureas control arm, 117,989 in the DPP4i control arm, 258,614 in the SGLT2i control arm and 1,203,097 in the usual carecontrol arm.. We did not use any statistical methods to predetermine the sample size because we enrolled all veterans who met our inclusion criteria.
Data exclusions	We predefined our exclusion criteria and excluded participants who had a contraindication for any of the diabetes medications including those with history of medullary thyroid carcinoma, multiple endocrine neoplasia type II, gastroparesis, eGFR<30 mL/min/1.73m2, received dialysis or kidney transplant, hypoglycemia with coma and hypoglycemia requiring hospitalization.
Replication	The finding was not replicated because no external dataset with similar features is available to us.
Randomization	We conducted an observational study. Exposure allocation was not random. To balance the exposure groups, covariates were adjusted for through the inverse probability weighting method.
Blinding	We conducted an observational study. Blinding was not possible.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	Not applicable.
Novel plant genotypes	Not applicable.
Authentication	Not applicable.