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Long-term safety and efficacy of glucagon-like peptide-1 receptor agonists in individuals with obesity and without type 2 diabetes: A global retrospective cohort study

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Abstract

Aim: We aimed to investigate the long-term impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on thyroid function, cardiovascular health, renal outcomes and adverse events in individuals with obesity and without type 2 diabetes (T2D).

Materials and Methods: In this observational cohort study, we used propensity score matching to construct comparable cohorts of individuals with obesity and without T2D who were new to GLP-1 RA treatment and those who did not receive glucose-lowering medications. In total, 3,729,925 individuals with obesity were selected from the TriNetX Global Network, with an index event between 1 January 2016 and 31 March 2024. The primary outcomes were safety, cardiovascular, thyroid and clinical biochemical profile outcomes occurring within 5 years following the index event.

Results: After propensity score matching, the study included 12,123 individuals in each group. GLP-1 RA treatment was associated with a significantly lower risk of all-cause mortality (hazard ratio 0.23; 95% confidence interval 0.15–0.34) and several cardiovascular complications, including ischaemic heart disease, heart failure, arrhythmias, hypertension, stroke and atrial fibrillation (all $p < 0.05$). GLP-1 RAs were also associated with a lower risk of acute kidney injury and allergic reactions. These protective effects were consistent across various subgroups and regions.

Conclusions: In this large observational study, GLP-1 RAs showed long-term protective effects on cardiovascular health, renal outcomes and adverse events in individuals with obesity and without T2D. Our findings suggest that GLP-1 RAs may offer a comprehensive approach to managing obesity and its related comorbidities, potentially improving overall health and survival in this population.

KEYWORDS
adverse effects, cardiovascular disease, glucagon-like peptide-1 receptor agonists, obesity management, thyroid dysfunction

1 | INTRODUCTION

Obesity, a complex metabolic disorder characterized by excessive adipose tissue accumulation, significantly increases the risk of comorbidities, including cardiovascular disease, thyroid dysfunction and renal impairment.[1–3] The rising global prevalence of obesity has become a major public health concern, prompting the development of effective therapeutic strategies to manage this condition and its complications.[2–4] While lifestyle modifications remain crucial, pharmacological interventions have emerged as valuable adjunctive therapies.[5–8]

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have gained attention as a promising class of obesity medications.[9–13] These agents mimic the effects of the endogenous incretin hormone GLP-1, secreted by the intestines in response to nutrient intake.[14] By activating the GLP-1 receptor, these drugs enhance glucose-dependent insulin secretion, suppress glucagon release, delay gastric emptying and promote satiety.[14–16] The well-documented weight loss effects of GLP-1 RAs in clinical trials make them an attractive option for individuals with obesity seeking to improve their metabolic health.[11–13,17–19]

The long-term impact of GLP-1 RAs on various organ systems and their potential adverse effects in individuals with obesity and without type 2 diabetes (T2D) remain incompletely understood.[20,21] While these medications have shown beneficial effects on cardiovascular risk factors, their influence on thyroid function, renal outcomes and adverse events requires further investigation.[11,20,22,23] Most studies evaluating GLP-1 RAs have focused on short-term outcomes, highlighting the need for longer-term assessments to fully characterize their safety and efficacy profile.[8,24] This lack of evidence restricts informed decision-making regarding the appropriateness of hypoglycaemic agents for weight management in obesity.[23,25]

This study aims to present the findings of a comprehensive 5-year investigation into the effects of GLP-1 RAs on thyroid function, cardiovascular health, renal outcomes and adverse events in individuals with obesity and without T2D.

2 | METHODS

2.1 | Data source

This study utilized real-world data from the TriNetX Global Collaborative Network, an international federated database containing de-identified electronic health records from over 100 health care organizations across the United States, Australia, Europe and Asia. To ensure individual data confidentiality and adhere to ethical standards, all data within the TriNetX network undergoes a rigorous de-identification process in accordance with HIPAA privacy regulations.[26]

To enhance transparency and reproducibility, we reported this study in accordance with the STROBE guidelines. The specific use of the TriNetX database for this study underwent review and received approval from the Institutional Review Board committee at Chung Shan Medical University Hospital (approval number CS2-24004).

2.2 | Study design

In this observational cohort study, we used a propensity score matching approach to construct comparable cohorts of individuals with obesity and without T2D treated with GLP-1 RAs and those who did not receive glucose-lowering medications (comparator). The primary cohort included individuals with a confirmed diagnosis of obesity (ICD-10 code: E66) and a body mass index ≥30 (TNX curated: 9083) without T2D (ICD-10 code: E11).

GLP-1 RA users were identified as those prescribed GLP-1 RAs for at least six consecutive months before the index event and still prescribed the medication at the index event. The mean durations for each GLP-RA were as follows: semaglutide (162 ± 42.8 days); liraglutide (174 ± 26.2 days); dulaglutide (112.1 ± 59.3 days); and total GLP-1 RA (167.5 ± 36.7 days) (Tables S1 and S2). Non-users had no history of GLP-1 RA use before and after the index event. The GLP-1 RA cohort included individuals who received a GLP-1 RA for at least 6 months and had a follow-up encounter with health services within 5 years post-drug initiation.

2.3 | Study cohort

The primary cohort was defined as all individuals who had a confirmed diagnosis of obesity (ICD-10 code: E66) and body mass index ≥30 (TNX curated: 9083; this term is curated by the TriNetX team to harmonize related codes) without T2D (ICD-10 code: E11; Figure 1). Individuals were excluded if they had a co-prescription of other glucose-lowering drugs or if they had used the study drugs for less than 6 months. In addition, individuals with target outcomes prior to the study baseline (6 months before the index event) were excluded. Those who had a history of undergone bariatric surgery or used other weight management medications were also excluded. Furthermore, individuals with a history of cancer, end-stage renal disease, HIV, pancreatitis and kidney transplant were excluded from the study.

2.4 | Statistical analysis

We employed propensity score matching using the 1:1 ratio nearest-neighbour algorithm to generate matched pairs of GLP-1 RA users and comparator. Standardized mean differences <0.1 were considered indicative of a well-balanced matching process, ensuring comparability between the two groups. We utilized both crude and multivariable-adjusted Cox proportional hazards models to assess the risk of various outcomes between the GLP-1 RA users and controls, presenting the results as hazard ratios (HRs) with 95% confidence intervals (CIs).

The underlying technology is protected by trade secrets, and the software languages and packages employed include Java 11.0.16

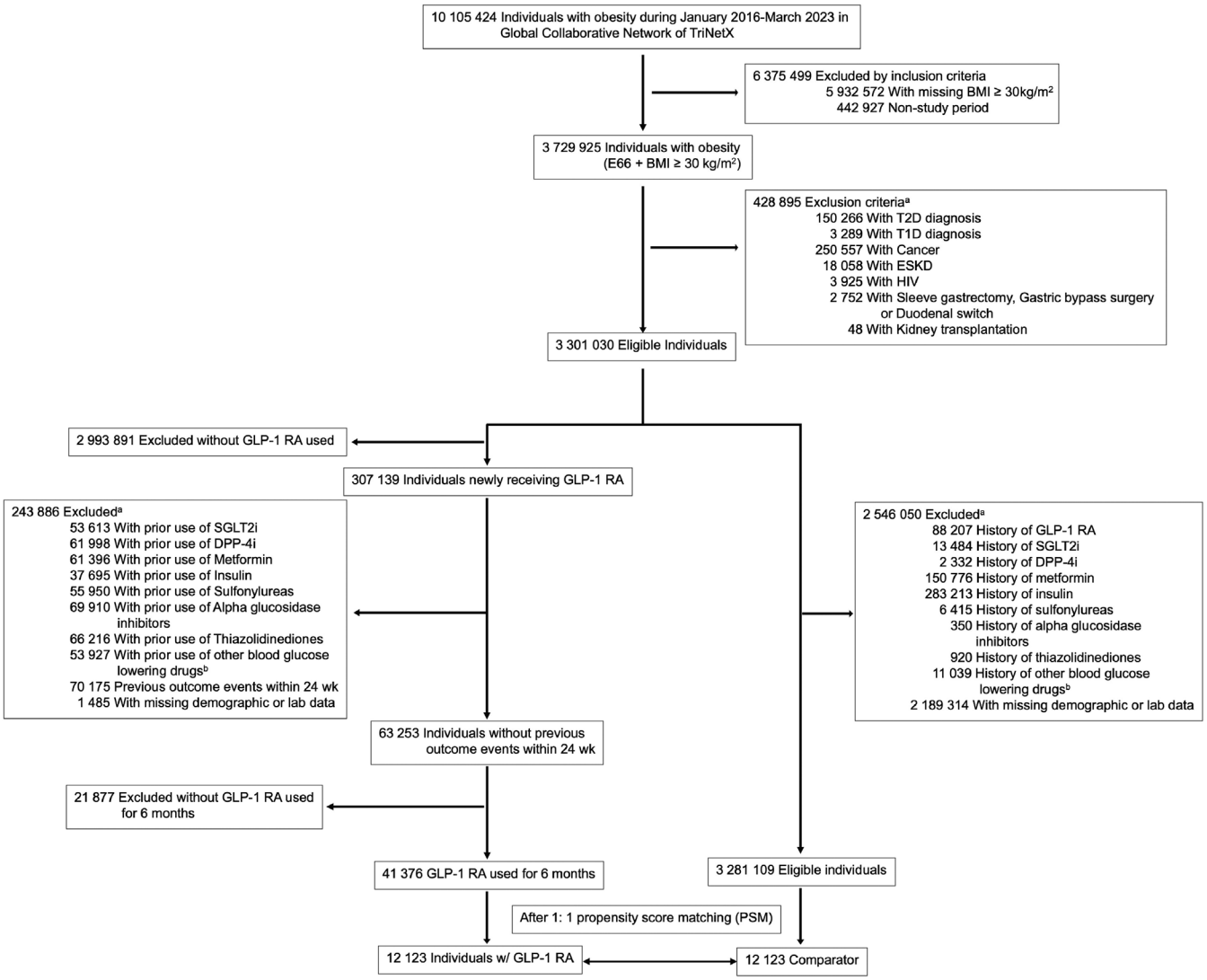


FIGURE 1 Flowchart for selection of individuals. BMI, body mass index; DPP-4i, dipeptidyl peptidase-4 inhibitor; ESKD, end stage kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HIV, human immunodeficiency virus; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T1D, type 1 diabetes; T2D, type 2 diabetes; wk, week. [a]Individuals could have met multiple exclusion criteria. [b]Including pramlintide, tirzepatide, guar gum, nateglinide and repaglinide.

(utilizing Apache Commons Math 3.6.1), R 4.0.2 (with the Hmisc1-1 and Survival 3.2–3 packages), and Python 3.7 (incorporating the lifelines 0.22.4, matplotlib 3.5.1, numpy 1.21.5, pandas 1.3.5, scipy 1.7.3 and statsmodels 0.13.2 packages). More detailed information in Data S1.

3 | RESULTS

3.1 | Baseline demographic and clinical characteristics of the cohort before and after matching

After 1:1 propensity score matching on key variables, the matched samples of 12,123 individuals per group were well balanced on nearly all measures. Standardized differences were <0.1 for all variables, confirming a good balance between the groups (Table 1). The matching process effectively eliminated the significant differences in age (mean 42.9 vs. 41.6 years), sex (80.2% vs. 81.0% female) and race that were observed before matching.

3.2 | Five years of safety, cardiovascular and thyroid adverse risk

We provide a thorough examination of the progression and impacts of GLP-1 RA on various outcomes over 5 years in individuals with obesity. GLP-1 RA users had a consistent and significant decrease in all-cause mortality compared with non-users, with a 5-year HR of 0.23 (95% CI 0.15–0.34; $p < 0.001$), suggesting a marked reduction in mortality risk that persisted across all analysed time frames (Figures 2 and S1).

Individuals treated with GLP-1 RAs (all brands) had a lower risk of ischaemic heart disease (HR 0.78; 95% CI 0.63–0.96; $p = 0.02$),

TABLE 1 Demographic and baseline characteristics of individuals with obesity treated with GLP-1 RA and matched comparators of individuals with obesity.

	Before matching			After matching		
	OB w/GLP-1 RA cohort ($n = 12,131$)	OB comparators cohort ($n = 735,059$)	Std Diff.	OB w/GLP-1 RA cohort ($n = 12,123$)	OB comparators cohort ($n = 12,123$)	Std Diff.
Age at index						
Mean ± SD	42.9 ± 13.0	36.0 ± 17.3	0.45	42.9 ± 13.0	41.6 ± 15.3	0.09
Sex (%)						
Female	9735 (80.2)	469,225 (63.8)	0.37	9729 (80.2)	9816 (81.0)	0.02
Male	2328 (19.2)	264,122 (35.9)	0.38	2327 (19.2)	2232 (18.4)	0.02
Missing	68 (0.6)	1712 (0.3)		68 (0.6)	76 (0.6)	
Race (%)						
White	7829 (64.5)	426,208 (58.0)	0.14	7822 (64.5)	7961 (65.7)	0.02
Black or African American	2122 (17.5)	151,774 (20.6)	0.08	2122 (17.5)	1946 (16.1)	0.04
Asian	145 (1.2)	10,409 (1.4)	0.02	145 (1.2)	149 (1.2)	0.01
Missing or unknown	2035 (16.8)	146,668 (20)		2035 (16.8)	2068 (17)	
Ethnicity (%)						
Hispanic or Latino	1318 (10.9)	130,651 (17.8)	0.20	1318 (10.9)	1152 (9.5)	0.05
Not Hispanic or Latino	9218 (76.0)	502,525 (68.4)	0.17	9211 (76.0)	9419 (77.7)	0.04
Missing or unknown	1595 (13.1)	101,883 (13.8)		1595 (13.1)	1553 (12.8)	
Socio-economic status						
Persons with potential health hazards related to socio-economic and psychosocial circumstances	1072 (8.8)	34,261 (4.7)	0.17	1068 (8.8)	970 (8.0)	0.03
Lifestyle						
Nicotine dependence (smoking)	1507 (12.4)	60,387 (8.2)	0.14	1505 (12.4)	1495 (12.3)	0.01
Problems related to lifestyle	1739 (14.3)	40,695 (5.5)	0.30	1735 (14.3)	1627 (13.4)	0.03
Comorbidities						
Asthma	2532 (20.9)	95,565 (13.0)	0.21	2527 (20.8)	2538 (20.9)	0.01
Hypertensive diseases	2415 (19.9)	63,749 (8.7)	0.33	2411 (19.9)	2350 (19.4)	0.01
Hyperlipidaemia	2700 (22.3)	67,193 (9.1)	0.37	2693 (22.2)	2807 (23.2)	0.02
Diseases of liver	1119 (9.2)	23,811 (3.2)	0.25	1114 (9.2)	1066 (8.8)	0.01
Ischaemic heart diseases	514 (4.2)	12,567 (1.7)	0.15	512 (4.2)	493 (4.1)	0.01
Other forms of heart disease	1679 (13.8)	48,163 (6.6)	0.24	1678 (13.8)	1652 (13.6)	0.01
AKI	119 (1.0)	4499 (0.6)	0.04	119 (1.0)	124 (1.0)	0.01
CKD	506 (4.2)	8843 (1.2)	0.18	503 (4.1)	431 (3.6)	0.03
Vitamin D deficiency	3234 (26.7)	56,108 (7.6)	0.52	3227 (26.6)	3214 (26.5)	0.01
Mental and behavioural disorders because of psychoactive substance use	2219 (18.3)	81,806 (11.1)	0.20	2216 (18.3)	2181 (18.0)	0.01
Medication						
Aspirin	1916 (15.8)	67,313 (9.2)	0.20	1914 (15.8)	1930 (15.9)	0.01
Thyroid modifiers	925 (7.6)	21,952 (3.0)	0.21	922 (7.6)	917 (7.6)	0.01
Thyroid therapy	855 (7.0)	21,001 (2.9)	0.19	854 (7.0)	852 (7.0)	0.01
Thyroid supplements	899 (7.4)	21,363 (2.9)	0.21	897 (7.4)	895 (7.4)	0.01
Beta-blockers	2267 (18.7)	51,991 (7.1)	0.35	2264 (18.7)	2276 (18.8)	0.01
ACE inhibitors	816 (6.7)	26,218 (3.6)	0.14	816 (6.7)	830 (6.8)	0.01
Antiarrhythmics	5081 (41.9)	157,358 (21.4)	0.45	5076 (41.9)	4998 (41.2)	0.01
Antihypertensives, other	1123 (9.3)	35,809 (4.9)	0.17	1120 (9.2)	1112 (9.2)	0.01

(Continues)

TABLE 1 (Continued)

	Before matching			After matching		
	OB w/GLP-1 RA cohort ($n = 12,131$)	OB comparators cohort ($n = 735,059$)	Std Diff.	OB w/GLP-1 RA cohort ($n = 12,123$)	OB comparators cohort ($n = 12,123$)	Std Diff.
Platelet aggregation inhibitors	1945 (16.0)	67,984 (9.2)	0.21	1943 (16.0)	1973 (16.3)	0.01
Atorvastatin	1164 (9.6)	29,635 (4.0)	0.22	1163 (9.6)	1208 (10.0)	0.01
Rosuvastatin	576 (4.7)	9451 (1.3)	0.20	573 (4.7)	576 (4.8)	0.01
Cardiovascular agents, other	329 (2.7)	9342 (1.3)	0.10	327 (2.7)	327 (2.7)	< 0.001
Laboratory						
BMI, 30–40 kg/m^2; *n* (%)	9356 (77.1)	370,829 (50.4)	0.58	9349 (77.1)	9575 (79.0)	0.05
Glycated haemoglobin >7%, *n* (%)	7432 (61.3)	178,274 (24.3)	0.05	7426 (61.3)	4688 (38.7)	0.07

Note: Characteristics were considered adequately matched between the cohorts when the standardized mean difference was <0.1.
If the number of individuals is ≤10, the result is displayed as 10 for privacy protection purposes.
Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; BMI, body mass index; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; OB, individuals with obesity; SD, standard deviation; Std Diff, standardized difference.

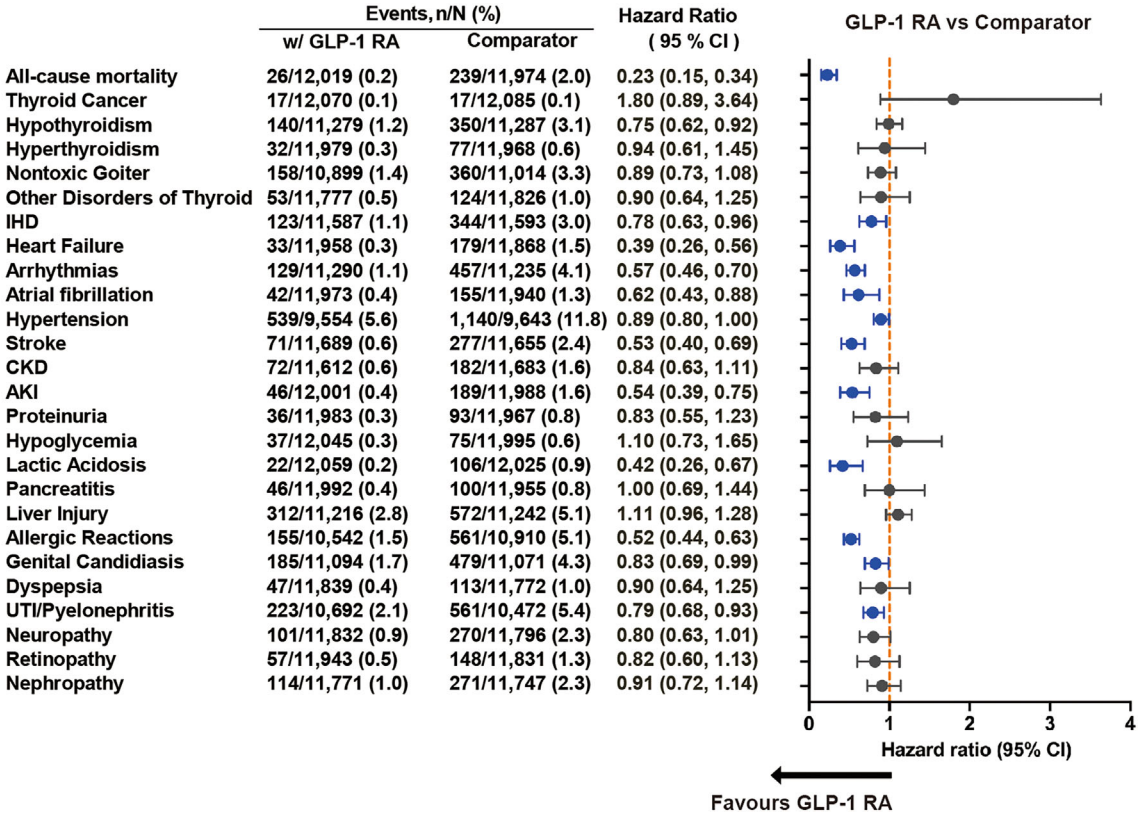


FIGURE 2 Forest plot depicting the 5-year HRs for thyroid disorders, cardiovascular outcomes, renal complications and adverse events associated with GLP-1 RA monotherapy compared with no glucose-lowering medication in propensity score-matched cohorts of obese individuals without type 2 diabetes (comparator). Incidence rates (IRs) are presented per 100 person-years. AKI, acute kidney injury; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IHD, ischaemic heart disease.

heart failure (HR 0.39; 95% CI 0.26–0.56; $p < 0.001$), arrhythmias (HR 0.57; 95% CI 0.46–0.70; $p < 0.001$), hypertension (HR 0.89; 95% CI 0.80–0.99; $p = 0.04$), stroke (HR 0.53; 95% CI 0.40–0.69; $p < 0.001$) and atrial fibrillation (HR 0.62; 95% CI 0.43–0.88; $p = 0.01$).

Semaglutide exhibited strong cardiovascular protective effects, including a 53% reduction in heart failure risk (HR 0.47, 95% CI 0.33–0.69), a 50% reduction in stroke risk (HR 0.50, 95% CI 0.37–0.66), and a 32% reduction in atrial fibrillation risk (HR 0.68, 95% CI 0.48–0.98). Semaglutide also showed significant renal benefits, with a 44% reduction

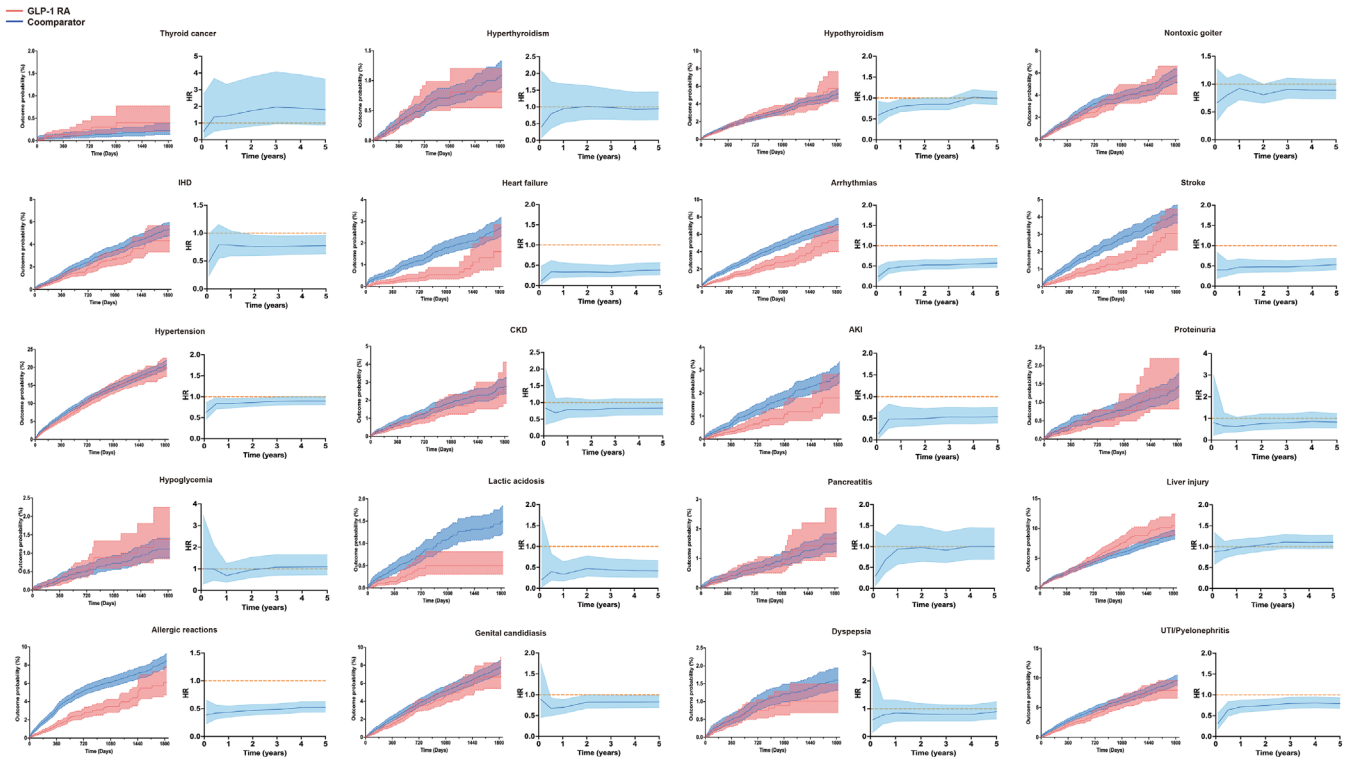


FIGURE 3 Outcome probabilities and time-varying HR comparing the incidence of various outcomes over a 5-year follow-up period between propensity score-matched cohorts of obese individuals treated with GLP-1 RAs and obese individuals (comparator) not receiving any glucose-lowering medications. AKI, acute kidney injury; CKD, chronic kidney disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; IHD, ischaemic heart disease.

in acute kidney injury (AKI) risk (HR 0.57, 95% CI 0.40–0.81) and a 32% reduction in chronic kidney disease risk (HR 0.68, 95% CI 0.50–0.92).

Liraglutide showed significant cardiovascular benefits, with a 29% reduction in ischemic heart disease risk (HR 0.72, 95% CI 0.53–0.96) and a 69% reduction in heart failure risk (HR 0.31, 95% CI 0.16–0.62). It also showed a 44% reduction in stroke risk (HR 0.56, 95% CI 0.38–0.84) and a 38% reduction in arrhythmias (HR 0.62, 95% CI 0.47–0.81). Renal outcomes improved with liraglutide use, evidenced by a 60% reduction in chronic kidney disease risk (HR 0.40, 95% CI 0.24–0.68).

Dulaglutide showed a notable 66% reduction in heart failure risk (HR 0.34, 95% CI 0.14–0.85). While other cardiovascular and renal outcomes trended towards improvement, they did not reach statistical significance, possibly because of a smaller sample size or shorter follow-up period for this newer agent.

Interestingly, all three GLP-1RAs showed significant reductions in mortality risk: liraglutide (HR 0.17, 95% CI 0.07–0.40), semaglutide (HR 0.19, 95% CI 0.10–0.38) and dulaglutide (HR 0.27, 95% CI 0.08–0.91).

3.3 | Kaplan–Meier curves and time-varying hazard ratios over the 5-year follow-up

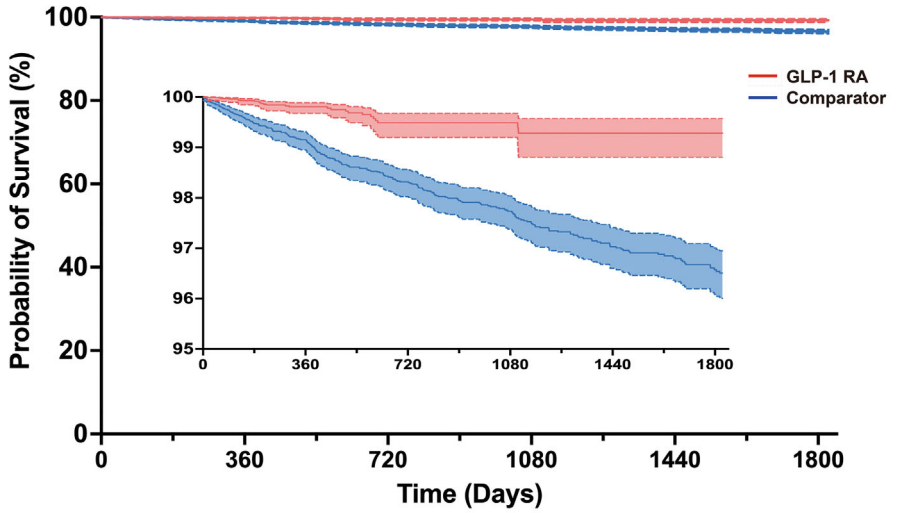
We examined the long-term effects of GLP-1 RAs on thyroid, cardiovascular, renal outcomes and adverse events in individuals with obesity and without T2D over a 5-year period, including outcome probabilities and HRs (Figure 3).

The Kaplan–Meier analysis for thyroid cancer showed the 5-year HR of 1.80 (95% CI 0.89–3.64; $p = 0.10$) suggested an increased risk that did not reach statistical significance. Other thyroid disorders showed no significant long-term impact observed in the HR or Kaplan–Meier analysis.

GLP-1 RAs had a significant impact on cardiovascular outcomes. For ischaemic heart disease (HR 0.84; 95% CI 0.76–0.93; $p = 0.01$), heart failure (HR 0.89; 95% CI 0.81–0.97; $p = 0.01$), arrhythmias (HR 0.76; 95% CI 0.69–0.84; $p < 0.001$), atrial fibrillation (HR 0.88; 95% CI 0.79–0.98; $p = 0.02$), hypertension (HR 0.92; 95% CI 0.87–0.97; $p = 0.01$) and stroke (HR 0.85; 95% CI 0.77–0.94; $p = 0.001$), the outcome probability data indicated stable trends over 5 years, suggesting protective effects.

AKI showed reduced incidence in the GLP-1 RA-treated group, with an HR of 0.79 (95% CI 0.70–0.89; $p = 0.001$). However, no significant differences were observed for CKD and proteinuria.

The 5-year study of GLP-1 RAs in individuals with obesity and without T2D revealed several noteworthy findings regarding adverse events. Hypoglycaemia, lactic acidosis, pancreatitis, liver injury and dyspepsia showed no significant risk increase. Allergic reactions and genital candidiasis were significantly less likely in treated individuals, with HRs of 0.52 (95% CI 0.44–0.63; $p < 0.001$) and 0.83 (95% CI 0.69–0.99; $p = 0.04$), respectively. The risk for urinary tract infections



No. at Risk						
GLP-1 RA	12109	12004	11995	11995	11993	11993
Comparator	11974	11887	11821	11784	11752	11735

FIGURE 4 Kaplan–Meier survival curves illustrating the cumulative incidence of all-cause mortality over a 5-year follow-up period in obese individuals treated with glucagon-like peptide 1 receptor agonists (GLP-1 RAs). The cumulative incidence of all-cause mortality within the two groups is shown in this Kaplan–Meier plot. We observed a total of 265 all-cause mortality events. There were 239 events in GLP-1 RA users (incidence ratio, 2.00 events per 100 person-years) compared with 26 in matched comparator (incidence ratio, 0.2 events per 100 person-years). GLP-1 RA use was with associated low risk of all-cause mortality compared with matched comparator (hazard ratio, 0.23; 95% CI 0.15–0.34).

and pyelonephritis remained moderate over 5 years, with a statistically significant risk decrease (HR 0.79; 95% CI 0.68–0.93; $p = 0.01$). However, vigilance in monitoring these conditions in GLP-1 RA therapy is still recommended.

Our analysis of kidney function markers (estimated glomerular filtration rate, BUN and creatinine) showed no evidence of clinically significant deterioration in kidney function among GLP-1 RA (all brands) treated individuals compared with matched comparators over a 5-year period (Table S3). Notably, individuals treated with semaglutide showed a small but significant improvement in estimated glomerular filtration rate at 5 years compared with 6 months. While we did not directly measure AKI severity, the stability and even improvement of these markers suggest that GLP-1 RA treatment, in particular semaglutide, may have a protective effect on kidney function over time.

3.4 | All-cause mortality

Over the 5-year follow-up period, the use of GLP-1 RAs was associated with a significantly lower risk of all-cause mortality compared with the comparator group (Figure 4 and Table S4).

At 1 month, the HR for all-cause mortality was 0.08 (95% CI 0.01–0.59; $p = 0.001$), indicating a 92.3% lower risk in the GLP-1 RA group. This trend continued at 6 months (HR 0.14; 95% CI 0.06–0.31; $p < 0.001$) and 1 year (HR 0.21; 95% CI 0.12–0.37; $p < 0.001$), with the GLP-1 RA cohort exhibiting an 86.1% and 78.8% lower risk of all-cause mortality, respectively. The protective effect of GLP-1 RAs on all-cause mortality persisted throughout the study period, with HRs remaining stable at 0.23 (95% CI 0.15–0.34; $p < 0.001$) at 5 years, showing a consistent and significant reduction in all-cause mortality risk among individuals with obesity and without T2D treated with GLP-1 RAs. The sensitivity analysis, excluding those who were dead within half a year, showed similar results (Table S4).

3.5 | Clinical biochemical profiles

GLP-1 RAs showed significant effects on various laboratory parameters in individuals with obesity and without T2D over a 5-year follow-up period (Table S5). GLP-1 RAs consistently showed a significant reduction in glycated haemoglobin levels compared with the comparator group ($p < 0.001$ at all time points), with a mean glycated haemoglobin of 5.44 ± 0.62% in the GLP-1 RA group versus 5.57 ± 0.83% in the comparator group at year 5, indicating a sustained glucose-lowering effect. Triglyceride levels were also significantly lower in the GLP-1 RA group at all time points ($p < 0.001$).

Thyroid function tests showed that free T3 levels were significantly higher in the GLP-1 RA group at year 1 (3.29 ± 0.78 pg/mL vs. 3.00 ± 0.94 pg/mL, $p = 0.02$). Total T3 levels did not differ between groups. Free T4 was significantly lower in the GLP-1 RA group at years 1, 2, 4, and 5 (1.07 ± 0.27 ng/dL vs. 1.10 ± 0.34 ng/dL at year 5, $p = 0.01$), while total T4 was significantly higher in the GLP-1 RA group at those same time points (8.09 ± 2.18 μg/dL vs. 7.36 ± 3.03 μg/dL at year 5, $p = 0.02$). Thyroid-stimulating

hormone (TSH) levels were significantly lower in individuals receiving GLP-1 RAs at all assessments (1.84 ± 1.97 μIU/mL vs. 2.53 ± 14.02 μIU/mL at year 5; $p = 0.01$).

3.6 | Subgroup analysis

Subgroup analyses were stratified by clinically relevant factors such as sex, age, race and cardiovascular disease status (Figure S2). GLP-1 RAs were associated with a significantly lower risk of all-cause mortality in both age subgroups, males and females, and White and Black individuals, and those with and without cardiovascular disease (all $p < 0.05$).

3.7 | Sensitivity analysis

Sensitivity analyses were conducted to compare the effects of GLP-1 RA on various outcomes in the global and US regions (Figure S3).

In both the global and US regions, GLP-1 RAs were associated with a significantly lower risk of all-cause mortality and consistent protective effects against several cardiovascular and renal outcomes, as well as adverse events, in both the global and US regions.

3.8 | Weight changes in different glucagon-like peptide 1 receptor agonist brands

Our analysis of weight changes across different GLP-1 RA brands revealed significant and sustained weight loss effects over the 5-year follow-up period (Figure S4). The GLP-1 RA group maintained a 5.43% weight loss from baseline, with the most substantial decrease occurring in the first year. Among individual brands, semaglutide showed the most pronounced effect with a 6.93% weight reduction, followed closely by liraglutide at 6.58%, while dulaglutide showed a more modest 3.11% reduction. In contrast, comparator groups exhibited minimal weight changes, ranging from a slight increase of 0.8% to minor decreases of 2.83%, 2.45% and 0.59% for the semaglutide, liraglutide and dulaglutide comparator groups, respectively.

4 | DISCUSSION

This large-scale observational cohort study evaluated the long-term effects of GLP-1 RAs on thyroid function, cardiovascular health, renal outcomes and adverse events in individuals with obesity and without T2D over a 5-year period. Different GLP-1RAs showed varying effects on cardiac and renal outcomes, with semaglutide and liraglutide showing more consistent benefits across multiple endpoints.

Our results are consistent with previous studies that have shown the weight loss effects and cardiovascular benefits of GLP-1 RAs in individuals with overweight and obese,[9–13,17,19,24,27–31] but our study extends these findings by providing a comprehensive assessment of the long-term impact of GLP-1 RAs on multiple organ systems and adverse events in individuals with obesity and without T2D. The observed reduction in all-cause mortality risk suggests that GLP-1 RAs may have a significant impact on overall health and survival in this population.[9]

Regarding the controversial association between GLP-1 RAs and thyroid cancer,[32] our results align with the latest findings from other research teams, showing a trend towards increased risk that does not reach statistical significance.[33–39] Our findings suggest a complex interplay between GLP-1 RAs and thyroid function. Several mechanisms may explain these observations. GLP-1 receptors are expressed in the hypothalamus and pituitary gland.[40] GLP-1 RA activation of these receptors may modulate the release of thyrotropin-releasing hormone and TSH, potentially explaining the observed lower TSH levels.[40] GLP-1 RAs may influence the activity of deiodinase enzymes, which are responsible for converting T4 to T3.[41] The observed increase in free T3 levels, coupled with decreased free T4 levels, suggests enhanced peripheral conversion of T4 to T3. GLP-1 RA-induced weight loss may lead to changes in leptin and other adipokines, which are known to influence thyroid function.[42,43] The observed changes in thyroid function parameters underscore the importance of monitoring thyroid function in patients receiving long-term GLP-1 RA treatment. Future mechanistic studies are needed to elucidate the precise pathways by which GLP-1 RAs influence thyroid function and to determine the clinical significance of these changes.

The relationship between GLP-1RA use, weight loss and clinical outcomes is indeed complex. Chen et al. showed a U-shaped association between weight change and mortality, with both weight gain and weight loss associated with increased mortality risk.[44] This relationship varied across different life stages, suggesting that the impact of weight change on mortality is not straightforward.[44] Yuan et al. further complicated this picture by showing that different patterns of weight and waist circumference changes had varying impacts on mortality risk.[45] Notably, they found that weight loss accompanied by waist circumference gain was associated with the highest mortality risk.[45] This highlights the importance of considering body composition changes beyond just overall weight loss. Regarding GLP-1RAs specifically, the STEP 1 trial extension provided valuable insights.[46] While significant weight loss was achieved with semaglutide treatment, much of this weight was regained after treatment discontinuation. However, some cardiometabolic benefits persisted despite weight regain. This suggests that the relationship between GLP-1RA use, weight loss and clinical outcomes is not solely mediated by absolute weight changes. The SURMOUNT-4 trial similarly showed substantial weight regain after tirzepatide discontinuation, yet some participants maintained clinically meaningful weight loss at 120 weeks.[47] This further supports the complex nature of the relationship between GLP-1RA-induced weight loss and long-term outcomes.

Given these findings, it seems unlikely that weight change alone fully mediates the association between GLP-1RA use and all-cause mortality or other adverse events. To definitively assess the mediating role of weight loss, formal mediation analyses would be necessary in the future. These analyses should account for time-varying

confounding and potential bidirectional relationships. In addition, studies comparing GLP-1RAs to other weight loss interventions achieving similar degrees of weight loss could help isolate weight-dependent and weight-independent effects.

Another key finding of our study is the consistent protective effect of GLP-1 RAs against several cardiovascular complications. This aligns with the growing body of evidence suggesting that GLP-1 RAs may have cardioprotective properties beyond their glucose-lowering effects.[48,49] The mechanisms underlying these benefits may involve improvements in endothelial function, reduction of inflammation and modulation of cardiac metabolism.[21,50] Future mechanistic studies are needed to elucidate the precise pathways by which GLP-1 RAs influence multiple organ function and to determine the clinical significance of these changes.

While our study showed several strengths, including a large sample size, a well-matched comparator group and a comprehensive assessment of various outcomes, it also has some limitations. As an observational study, we cannot establish a causal relationship between GLP-1 RA treatment and the observed outcomes. Furthermore, our study relied on electronic health records and ICD-10 codes for outcome ascertainment, which may not fully capture the nuances of individual experiences or the subtle changes in health status over time. Future research incorporating more comprehensive data sources, such as detailed clinical narratives or individual reported outcomes, could provide a more complete picture of the effects of GLP-1 RAs in this population. Furthermore, the small proportion of Asian patients (1.2%) in our study population limits the generalizability of our findings to Asian populations. Given potential differences in drug metabolism, body composition and cardiovascular risk profiles among different ethnic groups, our results should be interpreted with caution when applied to Asian individuals with obesity. Future studies with larger, more diverse cohorts or targeted investigations in Asian populations are needed to elucidate the efficacy and safety of GLP-1 RAs in this demographic. Another limitation is the potential for selection bias, as individuals prescribed GLP-1 RAs may have different characteristics or access to health care compared with those not receiving these medications. In addition, we did not have access to data on lifestyle factors, such as diet and physical activity, which could influence the outcomes of interest. Our exclusion of patients receiving glucose-lowering medications in the control group, while intended to create a more homogeneous comparison, may limit the generalizability of our results. This approach does not account for the growing trend of using these medications, particularly GLP-1 agonists, for weight management in non-diabetic individuals or for other off-label uses such as prediabetes management and cardiovascular risk reduction. Despite these limitations, our findings have important clinical and public health implications. The consistent protective effects of GLP-1 RAs across multiple organ systems and adverse events suggest that these medications may offer a comprehensive approach to managing obesity and its related comorbidities.

The findings of this study have significant implications for clinical practice in obesity management. GLP-1 RAs showed long-term protective effects on cardiovascular health, renal outcomes and adverse events in individuals with obesity and without T2D. This suggests that GLP-1 RAs may offer a comprehensive approach to managing obesity and its related comorbidities, potentially improving overall health and survival. Clinicians should consider GLP-1 RAs as a valuable treatment option for individuals with obesity, even in the absence of diabetes, particularly for those at high risk for cardiovascular complications. However, careful monitoring for potential side effects and individualized treatment plans remains essential.

5 | CONCLUSIONS

This retrospective cohort provides evidence for the long-term protective effects of GLP-1 receptor agonists on thyroid function, cardiovascular health, renal outcomes and adverse events in individuals with obesity and without T2D. These findings support the use of GLP-1 RAs as a promising therapeutic option for managing obesity.

AUTHOR CONTRIBUTIONS

YNH and PHS designed the study with unrestricted access to the TriNetX Analytics database, defining the inclusion, exclusion, and outcome criteria, as well as the analytical approaches. YNH conducted the data analyses with assistance from WLL, JYH, CHW and PHS. All authors contributed to interpreting the results. YNH, CHW and PHS drafted the initial manuscript, with input from YJL, SFY, CCH and CHW. YNH, WLL, CHW and PHS verified the data accuracy. PHS serves as the study guarantor. The corresponding author had the final responsibility for the decision to submit the findings for publication.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

De-identified participant data will be made available upon request to the corresponding author according to the regulation of Chung Shan Medical University Hospital.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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