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Comparative ocular outcomes of tirzepatide versus other anti-obesity medications in people with obesity

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Abstract

Background Obesity affects over one billion people worldwide and is associated with ocular complications, yet comparative effects of newer anti-obesity medications on eye health remain poorly understood. We examine ocular health outcomes among individuals with obesity receiving Tirzepatide, Semaglutide, Phentermine/Topiramate, Naltrexone/Bupropion, or Phentermine monotherapy.

Methods This propensity-score matched cohort study analyzed TriNetX US network data from November 2023 through April 2025. The study included matched pairs of obese individuals with a BMI ≥ 27 kg/m², comparing ocular outcomes between different anti-obesity medications. Primary outcomes included cataracts, oculomotor binocular dysfunction, visual disturbances, dry eye disease, ametropic accommodative dysfunction, and visual issues with blindness, assessed through Cox proportional hazards models with Bonferroni correction. Sensitivity analyses included BMI ≥ 30 kg/m² populations, subgroup stratification by clinical characteristics, and negative control outcomes to assess residual bias.

Results Here, we show that among 25,060 matched pairs comparing Tirzepatide with Semaglutide, no differences emerge across ocular outcomes. When compared with Naltrexone/Bupropion, Tirzepatide users show lower rates of cataracts (HR 0.46, 95% CI 0.23–0.92, $p = 0.025$) and oculomotor dysfunction (HR 0.31, 95% CI 0.16–0.60, $p = 2.3 \times 10^{-4}$). Semaglutide demonstrates similar patterns. Both medications show favorable profiles for visual disturbances, with Tirzepatide demonstrating lower rates versus Phentermine (HR 0.45, 95% CI 0.31–0.68, $p = 7 \times 10^{-5}$). Sensitivity analyses in the BMI ≥ 30 kg/m² population yield consistent results.

Conclusions Newer anti-obesity medications demonstrate differential associations with ocular outcomes compared to traditional agents. These findings may inform clinical decision-making regarding medication selection in obesity management, though prospective studies remain necessary to establish causal relationships.

Plain language summary

Obesity affects over one billion people worldwide and can cause eye problems. While newer weight-loss medications, including Tirzepatide and Semaglutide, work well for weight management, their effects on eye health compared to older treatments are unclear. We analyzed health records from over 2 million people with obesity using different weight-loss medications between 2023 and 2025. We compared eye problems between users of newer medications versus older medications, such as Phentermine combinations. We found that people using newer medications experienced fewer eye problems, including cataracts and dry eyes. Tirzepatide users had approximately half the cataract risk compared to some traditional medications. These results suggest newer weight-loss medications may provide benefits beyond weight reduction. This information could help people and their doctors make informed decisions about obesity treatments, considering both weight management and eye health protection.

Adult obesity rates have more than doubled since 1990, while childhood and adolescent obesity have risen from 8% in 1990 to 20% in 2022, making this expanding health crisis an urgent priority given its profound impact on global morbidity and mortality[1,2]. Obesity, a complex metabolic disorder, is associated with numerous comorbidities, including cardiovascular diseases, type 2 diabetes, and various ocular complications[3–8]. While diabetic retinopathy has received considerable research focus, other obesity-related ocular complications are now drawing increased clinical interest[9,10].

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Novel anti-obesity medications, including Tirzepatide and glucagon-like peptide-1 receptor agonists (GLP-1 RAs), have demonstrated effective weight reduction and glycemic control[11–13]. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist, and Semaglutide, a GLP-1 RA, have shown greater weight loss efficacy than traditional medications like Phentermine/Topiramate (Qsymia), Naltrexone/Bupropion (Contrave), and Phentermine[12,14,15]. However, the ocular effects of these medications remain inadequately characterized.

Obesity, metabolic dysfunction, and ocular pathology exhibit intricate interconnections that warrant further investigation[10,16]. Multiple eye disorders, namely cataracts, oculomotor binocular dysfunction, visual impairment and blindness, ametropic accommodative dysfunction, and visual disturbances, have been linked to obesity and its therapeutic interventions[5,7]. Despite the recognized associations, direct comparisons of anti-obesity medications' ocular effects remain limited. The clinical importance of these potential relationships necessitates systematic evaluation. We therefore examined the ocular safety profiles of Tirzepatide, Semaglutide, Phentermine/Topiramate, Naltrexone/Bupropion, and Phentermine among patients with obesity.

Using propensity-score matching (PSM), we controlled for confounding variables to establish reliable comparisons of ocular safety across these medications. We analyzed the incidence of cataracts, oculomotor binocular dysfunction, visual impairment and blindness, ametropic accommodative dysfunction, and visual disturbances in users of different anti-obesity agents.

Our findings demonstrate that newer anti-obesity medications, particularly Tirzepatide and Semaglutide, are associated with more favorable ocular outcomes compared to traditional treatments. Specifically, Tirzepatide users show lower rates of cataracts and oculomotor dysfunction when compared to Naltrexone/Bupropion, while both newer agents demonstrate reduced visual disturbances relative to Phentermine. These associations remain consistent across sensitivity analyses, suggesting that medication choice in obesity management may have implications extending beyond metabolic benefits to include ocular health considerations.

Methods

Ethics statement

Our study protocol was reviewed and approved by the Institutional Review Board of Chung Shan Medical University Hospital (CS2-24100; Title: Adverse Events and Complications of GLP-1 Receptor Agonists, Phentermine- Topiramate, and Naltrexone-Bupropion in Obese Patients with and without Prediabetes, Type 1 diabetes or Type 2 diabetes). This research utilized the TriNetX US Collaborative Network, a federated research platform that aggregates de-identified electronic health records from over 66 healthcare organizations across the United States through standardized data collection protocols. The TriNetX platform employs rigorous de-identification procedures that exceed HIPAA Safe Harbor requirements, including advanced statistical methods that automatically blur small population counts (1–10 participants) to the nearest decuple to prevent potential re-identification. The system restricts access to aggregate statistical analyses only, with no capability to view individual patient records or personally identifiable information. Independent privacy experts have verified that these de-identification protocols meet federal standards for research exemption. Given the comprehensive de-identification of all data elements and the impossibility of linking results to individual patients, this study qualified for exemption from individual informed consent requirements under 45 CFR 46.104(d)(4). The reviewing TriNetX IRB confirmed that the research posed no more than minimal risk to participants and could not reasonably be conducted with identifiable data. All research activities adhered to the ethical principles outlined in the Declaration of Helsinki regarding medical research involving human subjects.

Data source

Data came from the TriNetX US Collaborative Network, containing de-identified electronic health records from 66+ healthcare organizations nationwide. This repository includes over 100 million patients with demographics, diagnoses (ICD-10-CM), procedures (ICD-10-PCS and CPT), medications (RxNorm), laboratory results (LOINC and TNX), and healthcare utilization data[17]. Race and ethnicity information in the TriNetX database comes from electronic health records maintained by participating healthcare organizations. This information represents patient self-reported data collected during standard clinical encounters, which TriNetX subsequently maps to standardized HL7/OMB racial and ethnic categories. When race or ethnicity information was not documented in the original medical records, these fields were designated as 'Unknown'. TriNetX does not verify or independently assign race/ethnicity classifications beyond this standardization process.

Cohort design, covariates, and outcomes

This retrospective, propensity-score-matched cohort study included obese patients (BMI ≥ 27 kg/m²) initiating Tirzepatide, Semaglutide, Phentermine/Topiramate, Naltrexone/Bupropion, or Phentermine from November 1, 2023, through April 31, 2025. The index date corresponded to the initial medication prescription (Fig. 1).

Exclusion criteria included prior ocular conditions within three months, type 1 or type 2 diabetes, HIV, ESKD, and previous use of other study medications within six months. Follow-up started at medication initiation and concluded at the earliest occurrence of study outcomes, loss to follow-up, or administrative censoring (November 1, 2023, to April 30, 2025), with primary analyses including BMI ≥ 27 kg/m² and sensitivity analyses BMI ≥ 30 kg/m². No minimum follow-up duration was required (Supplementary Data 1).

PSM incorporated demographic factors (age, sex, race, ethnicity), comorbidities (hypertension, dyslipidemia, cardiovascular disease), medications (antihypertensives, lipid-lowering agents, antidiabetics), laboratory parameters (HbA1c, lipid profile), and BMI (Supplementary Data 2).

Primary endpoints included cataracts, oculomotor binocular dysfunction, visual impairment and blindness, visual disturbances, dry eye disease, and ametropic accommodative dysfunction, all identified through ICD-10-CM coding (Supplementary Data 3).

Statistics and reproducibility

Statistical analyses were conducted via the TriNetX platform, incorporating Java 11.0.16 (Apache Commons Math 3.6.1), R 4.0.2 (Hmisc1-1, Survival 3.2-3), and Python 3.7 (lifelines, matplotlib, numpy, pandas, scipy, statsmodels).

Sample sizes reflected the number of available matched pairs after implementing 1:1 PSM through nearest-neighbor algorithms. Our primary comparison between Tirzepatide and Semaglutide yielded 25,060 matched pairs, while other treatment comparisons produced cohorts of varying sizes, from 7240 pairs for Tirzepatide versus Naltrexone/Bupropion to 18,892 pairs for Tirzepatide versus Phentermine (Fig. 1). We assessed matching quality by examining standardized mean differences, with values below 0.1 indicating adequate balance between treatment groups. We set statistical significance at two-sided p-values less than 0.05 for initial assessment, then applied Bonferroni correction across our six prespecified primary ocular outcomes (adjusted $\alpha = 0.0083$) to maintain appropriate family-wise error control. Hazard ratios and corresponding 95% confidence intervals were calculated using Cox proportional hazards models. We generated Kaplan–Meier survival curves to examine cumulative outcome incidence patterns over time and applied log-rank tests to evaluate between-group differences. Data reproducibility was maintained through our use of the TriNetX US Collaborative Network, which houses standardized electronic health records from more than 66 healthcare organizations across the United States. We applied consistent inclusion and exclusion criteria throughout all analyses and conducted multiple sensitivity assessments, including BMI-stratified subgroup analyses and clinical characteristic stratification, to verify the robustness of our findings across different patient populations.

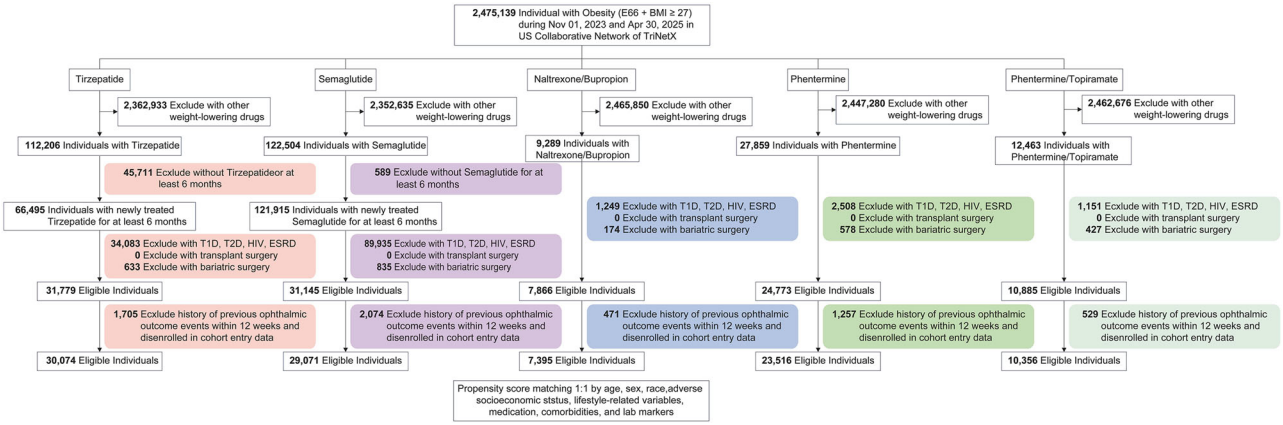

Fig. 1 | Flowchart of individual selection and propensity score matching process. The diagram illustrates the systematic selection process from the initial TriNetX database population to the final matched analytical cohorts for the calendar-aligned analysis (November 2023–April 2025). Following application of inclusion and exclusion criteria for individuals with BMI ≥ 27 kg/m^2, the pre-matching cohorts comprised: Tirzepatide (n = 30,074), Semaglutide (n = 29,071), Naltrexone/Bupropion (n = 7395), Phentermine/Topiramate (n = 10,356), and Phentermine (n = 23,516). These pre-matching cohorts were subsequently subjected to 1:1 propensity score matching using nearest-neighbor algorithms for pairwise comparative analyses. The matching process resulted in balanced analytical cohorts with substantially reduced sample sizes to ensure optimal covariate balance. Specifically, the Tirzepatide versus Semaglutide comparison yielded 25,060 matched pairs from the original pre-matching cohorts of 30,074 and 29,071 participants, respectively. Similarly, other treatment comparisons produced matched cohorts ranging from 7240 pairs (Tirzepatide versus Naltrexone/Bupropion) to 18,892 pairs (Tirzepatide versus Phentermine). This systematic matching approach eliminated participants who could not be adequately matched on baseline characteristics, ensuring comparability between treatment groups while maintaining statistical power for outcome analyses. BMI body mass index, T1D type 1 diabetes, T2D type 2 diabetes, ESRD end-stage renal disease, HIV human immunodeficiency virus, PSM propensity score matching.

Analytical methodology and secondary analyses

Risk assessment utilized crude and multivariable-adjusted Cox proportional hazards models, with results reported as hazard ratios (HRs) and 95% confidence intervals (CIs). Kaplan–Meier curves depicted cumulative incidence patterns, while t-tests evaluated biochemical profile changes. Negative control outcome (NCO) analyses employed unadjusted p-values to prevent false negatives from excessive multiple comparison correction. Subgroup, competing-risk, BMI-stratified, and other sensitivity analyses are designated exploratory and reported with unadjusted p-values, with emphasis on effect sizes and confidence intervals. E-values were calculated for significant associations to assess unmeasured confounding sensitivity[18].

Secondary analyses included stratification by demographic and clinical variables (sex, age, race, eGFR, HbA1c, hypertension, medication use), and extended follow-up for long-term drug effect assessment.

Reporting summary

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

Results

Baseline characteristics in the study population

This analysis compared five anti-obesity medications, examining demographic characteristics, comorbidities, medication use, and laboratory markers before and after PSM (Supplementary Fig. 1). Initial cohorts exhibited substantial imbalances across treatment groups, with the Tirzepatide vs. Semaglutide comparison including 30,074 and 29,071 individuals, respectively, before matching (Supplementary Data 4). Mean age showed modest differences (47.3 ± 12.6 vs. 46.8 ± 14.6 years, SMD = 0.038), while more substantial disparities existed in racial distribution, with white individuals comprising 74.4% vs. 68.4% (SMD = 0.132). PSM substantially improved the balance between groups. The matched cohorts comprised 25,060 patients each, achieving excellent equilibrium across most variables. Age differences became negligible (47.5 ± 13.0 vs. 47.5 ± 13.2 years, SMD = 0.004), and racial distribution achieved balance (white: 72.6% vs. 72.3%, SMD = 0.006). Clinical conditions showed improved matching, with hypertensive disease prevalence (45.7% vs. 45.8%, SMD = 0.001) and most comorbidities reaching optimal balance.

The mean follow-up periods after matching; these durations remained relatively stable, with means ranging from 376.04 to 422.37 days, depending on the specific treatment comparison. The Tirzepatide groups consistently showed shorter mean follow-up periods (390.09–395.18 days), which corresponds to its more recent market introduction compared to the other medications studied (Supplementary Table 1).

Differential ocular outcomes: tirzepatide and semaglutide versus traditional anti-obesity medications

Our calendar-aligned analysis examining the period when all medications were simultaneously available in the market revealed several notable patterns in ocular outcomes (Figs. 2, 3, Supplementary Fig. 2, Table 1, and Supplementary Tables 2–7). Tirzepatide was associated with a significantly lower incidence of cataract development compared to Naltrexone/Bupropion (HR 0.46; 95% CI: 0.23–0.92; p = 0.025). When compared to Phentermine/Topiramate, Tirzepatide showed a lower cataract incidence (HR 0.76; 95% CI: 0.38–1.52; p = 0.433), though this did not reach statistical significance. Tirzepatide also demonstrated significant associations with reduced incidence of oculomotor binocular dysfunction compared to Naltrexone/Bupropion (HR 0.31; 95% CI: 0.16–0.60; $p = 2.0 \times 10^{-4}$), Phentermine (HR 0.44; 95% CI: 0.28–0.67; $p = 1.0 \times 10^{-4}$), visual issues and blindness versus Naltrexone/Bupropion (HR 0.44; 95% CI: 0.26–0.76; p = 0.003) and phentermine (HR 0.51; 95% CI: 0.35–0.74; $p = 3.0 \times 10^{-4}$), and visual disturbances against Naltrexone/Bupropion (HR 0.46; 95% CI: 0.26–0.83; $p = 8.0 \times 10^{-3}$) and Phentermine (HR 0.45; 95% CI: 0.31–0.68; $p = 5.0 \times 10^{-5}$; Fig. 2).

Semaglutide demonstrated lower cataract rates versus Naltrexone/Bupropion (HR 0.37; 95% CI: 0.18–0.75; p = 0.004), decreased oculomotor binocular dysfunction versus both Naltrexone/Bupropion (HR 0.46; 95% CI: 0.27–0.79; p = 0.004) and Phentermine (HR 0.42; 95% CI: 0.27–0.66; $p = 1.0 \times 10^{-4}$), and reduced visual disturbances versus Phentermine/Topiramate (HR 0.61; 95% CI: 0.38–0.97; p = 0.037) and Phentermine (HR 0.71; 95% CI: 0.51–0.98; p = 0.038; Fig. 2 and Supplementary Fig. 2).

In the Tirzepatide versus Semaglutide cohort of 25,060 matched pairs, no statistically significant differences emerged across ocular outcomes, though Tirzepatide showed a non-significant trend (HR 0.87, 95% CI: 0.55–1.37, p = 0.540; Fig. 3). When compared to Naltrexone/Bupropion, Tirzepatide demonstrated associations with lower incidence across multiple

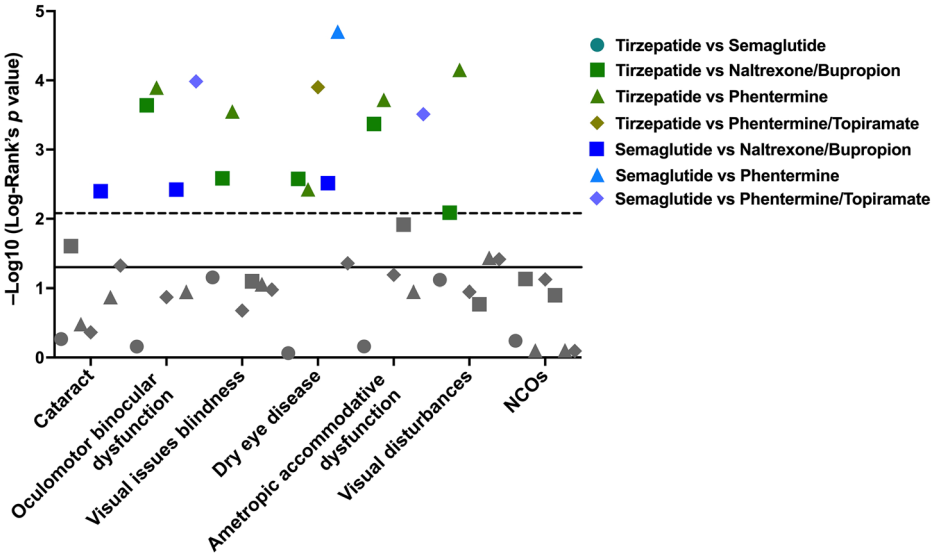

Fig. 2 | Negative log-transformed *p*-values comparing the incident risks of ocular-adverse events between Tirzepatide versus Semaglutide and other anti-obesity medications with negative control outcomes. Statistical significance thresholds are indicated by horizontal reference lines on the negative log10 scale. The solid line represents the conventional exploratory significance level (−log10[0.05] = 1.30), while the dashed line denotes the Bonferroni-corrected threshold within each drug comparison (−log10[0.0083] = 2.08). The Bonferroni adjustment was applied to account for multiple testing across the six primary ocular outcomes, resulting in a revised significance threshold of 0.0083 (α = 0.05/6). Outcomes plotted above the dashed line meet the more stringent multiple comparison-adjusted criterion, whereas those between the solid and dashed lines achieve nominal statistical significance but require cautious interpretation in the context of multiple hypothesis testing.

ocular outcomes. Cataract incidence was notably reduced (HR 0.46, 95% CI: 0.23–0.92, $p = 0.025$), representing a 54% lower observed rate. Similarly, oculomotor binocular dysfunction (HR 0.31, 95% CI: 0.16–0.60, $p = 2 \times 10^{-4}$), visual issues and blindness (HR 0.44, 95% CI: 0.26–0.76, $p = 0.003$), dry eye disease (HR 0.33, 95% CI: 0.15–0.71, $p = 0.003$), ametropic accommodative dysfunction (HR 0.31, 95% CI: 0.16–0.62, $p = 2.3 \times 10^{-4}$), and visual disturbances (HR 0.46, 95% CI: 0.26–0.83, $p = 0.008$) all showed statistically significant associations favoring Tirzepatide.

Against Phentermine/Topiramate, Tirzepatide demonstrated a significant association only with dry eye disease (HR 0.29, 95% CI: 0.15–0.57, $p = 1.3 \times 10^{-4}$), while other outcomes including cataracts (HR 0.76, 95% CI: 0.38–1.52, $p = 0.433$) and oculomotor binocular dysfunction (HR 0.63, 95% CI: 0.34–1.16, $p = 0.134$) showed non-significant trends. Compared to Phentermine alone, Tirzepatide showed significant associations with reduced oculomotor binocular dysfunction (HR 0.44, 95% CI: 0.28–0.67, $p = 1.3 \times 10^{-4}$), visual issues and blindness (HR 0.51, 95% CI: 0.35–0.74, $p = 2.8 \times 10^{-4}$), dry eye disease (HR 0.46, 95% CI: 0.27–0.79, $p = 0.004$), ametropic accommodative dysfunction (HR 0.44, 95% CI: 0.28–0.68, $p = 1.9 \times 10^{-4}$), and visual disturbances (HR 0.45, 95% CI: 0.31–0.68, $p = 7 \times 10^{-5}$).

Semaglutide comparisons with Naltrexone/Bupropion revealed significant associations with lower cataracts (HR 0.37, 95% CI: 0.18–0.75, $p = 0.004$), oculomotor binocular dysfunction (HR 0.46, 95% CI: 0.27–0.79, $p = 0.004$), dry eye disease (HR 0.36, 95% CI: 0.18–0.73, $p = 0.003$), and ametropic accommodative dysfunction (HR 0.50, 95% CI: 0.29–0.87, $p = 0.012$). Against Phentermine/Topiramate, Semaglutide showed significant associations with reduced dry eye disease (HR 0.26, 95% CI: 0.13–0.50, $p = 2 \times 10^{-5}$) and visual disturbances (HR 0.61, 95% CI: 0.38–0.97, $p = 0.037$). When compared to Phentermine, Semaglutide demonstrated significant associations with lower oculomotor binocular dysfunction (HR 0.42, 95% CI: 0.27–0.66, $p = 1 \times 10^{-4}$), dry eye disease (HR 0.61, 95% CI: 0.38–0.99, $p = 0.044$), ametropic accommodative dysfunction (HR 0.44, 95% CI: 0.28–0.70, $p = 3.1 \times 10^{-4}$), and visual disturbances (HR 0.71, 95% CI: 0.51–0.98, $p = 0.038$), while cataracts (HR 0.56, 95% CI: 0.31–1.00, $p = 0.047$) and visual issues and blindness (HR 0.77, 95% CI: 0.57–1.06, $p = 0.105$) showed borderline or non-significant associations.

The sensitivity analysis (individuals with BMI ≥ 30 kg/m^2) generally reinforced findings from the BMI ≥ 27 kg/m^2 population, with both GLP-1 RAs demonstrating consistent associations with better ocular outcomes compared to traditional anti-obesity medications (Fig. 3 and Supplementary Fig. 2).

Kaplan–Meier curves

The survival analysis approach through Kaplan–Meier estimation demonstrated distinct patterns in ocular health outcomes across different anti-obesity treatments (Supplementary Figs. 3–9).

Tirzepatide showed an observed association with lower incidence rates across multiple ocular conditions. When compared to Naltrexone/Bupropion combinations, the survival curves showed sustained separation throughout the observation period, with the most pronounced associations observed for oculomotor binocular dysfunction (HR 0.31, 95% CI: 0.16–0.60, $p = 2.3 \times 10^{-4}$), cataracts (HR 0.46, 95% CI: 0.23–0.92, $p = 0.025$), visual issues and blindness (HR 0.44, 95% CI: 0.26–0.76, $p = 0.003$), dry eye disease (HR 0.33, 95% CI: 0.15–0.71, $p = 0.003$), ametropic accommodative dysfunction (HR 0.31, 95% CI: 0.16–0.62, $p = 4.3 \times 10^{-4}$), and visual disturbances (HR 0.46, 95% CI: 0.26–0.83, $p = 0.008$). The temporal progression remained stable, indicating consistent associations rather than early transient effects. Compared to Phentermine/Topiramate, Tirzepatide showed an observed association with reduced incidence only for dry eye disease (HR 0.29, 95% CI: 0.15–0.57, $p = 1.3 \times 10^{-4}$), with other outcomes showing non-significant trends, including cataracts (HR 0.76, 95% CI: 0.38–1.52, $p = 0.433$).

Semaglutide was associated with a lower incidence across multiple comparisons. Against Naltrexone/Bupropion, observed associations with reduced incidence emerged for cataracts (HR 0.37, 95% CI: 0.18–0.75, $p = 0.004$), oculomotor binocular dysfunction (HR 0.46, 95% CI: 0.27–0.79, $p = 0.004$), dry eye disease (HR 0.36, 95% CI: 0.18–0.73, $p = 0.003$), and ametropic accommodative dysfunction (HR 0.50, 95% CI: 0.29–0.87, $p = 0.012$).

When compared to Phentermine/Topiramate, Semaglutide showed observed associations with lower incidence for dry eye disease (HR 0.26, 95% CI: 0.13–0.50, $p = 2 \times 10^{-5}$) and visual disturbances (HR 0.61, 95% CI: 0.38–0.97, $p = 0.037$).

Subgroup analysis

Based on the supplemental subgroup analyses, several notable patterns emerged regarding the associations between Tirzepatide and Semaglutide vs traditional anti-obesity medications across different patient characteristics and clinical contexts (Supplementary Data 5–22).

Among individuals with preserved renal function (eGFR ≥45 mL/min/1.73 m^2), Tirzepatide demonstrated associations with reduced visual issues and blindness (HR 0.62, 95% CI 0.44–0.89) and visual disturbances (HR 0.58, 95% CI 0.39–0.86) compared to semaglutide. Among individuals without heart failure, Tirzepatide showed associations with reduced visual

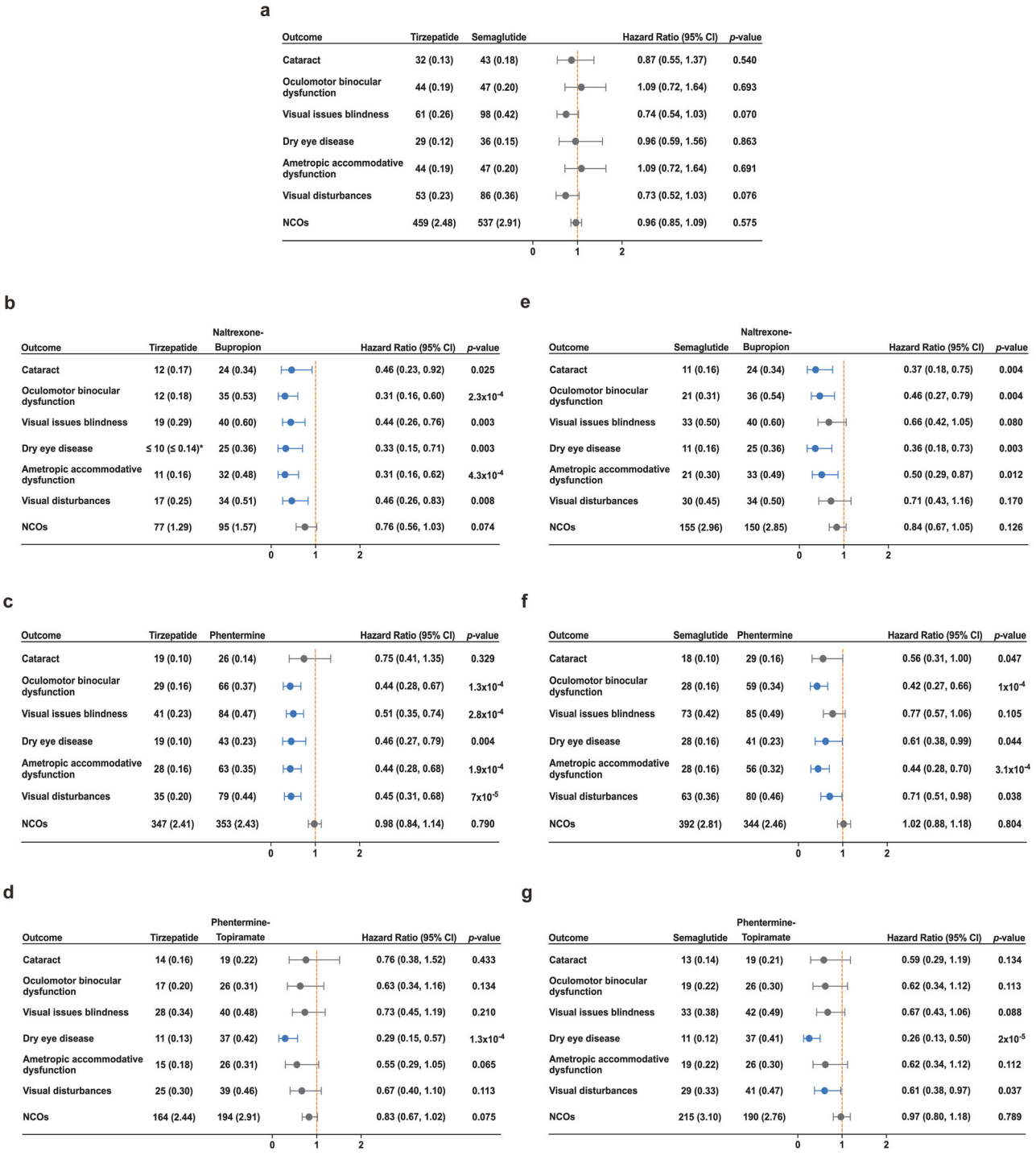

Fig. 3 | Forest plot of comparative ocular outcomes in obesity with Tirzepatide and Semaglutide versus other weight-lowering medications. Forest plot shows hazard ratios with 95% confidence intervals for ocular outcomes comparing anti-obesity medications in individuals with BMI ≥ 27 kg/m² (November 2023–April 2025). **a** presents Tirzepatide versus Semaglutide comparisons. **b**–**g** show comparisons against traditional medications: **b** Tirzepatide versus Naltrexone/Bupropion, **c** Phentermine, and **d** Phentermine/Topiramate; **e** Semaglutide versus Naltrexone/Bupropion, **f** Phentermine, and **g** Phentermine/Topiramate. Event counts appear below treatment names, with matched cohort percentages in parentheses. Horizontal error bars represent 95% confidence intervals from Cox proportional hazards models. Hazard ratios below 1.0 favor the first medication listed. Statistical testing used log-rank analysis with Bonferroni correction ($p < 0.0083$). NCOs negative control outcomes.

issues and blindness (HR 0.56, 95% CI 0.39–0.81) and visual disturbances (HR 0.52, 95% CI 0.35–0.78) compared to Semaglutide.

For Naltrexone/Bupropion comparisons, Tirzepatide showed associations with reduced cataract incidence, particularly in individuals without prior GLP-1 RA exposure (HR 0.18, 95% CI 0.05–0.60) and those without proteinuria (HR 0.34, 95% CI 0.13–0.85). Against Phentermine, Tirzepatide demonstrated associations with reduced oculomotor binocular dysfunction across most subgroups, with particularly strong associations in individuals with preserved renal function (HR 0.60, 95% CI 0.34–1.03) and those without ischemic heart disease (HR 0.55, 95% CI 0.30–0.98).

Semaglutide comparisons with traditional anti-obesity medications showed similar patterns. Against Naltrexone/Bupropion, Semaglutide

Table 1 | Comparison of Tirzepatide vs Semaglutide for ocular outcomes

	Tirzepatide	Semaglutide	Risk Difference (95% CI)	ARD (%)	HR-Based RRR (%)	HR (95%CI)	*P*-Value	*E*-value For HR	*E*-value for lower CI of HR
Cataract	32/24,377 (0.1)	43/24,385 (0.2)	−0.0005 (−0.0011 to 0.0002)	0.05	N/A	0.87 (0.55, 1.37)	0.540	N/A	N/A
Oculomotor binocular dysfunction	44/23,568 (0.2)	47/23,789 (0.2)	−0.0001 (−0.0009 to 0.0007)	0.01	N/A	1.09 (0.72, 1.64)	0.693	N/A	N/A
Visual issues blindness	61/23,218 (0.3)	98/23,413 (0.4)	−0.0016 (−0.0026 to −0.0005)	0.16	N/A	0.74 (0.54, 1.03)	0.070	N/A	N/A
Dry eye disease	29/24,367 (0.1)	36/24,464 (0.1)	−0.0003 (−0.0009 to 0.0004)	0.03	N/A	0.96 (0.59, 1.56)	0.863	N/A	N/A
Ametropic accommodative dysfunction	44/23,662 (0.2)	47/23,880 (0.2)	−0.0001 (−0.0009 to 0.0007)	0.01	N/A	1.09 (0.72, 1.64)	0.691	N/A	N/A
Visual disturbances	53/23,419 (0.2)	86/23,606 (0.4)	−0.0014 (−0.0024 to −0.0004)	0.14	N/A	0.73 (0.52, 1.03)	0.076	N/A	N/A
NCOs	459/18,494 (2.5)	537/18,484 (2.9)	−0.0042 (−0.0075 to −0.0009)	0.42	N/A	0.96 (0.85, 1.09)	0.575	N/A	N/A

Percentages of individual numbers are rounded to one decimal place following conventional rounding rules.
ARD absolute risk difference, *RRR* relative risk reduction, *NCOs* negative control outcomes.

demonstrated associations with reduced oculomotor binocular dysfunction, particularly in individuals with preserved renal function (HR 0.22, 95% CI 0.08–0.60) and those without prior GLP-1 RA exposure (HR 0.19, 95% CI 0.06–0.56).

Weight and HbA1c changes

Weight loss trajectories differed across medications (Supplementary Figs. 10 and 11). Tirzepatide produced 8.1% weight reduction from baseline (*T*-test, $p = 9 \times 10^{-4}$), exceeding Semaglutide's 6.0% decrease (*T*-test, $p = 2.45 \times 10^{-8}$). Similarly, HbA1c reductions favored Tirzepatide at 5.1% versus Semaglutide's 3.9% (*T*-test, $p = 1.94 \times 10^{-9}$; Supplementary Fig. 12).

Analysis of surgical interventions

To assess whether observed differences in cataract diagnosis translated into measurable healthcare utilization, we examined cataract surgery rates across treatment groups using CPT procedure codes (Supplementary Fig. 13). Surgical intervention rates remained comparable between Tirzepatide and Semaglutide (HR 1.92, 95% CI 0.63–5.87, $p = 0.25$). Tirzepatide showed no significant differences in surgery rates when compared with other agents: Naltrexone/Bupropion (HR 0.81, 95% CI 0.63–1.05, $p = 0.11$), Phentermine/Topiramate (HR 0.43, 95% CI 0.08–2.23, $p = 0.30$), or Phentermine (HR 3.21, 95% CI 0.61–16.91, $p = 0.15$).

Among Semaglutide comparisons, surgical rates showed no significant differences between Phentermine/Topiramate (HR 0.18, 95% CI 0.02–1.55, $p = 0.08$). Comparisons with Naltrexone/Bupropion (HR 0.55, 95% CI 0.16–1.95, $p = 0.35$) and Phentermine (HR 1.87, 95% CI 0.34–10.23, $p = 0.46$) showed no significant differences.

BMI-stratified analysis: medication-specific ocular protection patterns

The BMI-stratified subgroup analysis revealed no statistically significant differences between Tirzepatide and Semaglutide across primary ocular outcomes (Supplementary Fig. 14 and Supplementary Data 5–22). However, several statistically significant associations emerged when comparing these agents against traditional anti-obesity medications across different BMI categories.

Against Naltrexone/Bupropion, Tirzepatide demonstrated significant protective associations in specific BMI strata. For visual issues and blindness, the BMI 30–34.9 kg/m² group showed notable protection (HR 0.20, 95% CI 0.06–0.67). Visual disturbances outcomes favored Tirzepatide in the BMI 30–34.9 kg/m² category (HR 0.21, 95% CI 0.06–0.72). For visual disturbances, the BMI 30–34.9 kg/m² group demonstrated protective effects (HR 0.21, 95% CI 0.06–0.72). Against Naltrexone/Bupropion, Semaglutide exhibited significant protective associations in the BMI 30–34.9 kg/m² group for cataracts (HR 0.11, 95% CI 0.01–0.87). The comparison with Phentermine revealed significant protective associations for oculomotor binocular dysfunction in the BMI 27–29.9 kg/m² group (HR 0.12, 95% CI 0.01–0.93). Against Phentermine/Topiramate, Semaglutide demonstrated significant protection for dry eye disease in the BMI 35–39.9 kg/m² group (HR 0.18, 95% CI 0.04–0.83), representing a protective association in this specific weight category.

Discussion

This study demonstrates that newer anti-obesity medications, particularly Tirzepatide and Semaglutide, show superior ocular safety profiles relative to traditional agents like Phentermine/Topiramate, Naltrexone/Bupropion, and Phentermine in people with obesity. These results inform clinical decision-making and expand knowledge of incretin-based therapy's broader health benefits.

Tirzepatide's association with reduced cataract incidence represents a notable finding, given sparse evidence for GLP-1 RA effects on cataract formation in people with obesity. Prior GLP-1 RA research has emphasized diabetic retinopathy (DR) and other ocular complications rather than cataract development[7,19–22]. The SUSTAIN trials reported DR worsening in some Semaglutide-treated patients, particularly those with

pre-existing DR[23]. However, Tirzepatide's dual GIP and GLP-1 receptor agonism may confer cataract protection through GIP's anti-inflammatory properties[24].

Our analysis also revealed important findings regarding dry eye disease and other ocular outcomes that merit specific attention. Dry eye disease, a prevalent condition affecting quality of life, showed differential responses to the medications studied[25]. Tirzepatide and Semaglutide were associated with a lower incidence of dry eye disease compared to both Phentermine/Topiramate and Naltrexone/Bupropion. Dry eye disease in obesity has been linked to chronic low-grade inflammation and altered tear film composition, potentially through pro-inflammatory cytokines associated with adipose tissue[10]. The association between Semaglutide and lower dry eye incidence aligns with its documented anti-inflammatory properties, which may extend to ocular surface tissues[26].

Regarding the other ocular outcomes studied, our findings on visual disturbances and oculomotor binocular dysfunction further enhance the understanding of anti-obesity medications' ocular profile. Semaglutide was consistently associated with lower rates of visual disturbances across all comparisons, potentially reflecting its neuroprotective properties that may extend to visual pathways[27]. This observation is clinically meaningful, as visual disturbances impact daily functioning and quality of life[28]. The oculomotor binocular dysfunction findings complement these observations, with both Tirzepatide and Semaglutide showing lower associated rates compared to Naltrexone/Bupropion. These patterns suggest that GLP-1 receptor activation may influence not only metabolic parameters, but also neural pathways involved in visual processing and oculomotor control, though the precise mechanisms require further investigation.

Slower-than-expected progression to surgery is a plausible explanation for the discordant findings between the observed association with lower incidence of cataract diagnosis and the neutral trend for CPT-coded extraction. Population-based Medicare data involving 1.3 million beneficiaries show a weighted median of 194 days and a range of 17–367 days across hospital-referral regions, between the first H25/H26 diagnosis and subsequent cataract surgery[29]. Such lags mean that a follow-up can readily register incident diagnoses but may be underpowered to register procedure codes. In addition, modern phacoemulsification is elective and largely patient-driven, so modest delays in lens opacification seldom trigger immediate surgery[30,31].

The observed differential effects between Tirzepatide and Semaglutide likely stem from their distinct receptor activation profiles. These medications differ fundamentally in their target receptors. Tirzepatide functions as a dual GIP and GLP-1 RA, whereas Semaglutide exclusively activates GLP-1 receptors[32–34]. Structurally, Tirzepatide is engineered as a hybrid incretin agonist combining the first 14 amino acid residues from native GIP with a GLP-1-derived C-terminal segment (residues 15–39)[32]. Its structure incorporates two Aib substitutions (positions 2 and 12) that enhance resistance to DPP-4 degradation, along with an amido-linked C-20 di-acid fatty chain at Lys20 that facilitates high-affinity albumin binding, resulting in a half-life of approximately five days[32,34]. In contrast, Semaglutide maintains the GLP-1 (7–37) backbone, incorporates Aib8 and Arg34 modifications, and features a shorter C-18 lipid chain at Lys26, achieving weekly dosing while targeting only GLP-1 receptors[33].

Tirzepatide promotes cAMP generation while minimally recruiting β-arrestin, which reduces receptor internalization and extends surface signaling duration[35]. Semaglutide, however, produces a more balanced cAMP/β-arrestin response[35]. Pharmacological studies demonstrate that blocking either GLP-1R or glucose-dependent insulinotropic polypeptide receptor (GIPR) partially reduces Tirzepatide-induced insulin secretion, but only simultaneous blockade of both receptors eliminates this effect[36]. Semaglutide's action, by comparison, relies solely on GLP-1 receptors[36]. These cellular findings correlate with the superior glycemic control and weight reduction observed in the SURPASS-2 trial[37]. Research has shown that induced GIPR expression in white adipocytes triggers sarco-endoplasmic calcium ATPase (SERCA)-dependent futile calcium cycling[38]. CRISPR deletion of SERCA2 eliminates this effect, demonstrating that GIPR connects to a SERCA/sarcolipin pathway that supports energy expenditure and weight reduction[38]. Sustained GIPR agonism shifts post-prandial glucose toward glycerol production and promotes lipolysis during fasting, enhancing lipid clearance and mobilization beyond what GLP-1R agonism achieves alone[14].

Current evidence confirms GLP-1 receptors in human retinal neurons, glia, and choroidal endothelium, where they modulate hyperglycemia-induced apoptosis and oxidative stress[39–41]. In contrast, ocular localization of the GIPR remains speculative; only neuro-anatomical studies demonstrate GIPR in central neurons and glia, suggesting but not establishing its presence in the retina, a CNS extension[42]. GLP-1R agonists notably reduce retinal inflammation, suppress reactive oxygen species, and maintain the blood/retina barrier; topical application prevents diabetic retinal neurodegeneration in rodent models[40]. Both pre-clinical and clinical observations suggest that GLP-1R activation may modestly reduce intraocular pressure (IOP) by decreasing ocular inflammation, although human evidence remains limited[43,44].

The divergent ocular profiles of these medications emerged unexpectedly in clinical trials. In people with T2D, SUSTAIN-6 revealed increased diabetic-retinopathy complications with semaglutide, primarily in subjects with pre-existing retinopathy and rapid HbA1c reduction[45,46]. Later analysis suggested this risk relates more to the rate of glycemic improvement than direct retinal toxicity, a pattern observed historically with intensive insulin therapy[46,47]. Current evidence, including the retrospective research by Stevens et al., suggests that Semaglutide use was not associated with increased risk of DR progression, visual loss, or increased intravitreal injections over a 3-year period[48]. The current understanding points to a potential biphasic pattern in GLP-1 RA studies, where any observed early worsening may be related to rapid glycemic improvement rather than direct retinal toxicity, particularly in patients with pre-existing retinopathy, poor glycemic control, and those undergoing HbA1c reduction[47]. This parallels the "early worsening" phenomenon documented with intensive insulin therapy in landmark trials like DCCT, where temporary deterioration was followed by long-term benefits with sustained glycemic control[47].

Throughout the SURPASS program, Tirzepatide's overall ocular-adverse-event profile was comparable to comparators, and adjudicated analyses detected no signal for early diabetic-retinopathy worsening[37]. Two key mechanisms may explain this divergence from Semaglutide: (i) SURPASS enrolled participants with less severe baseline diabetic retinopathy compared to SUSTAIN; and (ii) GIPR co-activation may exert unique vascular effects. The latter hypothesis derives from observations that GIP modulates vascular tone across peripheral vascular beds by enhancing endothelial nitric-oxide synthesis through eNOS activation—an effect abolished by CaMKK, PLC, or AMPK inhibition—and demonstrates anti-inflammatory actions in adipose tissue and endothelium that correlate with increased cAMP signaling in select vascular beds, though a direct cAMP-dependent mechanism underlying its anti-inflammatory effect has yet to be conclusively established[49]. If similar mechanisms operate in retinal vessels, dual agonism might be associated with reduced transient hypoperfusion, believed to trigger early worsening.

Current literature supports GLP-1R-mediated anti-inflammatory and neuroprotective effects in the retina[43]. To attribute additional benefit to Tirzepatide's GIP component, ocular expression and functionality of GIPR must be demonstrated. Semaglutide's early retinopathy signal appears specific to diabetes and influenced by HbA1c kinetics; evidence in non-diabetic populations remains reassuring, though sparse. Future research should characterize GIPR with single-cell ocular transcriptomics, directly compare Tirzepatide with pure GLP-1 RAs for IOP and retinal outcomes across metabolic contexts, and incorporate ophthalmic endpoints in cardiometabolic trials to better define the risk-benefit profile.

Despite the robust design of our study, several limitations must be acknowledged. Unmeasured confounders, particularly lifestyle factors such as dietary patterns, physical activity levels, smoking status, and alcohol

consumption, could influence both treatment selection and observed ocular outcomes. These factors are rarely captured comprehensively in electronic health records, yet they represent critical determinants of ocular health in obesity. For instance, Mediterranean diet adherence has been associated with reduced cataract risk through its antioxidant properties, while smoking accelerates cataract formation through oxidative stress mechanisms. Similarly, physical activity might influence intraocular pressure and vascular health independently of weight loss medications. To mitigate these concerns, we included several proxy indicators in our propensity score matching, such as socioeconomic determinants (captured through ICD codes related to employment status, housing circumstances, and social environment), lifestyle counseling codes, and medication profiles that often correlate with health behaviors. While these proxies provide some adjustment, they incompletely capture the complex lifestyle patterns that might differ between treatment groups. Additionally, the possibility of treatment selection bias based on unmeasured clinical factors remains. Clinicians might preferentially prescribe newer agents like Tirzepatide to patients with certain unmeasured characteristics that independently correlate with better ocular outcomes. Despite using comprehensive propensity score matching that achieved excellent balance on measured variables (most SMDs <0.1), residual confounding from unmeasured factors cannot be definitively excluded. Future studies incorporating direct measurement of dietary patterns, physical activity levels, and other lifestyle indicators would provide valuable complementary evidence to our findings. Tirzepatide's recent market entry resulted in smaller sample sizes, potentially reducing power to detect subtle ocular changes. Additionally, ICD-10 coding may miss subclinical or undiagnosed early-stage ocular conditions. While we expanded our analysis to include additional follow-up data and performed sensitivity analyses with broader inclusion criteria, we acknowledge that limitations related to sample size remain, particularly for certain subgroup analyses. The relatively recent introduction of Tirzepatide into clinical practice inherently constrains both sample size and follow-up duration compared to more established medications, potentially limiting our ability to detect rare events or effects that may emerge only after longer exposure periods. The inherent challenges of comparing newer medications like Tirzepatide with established treatments are due to differences in market availability periods. However, our methodological safeguards, including propensity score matching, time-to-event analysis, and calendar-restricted sensitivity analyses—provide robust evidence that observed differences in ocular outcomes represent true medication effects rather than artifacts of differential follow-up.

Our statistical framework employed Bonferroni correction across six primary ocular outcomes, yielding an adjusted significance threshold of $p < 0.0083$. While this conservative approach controls family-wise error rate, we recognize the importance of evaluating effect magnitude and confidence intervals alongside significance testing. Results approaching our adjusted threshold require nuanced interpretation beyond binary significance classification. For example, Tirzepatide's association with reduced cataract incidence versus Naltrexone/Bupropion (HR 0.46, 95% CI: 0.23–0.92, $p = 0.025$) demonstrates both statistical significance and substantial effect size, with the confidence interval excluding unity while encompassing clinically meaningful reductions. The consistency of effect directions across sensitivity analyses provides additional confidence in our findings, independent of individual p-value thresholds. This multi-dimensional analytical approach acknowledges that statistical significance testing represents one component of evidence evaluation, particularly in observational studies where effect size and precision estimates offer essential clinical context. Future research with advanced imaging and extended follow-up may better elucidate long-term ocular effects of these medications. This study offers important strengths, including large sample sizes and real-world TriNetX data that enhance generalizability. The broad range of ocular outcomes examined provides a thorough assessment of anti-obesity medications' ophthalmic effects. Time-varying hazard ratios and Kaplan–Meier curves captured temporal treatment dynamics. These findings carry clinical significance for obesity management. As obesity prevalence rises alongside ocular complications, anti-obesity medications offering both metabolic and ocular benefits may reduce eye disease burden in affected populations. In conclusion, Tirzepatide and Semaglutide demonstrate favorable ocular safety profiles compared to traditional anti-obesity treatments. These results support incorporating ocular considerations into obesity management decisions and indicate that newer incretin-based therapies may offer benefits beyond metabolic effects.

Data availability

All data supporting the findings of this study are available within the paper and its Supplementary Information. Raw data are available from the corresponding author upon reasonable request, subject to compliance with Chung Shan Medical University Hospital and TriNetX regulatory requirements and data sharing policies. Data from TriNetX are available to researchers on application to TriNetX following the steps outlined here: https://live.trinetx.com. Source data for Figs. 2 and 3 are provided in Supplementary Data 23 and 24, respectively.

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Authors contributions

Y.N.H. Conceptualization, Methodology, Formal analysis, Data Curation, Writing – Original Draft, Writing – Review & Editing; J.C.C. Methodology, Formal analysis, Data Curation, Writing – Original Draft, Writing – Review & Editing; P.H.L. Methodology, Formal analysis, Data Curation, Writing – Original Draft, Writing – Review & Editing; M.Y.H. Writing – Review & Editing; C.W.C. Writing – Review & Editing; G.M.K. Conceptualization, Writing – Review & Editing; P.H.S. Conceptualization, Methodology, Writing – Review & Editing, Supervision, Project Administration, Funding Acquisition.

Competing interests

The authors have no conflicts of interest to declare. The funders had no role in the design, execution, interpretation, or writing of this study, and the authors maintain no personal or financial relationships that could potentially influence the work presented here.

Additional information

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