

Risk of suicidal thoughts and dizziness associated with tirzepatide: A systematic review and meta-analysis

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ABSTRACT

Tirzepatide, a dual GLP-1 and GIP receptor agonist, is effective in managing type 2 diabetes and obesity. However, concerns about neuropsychiatric adverse events (AEs), particularly dizziness and suicidal ideation, warrant further investigation. To evaluate the risk of suicidal thoughts and dizziness associated with once-weekly subcutaneous tirzepatide in patients with type 2 diabetes mellitus or obesity, compared to placebo. A systematic review and meta-analysis were conducted according to PRISMA guidelines. Databases including PubMed, EMBASE, Web of Science, and ClinicalTrials.gov were searched thoroughly till July 15, 2025. Only randomized controlled trials comparing tirzepatide with placebo and reporting AEs were included. Data were analyzed using Review Manager 5.4. Thirteen RCTs met the inclusion criteria. Tirzepatide was associated with a significantly increased risk of dizziness (OR = 2.12, 95% CI: 1.67–2.68). The risk was consistent across both low (<10 mg) and high (>10 mg) doses. No significant association was found between tirzepatide and suicidal ideation (OR = 1.96, 95% CI: 0.76–5.05), though wide confidence intervals reflect limited data. Tirzepatide is associated with a higher risk of dizziness, irrespective of dose. No clear link to suicidal thoughts was observed; however, the low event rate limits firm conclusions. Ongoing surveillance and further research are needed to better understand potential neuropsychiatric risk.

1. INTRODUCTION

Diabetes mellitus and obesity are major global health challenges, with significant impact on morbidity, mortality, and healthcare expenditures [1]. In recent years, incretin-based therapies have emerged as a game-changer in the management

of these conditions. Tirzepatide, a novel drug, is also known as a dual agonist for glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors or a twincretin. At a once weekly injectable dose, the drug stimulates the GIP and GLP-1 receptors synergistically to increase insulin secretion, suppress glucagon release, and delay gastric emptying, resulting in a significant reduction in HbA1c and weight loss [2-4]. With a worldwide increase in use of tirzepatide, concerns have arisen regarding its long-term safety profile beyond its well-documented common gastrointestinal side effects like nausea, vomiting, and diarrhea [5]. The pressing matter is the neuropsychiatric adverse events (AEs), including suicidal ideation and dizziness, which, though

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often deemed mild, may significantly impact patient safety, quality of life, and treatment adherence. Growing reports and the World Health Organization's (WHO) safety signals imply a possible link between GLP-1 receptor agonists (RAs) and suicidal behavior [6,7]. Tirzepatide is structurally similar to GLP-1 RAs, uniquely activating both GIP and GLP-1 receptors to regulate mood and appetite, but the specific molecular mechanism in the brain remains unclear [8]. Modulating these pathways might alter neurotransmitters and stress responses, possibly affecting mental health in certain patients [9]. Suicidal ideation and dizziness have been reported with GLP-1 RAs, but the data on tirzepatide remain limited and inconsistent. No systematic review has yet assessed these risks. Therefore, we undertook this review to evaluate the risk of suicidal thoughts and dizziness associated with tirzepatide.

1.1. Review question

Does treatment with once-weekly subcutaneous tirzepatide increase the risk of suicidal thoughts and dizziness in subjects with type 2 diabetes mellitus or obesity compared to placebo?

2. METHODOLOGY

This systematic review and meta-analysis protocol was prospectively registered in PROSPERO (registration number: CRD420251085759). This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines

[10]. The CONSORT flow chart illustrates the study selection process. A total of 13 studies were included in the current review (Fig. 1).

2.1. Search strategy

This review was conducted by systematically searching PubMed, EMBASE, Web of Science, and Clinical Trials databases for English language studies from their inception to July 15, 2025, using the search terms "Tirzepatide" [MeSH] OR "LY3298176" OR "Mounjaro." Three researchers independently screened titles and abstracts in accordance with the predefined inclusion and exclusion criteria and subsequently selected full-text articles that potentially met the eligibility criteria. Any disagreements were resolved through discussion and confirmed by the fourth researcher. Studies were included for the meta-analysis if they met the following criteria: randomized control trials (RCTs); adult participants with obesity alone, obesity with or without type 2 diabetes mellitus (T2DM) or T2DM alone; and tirzepatide as the intervention and placebo as the comparator and safety outcomes. Data extracted from all included studies comprised of authorship, year of publication, randomization method, intervention details, number of participants, study design, study duration, study site, study population, treatment duration, and the risk of AEs, specifically suicidal thoughts and dizziness. Conference abstracts, unpublished data, and other non-peer-reviewed sources were excluded from the review to ensure transparency and methodological rigor. Our analysis was restricted to articles in the English language.

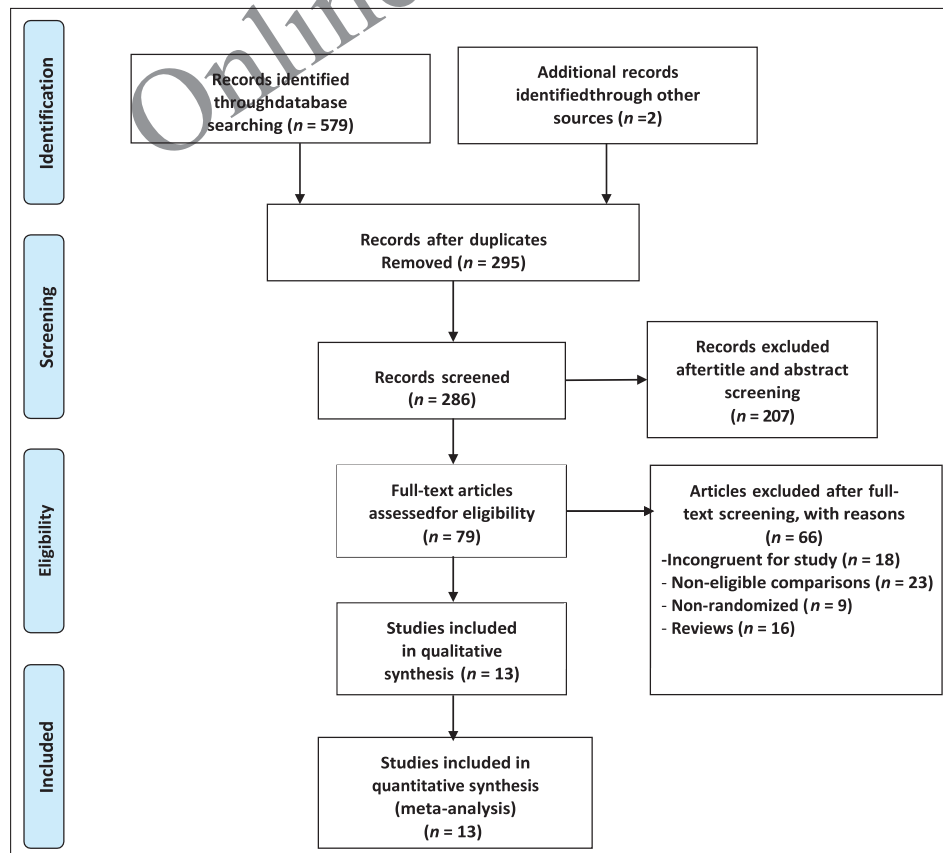


Figure 1. PRISMA flowchart outlining literature search.

2.2. Outcome indicators and the risk of bias assessment

Suicidal thoughts were considered the primary outcome, and dizziness was designated the secondary outcome. The risk of bias of the included studies was independently assessed by two reviewers using the Cochrane Collaboration risk of bias assessment tool and categorized as low risk, high risk, or unclear risk.

2.3. Statistical analysis

The statistical analysis was done using Review Manager 5.4 software. The effect analysis statistics for the dichotomous variables were expressed with odds ratio (OR) at 95% confidence interval (CI) for each effect. Chi-square (χ^2) test was used to analyze the statistical heterogeneity between the results, and the heterogeneity was quantitatively judged by I^2 . The fixed effect model was applied for $I^2 \leq 50\%$ and $p > 0.1$, and the random effect model for $I^2 > 50\%$ and $p < 0.1$. To verify the robustness of the results, sensitivity analysis was conducted using R software (version 4.2) employing the leave-one-out method, whereby each study was sequentially excluded to assess the influence

of individual publications on the overall pooled effect estimate. Publication bias was assessed using visual inspection of funnel plots and statistical assessment with Egger's and Begg's tests for both suicidal thoughts and dizziness outcomes. Egger's regression quantified small-study effects, while Begg's rank correlation assessed funnel plot asymmetry. A p -value < 0.05 was considered indicative of significant publication bias.

2.4. Eligibility criteria

Studies were eligible if they met the following criteria: (1) randomized controlled trials (RCTs) comparing any approved dose of once-weekly subcutaneous (SC) tirzepatide with placebo in adults with obesity and/or type 2 diabetes mellitus (T2DM); placebo consisted of an inert SC injection identical in appearance, volume, excipients, injection device, and dosing schedule to tirzepatide, ensuring adequate blinding; (2) minimum follow-up duration of 24 weeks; and (3) publication in English. Studies with duplicate or overlapping data were excluded. The following PICOS was used to retrieve the literature: Population: Adults with type 2 diabetes mellitus or obesity with or without

Table 1. Baseline characteristics and description of included studies.

Author, Year	Tirzepatide Dose	Sample size	Tirzepatide (T)/ Placebo (P)	Female/ Males	Duration of DM*	HbA1c%*	Study duration	Discontinuations from study because of AEs†	Treatment-emergent AEs	Deaths
Feng <i>et al.</i> [11]	2.5 to 15mg	24	T = 20 P = 4	M=14	6.6 5.3	7.95 7.8	28 weeks	T=0 P = 1	T = 67 P = 8	0/0
Frias <i>et al.</i> [12]	1, 5, 10, 15 mg	316	T = 302 P = 14	M=159	8.3 6.8	8.1 8.1	26 weeks	T = 4 P = 1	T = 151 P = 27	0/0
Frias <i>et al.</i> [13]	5, 10, 15 mg	478	T = 358 P = 120	M = 180	9.2 8.8	8.4 8.2	40 weeks	T = 2 P = 1	T = 66 P = 13	0/0
Garvey <i>et al.</i> [14]	10, 15 mg	938	T = 626 P = 312	M = 223	8.4 8.8	8.0 7.9	72 weeks	T = 35 P=12	T = 421 P = 111	T = 2
Heise <i>et al.</i> [15]	15mg	73	T = 45 P = 28	M = 52	10.2 10.9	7.8 7.9	28 weeks	T = 1 P = 3	T = 62 P = 11	0/0
Jastreboff <i>et al.</i> [16]	5, 10, 15 mg	2539	T = 1906 P = 633	M = 826	NA	NA	72 weeks	T = 111 P = 12	T = 616 P = 34	0/0
Kadowaki <i>et al.</i> [17]	10, 15 mg	225	T = 150 P = 75	M = 133	NA	5.6 5.6	52 weeks	T = 16 P = 8	T = 90 P = 8	0/0
Krumholz <i>et al.</i> [18]	5/10/15 mg	2539	T = 1896 P = 643	F = 1714	NA	NA	72 weeks	NR NR	NR NR	0/0
Loomba <i>et al.</i> [19]	5, 10, 15 mg	190	T = 142 P = 48	F = 109	NA	NA	52 weeks	T = 6 P=8	T=131 P=40	0/0
Malhotra <i>et al.</i> [20]	10/15 mg	467	T = 233 P=234	F = 139	NA	5.6	52 weeks	T = 1 P = 7	T = 16 P = 19	0/0
Wadden <i>et al.</i> [21]	10/15 mg	579	T = 287 P = 292	F = 364	NA	5.4 5.4	72 weeks	T = 30 P = 6	NR NR	T = 1 P = 1
Zhao <i>et al.</i> [22]	10, 15 mg	210	T = 141 P = 69	F = 103	NA	5.6 5.6	52 weeks	T = 7 P = 1	T = 235 P = 42	0/0
Jastreboff <i>et al.</i> [23]	5, 10, 15 mg	1032	T = 762 P=270	F = 659	NA	5.7 5.7	176 weeks	T = 74 P = 16	T = 227 P=34	0/0

*: Mean values; T = Tirzepatide; P = Placebo; † = Discontinuations from study because of AEs/ Serious AEs/ Discontinuation of study treatment drug because of AEs; NA = Not applicable

diabetes; Intervention: Once-weekly subcutaneous tirzepatide at any approved dose; Comparator: Once-weekly subcutaneous placebo; Outcomes: risk of suicidal thoughts and dizziness; and Study design: randomized control trials.

3. RESULTS

A total of 13 studies were included in our review [11–23], of which 12 studies reported dizziness and 6 studies [14,15,20–23] reported suicidal ideations. The demographic data of the included studies are represented in Table 1.

3.1. The risk of dizziness with Tirzepatide

A pooled analysis of 13 studies demonstrated that tirzepatide is associated with a significantly increased risk of dizziness compared to placebo. The combined odds ratio (OR) was 2.06 (95% CI: 1.63–2.62; $p < 0.00001$), indicating that the patients treated with tirzepatide had nearly twice the odds of experiencing dizziness relative to those receiving placebo. The test for heterogeneity was not significant ($\chi^2 = 11.29$, $df = 20$, $p = 0.94$; $I^2 = 0\%$), suggesting that the effect estimates were consistent and robust across the included studies (Fig. 2). The subgroup

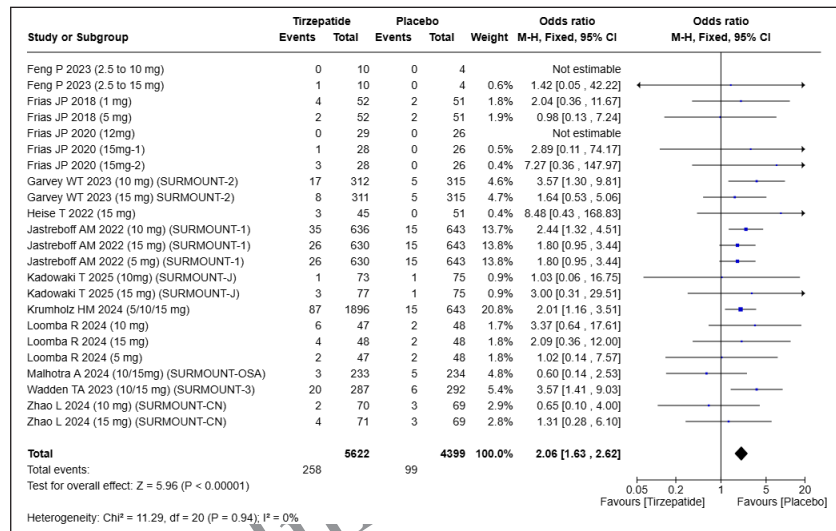


Figure 2. Forest plot comparing the risk of dizziness in treatment with tirzepatide versus placebo.

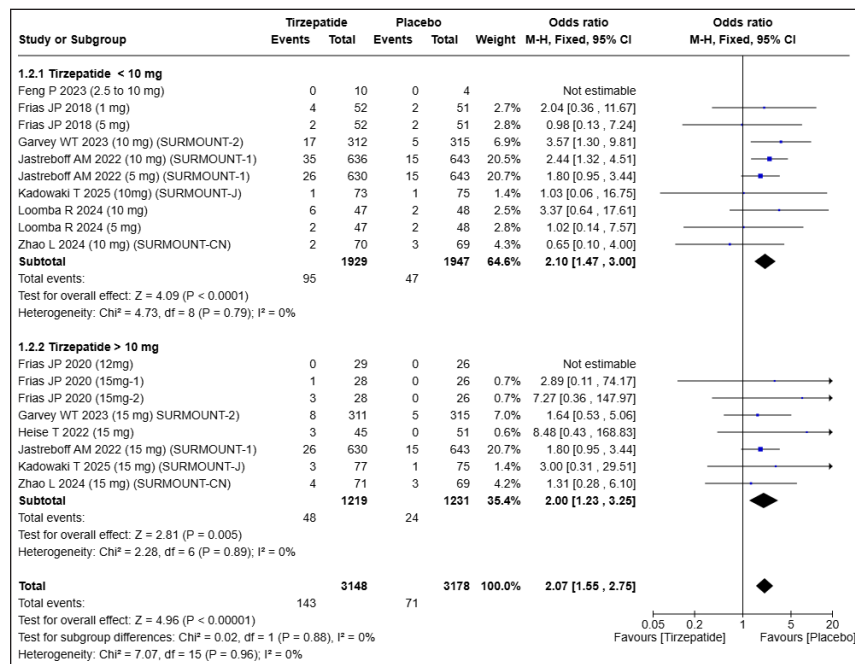


Figure 3. Forest plot comparing the risk of dizziness in treatment with tirzepatide < 10 mg versus > 10 mg and placebo.

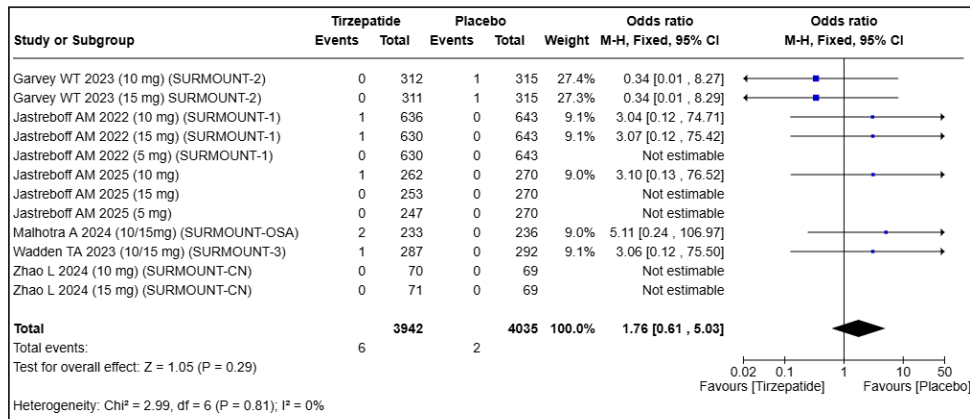


Figure 4. Forest plot comparing the risk of suicidal thoughts in treatment with tirzepatide versus placebo.

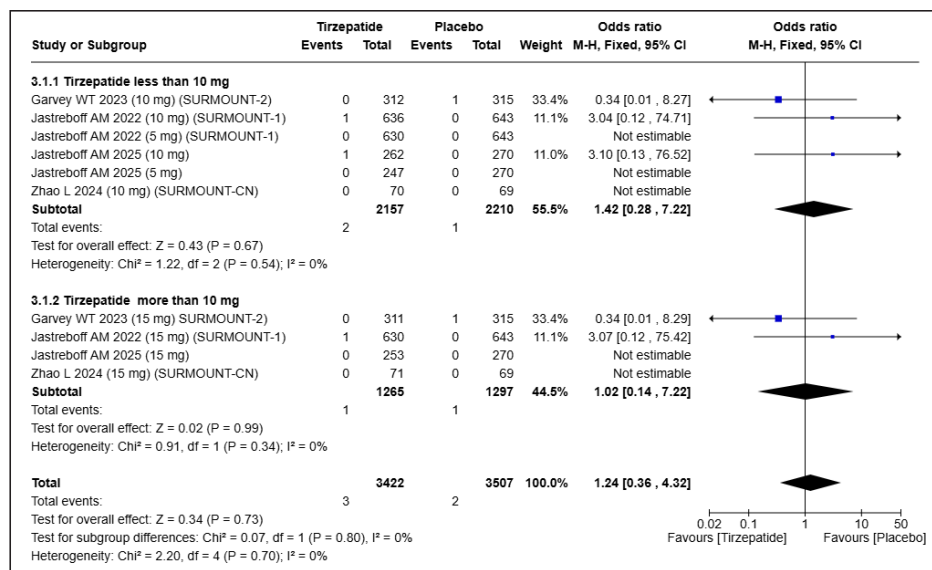


Figure 5. Forest plot comparing the risk of suicidal thoughts in treatment with tirzepatide < 10 mg versus > 10 mg and placebo.

analysis showed that both lower (<10 mg) and higher (>10 mg) doses of tirzepatide were associated with a significantly increased risk of dizziness compared to placebo, with odds ratios of 2.10 (95% CI: 1.47–3.00) and 2.00 (95% CI: 1.23–3.25), respectively. There was no significant difference between dose subgroups ($p = 0.88$), indicating a comparable risk across dose ranges (Fig. 3).

3.2. The risk of suicidal ideation with Tirzepatide

There was no statistically significant increase in the risk of suicidal ideation among patients on treatment with tirzepatide compared to placebo in the overall pooled analysis (OR = 1.76, 95% CI: 0.61–5.03; $p = 0.29$). The confidence interval includes the null value, reflecting substantial uncertainty due to the smaller number of reported events. There was no evidence of heterogeneity among the studies ($\chi^2 = 3.16$, $df = 8$, $p = 0.92$; $I^2 = 0\%$) (Fig. 4). Subgroup analysis demonstrated no statistically significant increase in the risk of suicidal intentions with tirzepatide, either at doses below 10 mg (OR = 1.42, 95% CI:

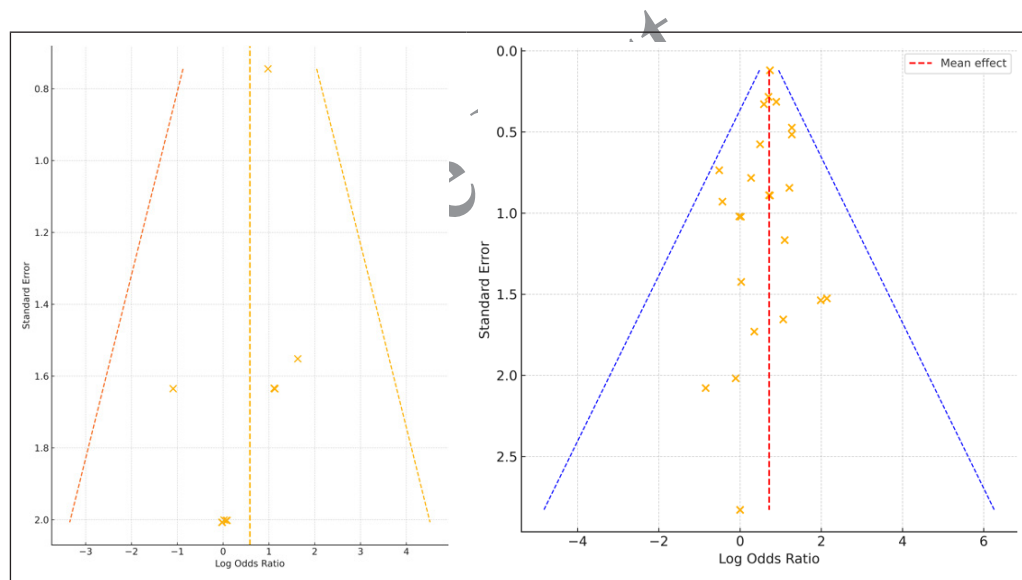
0.28–7.22) or at doses above 10 mg (OR = 1.02, 95% CI: 0.14–7.22) compared to placebo. Analysis of subgroup differences was not statistically significant ($p = 0.80$), indicating no evidence of a dose-dependent difference in risk. The analysis is limited by the smaller number of events and wider confidence intervals (Fig. 5).

3.2.1 Literature quality assessment

As shown in Table 2, all 13 studies [11–23] reported random sequence generation and were rated as “low risk.” Three studies [11,12,20] had unclear allocation concealment and were marked as “some concerns.” Twelve trials [12-23] were double-blinded and rated as “low risk,” while one study [11] had some concerns regarding blinding. Detection bias was at low risk in all but one study [11], which had some concerns. No significant attrition bias was observed, and all studies were marked “low risk” for incomplete outcome data. Three studies [11,12,20] had some concerns for selective reporting; all others were of low risk (Table 2).

Table 2. Risk of bias assessment.

S. No	Study Name	Random Sequence generation (Selection bias)	Allocation Concealment (Selection bias)	Blinding of participants and personnel	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias)	Selective reporting (Reporting bias)	Overall bias
1	Feng <i>et al.</i> [11]	Low risk	Some concerns	Some concerns	Some concerns	Low risk	Some concerns	Low risk
2	Frias <i>et al.</i> [12]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
3	Frias <i>et al.</i> [13]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
4	Garvey <i>et al.</i> [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
5	Heise <i>et al.</i> [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
6	Jastreboff <i>et al.</i> [16]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
7	Kadowaki <i>et al.</i> [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
8	Krumholz <i>et al.</i> [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
9	Loombar <i>et al.</i> [19]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
10	Malhotra <i>et al.</i> [20]	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
11	Wadden <i>et al.</i> [21]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
12	Zhao <i>et al.</i> [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
13	Jastreboff <i>et al.</i> [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

**Figure 6.** a: Publication bias assessment (Suicidal thoughts). b: Publication bias assessment (Dizziness).

3.2.2. Sensitivity analysis

Leave-one-out sensitivity analyses were conducted for both dizziness and suicidal thoughts by sequentially excluding individual studies and recalculating pooled estimates using a fixed-effect inverse-variance model based on log-transformed odds ratios. Across all iterations, the effect sizes and confidence intervals remained consistent, with no change in effect direction or statistical significance. These findings confirm the robustness of the results and demonstrate that the results are not driven by any individual study (Supplementary Fig. a and b).

3.2.3. Risk of bias assessment

Assessment of publication bias for suicidal thoughts and dizziness associated with tirzepatide showed no significant

asymmetry in funnel plots. Egger's tests ($p = 0.29$ and $p = 0.61$) and Begg's tests ($p = 0.35$ and $p = 0.22$) indicated no evidence of small-study effects, suggesting that the pooled estimates are robust and unlikely influenced by publication bias (Fig. 6a and b).

4. DISCUSSION

Tirzepatide, a novel dual GLP-1 and GIP receptor agonist, has garnered significant attention for its most substantial clinical outcomes on glycemic control and weight loss in individuals with T2DM and obesity. However, with its growing global use, there is an urgent need to thoroughly assess its safety profile, particularly in relation to neuropsychiatric and neurological AEs such as dizziness and suicidal ideation.

The present meta-analysis of twelve randomized controlled trials (RCTs) demonstrated a significantly increased risk of dizziness with tirzepatide compared to placebo, yielding a pooled OR of 2.06 (95% CI: 1.63–2.62). Subgroup analyses indicated that both lower (<10 mg) and higher (>10 mg) doses were associated with a similarly elevated risk, with no observation of statistically significant dose-dependent difference ($p = 0.88$). These findings are consistent with previous observational studies that have reported central nervous system adverse effects associated with incretin-based therapies, particularly GLP-1 RAs [24,25]. Dizziness may be attributed to GLP-1 receptor expression in brain regions such as the area postrema and the nucleus tractus solitarius, which regulate vestibular function and autonomic balance [26]. Activation of these receptors may influence central nervous system activity, thus leading to light-headedness, vertigo, or balance disturbances. Furthermore, tirzepatide's delayed gastric emptying and fluid shifts may indirectly contribute to hypotension-related dizziness, especially in patients with intensive weight loss [27]. Although dizziness is typically categorized as a non-serious AE, its clinical significance should not be overlooked. Persistent or severe dizziness can impair daily functioning, increase the risk of falls, particularly in older adults, and negatively affect treatment adherence [28]. Considering the consistency of this adverse effect across studies and doses, clinicians should counsel patients accordingly, monitor for symptom onset, and consider dose titration strategies where appropriate.

Unlike dizziness, the present analysis observed no statistically significant increase in the risk of suicidal ideation or thoughts with tirzepatide use (OR = 1.76, 95% CI: 0.61–5.03; $p = 0.29$). Subgroup analysis across different doses also failed to demonstrate a dose-response relationship. However, the limited number of events and wide confidence intervals underscore the uncertainty of these findings, precluding firm conclusions. This uncertainty is consistent with previously reported data for other GLP-1 RAs. Although early post-marketing surveillance raised concerns about mood changes and suicidal thoughts, subsequent pooled analyses and regulatory reviews have largely been inconclusive. The European Medicines Agency (EMA), for instance, launched a class-wide investigation in 2023 after spontaneous reports of suicidal ideation in patients using GLP-1 RAs such as semaglutide and liraglutide, but no clear causal relationship was established [29,30]. Of note, a recent disproportionality analysis using the WHO global pharmacovigilance database reported a signal linking semaglutide to suicidal ideation, warranting further investigation. This was a case-control study that included the global reports of adverse drug reactions attributed to semaglutide or liraglutide [7]. Although the present meta-analysis does not confirm this association for tirzepatide, the signal detected for other GLP-1 RAs highlights the importance of long-term safety monitoring and mental health assessment, especially in vulnerable populations often excluded from ClinicalTrials.

GLP-1 and GIP receptors are present in brain regions regulating mood, affecting neurotransmission, neuroinflammation, and the Hypothalamic Pituitary Adrenal (HPA) axis. Dysregulation of these systems has been associated with mood disorders such as depression and anxiety [9,26]. Preclinical studies indicate that GLP-1 signaling may influence mood and behavioral responses; however, evidence

in the human population remains limited and inconclusive [31]. Tirzepatide activates both GLP-1 and GIP receptors, so its neuropsychiatric effect may be distinct from that of GLP-1 RAs alone. It is still unclear whether GIP helps, worsens, or has its own effect on mental health. This emphasizes the need for mechanistic studies and long-term data in humans. Overall, our meta-analysis identified two important safety considerations associated with tirzepatide. First, dizziness appears to be a relatively common AE that may affect treatment adherence, particularly in older adults. Second, while no significant association with suicidal ideation was observed, limited data preclude exclusion of a rare but serious risk. Therefore, the clinical implications of these findings are significant, as dizziness can impair daily functioning and increase fall risk, particularly among older adults or those with intensive weight loss. Clinicians should routinely monitor for dizziness after initiation or dose escalation and provide counselling regarding hydration, posture change, and fall precautions. The absence of a dose-response effect suggests a pharmacological mechanism related to central GLP-1 receptor activation rather than dose-dependent systemic exposure, aligning with prior evidence of CNS involvement [26]. Although no increased risk of suicidal ideation was identified, patients with prior psychiatric history should be closely monitored and referred promptly if symptoms emerge [7,30]. The present review has several notable strengths. Only randomized controlled trials were included, minimizing confounding and enhancing internal validity. The review was prospectively registered in PROSPERO and conducted in accordance with PRISMA guidelines, ensuring methodological transparency and reproducibility. Comprehensive literature searching across multiple databases reduced the risk of study omission. Low statistical heterogeneity across analyses, along with subgroup, leave-one-out sensitivity, and publication bias assessments, further supports the robustness and reliability of the pooled estimates. Hence, future research should require beyond short-term trial data and focus on long-duration randomized studies and real-world surveillance to capture rare neuropsychiatric events. Dedicated mechanistic studies are needed to clarify GLP-1/GIP effects on central nervous system pathways. Inclusion of high-risk populations, standardized assessment of psychiatric outcomes, and consistent reporting frameworks will be essential to guide clinically meaningful and true safety profile of Tirzepatide to strengthen causal inference.

5. CONCLUSION

Tirzepatide is associated with a significantly increased risk of dizziness irrespective of dose. However, no significant association with suicidal thoughts was observed. The suicidal intention findings remain inconclusive due to limited events and wide confidence intervals. Continued post-marketing surveillance and high-quality studies are essential to clarify these potential safety concerns.

6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising

it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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8. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

10. DATA AVAILABILITY

All the data is available with the authors and shall be provided upon request.

11. PUBLISHER'S NOTE

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12. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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SUPPLEMENTARY MATERIAL

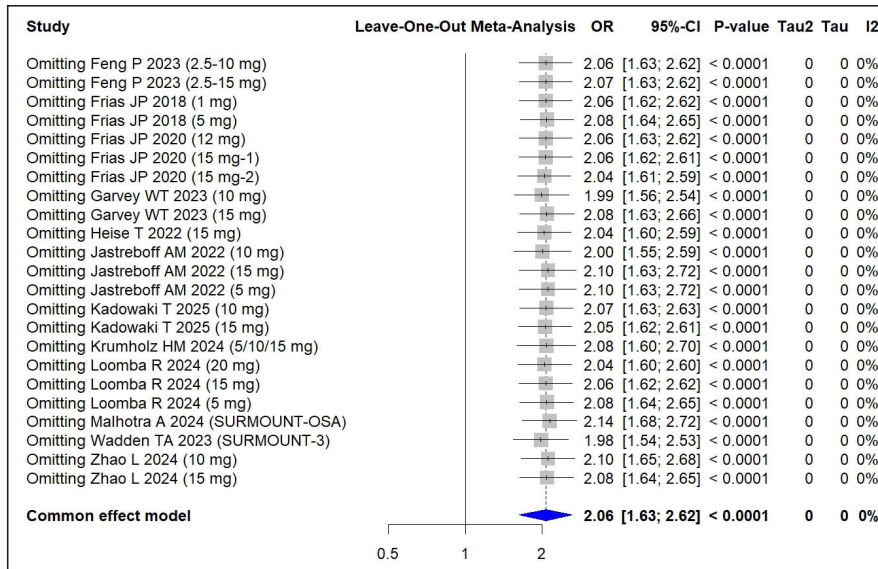


Figure a. Sensitivity analyses for risk of dizziness.

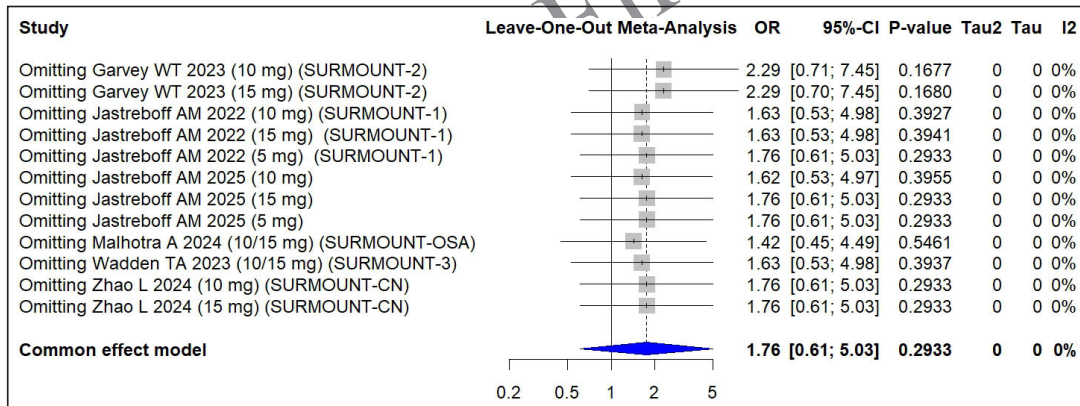


Figure b. Sensitivity analyses for risk of suicidal thoughts.