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Association between tirzepsatide use and risk of suicidal ideation among individuals with obesity and major depressive disorder

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Abstract

Obesity and major depressive disorder (MDD) frequently co-occur and confer mutually reinforcing risks, including elevated suicidality. Tirzepatide has demonstrated substantial metabolic benefits, yet its psychiatric safety in high-risk populations with MDD remains uncertain. This study aimed to compare suicidal ideation outcomes among adults with comorbid obesity and MDD initiating tirzepatide versus non–GLP-1RA anti-obesity medications. This retrospective, propensity score–matched cohort study used deidentified electronic health record data from the TriNetX Global Collaborative Network. Adults (≥18 years) with diagnosed obesity and MDD who initiated tirzepatide or non–GLP-1RA anti-obesity medications were included. The primary outcome was suicidal ideation. Secondary outcomes included anxiety disorders, insomnia disorders, all-cause mortality, and emergency department or inpatient encounters. Among 24,103 matched pairs, tirzepatide use was associated with lower risk of suicidal ideation (HR, 0.63; 95% CI, 0.42–0.93), anxiety disorders (HR, 0.83; 95% CI, 0.81–0.86), insomnia disorders (HR, 0.92; 95% CI, 0.86–0.98), all-cause mortality (HR, 0.38; 95% CI, 0.25–0.58), and emergency department visits or hospitalizations (HR, 0.94; 95% CI, 0.89–0.99). Risk reduction was generally consistent across prespecified subgroups. Control outcome analyses supported the internal validity of the findings. In conclusion, this study provides real-world evidence that tirzepatide initiation was associated with a lower recorded risk of suicidal ideation, as well as reduced anxiety, insomnia, all-cause mortality, emergency department visits, and hospitalizations, among adults with comorbid obesity and MDD. This observational association should not be interpreted as evidence of a direct antisuicidal effect. These findings support the potential for tirzepatide to serve as a metabolically favorable treatment option associated with a lower risk of suicidal ideation in this vulnerable, high-risk population.

Introduction

Obesity and major depressive disorder (MDD) frequently co-occur and exhibit a bidirectional relationship: individuals with obesity are 55% more likely to develop MDD, while those with depression have a 71% increased risk of becoming obese [1]. This reciprocal link is driven by shared biological mechanisms, including chronic inflammation and neuroendocrine dysregulation, as well as behavioral and psychosocial factors including emotional eating, reduced physical activity, and social stigma [2–4]. The coexistence of these conditions not only compounds disease burden

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but also complicates treatment, particularly given that many antidepressants and antipsychotics may induce weight gain, perpetuating a self-reinforcing cycle of worsening metabolic and psychiatric health [1].

In recent years, glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have revolutionized obesity pharmacotherapy, with tirzepatide, a dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist, demonstrating unprecedented efficacy. In the SURMOUNT-1 trial, tirzepatide led to an average weight loss of approximately 20% over 72 weeks, significantly outperforming previous agents [5–7]. However, emerging post-marketing reports of suicidal ideation and self-injury associated with GLP-1 RAs have prompted regulatory scrutiny in both Europe and the United States [8, 9]. While several large observational studies have shown neutral or even protective associations between GLP-1 RAs use and suicidality, with some data suggesting concurrent improvements in mood and anxiety symptoms, the evidence remains mixed [10, 11]. For instance, a recent pharmacovigilance study by Nishida et al. reported that semaglutide was associated with an elevated risk of depression and suicidality, highlighting the need for continued clinical vigilance [12].

Given these mixed findings, evidence regarding the psychiatric safety of GLP-1 RAs, specifically whether they confer a protective or adverse effect on suicidality, remains critically limited in high-risk psychiatric populations. Individuals with coexisting obesity and MDD, who face elevated baseline risks of suicidality, have not been the focus of prior investigations. To address this critical evidence gap, we conducted a real-world, propensity score–matched cohort study to compare the risk of suicidal ideation in adults with obesity and MDD initiating tirzepatide versus those starting traditional non–GLP-1 anti-obesity medications.

Methods

Data source

This retrospective cohort study was conducted using the TriNetX Global Collaborative Network, a federated research platform containing de-identified electronic health records (EHRs) from participating healthcare organizations (HCOs) across North America, Europe, Asia, and other regions. The database includes longitudinal information on demographics, diagnoses, procedures, medications, laboratory values, and healthcare utilization. All analyses were executed within the secure TriNetX environment, which prohibits access to patient-level identifiable data. This study was reviewed and approved by the Institutional Review Board of Chi Mei Medical Center (IRB No. 11412-E03). The requirement for written informed consent was waived because the study used anonymized, de-identified data. All methods were performed in accordance with the relevant guidelines and regulations, including the principles of the Declaration of Helsinki.

Cohort definitions

Tirzepatide group

The tirzepatide cohort consisted of adults aged 18 years or older who initiated tirzepatide therapy for obesity management. To ensure that tirzepatide was prescribed for a relevant metabolic indication, eligible patients were required to have a recorded diagnosis of overweight or obesity (ICD-10-CM E66) within the 30 days preceding or on the date of their first tirzepatide prescription. Individuals were additionally required to have a diagnosis of major depressive disorder within the year before treatment initiation, defined as either a depressive episode (F32) or recurrent major depressive disorder (F33). To ensure that the primary endpoint represented new-onset suicidality rather than continuation of a recent crisis, patients were excluded if they had any documentation of suicidal ideation (R45.851), suicide attempt (T14.91), inpatient hospitalization, or emergency department encounters during the six months preceding tirzepatide initiation [13]. To establish incident exposure, individuals with evidence of tirzepatide use before the defined index date were excluded. Patients were also excluded if they had ever been prescribed other

anti-obesity medications, including phentermine, orlistat, topiramate, naltrexone, or bupropion, to prevent contamination from comparator therapies.

Non-GLP-1RA anti-obesity medication group

The comparator cohort consisted of adults aged 18 years or older who initiated one of five commonly prescribed anti-obesity medications, phentermine, orlistat, topiramate, naltrexone, or bupropion. As with the tirzepatide cohort, patients were required to have a diagnosis of overweight or obesity (E66) within 30 days before or on the date of treatment initiation, as well as a diagnosis of major depressive disorder (F32–F33) within the preceding year. To maintain parallel baseline risk profiles, exclusion criteria mirrored those applied to the tirzepatide cohort. Patients were excluded if they had documented suicidal ideation, suicide attempt, inpatient hospitalization, or emergency encounters within the six months before index medication use. Additionally, patients with any history of tirzepatide exposure were removed to ensure mutually exclusive cohorts. Full code lists and definitions are provided in Supplementary Table 1.

To capture incident suicidal ideation and reduce the likelihood that post-index events reflected continuation of an ongoing suicidal crisis, patients with documented suicidal ideation, suicide attempt, inpatient hospitalization, or emergency department encounter during the six months before the index date were excluded. This six-month baseline outcome-free period was selected as an operational washout window to improve outcome temporality in the EHR-based new-user design. Because the duration of washout may influence cohort representativeness, we additionally performed a sensitivity analysis using a shorter baseline outcome-free period of 3 months, 1 month and no outcome free period.

Index event

For each cohort, the index date was defined as the date on which a patient fulfilled both the medication exposure criterion and the obesity criterion. This date served as the starting point for all subsequent analyses.

Outcome definitions

The primary outcome was the first recorded diagnosis of suicidal ideation (ICD-10-CM R45.851) occurring after the index date. A composite of suicidal ideation or suicide attempt (T14.91) was an exploratory outcome. Secondary psychiatric outcomes included anxiety disorders, insomnia disorders, all-cause mortality and all-cause emergency or inpatient encounters.

Patients were followed from the index date until the earliest of outcome occurrence, death, loss to follow-up, or completion of the prespecified observation window. To reduce protopathic bias, outcomes were assessed beginning 30 days after the index date. Analyses were conducted over several prespecified follow-up windows, 6 months (0.5 years), 1 year, and 2 years after the start of outcome surveillance, to evaluate the temporal stability of associations.

In accordance with TriNetX privacy requirements, analyses were automatically suppressed if either cohort contained fewer than ten individuals experiencing a given outcome during the observation window.

Stratified analyses

Baseline characteristics were summarized descriptively. To reduce confounding, 1:1 propensity score matching was performed using a greedy nearest-neighbor algorithm with a caliper of 0.1 of the propensity-score logit, and covariate balance was assessed using standardized differences (<0.1 considered acceptable) [14]. Time-to-event outcomes, were analyzed using Kaplan–Meier estimators, log-rank tests, and Cox proportional hazards models to obtain hazard ratios and 95% confidence intervals across the 6-month, 1-year, and 2-year follow-up windows. Continuous outcomes such as BMI were compared using the TriNetX laboratory distribution analysis. All analyses were conducted within

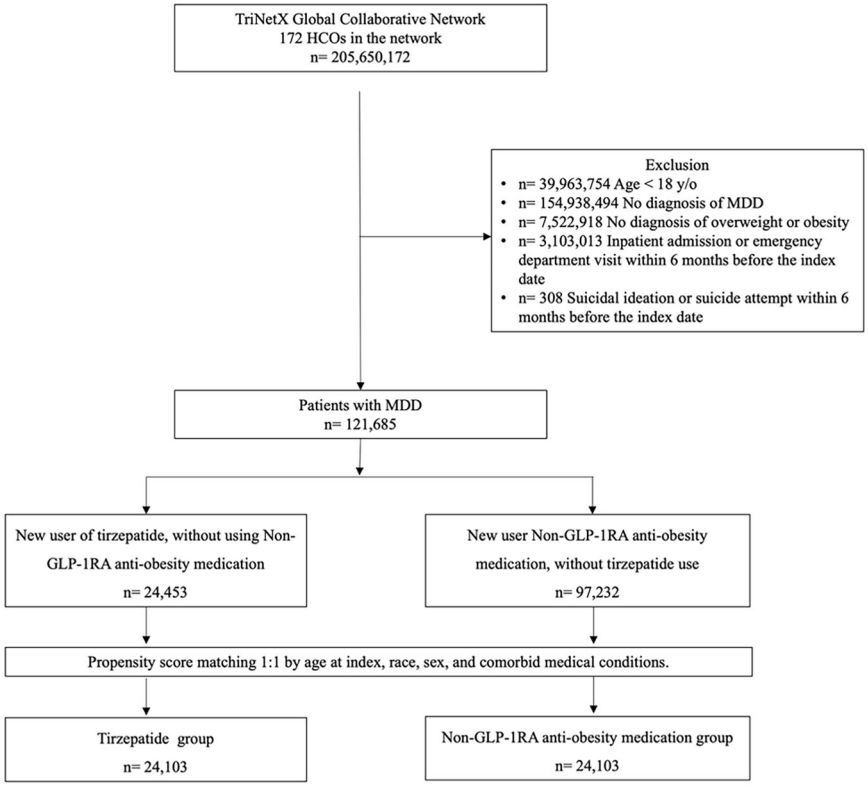


Fig. 1 Flowchart of patient selection and cohort construction.

the TriNetX platform, which does not permit access to individual-level data. To assess the potential influence of unmeasured confounding on our estimates, we additionally calculated E-values for both primary and secondary outcomes [15].

Stratified analyses

To examine potential effect heterogeneity, prespecified subgroup analyses were conducted across clinically relevant patient characteristics. Stratified analyses were performed by sex (male, female), age group (18–64 years, ≥65 years), race (White, other races), type 2 diabetes status (T2DM) (present vs absent), baseline BMI category (BMI ≥ 30 kg/m² vs <30 kg/m²), and baseline antipsychotic exposure. Within each subgroup, new 1:1 propensity score–matched cohorts were constructed using the same matching specifications as the primary analysis. A complete list of covariates codes and corresponding definitions is provided in Supplementary Table 3. Hazard ratios and 95% confidence intervals were estimated separately for each stratum, and results were summarized using forest plots to facilitate comparison of treatment effects across subgroups.

Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the study findings. First, fracture was evaluated as a negative control outcome to detect residual confounding or model misspecification, given its lack of biological association with tirzepatide use or depressive illness. Second, BMI change was analyzed as a positive control outcome to confirm the expected metabolic response to tirzepatide and to verify that the analytic framework detected known treatment effects.

Table 1 Baseline characteristics of tirzepatide and non-GLP1RA anti-obesity medication groups before and after matching.

Variables	Before matching			After matching		
	Tirzepatide group ($n = 24,453$)	Non-GLP-1RA anti-obesity medication group ($n = 97,232$)	Standardized difference	Tirzepatide group ($n = 24,103$)	Non-GLP-1RA anti-obesity medication group ($n = 24,103$)	Standardized difference
Age at index, years						
Mean (SD)	50.8 (14.8)	45.5 (15.1)	0.359	50.6 (14.8)	50.4 (15.2)	0.012
Sex, n (%)						
Male	6095 (24.9)	20,769 (21.4)	0.085	5963 (24.7)	5808 (24.1)	0.015
Female	18,348 (75)	76,424 (78.6)	0.085	18,131 (75.2)	18,281 (75.8)	0.014
Race, n (%)						
White	19,746 (80.8)	74,198 (76.3)	0.108	19,436 (80.6)	19,627 (81.4)	0.021
Not Hispanic or Latino	19,098 (78.1)	69,264 (71.2)	0.158	18,768 (77.9)	18,700 (77.6)	0.007
Black or African American	2493 (10.2)	12,814 (13.2)	0.093	2485 (10.3)	2395 (9.9)	0.012
Asian	346 (1.4)	817 (0.8)	0.054	327 (1.4)	305 (1.3)	0.008
Hispanic or Latino	1672 (6.8)	7158 (7.4)	0.021	1661 (6.9)	1635 (6.8)	0.004
Other Race	752 (3.1)	3695 (3.8)	0.041	745 (3.1)	702 (2.9)	0.011
Comorbidities, n (%)						
Type 2 diabetes mellitus	7395 (30.2)	13,777 (14.2)	0.394	7076 (29.4)	7008 (29.1)	0.006
Hyperlipidemia	6739 (27.6)	17,428 (17.9)	0.231	6552 (27.2)	6475 (26.9)	0.007
Hypertensive diseases	12,536 (51.3)	33,659 (34.6)	0.341	12,219 (50.7)	12,281 (51)	0.005
Ischemic heart diseases	2216 (9.1)	4659 (4.8)	0.169	2102 (8.7)	2039 (8.5)	0.009
Cerebral infarction	287 (1.2)	766 (0.8)	0.039	278 (1.2)	258 (1.1)	0.008
Chronic lower respiratory diseases	4883 (20)	15,998 (16.5)	0.091	4772 (19.8)	4780 (19.8)	0.001
Chronic kidney disease	1671 (6.8)	3410 (3.5)	0.151	1593 (6.6)	1567 (6.5)	0.004
Neoplasms	4257 (17.4)	10,612 (10.9)	0.187	4107 (17)	4051 (16.8)	0.006
Chronic pain	4397 (18)	13,120 (13.5)	0.123	4301 (17.8)	4204 (17.4)	0.011
Anxiety disorders	13,099 (53.6)	38,527 (39.6)	0.282	12,826 (53.2)	13,101 (54.4)	0.023
Sleep disorders	9057 (37)	24,278 (25)	0.263	8810 (36.6)	8724 (36.2)	0.007
Major depressive disorder, severe with psychotic features	22 (0.1)	113 (0.1)	0.008	22 (0.1)	21 (0.1)	0.001
Major depressive disorder, recurrent	7302 (29.9)	17,561 (18.1)	0.279	7067 (29.3)	6970 (28.9)	0.009
Suicidal ideations	63 (0.3)	356 (0.4)	0.019	62 (0.3)	54 (0.2)	0.007
Schizophrenia spectrum disorders	161 (0.7)	725 (0.7)	0.011	156 (0.6)	143 (0.6)	0.007
Personality disorder	227 (0.9)	1032 (1.1)	0.013	225 (0.9)	226 (0.9)	<0.001
Alcohol related disorders	421 (1.7)	2070 (2.1)	0.031	419 (1.7)	401 (1.7)	0.006
Nicotine dependence	1510 (6.2)	8352 (8.6)	0.092	1507 (6.3)	1447 (6)	0.011
Previous medication prescription or procedures, n (%)						
Antidepressants	14,010 (57.3)	41,048 (42.2)	0.305	13,720 (56.9)	13,951 (57.9)	0.019
Antipsychotics	2361 (9.7)	7748 (8)	0.061	2311 (9.6)	2205 (9.1)	0.015
Bariatric surgery status	781 (3.2)	3520 (3.6)	0.024	779 (3.2)	706 (2.9)	0.018
Laboratory examination and BMI						
Hemoglobin A1c, Mean (SD)	6.4 (1.5)	6 (1.3)	0.245	6.3 (1.5)	6.2 (1.4)	0.099
BMI kg/m^2, Mean (SD)	39.6 (7.7)	39.4 (8)	0.026	39.6 (7.7)	39.4 (8)	0.025

Table 1 continued

Variables	Before matching			After matching		
	Tirzepatide group ($n = 24,453$)	Non-GLP-1RA anti-obesity medication group ($n = 97,232$)	Standardized difference	Tirzepatide group ($n = 24,103$)	Non-GLP-1RA anti-obesity medication group ($n = 24,103$)	Standardized difference
Visit						
Emergency room visit	2233 (9.1)	6420 (6.6)	0.094	2154 (8.9)	2064 (8.6)	0.013
Inpatient Encounter	1577 (6.4)	3659 (3.8)	0.122	1496 (6.2)	1469 (6.1)	0.005

To assess whether the six-month baseline outcome-free period affected the representativeness and robustness of the findings, we conducted an additional sensitivity analysis using shorter baseline exclusion window for suicidal ideation, suicide attempt, inpatient hospitalization, and emergency department encounter before the index date.

To address potential residual psychiatric confounding from comparator agents with known central nervous system activity or psychiatric warnings (i.e., bupropion, topiramate, and naltrexone), a restricted sensitivity analysis was performed by comparing tirzepatide against a narrower comparator group consisting solely of orlistat and phentermine.

To address potential confounding by lithium use, we conducted an additional sensitivity analysis including baseline lithium prescription as a covariate in the propensity score model, given lithium's established anti-suicidal properties.

Results

Patient selection

A total of 205,650,172 individuals were identified from the TriNetX Global Collaborative Network across 172 healthcare organizations. Of these, 205,528,487 individuals were excluded for meeting at least one of the following criteria: age <18 years, no diagnosis of MDD, no diagnosis of overweight or obesity, inpatient admission or emergency department visit within 6 months before the index date, or documented suicidal ideation or suicide attempt within 6 months before the index date. The remaining 121,685 eligible patients with MDD and overweight or obesity were included for cohort construction. Among them, 24,453 were new users of tirzepatide without exposure to non–GLP-1RA anti-obesity medications, and 97,232 were new users of non-GLP-1RA anti-obesity medications without prior tirzepatide use. After 1:1 propensity score matching on age at index date, sex, race, and baseline medical comorbidities, 24,103 matched pairs were retained for the final analysis (Fig. 1).

Demographic characteristics

Before propensity score matching, patients initiating tirzepatide differed substantially from those receiving non–GLP-1 anti-obesity medications. The tirzepatide cohort was older (50.8 ± 14.8 vs. 45.5 ± 15.1 years) and included a higher proportion of White patients (80.8 vs. 76.3%), whereas Black individuals were less represented (10.2 vs. 13.2%). Several medical comorbidities were more common in the tirzepatide group, including T2DM (30.2 vs. 14.2%), hyperlipidemia (27.6 vs. 17.9%), hypertension (51.3 vs. 34.6%), ischemic heart disease (9.1 vs. 4.8%), chronic kidney disease (6.8 vs. 3.5%), chronic pain (18.0 vs. 13.5%), neoplasms (17.4 vs. 10.9%), and chronic lower respiratory diseases (20.0 vs. 16.5%). Psychiatric conditions were also more prevalent in the tirzepatide group, including anxiety disorders (53.6 vs. 39.6%), sleep disorders (37.0 vs. 25.0%), recurrent major depressive disorder (29.9 vs. 18.1%), nicotine dependence (6.2 vs. 8.6% in comparison), and prior antidepressant use (57.3 vs. 42.2%). Emergency room visits (9.1 vs. 6.6%) and inpatient encounters (6.4 vs. 3.8%) were also more frequent among

Table 2 Hazard ratio of outcomes between tirzepatide and the non-GLP-1RA anti-obesity medication groups within a 6-month time window after the index event.

Outcomes	Tirzepatide group	Non-GLP-1RA anti-obesity medication group	HR (95% CI)	P-value	E-value (95% LCL)
Primary outcome					
Suicidal ideation	0.15% (37/24103)	0.29% (71/24103)	0.63 (0.42, 0.93)	0.021	2.57 (1.35)
Secondary outcomes					
Anxiety	26.47% (6380/24103)	34.95% (8424/24103)	0.83 (0.81, 0.86)	<0.001	1.69 (1.59)
Insomnia	6.77% (1631/24103)	8.61% (2076/24103)	0.92 (0.86, 0.98)	0.007	1.41 (1.18)
All-cause mortality	0.12% (29/24103)	0.38% (92/24103)	0.38 (0.25, 0.58)	<0.001	4.65 (2.83)
ER visit or hospitalization	8.94% (2154/24103)	11.28% (2720/24103)	0.94 (0.89, 0.99)	0.026	1.33 (1.10)
Exploratory outcome					
Suicidal-related events	0.16% (39/24103)	0.32% (77/24103)	0.61 (0.41, 0.89)	0.011	2.69 (1.49)

tirzepatide users. Mean HbA1c was slightly higher in the tirzepatide group (6.4 ± 1.5 vs. 6.0 ± 1.3), while BMI was similar between groups (39.6 ± 7.7 vs. 39.4 ± 8.0 kg/m²).

After 1:1 propensity score matching, the tirzepatide and comparator cohorts each included 24,103 patients and were well balanced across all measured baseline variables, with standardized mean differences <0.1 for every covariate (Table 1).

Primary outcome

For the primary outcome, suicidal ideation occurred in 37 patients (0.15%) in the tirzepatide group and 71 patients (0.29%) in the non–GLP-1RA anti-obesity medication group during the 1–180-day interval (HR, 0.63; 95% CI, 0.42–0.93; $p = 0.021$; E-value, 2.57 [95% LCL, 1.35]) (Table 2). In the exploratory composite analysis, suicidal ideation or suicide attempt occurred in 39 patients (0.16%) and 77 patients (0.32%), respectively (HR, 0.61; 95% CI, 0.41–0.89; $p = 0.011$). Because the difference between the composite and suicidal-ideation counts was small and suicide-attempt counts were below the TriNetX reporting threshold in both cohorts, no formal inference was made for suicide attempt alone. Kaplan–Meier analyses showed separation of the survival curves beginning early in follow-up and persisting through longer intervals. At 1–365 days and 1–730 days, cumulative incidence remained lower in the tirzepatide group compared with the comparator cohort, with statistically significant differences on log-rank testing ($p < 0.001$ for both time windows) (Fig. 2).

Secondary outcomes

Across secondary outcomes, event rates were consistently lower in the tirzepatide group compared with the non–GLP-1RA anti-obesity medication group. The incidence of anxiety disorders was also reduced (26.47 vs. 34.95%; HR, 0.83; 95% CI, 0.81–0.86; $p < 0.001$; E-value 1.69 [95% LCL, 1.59]), as was insomnia (6.77 vs. 8.61%; HR, 0.92; 95% CI, 0.86–0.98; $p = 0.007$; E-value 1.41 [95% LCL, 1.18]). All-cause mortality occurred less frequently in the tirzepatide cohort (0.12 vs. 0.38%; HR, 0.38; 95% CI, 0.25–0.58; $p < 0.001$; E-value 4.65 [95% LCL, 2.83]). In addition, the risk of emergency room visit or hospitalization was lower among tirzepatide users (8.94 vs. 11.28%; HR, 0.94; 95% CI, 0.89–0.99; $p = 0.026$; E-value 1.33 [95% LCL, 1.10]) (Table 2).

Subgroup analyses

In subgroup analyses, the association between tirzepatide use and suicidal-related events was generally consistent across most strata (Fig. 3). Among males, event rates were lower in the tirzepatide group (0.17 vs. 0.52%; HR, 0.39; 95% CI, 0.20–0.77; $p = 0.004$), and a similar pattern was observed among females (0.13 vs. 0.29%; HR, 0.53; 95%

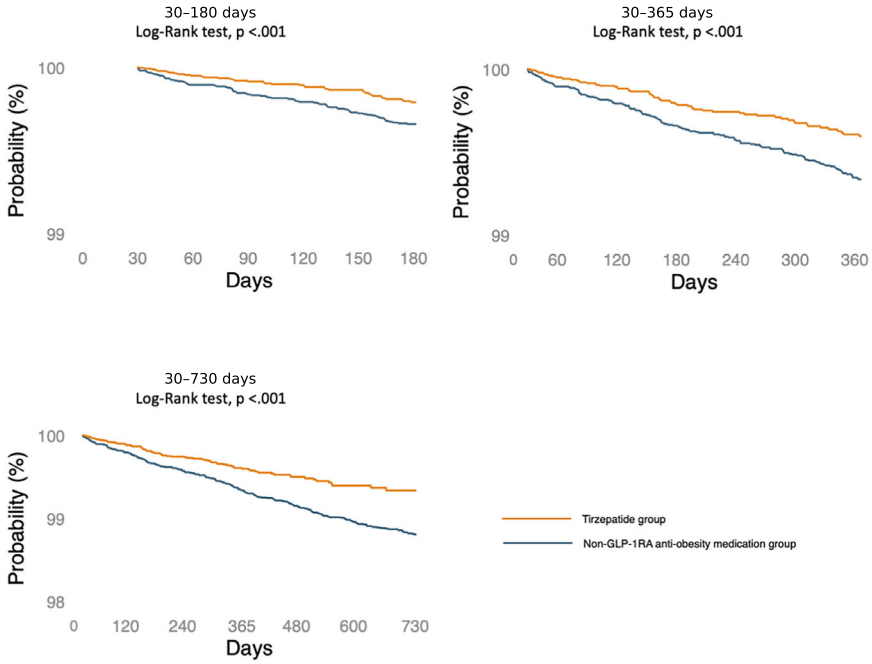


Fig. 2 Kaplan–Meier curves of suicidal-related outcomes in the tirzepatide group versus the non-GLP-1RA anti-obesity medication group across follow-up intervals of 1–180, 1–365, and 1–730 days.

CI, 0.33–0.84; $p = 0.006$). For individuals aged 18–64 years, tirzepatide users also had lower event rates (0.16 vs. 0.36%; HR, 0.53; 95% CI, 0.35–0.81; $p = 0.002$). Among White patients, the incidence was likewise lower (0.14 vs. 0.32%; HR, 0.52; 95% CI, 0.33–0.81; $p = 0.003$).

Stratification by metabolic factors showed reduced risk among patients without T2DM (0.14 vs. 0.33%; HR, 0.52; 95% CI, 0.32–0.84; $p = 0.006$), whereas the association did not reach statistical significance among those with diabetes (0.15 vs. 0.31%; HR, 0.56; 95% CI, 0.29–1.05; $p = 0.067$). By BMI category, tirzepatide was associated with lower event rates among patients with BMI ≥ 30 kg/m² (0.16 vs. 0.29%; HR, 0.66; 95% CI, 0.44–1.00; $p = 0.044$), while no significant difference was observed for BMI < 30 kg/m² (0.26 vs. 0.39%; HR, 0.82; 95% CI, 0.42–1.61; $p = 0.555$).

For psychiatric treatment strata, patients without antipsychotic exposure showed lower rates in the tirzepatide group (0.10 vs. 0.22%; HR, 0.51; 95% CI, 0.30–0.88; $p = 0.013$), whereas the association did not reach statistical significance among those receiving antipsychotics (0.28 vs. 0.57%; HR, 0.59; 95% CI, 0.34–1.02; $p = 0.055$).

Sensitivity analyses

To evaluate residual confounding, we included a negative control outcome (fracture) and a positive control outcome (BMI change). There was no statistically significant difference in the incidence of fracture between the tirzepatide group and the non-GLP-1RA anti-obesity medication group (0.08 vs. 0.05%; HR, 2.02; 95% CI, 0.96–4.24; $p = 0.059$). In contrast, the tirzepatide group had significantly greater BMI reduction compared to the comparator group (-1.31 ± 7.93 vs. -0.68 ± 7.99 kg/m²; $p < 0.001$). These findings support the specificity and internal validity of the primary results (Supplementary Table 3).

To address concerns that the 6-month baseline outcome-free period might have influenced the findings by selecting a more stable patient population, we conducted further sensitivity analyses using shorter washout periods. The results remained highly consistent with the primary analysis. Tirzepatide use was associated with a significantly lower risk of suicidal ideation when using a 3-month outcome-free period (0.17 vs. 0.36%; HR, 0.54; 95% CI, 0.38–0.76; $p < 0.001$), a 1-month outcome-free period (0.20 vs. 0.35%; HR, 0.67; 95% CI, 0.48–0.94; $p = 0.018$), and when no outcome-free period was applied (0.28 vs. 0.61%; HR, 0.51; 95% CI, 0.40–0.65; $p < 0.001$) (Supplementary Fig. 1).

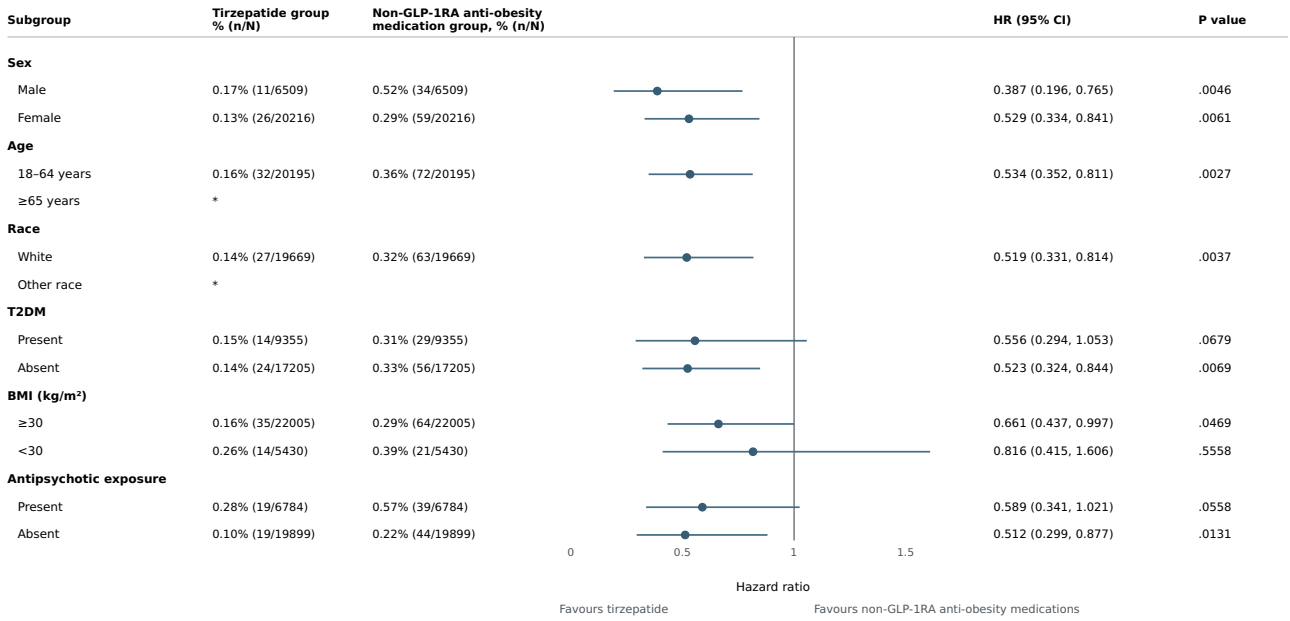


Fig. 3 Subgroup analyses of the association between tirzepatide use and the risk of suicide-related outcomes compared with non–glucagon-like peptide-1 receptor agonist anti-obesity medications. GLP-1 RA glucagon-like peptide-1 receptor agonist, HR hazard ratio, CI confidence interval, T2DM type 2 diabetes mellitus, BMI body mass index.

The restricted sensitivity analysis excluding comparators with strong CNS activity (bupropion, topiramate, and naltrexone) yielded consistent results. When compared specifically against a narrower comparator group consisting solely of orlistat and phentermine, tirzepatide use remained associated with a significantly lower risk of suicidal ideation (0.14 vs. 0.27%; HR, 0.58; 95% CI, 0.36–0.93; $p = 0.023$).

To account for the potential confounding effect of medications with known anti-suicidal properties, we conducted a sensitivity analysis including baseline lithium prescription as a covariate in the propensity score model. The association between tirzepatide use and reduced risk of suicidal ideation remained robust (0.14 vs. 0.32%; HR, 0.52; 95% CI, 0.36–0.77; $p < 0.001$).

Discussion

To our knowledge, this is the first large-scale real-world study to evaluate the psychiatric safety of tirzepatide in individuals with comorbid MDD and obesity, a high-risk population that has been largely excluded from pivotal GLP-1RAs trials, thereby leaving a critical gap in the evidence base regarding neuropsychiatric effects of these agents [16–19]. By leveraging a large, real-world electronic health record cohort and employing rigorous propensity score matching, our study addresses this gap and provides timely insight into the psychiatric safety profile of modern metabolic therapies in vulnerable populations.

Our first major finding was that tirzepatide use was associated with a significantly lower risk of suicidal ideation compared to other obesity treatments in patient with obesity and MDD. This observation is clinically relevant given the markedly elevated risk of suicidality among individuals with MDD, whose lifetime risk of suicide is estimated to be 8-–17-fold higher than in the general population [20]. The observed protective association suggests that, in addition to its metabolic benefits, tirzepatide may offer ancillary psychiatric advantages for this high-risk group. Several mechanisms may be hypothesized, including indirect metabolic benefits and possible central neurobiological pathways. Indirectly, weight reduction has been associated with improvements in depressive symptoms, potentially through improvements in quality of life and physical functioning [21–23]. However, because the active comparator group also received anti-obesity medications, differences in outcomes may not be attributable to weight loss alone. As

demonstrated by our positive control analysis, tirzepatide was associated with a greater mean reduction in BMI than older non-incretin agents, although the absolute between-group difference was modest. In addition, preclinical studies have shown that GLP-1 and GIP receptors are expressed in mood-regulating brain regions, including the hippocampus and prefrontal cortex, and that activation of incretin-related pathways may influence neuroinflammation, microglial activity, brain-derived neurotrophic factor expression, and neuroplasticity [24–27]. A recent cross-sectional analysis of National Health and Nutrition Examination Survey data reported that C-reactive protein mediated part of the association between obesity and depressive symptoms. This observation supports inflammation as one possible link between obesity and depressive symptoms, but it does not demonstrate that tirzepatide reduces suicidal ideation through weight loss, inflammation, or a direct central mechanism[28]. Given the modest mean BMI difference observed in our study and the absence of outcome-stratified longitudinal weight analyses, the disproportionate association with suicidal ideation may also reflect residual confounding, including differences in continuity of care, healthcare engagement, treatment adherence, or other unmeasured clinical factors. The mechanistic interpretation of our findings should therefore remain hypothesis-generating.

Emerging clinical data suggest that GLP-1 receptor agonists may exert broader neuropsychiatric effects, although their relationship with suicidality remains uncertain. A recent meta-analysis of randomized controlled trials in patients with T2DM found modest reductions in depressive symptoms among GLP-1RA users compared with placebo [25]. Nevertheless, depressive symptoms and suicidality are related but distinct constructs, and improvement in depressive symptom severity cannot be assumed to translate into reduced suicidal ideation or suicide attempt. Therefore, these findings should be viewed only as supportive evidence for possible mood-related effects, not as evidence of anti-suicidal benefit. More directly relevant to suicide-related safety, available regulatory and pharmacovigilance evidence has not consistently shown an increased risk of suicidality with GLP-1RA use, but the evidence remains inconclusive [29]. Our study addresses this gap by directly evaluating suicidal ideation in patients with comorbid obesity and MDD using real-world data and an active comparator.

Beyond suicidality, we found that tirzepatide-treated patients had significantly lower incidences of new-onset anxiety disorders and insomnia compared to matched controls. This suggests a broader positive impact on mental health symptoms. Potential mechanisms for anxiolytic and sleep-improving effects are multifactorial. GLP-1 receptors in the central nervous system modulate stress circuits; agonism of these receptors can reduce HPA-axis hyperactivity and normalize stress responses in preclinical models [30, 31]. Improved metabolic health may further relieve anxiety and insomnia. Weight loss leads to better respiratory function and often alleviates obstructive sleep apnea, which in turn can improve sleep quality [32, 33]. Enhanced insulin sensitivity and fewer glycemic fluctuations might also stabilize energy and mood levels, reducing anxiety and irritability [34]. Additionally, improvements in depressive symptoms often translate into downstream reductions in anxiety and better sleep, as these conditions are interrelated. Our results echo prior observational data indicating lower risks of anxiety among patients using GLP-1RAs. In a nationwide cohort of diabetic patients, those on GLP-1RA had a 59% lower hazard of developing anxiety than non-users[34]. These results highlight tirzepatide's potential to improve anxiety and sleep symptoms, and our study's real-world design and focus on patients with MDD provide unique evidence in a population often excluded from clinical trials.

Beyond psychiatric outcomes, tirzepatide has demonstrated significant improvements in broader clinical endpoints. All-cause mortality was lower in the tirzepatide group, alongside reduced emergency room visits and hospitalizations. These findings are consistent with prior large-scale trials in T2DM and obesity populations, including the SURPASS and SELECT trials, which have shown that GLP-1 based therapies reduce cardiovascular events, mortality, and healthcare utilization through mechanisms including improved glycemic control, reduced blood pressure, anti-inflammatory effects, and sustained weight loss [35–37]. Further supporting this evidence base, a recent comprehensive meta-analysis by Lee et al., encompassing over 71,000 individuals across 10 randomized trials, confirmed that long-acting GLP-1RAs reduce major adverse cardiovascular events by 14%, heart failure hospitalization by 14%, and all-cause mortality by 12%. Our results extend these benefits into a high-risk psychiatric subgroup, patients with comorbid MDD and obesity [38]. Unlike prior studies that focused exclusively on cardiometabolic endpoints in general populations, our study incorporates psychiatric comorbidity as a core component of the clinical profile and

outcomes assessment. This dual focus provides a more comprehensive understanding of tirzepatide's real-world utility in complex patients.

Subgroup analyses generally showed point estimates in the same direction across major demographic and clinical categories. The association between tirzepatide use and reduced suicidal ideation was generally consistent across sex and age strata; however, among patients receiving antipsychotics, the point estimate favored tirzepatide but the confidence interval included the null. Importantly, a significant protective effect was observed among patients without T2DM, whereas no statistically significant association was found in those with T2DM. This difference may reflect variation in baseline risk, chronic disease burden, or cumulative medication exposure. Patients with T2DM often contend with more advanced metabolic dysfunction and polypharmacy, which could attenuate or obscure the neuropsychiatric benefits of tirzepatide [39]. In contrast, those without diabetes may experience greater psychological gains from metabolic improvements. The association was statistically significant among patients without antipsychotic exposure but did not reach statistical significance among those receiving antipsychotics; these subgroup findings should therefore be interpreted cautiously. These findings highlight tirzepatide's potential to confer dual benefit, metabolic and psychiatric, even in populations at heightened clinical risk.

Several limitations should be acknowledged. First, the use of EHR data introduces inherent challenges, including potential misclassification of exposures and outcomes, underreporting of suicidality, and variability in diagnostic coding practices. Nonetheless, our study leveraged a large, multi-institutional, population-based EHR database that captures real-world treatment patterns across diverse healthcare settings, enhancing generalizability. To reduce residual confounding not fully addressed by propensity score matching, we employed a new-user design and anchored the index date at the time of tirzepatide initiation, thereby minimizing biases related to prior treatment exposure and immortal time. In addition, we incorporated both positive and negative control outcomes to strengthen causal inference and assess the robustness of our findings against unmeasured confounding. Second, we lacked access to detailed information on tirzepatide dosage, treatment adherence, socioeconomic status, educational level, and psychiatric symptom severity at baseline. These unmeasured factors could influence both treatment allocation and clinical outcomes, and the absence of structured psychiatric assessments (e.g., validated symptom scales) limits our ability to detect more detailed mental health changes. Baseline depressive symptom severity could not be directly assessed because structured depression rating scales were not consistently available in the EHR database. Although we balanced available psychiatric severity proxies, including recurrent MDD, severe MDD with psychotic features, anxiety disorders, sleep disorders, psychotropic medication use, prior suicidal ideation, and healthcare utilization, residual confounding by unmeasured depression severity cannot be excluded. Additionally, while we matched for baseline emergency room and inpatient encounters, the database lacks data on outpatient visit frequency. Thus, we could not adjust for differences in continuity of care, such as the intensive specialist follow-up typical for tirzepatide users, which improves MDD outcomes. Third, our use of a six-month baseline outcome-free period may limit the generalizability of the findings. Although the six-month baseline outcome-free period improved temporality for incident suicidal ideation, it may have selected for patients with a more stable or less acutely suicidal course of MDD. We therefore performed a sensitivity analysis using a shorter baseline outcome-free period, which yielded consistent findings. Nevertheless, the results should not be generalized to patients with active suicidal ideation, recent suicide attempt, psychiatric crisis, or severe unstable depression. Finally, the modest BMI reduction observed in our study, compared with that reported in clinical trials, may reflect real-world conditions, including variable treatment adherence, the absence of protocol-driven lifestyle interventions, and the concurrent use of weight-promoting psychotropic medications. Importantly, we did not have an outcome-stratified analysis linking longitudinal BMI or weight change to subsequent suicidal ideation within each treatment group. We therefore could not determine whether the observed association with suicidal ideation differed according to the magnitude of weight change. Accordingly, the discordance between the modest mean BMI change and the observed association with suicidal ideation should not be interpreted as evidence of a direct, weight-independent central neuropharmacological effect. Residual confounding related to continuity of care, healthcare engagement, treatment adherence, and other unmeasured clinical factors remains a plausible explanation.

In conclusion, this study provides real-world evidence that tirzepatide initiation was associated with a lower recorded risk of suicidal ideation, as well as reduced anxiety, insomnia, all-cause mortality, emergency department

visits, and hospitalizations, among adults with comorbid obesity and MDD. This observational association should not be interpreted as evidence of a direct antisuicidal effect. These findings support the potential for tirzepatide to serve as a metabolically favorable treatment option associated with a lower risk of suicidal ideation in this vulnerable, high-risk population.

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Author contributions Ting-Hui Liu and Chia-Chun Chu contributed equally to this work and were responsible for study conception and design, data acquisition, statistical analysis, interpretation of the data, and drafting of the manuscript. Chia-Yu Liu, Jheng-Yan Wu, and Ya-Wen Tsai contributed to data interpretation, critical revision of the manuscript for important intellectual content, and approval of the final version. Hsin-An Chang contributed to study supervision, methodology development, manuscript revision, and overall project administration. Chih-Cheng Lai contributed to study conception and design, interpretation of the findings, manuscript revision, and supervision of the study. All authors reviewed and approved the final manuscript.

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Data availability The data that support the findings of this study were obtained from the TriNetX Research Network. Access to the TriNetX platform is available to participating institutions under a data use agreement; therefore, the underlying data cannot be made publicly available. Researchers affiliated with institutions that have access to TriNetX may obtain the data directly from the TriNetX Research Network (Cambridge, MA, USA) using the same methodology described in this article.

Competing interests The author declare no competing interests.

Ethics approval and consent to participate statement This retrospective cohort study was approved by the Institutional Review Board of Chi Mei Medical Center (IRB No. 11412-E03). The requirement for written informed consent was waived because all data used in this study were de-identified and anonymized.

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