STUDY PROTOCOL WITH STATISTICAL ANALYSIS PLAN

Official Title:
Pre-Diagnosis GLP-1 Receptor Agonist Use and Post-Cancer Mortality in Adults With Obesity and Type 2 Diabetes: A Target Trial Emulation

NCT Number:
NCT07513259

Document Date:
April 6, 2026

Sponsor:
Chung Shan Medical University Hospital

Funding Source:
Chung Shan Medical University Hospital
National Science and Technology Council, Taiwan

Responsible Party:
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Study Protocol with Statistical Analysis Plan

1. Background and Rationale

Adults with obesity and type 2 diabetes who develop obesity-associated cancer are at increased risk of mortality and serious clinical complications after cancer diagnosis. Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are widely used in the management of obesity and type 2 diabetes and may be associated with differences in post-diagnosis outcomes through metabolic and clinical pathways. However, whether pre-diagnosis initiation of GLP-1 RA is associated with subsequent mortality and major complications after obesity-associated cancer diagnosis remains unclear in routine clinical practice. This study uses a target-trial emulation framework and de-identified electronic health record data from the TriNetX US Collaborative Network to compare post-diagnosis outcomes according to pre-diagnosis glucose-lowering treatment strategies.

2. Study Objective

To compare the 36-month risks of all-cause mortality and major post-cancer clinical outcomes among adults with obesity and type 2 diabetes who developed obesity-associated cancer, according to pre-diagnosis glucose-lowering treatment strategy, with a primary focus on glucagon-like peptide-1 receptor agonist initiation.

3. Data Source

The study data were obtained from the TriNetX US Collaborative Network, a distributed research platform containing de-identified electronic health records contributed by participating healthcare organizations.

4. Study Period / Follow-up End Date

Eligible medication initiation was required to occur between January 1, 2018 and October 31, 2025. Follow-up continued until the earliest of the outcome event, death, last recorded encounter, or October 31, 2025.

5. Study Design

This study is a retrospective observational cohort study designed using a new-user, target-trial emulation framework. The overall study population was classified into two mutually exclusive cohorts according to pre-diagnosis GLP-1 RA use: participants who initiated a GLP-1 RA before obesity-associated cancer diagnosis and participants who did not initiate a GLP-1 RA before obesity-associated cancer diagnosis. The first qualifying obesity-associated cancer diagnosis defined the index date (time zero). Baseline exposure status,

covariates, and eligibility criteria were fixed at the index date, and the primary analytic framework followed an intention-to-treat approach. Within the overall source population, comparator-specific propensity score-matched cohorts were defined for prespecified pairwise outcome analyses comparing GLP-1 RA initiators with initiators of SGLT2 inhibitors, DPP-4 inhibitors, sulfonylureas, metformin, and usual care without GLP-1 RA use.

6. Study Population

Adults aged 18 years or older with obesity and type 2 diabetes identified from the TriNetX US Collaborative Network who developed an obesity-associated cancer after initiation of a glucose-lowering medication during the study period. Obesity was defined using diagnosis codes or body mass index values of 27 kg/m^2 or higher.

7. Inclusion Criteria

1. Age ≥ 18 years
2. BMI ≥ 27 kg/m^2, or diagnosis codes consistent with obesity
3. Type 2 diabetes mellitus
4. Initiation of a glucose-lowering medication before obesity-associated cancer diagnosis
5. Incident obesity-associated cancer diagnosed after medication initiation
6. No dispensing of the study drug classes during the 6-month washout period before the first qualifying prescription

8. Exclusion Criteria

1. Type 1 diabetes or other specified diabetes types
2. Human immunodeficiency virus infection
3. End-stage renal disease
4. Prior bariatric surgery
5. Prior organ transplantation
6. Transplant-related complications
7. Any use of tirzepatide before cohort entry

9. Exposure Groups and Pairwise Analysis Cohorts

The overall study population consisted of two mutually exclusive cohorts: GLP-1 RA and usual care without GLP-1 RA. The GLP-1 RA cohort included adults with obesity and type 2 diabetes who developed an obesity-associated cancer after initiating a GLP-1 receptor

agonist before cancer diagnosis. The usual care without GLP-1 RA cohort included adults with obesity and type 2 diabetes who developed an obesity-associated cancer and had no GLP-1 receptor agonist prescriptions before cancer diagnosis. Participants in the usual care without GLP-1 RA cohort could receive routine clinical care, including other non-GLP-1 RA glucose-lowering medications.

Within this overall source population, the study evaluated the following prespecified pairwise comparisons for outcome analyses:

- GLP-1 RA initiators versus SGLT2 inhibitor initiators
- GLP-1 RA initiators versus DPP-4 inhibitor initiators
- GLP-1 RA initiators versus sulfonylurea initiators
- GLP-1 RA initiators versus metformin initiators
- GLP-1 RA initiators versus usual care without GLP-1 RA use

For each pairwise comparison, comparator-specific propensity score-matched cohorts were defined. The GLP-1 RA analysis cohort included individuals who initiated a GLP-1 RA and had no prescriptions for the comparator drug class during the prespecified comparator-specific restriction period. The comparator analysis cohort included individuals who initiated the comparator drug class and had no GLP-1 RA prescriptions during the same restriction period. For the usual care comparison, individuals in the comparator analysis cohort had no GLP-1 RA prescriptions, while other diabetes management was permitted. Because these pairwise analysis cohorts were comparison-specific, they were analyzed separately.

10. Outcomes

10.1 Primary Outcome

- All-cause mortality within 36 months after obesity-associated cancer diagnosis.

10.2 Secondary Outcomes

Major secondary outcomes included:

- Inpatient
- Pericardial effusion
- Pulmonary embolism
- Sepsis

11. Follow-up

Follow-up started on the index date, defined as the date of the first qualifying obesity-

associated cancer diagnosis, and continued until the earliest occurrence of the outcome event, death, last recorded encounter, or October 31, 2025. Outcomes were assessed through 36 months after the obesity-associated cancer diagnosis date.

12. Statistical Analysis Plan

12.1 General Approach

Each pairwise comparison was analyzed within its own target-trial emulation cohort using an intention-to-treat framework. Comparative associations were assessed over follow-up extending to 36 months after the index date. Propensity score matching and outcome modeling were performed separately for each prespecified comparison.

12.2 Covariates

Baseline covariates were assessed during the 12 months before the index date. Prespecified covariates included demographic factors, race and ethnicity, BMI-related measures, selected socioeconomic or psychosocial indicators, comorbidities, cancer site indicators, healthcare utilization proxies, concurrent medication classes, and selected laboratory variables when available. Missing laboratory information was handled by retaining explicit unavailable categories rather than applying imputation.

12.3 Propensity Score Methods

Propensity scores were estimated separately for each pairwise comparison using logistic regression with prespecified baseline covariates.

12.4 Matching

One-to-one greedy nearest-neighbor propensity score matching was performed using a caliper of 0.1 pooled standard deviations. Covariate balance after matching was evaluated using standardized mean differences, with values below 0.1 considered acceptable.

12.5 Main Outcome Models

Time-to-event analyses were conducted using Cox proportional hazards models and reported as hazard ratios with 95% confidence intervals. Kaplan-Meier methods were used to estimate cumulative event rates, and log-rank tests were used for between-group comparisons. Absolute risk differences were derived from Kaplan-Meier cumulative incidence estimates at 12, 24, and 36 months after obesity-associated cancer diagnosis.

12.6 Multiplicity and Unmeasured Confounding

Two-sided *p* values were used. The Benjamini-Hochberg procedure was applied to account

for multiple testing across outcomes within each comparison. E-values were calculated to quantify the minimum strength of association that an unmeasured confounder would need with both exposure and outcome to explain the observed associations.

12.7 Subgroup Analyses

Prespecified subgroup analyses evaluated whether associations differed across strata defined by age, sex, BMI category, and cancer type.

12.8 Sensitivity Analyses

Sensitivity analyses included as-treated analyses according to post-diagnosis GLP-1 RA continuation patterns, landmark analyses redefining outcome assessment from 3 months and 6 months after index date, extended follow-up analyses where data permitted, and analyses restricted to semaglutide exposure definitions.

13. Ethical Considerations

This study was reviewed and approved by the Institutional Review Board of Chung Shan Medical University Hospital under approval number CS2-24004. The analysis used de-identified electronic health record data, and informed consent was waived in accordance with applicable regulatory criteria.

14. Data Privacy

The study used de-identified electronic health record data from the TriNetX US Collaborative Network. No directly identifiable individual-level information was available to the investigators.

15. Limitations

As a retrospective observational study, this analysis may be subject to residual confounding, exposure misclassification, outcome misclassification, and incomplete capture of clinical variables in routine healthcare data. Because eligibility was defined at first recorded obesity-associated cancer diagnosis, the study may also be affected by index-event bias. Observed associations should therefore not be interpreted as evidence of a treatment effect.