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# Treatment Intensification with GLP-1 Receptor Agonists and Digestive Cancer Risk in Type 2 Diabetes: A Global Target Trial Emulation

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**Research Article**

**Keywords:** GLP-1 receptor agonists, type 2 diabetes, digestive cancers, real-world evidence, target trial emulation

**Posted Date:** November 24th, 2026

**DOI:** https://doi.org/10.21203/rs.3.rs-11591019/v1

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**Additional Declarations:** No competing interests reported.

## Abstract

# Background

Type 2 diabetes mellitus (T2DM) substantially increases the risk of digestive malignancies. GLP-1 receptor agonists (GLP-1 RAs) exert great metabolic effects, yet evidence for cancer-related benefit in the early treatment intensification remains limited. We evaluated whether early treatment intensification GLP-1 RA is associated with a lower risk of major digestive cancers compared with other antidiabetic agents.

# Methods

Using the global TriNetX network, we emulated a target trial among treatment-naïve adults with type 2 diabetes who initiated metformin and subsequently required treatment intensification within 6 months. Comparators included insulin, sulfonylureas (SU), dipeptidyl peptidase-4 inhibitor (DPP-4i), and SGLT2 inhibitors (SGLT2i). After 1:1 propensity score matching on 71 pre-specified covariates, Cox proportional hazards models estimated hazard ratios (HRs) for incident digestive cancers, defined as a composite of hepatocellular carcinoma and pancreatic, colorectal, gastric, and esophageal cancer.

# Results

Among 223,159 eligible patients, 41,354 candidate GLP-1 RA users were separately 1:1 propensity-score matched against each comparator. GLP-1 RA use was associated with a lower risk of any digestive cancer versus insulin (HR 0.68, 95% CI 0.59–0.79), sulfonylureas (HR 0.75, 95% CI 0.64–0.88), DPP-4i (HR 0.81, 95% CI 0.64–0.99), and SGLT2i (HR 0.80, 95% CI 0.68–0.95). Associations were directionally consistent across subgroups defined by female, age (≥ 65 years), BMI (≥ 35 kg/m²), and HbA1c.

# Conclusions

In this large, global target trial emulation, early treatment intensification of GLP-1 RAs, compared with insulin, sulfonylureas, DPP-4i, or SGLT2i, was associated with a lower risk of digestive cancers among people with type 2 diabetes.

## Background

The global burden of digestive malignancies, including hepatocellular carcinoma (HCC), colorectal, pancreatic, gastric, and esophageal cancers, continues to escalate [1], with distinct geographic patterns documented by GLOBOCAN and Global Burden of Disease assessments[2]. In type 2 diabetes mellitus (T2DM), this oncogenic risk is further exacerbated: large European and Asian cohorts of over 80,000 gastrointestinal cancer patients show a high prevalence of comorbid diabetes, with pancreatic cancer

showing the strongest association (hazard ratio [HR] 1.54 vs non-diabetic individuals)[3, 4]. The American Diabetes Association (ADA) 2025 Standards of Care reiterates that diabetes confers elevated risk for liver, pancreatic, and colorectal cancers and recommends age-appropriate screening[5]. Rapid escalation of antidiabetic treatment within six months of new-onset diabetes has also been linked to increased pancreatic cancer risk [6].

Metformin remains the most widely used first-line therapy[7], with strong evidence for reduced risk of multiple digestive cancers [8–12], but progressive disease often necessitates second-line intensification, for which current guidelines do not prioritize a specific agent. GLP-1 RAs have gained prominence beyond glycemic control[13], offering pleiotropic benefits across multiple organ systems [14], including substantial weight reduction [15], attenuation of hepatic steatosis[16], and mitigation of systemic inflammation[17], all mechanisms relevant to cancer biology. However, most prior studies of GLP-1 RAs and cancer risk have examined first-line use [18, 19] or obesity-specific subpopulations[20], settings that do not reflect the second-line context in which GLP-1 RAs are increasingly initiated. Meta-analyses of randomized trials also lack head-to-head comparisons and rigorous washout periods, raising concern for protopathic bias and conflicting results[21, 22]. We therefore used the global TriNetX research network (> 200 million patients) to compare GLP-1 RAs against four active second-line antidiabetic agents, evaluating whether early second-line GLP-1 RA initiation is associated with digestive cancer incidence across five major malignancies in a real-world population.

# Methods

This retrospective cohort study used the TriNetX research network, aggregating de-identified data from 186 healthcare organizations in more than 50 countries (> 200 million patients), from January 1, 2018, to January 1, 2026. We followed the target trial emulation framework of Hernán and Robins[23, 24] (Supplementary Table S1), estimating the 5-year intention-to-treat-type effect of GLP-1 RA initiation vs each active comparator on incident digestive cancer, under assumptions of consistency, positivity, conditional exchangeability, and correct classification of treatment and outcomes.

Eligible participants were adults ≥ 18 years with T2DM who had been first treated with metformin and required early second-line intensification within 6 months, without prior digestive cancer (Supplementary Table S2). The exposure was GLP-1 RA initiation vs one of four active comparators: insulin, sulfonylureas (SU), DPP-4 inhibitors (DPP-4i), or SGLT2 inhibitors (SGLT2i), excluding patients with prior or concurrent use of another second-line agent (Supplementary Table S2). To approximate randomization, 1:1 propensity score matching was performed on 71 prespecified covariates (Supplementary Table S3), including demographics (age, sex, race/ethnicity, socioeconomic status); comorbidities and T2DM complications (eg, alcohol-related disorders, overweight, hyperlipidemia, nicotine dependence, ischemic heart disease, chronic kidney disease, cerebrovascular disease, heart failure); organ-specific cancer risk factors (eg, cirrhosis and chronic viral hepatitis B/C for HCC; inflammatory bowel disease and familial adenomatous polyposis for colorectal cancer; chronic pancreatitis for pancreatic cancer; H. pylori infection and gastric intestinal metaplasia for gastric cancer; GERD and Barrett's esophagus for

esophageal cancer); metabolic profile (BMI, HbA1c); renal function (glomerular filtration rate); cancer-surveillance procedures (ultrasound, CT); healthcare-utilization intensity (emergency department visits); and statin, aspirin, and proton-pump-inhibitor use. Laboratory and urinary biomarkers particularly relevant to the SGLT2i comparison (eg, urine albumin-to-creatinine ratio, serum albumin, fecal occult blood testing) were not included because they are not consistently captured as structured data across TriNetX sites (see Limitations). BMI and HbA1c were missing for 33% to 50% of patients and were matched and summarized using complete-case data without imputation. Covariate balance after matching was defined as a standardized mean difference (SMD) < 0.1. E-values were calculated to assess the robustness of the associations to unmeasured confounding (Supplementary Table S8).

Follow-up began at second-line initiation (index date) and continued until outcome, death, loss to follow-up, or 5 years (or October 10, 2026), whichever came first, emulating intention-to-treat (follow-up metrics are reported in Supplementary Table S5); lagged-outcome sensitivity analyses were also performed (Supplementary Figure S1). The outcome was incident digestive cancer (HCC, colorectal, pancreatic, gastric, or esophageal cancer) occurring after the index date (diagnostic codes in Supplementary Table S4). Cox proportional hazards models estimated HRs and 95% CIs within matched cohorts. Subgroup analyses were prespecified by sex, age, BMI, and HbA1c, with the index date defined as when patients first met the subgroup criterion and initiated a second-line agent. Because numerous HRs were estimated across 5 cancer subtypes, 4 comparator classes, and multiple subgroups without correction for multiplicity, all estimates are reported as point estimates with 95% CIs and interpreted associationally rather than as significance tests; subtype- and subgroup-specific estimates should be regarded as exploratory and hypothesis-generating.

All analyses were performed using the TriNetX analytic platform (R 4.0.2, survival package 3.2-3). Competing-risk models were not implemented because Fine-Gray methods are not supported by this platform; cell counts < 10 were masked per TriNetX policy. This study used de-identified data and did not require institutional review board approval.

# Results

Between January 1, 2018, and January 1, 2026, 9,037,564 adults with T2DM were identified, of whom 1,216,127 were treatment-naive metformin initiators. After excluding 986,050 patients who did not initiate a second-line agent within 6 months or who received only a thiazolidinedione (TZD) or acarbose, and 6,918 patients with prior digestive cancer, 223,159 patients entered the risk set. After excluding prior/concurrent use of other second-line agents, 41,354 candidate GLP-1 RA users were separately matched 1:1 to insulin, SU, DPP-4i, and SGLT2i users, yielding 33,395, 24,986, 12,116, and 22,217 matched pairs (Fig. 1); TZD and acarbose were not analyzed as comparators owing to insufficient sample size. All covariates achieved standardized mean differences < 0.1 after matching (Supplementary Table S9).

GLP-1 RA therapy was associated with lower risk of any digestive cancer vs insulin (HR 0.68, 95% CI 0.59–0.79), SU (HR 0.75, 95% CI 0.64–0.88), DPP-4i (HR 0.81, 95% CI 0.64–0.99), and SGLT2i (HR 0.80, 95% CI 0.68–0.95) over 5 years (Fig. 2); Kaplan Meier estimated cumulative event probability are shown in Fig. 3.

For HCC, point estimates favored GLP-1 RA vs insulin (HR 0.61, 95% CI 0.43–0.87) and SU (HR 0.69, 95% CI 0.46-1.00), while CIs for DPP-4i (HR 0.64, 95% CI 0.38–1.07) and SGLT2i (HR 0.90, 95% CI 0.59–1.36) crossed the null. For pancreatic cancer, risk was lower vs insulin (HR 0.56, 95% CI 0.43–0.73), SU (HR 0.75, 95% CI 0.56-1.00), and SGLT2i (HR 0.68, 95% CI 0.51–0.93), with a less precise estimate vs DPP-4i (HR 0.85, 95% CI 0.56–1.29). Colorectal cancer showed a similar pattern: lower risk vs insulin (HR 0.79, 95% CI 0.62-1.00), SU (HR 0.72, 95% CI 0.56–0.93), and SGLT2i (HR 0.74, 95% CI 0.57–0.96), with an imprecise estimate vs DPP-4i (HR 0.89, 95% CI 0.64–1.24).

Gastric and esophageal cancer estimates were imprecise and largely null (HRs 0.71–1.03), with CIs spanning 1.0 in nearly every comparison and point estimates at or above 1.0 for SU and SGLT2i on gastric cancer (Fig. 4); these site-specific findings do not support a consistent association and should be interpreted cautiously given few events. Crude incidence rates of digestive cancer among GLP-1 RA initiators ranged from 3.21 to 4.19 per 1,000 person-years across the four matched comparator cohorts, compared with 4.52 to 4.88 per 1,000 person-years among comparator initiators (Supplementary Table S6). These descriptive incidence rates were directionally consistent with the primary Cox proportional hazards estimates. However, differences in follow-up duration and the absence of competing-risk-adjusted cumulative incidence estimates precluded reliable estimation of 5-year absolute risk differences or numbers needed to treat.

## Stratified Analyses

The inverse association was directionally consistent across all four comparators in both sexes, age groups (< 65 vs ≥ 65 years), BMI strata (< 30, 30-<35, ≥ 35 kg/m²), and HbA1c strata (< 7% vs ≥ 7%) (Fig. 5). Associations vs insulin excluded the null in 8 of 9 strata, with the upper confidence limit reaching 1.00 for age < 65 years, whereas associations vs SU excluded the null in 7 of 9 strata and crossed the null only for male sex and age < 65 years. Associations vs DPP-4i and SGLT2i followed the same direction but less consistently excluded the null, with CIs crossing 1.0 for male sex, age < 65 years, and BMI 30-<35 kg/m² for both agents, and additionally for BMI < 30 kg/m² and HbA1c < 7% for DPP-4i. Estimates were most consistently precise among female patients, those ≥ 65 years, BMI ≥ 35 kg/m², and HbA1c ≥ 7%, concordant with exploratory tests of heterogeneity (Supplementary Table S7), which identified age and, for the SGLT2i comparison, sex as interaction terms least compatible with no effect modification (nominal P<.05, unadjusted). Point estimates in strata where CIs crossed the null remained below 1.0 (HRs 0.75–0.99), most likely reflecting reduced precision rather than true heterogeneity. Inverse associations were preserved among patients with BMI ≥ 35 kg/m² across all comparators (HRs 0.58–0.76), indicating the association was not confined to lower-weight patients, though subgroup findings alone cannot establish a weight-independent mechanism. Prespecified interaction tests were

exploratory and unadjusted for multiplicity, and should be interpreted as hypothesis-generating rather than confirmatory (Supplementary Table S7).

## Sensitivity Analysis

Associations remained directionally consistent across all sensitivity analyses, with attenuated but generally inverse HRs. Extending the lag period to 6, 12, and 24 months attenuated the estimates toward the null (for example, HR vs insulin 0.77, 0.84, and 0.89, respectively), although all point estimates remained below 1.0 and the 24-month estimate remained statistically significant only versus SGLT2i (HR 0.77, 95% CI 0.63–0.95) (Supplementary Figure S1). Restricting first-line metformin exposure to 3–6 months and 6–12 months yielded point estimates below 1.0 for all comparators (HRs 0.61–0.95), although the confidence intervals included 1.0 for SU, DPP-4i, and SGLT2i in the 3–6 month window and for DPP-4i and SGLT2i in the 6–12 month window (Supplementary Figures S2-S3). A negative-control analysis using basal cell carcinoma showed null associations across all comparators (all CIs spanning 1.0; Supplementary Figure S4). Specifying individual GLP-1 RA brands (semaglutide, Supplementary Figure S5; liraglutide/dulaglutide, Supplementary Figure S6) also yielded directionally consistent inverse associations. E-values for the primary estimates ranged from 1.77 to 2.30, with E-values for the lower confidence limits ranging from 1.11 to 1.85 (Supplementary Table S8).

## Discussion

To our knowledge, this is the largest head-to-head comparative effectiveness study evaluating digestive cancer risk across major second-line antidiabetic classes. Unlike prior studies of treatment-naive populations, we emulated the clinical decision point of second-line intensification. The GLP-1 RA vs insulin comparison is most susceptible to confounding by indication, as insulin is preferentially prescribed to patients with longer diabetes duration and greater metabolic burden, factors independently associated with cancer risk that may not be fully captured even after matching on 71 covariates. Comparisons with SU, DPP-4i, and SGLT2i, in which disease severity at initiation is more comparable between groups, are likely less susceptible to this bias and thus more informative for inferring an oncologic association of GLP-1 RAs.

Gastric and esophageal cancer estimates were imprecise and inconsistent (HRs 0.71–1.03, CIs spanning the null in nearly every comparison), probably reflecting few site-specific events rather than a true absence of association; these should not be read as evidence of benefit at these sites. The subgroup findings in Fig. 5 merit closer consideration. Inverse associations were preserved, and in several comparisons strengthened, among patients with BMI ≥ 35 kg/m² across all four comparator classes, consistent with reports that the oncologic benefit of GLP-1 RAs is most pronounced in obesity, where excess adiposity itself drives several digestive malignancies[20]; because weight reduction is also greatest in this subgroup, our data cannot dissociate a weight-mediated from a weight-independent pathway. The association was also more consistently precise in women than men, with a nominally

significant sex interaction for the GLP-1 RA-vs-SGLT2i comparison, consistent with reports that GLP-1 RAs produce greater relative weight loss in women [25], and sex differences in GLP-1 physiology and receptor signaling have been described[26], either of which could translate into a larger reduction in the hyperinsulinemia-IGF-1-PI3K/AKT/mTOR signaling that drives gastrointestinal carcinogenesis[26–29]. Similarly, the association was more consistently precise among patients ≥ 65 years, with a nominally significant age interaction for the insulin and SGLT2i comparisons; older patients carry a longer cumulative duration of hyperglycemic exposure and greater insulin resistance, both linked to higher digestive cancer risk [3, 26, 27], though more frequent surveillance and more complete comorbidity documentation in this group cannot be excluded as an alternative explanation. The association was directionally consistent across both HbA1c strata (HRs 0.61–0.77 for ≥ 7% and 0.63–0.75 for < 7%), with no interaction term approaching significance, suggesting the signal is not solely attributable to differential glycemic control and raising the possibility of a glucose-independent component, as proposed for GLP-1 RAs' anti-inflammatory and immunomodulatory actions. Together with the formal interaction testing (Supplementary Table S7), these patterns identify sex and age, rather than BMI or glycemic control, as the most likely effect modifiers in this cohort, and should motivate prospective studies testing sex- and age-stratified effects rather than being treated as confirmatory evidence of differential benefit.

The consistently lower risk across comparator cohorts probably reflects overlapping pathways. GLP-1 RAs have well-documented effects on weight reduction, insulin sensitivity, and systemic inflammation, all key drivers of gastrointestinal tumorigenesis. Obesity and hyperinsulinemia drive carcinogenesis through IGF-1 upregulation[27, 28], PI3K/AKT/mTOR pathway activation[29, 30], and chronic low-grade inflammation[31]. At the same time, GLP-1 RAs reduce pro-inflammatory cytokines such as TNF-α and IL-6, mitigating the chronic inflammation that facilitates the progression of preneoplastic lesions[32, 33]. GLP-1 signaling may also modulate the tumor immune microenvironment, enhancing NKT cell activity and reducing M2 macrophage polarization to bolster antitumor surveillance[34]. Reduction in hepatic steatosis and systemic inflammatory markers[35], together with improvement in MASLD [36] and suppression of lipotoxicity-driven fibrosis, offers one possible explanation for the strong inverse association observed for HCC.

Concerns about increased pancreatic cancer risk with incretin-based therapies derive from observational studies susceptible to detection bias and reverse causation [37]. Our extended lag analyses (6, 12, and 24 months) consistently showed inverse associations, arguing against a purely protopathic-bias explanation, though reverse causation from long-latency malignancies cannot be fully excluded. Prior database studies have often not specifically addressed GLP-1 RAs initiated as second-line therapy, and many used excessively long follow-up periods, which in real-world data increases loss to follow-up and attrition bias, undermining internal validity[18, 38].

While both GLP-1 RAs and SGLT2i improve cardiometabolic outcomes, their biological effects differ: GLP-1 RAs exert more pronounced effects on weight loss, visceral adiposity, hepatic steatosis, and inflammatory signaling, which may be more relevant to digestive carcinogenesis[33, 39], whereas SGLT2i

act primarily through glycosuria and hemodynamic mechanisms [40, 41] with less direct influence on insulin-IGF signaling and gut-liver inflammatory axes.

Compared with Kuo et al.[19], who analyzed GLP-1 RA users regardless of treatment line without restricting to metformin-experienced patients, our study specifically targeted the second-line prescribing scenario dominating real-world practice. In contrast to Wang et al[18] whose target trial emulation examined pancreatic cancer alone with early-generation agents, our analysis spans five digestive cancer subtypes across all approved GLP-1 RA classes and four comparator classes within a unified framework.

Several limitations warrant acknowledgment. First, as an observational study using electronic health records, residual confounding from unmeasured factors, most notably diabetes duration, frailty, recent unintentional weight loss, and genetic predisposition, cannot be entirely excluded, although our extensive propensity-score matching on 71 baseline covariates mitigated many known confounders. Diabetes duration in particular could not be reliably ascertained in TriNetX, because the platform captures the timing of diagnosis-code entry rather than true disease onset; cancer-surveillance and healthcare-utilization covariates were included as matched variables but remain coarse proxies for true screening and surveillance intensity rather than direct measures of it. Second, the study period (2018–2026) spans a period of substantial change in GLP-1 RA prescribing, with uptake concentrated in more recent years when cancer screening and general metabolic care were also more intensive; because this calendar-time trend could affect both exposure ascertainment and outcome detection in the same direction, it represents a potential source of residual confounding and detection bias that an active-comparator, propensity-matched design does not fully eliminate, and that we were unable to address with a calendar-period-stratified sensitivity analysis within the current TriNetX query structure; this should be pursued in future replications. Third, competing mortality was not explicitly accounted for using a competing-risk framework. Although Cox proportional hazards models were used to estimate the association between treatment initiation and subsequent digestive cancer diagnoses, death before cancer diagnosis represents a competing event that may influence the interpretation of cumulative event probabilities. Fine–Gray sub distribution hazard models were not available within the analytic platform, and treatment-specific mortality estimates were not separately obtained. Consequently, the direction and magnitude of potential bias arising from differential mortality between treatment groups could not be determined. The findings should therefore be interpreted as association with the hazard of diagnosed digestive cancer rather than definitive reductions in absolute cancer risk. Future studies incorporating cause-specific and sub distribution hazard analyses are warranted. Fourth, TriNetX's lack of a formal active-censoring mechanism precluded precise number-at-risk reporting. Fifth, BMI and HbA1c were missing for 33% to 50% of patients; informative missingness could leave residual imbalance despite matching on observed values. Finally, regional differences in screening and health care access may still influence findings despite TriNetX's global scope.

# Conclusions

In this global propensity-score-matched cohort study emulating the clinical decision to initiate second-line glucose-lowering therapy, GLP-1 receptor agonist initiation was associated with a lower hazard of diagnosed digestive cancer compared with insulin, sulfonylureas, DPP-4 inhibitors, and SGLT2 inhibitors. The associations were more apparent for hepatocellular, pancreatic, and colorectal cancers, whereas evidence for gastric and esophageal cancers was inconclusive. Given the observational design, potential residual confounding, and the lack of competing-risk-adjusted absolute risk estimates, these findings should not be interpreted as establishing a causal cancer-preventive effect. Further studies with longer follow-up and competing-risk analyses are warranted.

# Abbreviations

T2DM, type 2 diabetes mellitus; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, Sodium-Glucose Cotransporter 2 inhibitors; SU, sulfonylurea; TZD, thiazolidinedione; HCC, Hepatocellular Carcinoma; PSM, Propensity Score Matching; NNT, Number Needed to Treat; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; GERD, Gastroesophageal Reflux Disease; BMI, body mass index; HbA1c, glycated hemoglobin; HRs, Hazard ratios; CI, Confidence Interval.

# Declarations

### Conflict of interest disclosure

The authors declare no competing interests.

### Ethics approval statement

This study did not require institutional review board approval as it involved analysis of de-identified data from the TriNetX global health research network without access to identifiable personal information.

### Patient consent statement

Consent was waived because the study used de-identified data from the TriNetX research network.

### Funding Statement

This research is not supported by any funding.

### Author's contributions

Kuan-Yi Sung: Statistical analysis and interpretation of the data, figure preparation and drafting of the manuscript.

Yen-Po Wang: Data collection and revision of the manuscript.

Fang-Yu Chen, Chi-Yang Chang: Critical revision of the article for important intellectual content.

Chun-Ying Wu: Contributed to the study conception, critical revision of the article and final approval of the article

**Acknowledgements**

The authors have no acknowledgments to declare.

**Data Availability Statement**

The data used in this study were obtained from the TriNetX Research Network. Because of data-use and privacy restrictions, the underlying patient-level data cannot be shared directly by the authors. Researchers with appropriate access to TriNetX may reproduce the analyses using the cohort definitions and codes provided in the Supplementary Material.

**Declaration of Generative AI Use**

During the preparation of this manuscript, the authors used a generative AI tool (Claude, Anthropic) to assist with language editing. The AI tool was not used to generate, analyze, or interpret the underlying study data, and was not used as an author. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of this publication.

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# Figures

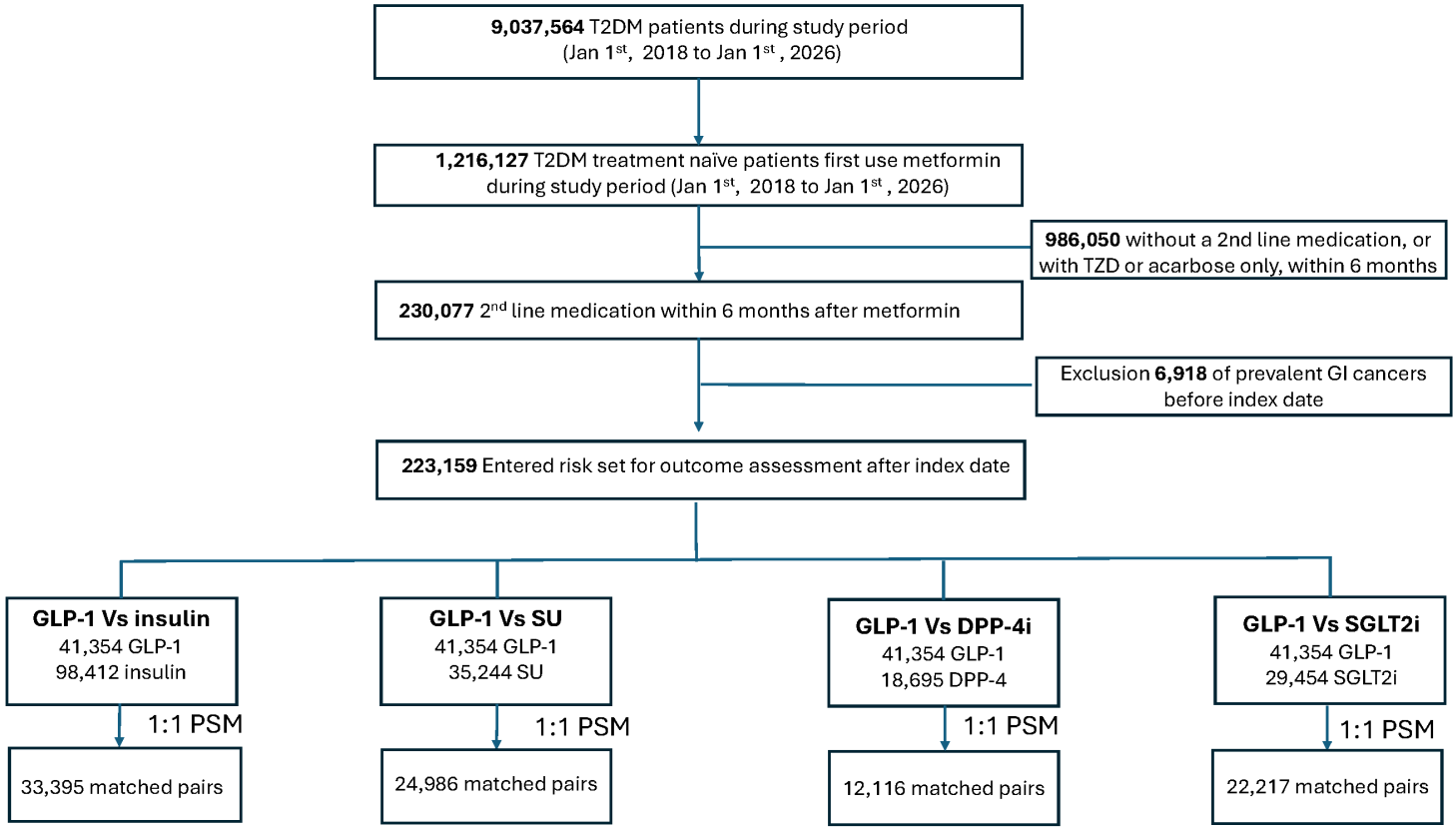
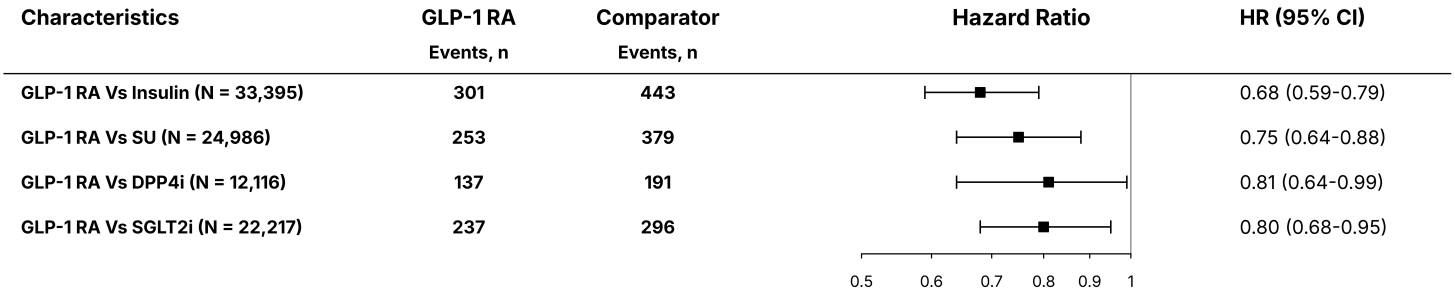



**Figure 1**

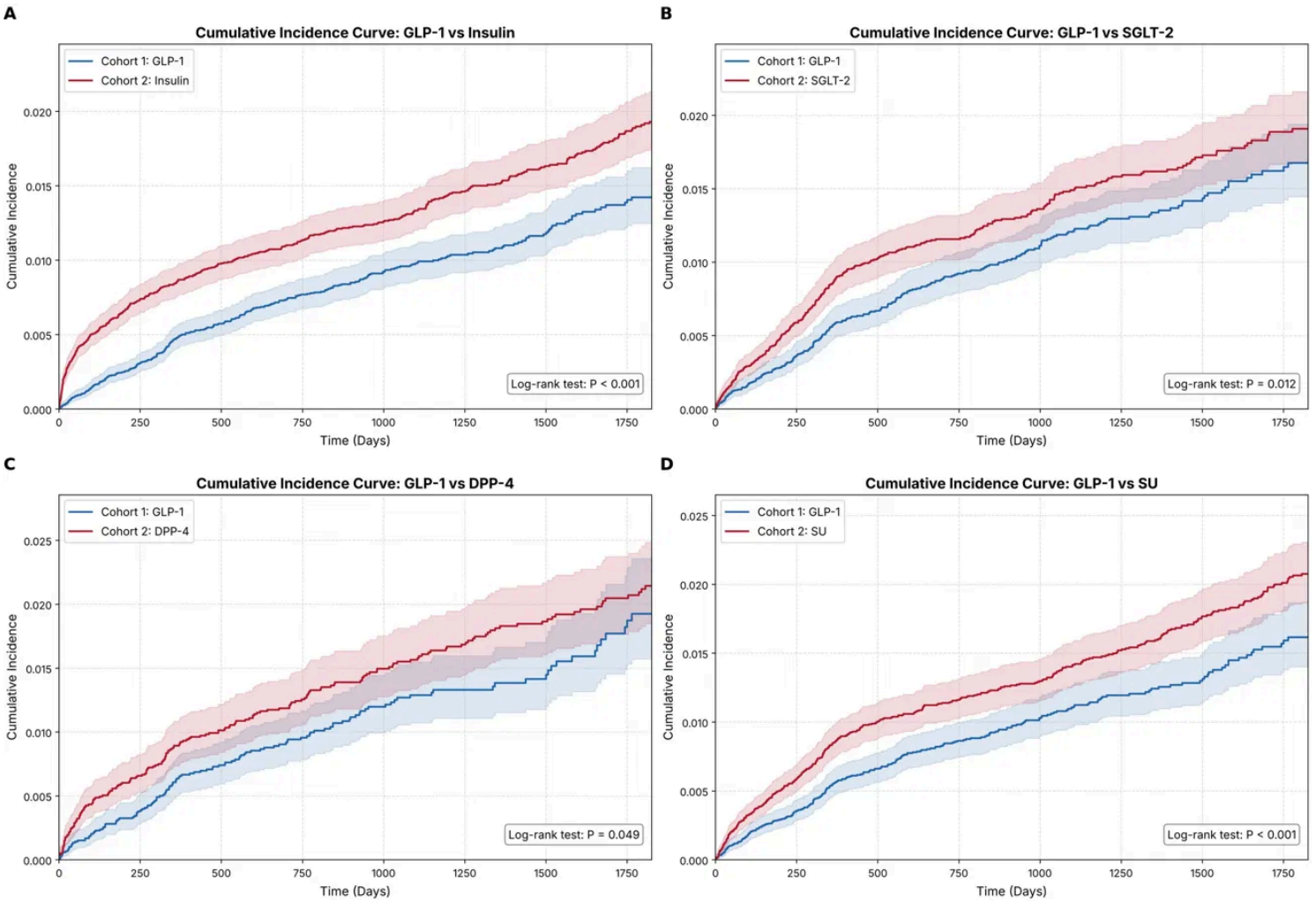
Flowchart of cohort selection and propensity score matching.
This flow diagram illustrates the identification and selection of study cohorts from the TriNetX database. A total of 9,037,564 patients with type 2 diabetes mellitus (T2DM) during the study period (January 1, 2018, to January 1, 2026) were screened. Among these, 1,216,127 treatment-naïve patients who initiated metformin were identified. Of these, 230,077 patients subsequently initiated a second-line glucose-lowering therapy and were eligible for inclusion, while 986,050 patients who did not receive a second-line agent within 6 months or who received only a thiazolidinedione (TZD) or acarbose were excluded. After excluding 6,918 patients with a diagnosis of digestive cancer prior to the index date, 223,159 patients entered the risk set for outcome assessment. Patients were categorized into four comparison cohorts based on second-line therapy exposure, excluding concurrent use of comparator medications. Propensity score matching (PSM) at a 1:1 ratio was performed separately for each of the four comparisons, starting from the same pool of 41,354 candidate GLP-1 RA initiators matched in turn

against each comparator-eligible pool (98,412 insulin, 35,244 SU, 18,695 DPP-4i, and 29,454 SGLT2i initiators); because the size of the comparator-eligible pool, and the degree of covariate overlap with GLP-1 RA initiators, differed across the four comparators, the number of patients retained after 1:1 matching also differed, yielding 33,395 matched pairs for GLP-1 RA versus insulin, 24,986 pairs for GLP-1 RA versus SU, 12,116 pairs for GLP-1 RA versus DPP-4i, and 22,217 pairs for GLP-1 RA versus SGLT2i. T2DM, type 2 diabetes mellitus; PSM, propensity score matching; GLP-1, glucagon-like peptide-1; SU, sulfonylurea; DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter-2 inhibitor.




## Figure 2

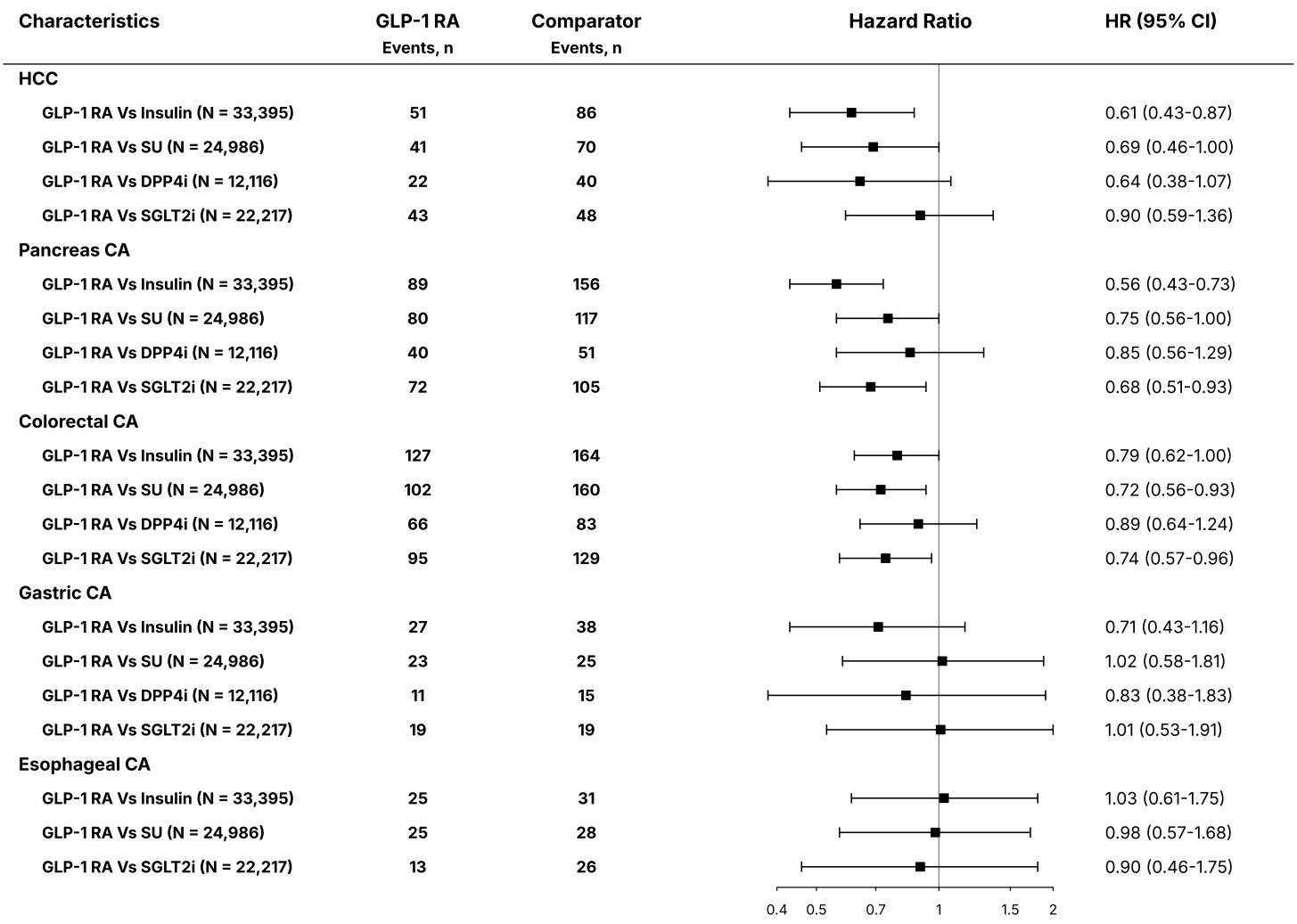
**Association between second-line GLP-1 receptor agonist use and risk of any digestive malignancy.** Forest plot showing the association between second-line use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and the risk of incident digestive malignancies compared with insulin, sulfonylureas (SU), dipeptidyl peptidase-4 inhibitors (DPP-4i), and sodium-glucose cotransporter-2 inhibitors (SGLT2i), after 1:1 propensity score matching. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models in the matched cohorts. Squares represent point estimates; horizontal lines indicate 95% CIs; the vertical reference line corresponds to an HR of 1.0. Event counts (cancer cases) in the GLP-1 RA and comparator groups are shown for each comparison.




## Figure 3

**Kaplan–Meier–estimated cumulative event probability of digestive cancer following second-line treatment initiation.**

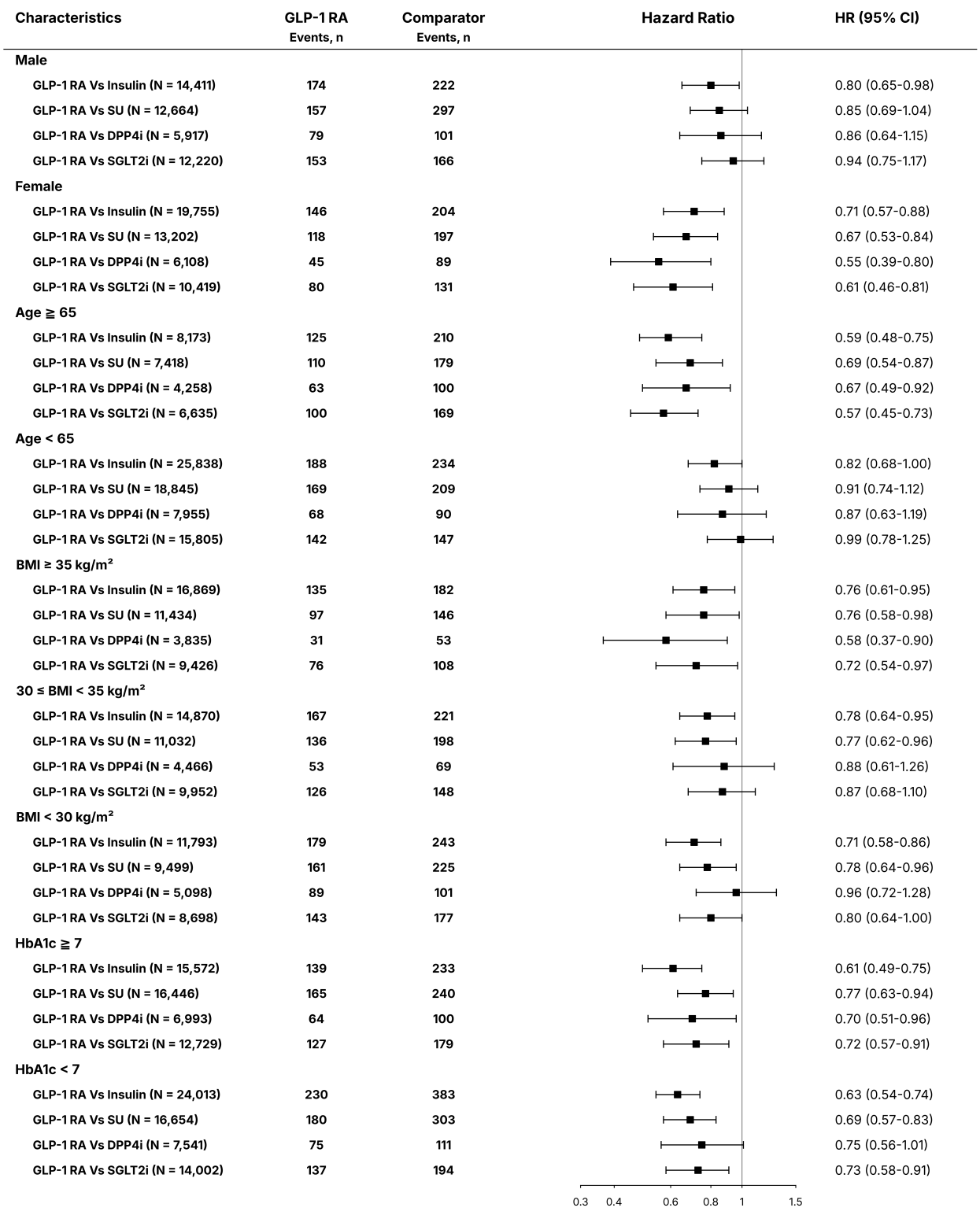
Kaplan–Meier curves display the estimated cumulative probability of a recorded digestive cancer diagnosis in propensity-score-matched cohorts comparing GLP-1 receptor agonists with (A) insulin, (B) sodium-glucose cotransporter-2 inhibitors, (C) dipeptidyl peptidase-4 inhibitors, and (D) sulfonylureas. Shaded areas represent 95% confidence intervals. Between-group differences were assessed using two-sided log-rank tests. These estimates were derived from conventional Kaplan–Meier analyses and were not adjusted for competing mortality; therefore, they should not be interpreted as competing-risk-adjusted absolute cancer risks.




## Figure 4

**Association between second-line GLP-1 receptor agonist use and risk of site-specific digestive malignancies.**

Forest plot showing the association between second-line GLP-1 RA use and the risk of hepatocellular carcinoma (HCC), pancreatic cancer, colorectal cancer, gastric cancer, and esophageal cancer, compared with insulin, SU, DPP-4i, and SGLT2i, after 1:1 propensity score matching. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazards models within each matched cohort. Squares represent point estimates; horizontal lines indicate 95% CIs; the vertical reference line corresponds to an HR of 1.0. The esophageal-cancer comparison with DPP-4i is not shown because one or more event cells contained fewer than 10 patients and were suppressed under the TriNetX privacy policy.




## Figure 5

**Subgroup analyses of the association between second-line GLP-1 receptor agonist use and risk of any digestive malignancy.**

Forest plot showing subgroup analyses stratified by sex (male, female), age (<65, ≥65 years), BMI (<30, 30–<35, ≥35 kg/m²), and glycemic control (HbA1c <7%, ≥7%), compared with insulin, SU, DPP-4i, and SGLT2i, after 1:1 propensity score matching within each subgroup. Hazard ratios (HRs) and 95%

confidence intervals (CIs) were estimated using Cox proportional hazards models. Squares represent point estimates; horizontal lines indicate 95% CIs; the vertical reference line corresponds to an HR of 1.0. HbA1c and BMI for subgroup analyses, propensity score matching was performed independently within each subgroup-specific cohort rather than by simply stratifying the overall matched cohort. Consequently, subgroup-specific matched sample sizes may not sum to the sample sizes of the corresponding overall matched cohorts.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementdata.docx