Management of Overweight and Obese People with the Dual GIP/GLP-1 Receptor Agonist Tirzepatide: A Systematic Review

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Abstract: *Purpose* Aimed to comprehensively investigate the efficacy and safety of the dual GIP/GLP-1 re-ceptor agonist Tirzepatide on overweight and obesity. *Methods* Embase, PubMed/Medline, Web of Science, Cochrane, CNKI, Wanfang and VIP databases were searched using standard key-words to identify all controlled trials investigating the weight loss effects of Tirzepatide. RevMan 5.3 was used for analysis. *Results* Eleven randomized controlled trials with 11710 participants were included in this systematic review and meta-regression analysis. The pooled findings showed that Tirzepatide vs control significantly reduced body weight (mean difference (MD): -7.38, 95% confidence interval (CI): -13.66 to -1.09, P=0.02). The results of subgroup analysis showed that the trend of weight loss is dose-dependent (5mg: MD: -6.87, 95%CI: -10.29 to -3.45, P<0.0001; 10 mg: MD: -9.62, 95%CI: -13.11 to -6.13, P<0.000 01; 15mg: MD: -11.00, 95%CI: -14.29 to -7.70, P<0.000 01). HbA1c (MD: -1.38, 95% CI: -1.52 to -1.23, P<0.000 01). The total incidence of adverse reactions in Tirzepatide vs control was significantly increased (Odds Ratio (OR): 1.57, 95%CI: 1.35 to 1.81, P<0.000 01), and these adverse reactions were even greater, especially with higher doses and duration of Tirzepatide. *Conclusions* The administration of Tirzepatide medication has demonstrated noteworthy effects on weight management, resulting in reductions in both body weight and HbA1c levels. These effects may potentially be dependent on the dosage administered. Consequently, for individuals with diabetes who experience significant impacts on body weight, the utilization of Tirzepatide can be regarded as a viable therapeutic approach for obese individuals.

Keywords: Tirzepatide; The Dual GIP/GLP-1 Receptor Agonist; Efficacy; Safety; Systematic Review

DOI: 10.57237/j.cmf.2026.01.001

1 Introduction

Overweight and obesity is the result of a prolonged imbalance in energy homeostasis, specifically between caloric intake and expenditure [1]. When there is an excess of calories, they are stored in the body as fat [2]. This excessive fat content or abnormal fat distribution in the human body can lead to various health issues, including type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), obstructive sleep apnea (OSA), increased risks of various cancers, mortality, reduced quality of life, and increased risk of death [1, 2]. Research has indicated that 44% of T2DM cases, 23% of CVD cases and 7% to 41% of specific cancers are associated with obesity [3]. Furthermore, it has been projected that a

Funding: This work was financially supported by grants from the Foundation of the People's Hospital of Jianyang (JYk202406).

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Received: 15 June 2025; Accepted: 8 September 2025; Published Online: 14 January 2026 http://www.clinmedfront.com

significant proportion of the global adult population will experience obesity by the year 2030. In the specific case of China, the prevalence of childhood obesity stands at approximately 30%, while a staggering 70% of the adult population is classified as either overweight or obese. It has been approximated that the economic burden of overweight and obesity in China will amount to ¥418 billion by 2023, constituting approximately 22% of the nation's total medical costs [4]. In cases where lifestyle interventions prove ineffective, drug therapy is often considered the primary treatment option. Currently, the Food and Drug Administration (FDA) has approved several medications, including Orlistat, Phentermine, Phentermine/Topiramate, Liraglutide and Semaglutide for the management of obesity. However, there are many side effects and limited therapeutic effects with long-term use, those treatment has some limitations [5].

Tirzepatide (TZP, LY3298176) is a peptide modified with fatty acids that exhibits dual agonist activity for glucose-dependent insulinotropic polypeptide (GIP)/ Glucagon-like peptide-1 (GLP-1) receptors. It was approved by the FDA in May 2022 and by the European Medicines Agency (EMA) in November 2022 for the purpose of enhancing glycemic control in adults diagnosed with T2DM [6, 7]. TZP has been observed to stimulate insulin secretion, suppress glucagon secretion, reduce hepatic gluconeogenesis, enhance insulin sensitivity, delay gastric emptying, decrease food intake, and promote weight loss [8, 9]. Furthermore, a phase 3 clinical trial involving 2539 individuals with obesity and overweight demonstrated that weekly administration of TZP at doses of 5mg, 10mg, or 15mg yielded significantly and continuously reduce body weight for 72 weeks [6]. However, the appropriate dose and duration of Tirzepatide therapy which is effective in weight loss is an issue that needs more comprehensive studies. The present systematic review, based on clinical trials, aimed to investigate the effects of Tirzepatide on weight loss and safety.

2 Materials and Methods

2.1 Search Strategy

Methods Protocol We followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) standards for conducting our systematic review. The Chi-nese biomedical literature database, CNKI, Wanfang data, PubMed, Embase, Web of sci-ence, and Cochrane Library and Clinical Trials website were searched from inception to December 31, 2023. Searches were designed using a combination of Medical Subject Heading (Medline), Emtree (Embase subject headings), and free-text terms such as SCLC, as follow (Tizepatide OR Ly3298176 OR TZP) AND ("weight" OR "Body Mass Index" OR "BMI" OR "diabetes mellitus" OR "type 2 diabetes mellitus" OR "T2DM") AND ("Clinical Trials as Topic" OR "Cross-Over Studies" OR "Double-Blind Method" OR "Single Blind Method" OR "Random Allocation" OR "Clinical Trial"). In order to discover potentially overlooked eligible trials, the reference lists of the papers found and associated review studies were also manually examined.

2.2 Inclusion and Exclusion Criteria

2.2.1 Types of Research

The dual GIP/GLP-1 receptor agonist Tirzepatide on body mass index (BMI)≥27kg/m^2 obesity randomized controlled trial (RCT).

2.2.2 Subjects

Obesity (BMI ≥28kg/m^2). Patients were older than 18 years old. No restrictions on gender, age, and ethnicity.

2.2.3 Interventions

Test group: Tirzepatide (5mg, 10mg, 15mg). Control group: placebo, Semaglutide, Dulaglutid, insulin.

2.2.4 Outcomes

Primary outcome indicators: bodyweight (kg). Secondary outcome indicators: glycated haemoglobin A 1c (HbA1c), adverse reactions, serious adverse event, diarrhea, nausea.

2.2.5 Exclusion Criteria

Non-RCT or semi-RCT trials, literature without relevant outcome indicators, phase 1 clinical experiments, clinical case reports, animal experiments, review papers, letters, laboratory studies, meta-analysis, reviews, or conference papers.

2.3 Literature Screening, Data Extraction and Quality Evaluation

The literature screening was conducted independently by two investigators according to the inclusion and exclusion

criteria. In case of disagreement, a third independent investigator made the final adjudication. The data extraction mainly includes the author, published literature year, test sample size, age, gender, basic condition, intervention measures, treatment methods, curative effect, and safety after treatment. The literature quality of the included studies was evaluated according to the quality evaluation method recommended by Cochrane System Reviewer Manual 5.1.0. The specific evaluation contents included the generation of random sequences, allocation concealment, blinding of subjects, blinding of result evaluators, data integrity, and selective reporting. And the improved Jadad rating scale was used to evaluate the literature quality.

2.4 Statistical Methods

Statistical analysis was performed using RevMan5.3. Assessment of heterogeneity the $\chi 2$ test was used to analyze heterogeneity, test level is $\alpha=0.1$, and the magnitude of heterogeneity was judged by combining the findings with the I^2 test. When no obvious heterogeneity exists ($P > 0.1$, $I^2 < 50\%$), we used a fixed effect model; otherwise, we used the random effects mode. The results were presented as relative risk (RR) and 95% credible intervals (CI). If $P \leq 0.05$ was considered to indicate a statistically significant difference; iv) the publication bias was identified with funnel plots.

3 Results

3.1 Database Search

The initial 716 articles were searched, and the duplicate literature was first removed with EndNote software, then the literature was further read for screening, and finally, the 11 studies that conformed to inclusion criteria were included [6, 10-19]. All 11 articles were RCT trials, including 11710 patients and published in English. See Figure 1 for literature screening diagram and Table 1 for basic characteristics of the included articles.

Table 1 Basic features of the included studies

Studies	Type	Course	Interventions	Cases	Age	Body weight (kg)	BMI (kg/m^2)
NCT03131687 [14]	Phase 2	26w	placebo	51	56.6 (8.9)	91.5 (23.1)	32.4 (6.0)
Frias 2018			TZP 5mg	55	57.9 (8.2)	92.8 (19.0)	32.9 (5.7)
			TZP 10mg	51	56.5 (9.9)	92.7 (19.5)	32.6 (5.8)
			TZP 15mg	53	56.0 (7.6)	89.1 (22.7)	32.2 (6.2)
			dulaglutid 1.5mg	54	58.7 (7.8)	89.8 (16.9)	32.4 (5.4)
NCT03311724 [13]	Phase 2	12w	placebo	26	56.0 (10.13)	89.6 (23.7)	32.5 (5.7)
Frias 2020			TZP 15mg^{-1}	28	55.5 (8.54)	88.7 (18.21)	32.0 (5.56)
			TZP 15mg^{-2}	28	56.6 (9.21)	89.6 (16.91)	31.1 (4.21)
NCT04184622 [6]	Phase 3	72w	TZP 5mg	630	45.6 (12.7)	102.9 (20.71)	37.4 (6.63)
Jastreboff 2022			TZP 10mg	636	44.7 (12.4)	105.8 (23.32)	38.2 (7.01)
			TZP 15mg	630	44.9 (12.3)	105.6 (22.92)	38.1 (6.69)
			placebo	643	44.4 (12.5	104.8 (21.37)	38.2 (6.89)
NCT04657003 [16]	Phase 3	72w	TZP 10mg	312	54.3 (10.7)	100.9 (20.9)	36.0 (6.4)
Garvey 2023			TZP 15mg	311	53.6 (10.6)	99.6 (20.1)	35.7 (6.1)
			placebo	315	54.7 (10.5)	101.7 (22.3)	36.6 (7.3)
NCT03861052 [17]	Phase 3	52w	TZP 5mg	159	56.8 (10.1)	78.5 (16.3)	28.6 (5.4)
Nobuya 2022			TZP 10mg	158	56.2 (10.3)	78.9 (13.7)	28.0 (4.1)
			TZP 15mg	160	56.0 (10.7)	78.9 (14.3)	28.1 (4.4)
			dulaglutid 0.75mg	159	57.5 (10.2)	76.5 (13.2)	27.8 (3.7)
NCT03954834 [19]	Phase 3	40w	TZP 5mg	121	54.1 (11.9)	87.0 (21.2)	32.2 (7.0)
Rosenstock 2021			TZP 10mg	121	55.8 (10.4)	86.2 (19.5)	32.2 (7.6)
			TZP 15mg	121	52.9 (12.3)	85.4 (18.5)	31.5 (5.5)
			placebo	115	53.6 (12.8)	84.8 (20.0)	31.7 (6.1)

Studies	Type	Course	Interventions	Cases	Age	Body weight (kg)	BMI (kg/m^2)
NCTO3882970 [18]	Phase 3	52w	TZP 5mg	358	57.2 (10.1)	94.4 (18.9)	33.6 (5.9)
Bernhard 2021			TZP 10mg	360	57.4 (9.7)	93.8 (19.8)	33.4 (6.2)
			TZP 15mg	359	57.5 (10.2)	94.9 (21.0)	33.7 (6.1)
			insulin degludec	360	57.5 (10.1)	94.0 (20.6)	33.4 (6.1)
NCT03730662 [11]	Phase 3	52w	TZP 5mg	329	62.9 (8.6)	90.3 (20.32)	32.6 (6.06)
Stefano 2021			TZP 10mg	328	63.7 (8.7)	90.6 (18.21)	32.8 (5.51)
			TZP 15mg	338	63.7 (8.6)	90.0 (16.34)	32.5 (5.02)
			insulin degludec	1000	63.8 (8.5)	90.2 (19.00)	32.5 (5.55)
NCT04039503 [10]	Phase 3	40w	TZP 5mg	116	62 (10)	95.8 (19.8)	33.6 (5.9)
Dominik 2022			TZP 10mg	119	60 (10)	94.5 (22.2)	33.4 (6.2)
			TZP 15mg	120	61 (10)	96.3 (22.8)	33.4 (5.9)
			placebo	120	60 (10)	94.1 (21.8)	33.2 (6.3)
NCT04093752 [15]	Phase 3	40w	TZP 5mg	230	53.1 (11.2)	77.7 (14.2)	28.1 (3.9)
Gao 2023			TZP 10mg	228	53.5 (11.1)	76.3 (15.0)	27.7 (3.8)
			TZP 15mg	229	54.3 (11.6)	76.2 (13.6)	27.8 (3.8)
			insulin glarginea	220	55.6 (11.4)	76.0 (15.2)	28.0 (4.6)
NCT03987919 [12]	Phase 3	40w	TZP 5mg	470	56.3 (10.0)	92.5 (21.76)	33.8 (6.85)
Juan 2021			TZP 10mg	469	57.2 (10.5)	94.8 (22.71)	34.3 (6.60)
			TZP 15mg	470	55.9 (10.4)	93.8 (21.83)	34.5 (7.11)
			semaglutide 1mg	469	56.9 (10.8)	93.7 (21.12)	34.2 (7.15)

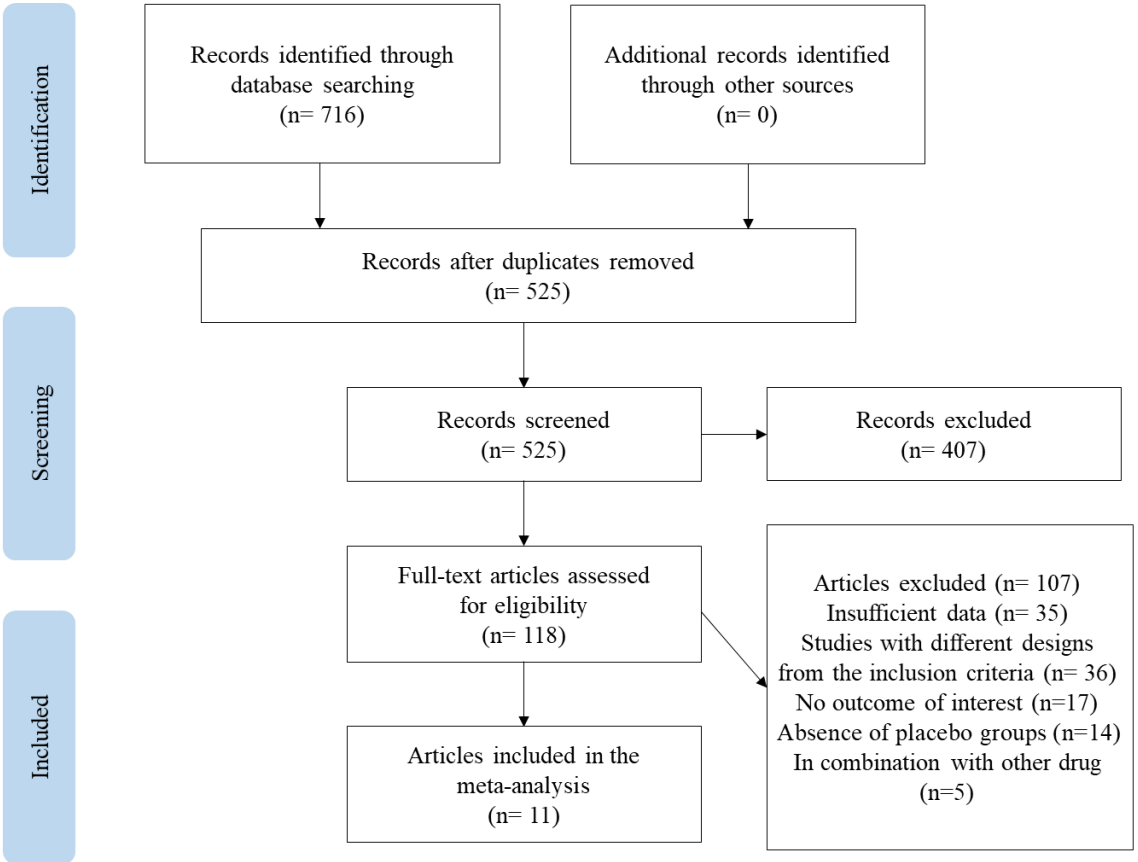

Figure 1 Literature screening process and results

3.2 Quality Assessment

All the included studies were double-blind, randomized clinical trial. Six studies described the specific methods used for random sequence generation; six studies described the allocation concealment in an acceptable manner. The number of patients lost to follow-up was reported in all studies. In all studies, the JADADscore was above 5, which is satisfactory for inclusion in this systematic review [6, 10-19]. The results are shown in Table 2. This is a figure. Schemes follow another format. If there are multiple panels, they should be listed as: (a) Description of what is contained in the first panel; (b) Description of what is contained in the second panel. Figures should be placed in the main text near to the first time they are cited.

Table 2 The quality assessment of included studies

Studies	Random sequence generation	Concealed versus	Blinded	Drop-out/lost to follow-up	Complete outcome data	Selective reporting	Other selection bias	JADAD score
NCT03131687 [14] Frias 2018	Unclear	Unclear	double-blind	Yes	Yes	Unclear	Unclear	5
NCT03311724 [13] Frias 2020	Unclear	Unclear	double-blind	Yes	Yes	Unclear	Unclear	5
NCT04184622 [6] Jastreboff 2022	Unclear	Unclear	double-blind	Yes	Yes	Unclear	Unclear	5
NCT04657003 [16] Garvey 2023	interactive web-response system	interactive web-response system	double-blind	Yes	Yes	Unclear	Unclear	7
NCT03861052 [17] Nobuya 2022	interactive web-response system	interactive web-response system	double-blind	Yes	Yes	Unclear	Unclear	7
NCT03954834 [19] Rosenstock 2021	interactive web-response system	interactive web-response system	double-blind	Yes	Yes	Unclear	Unclear	7
NCT03987919 [12] Juan 2021	Unclear	Unclear	double-blind	Yes	Yes	Unclear	Unclear	5
NCTO3882970 [18] Bernhard 2021	interactive web-response system	interactive web-response system	double-blind	Yes	Yes	Unclear	Unclear	7
NCT03730662 [11] Stefano 2021	interactive web-response system	interactive web-response system	double-blind	Yes	Yes	Unclear	Unclear	7
NCT04039503 [10] Dominik 2022	interactive web-response system	interactive web-response system	double-blind	Yes	Yes	Unclear	Unclear	7
NCT04093752 [15] Gao 2023	Unclear	Unclear	double-blind	Yes	Yes	Unclear	Unclear	5

3.3 Meta-analysis of Efficacy Outcome

3.3.1 Body Weight

Eleven studies [6, 10-19] reported the comparison of the changes in body weight about Tirzepatide vs. control group, significant heterogeneity among studies (P<0.000 01, I^2=100%), a random-effects model was used for meta-analysis. Compared to control, the difference was statistically significant (mean difference (MD): -7.38, 95% confidence inter-val (CI): -13.66 to -1.09, P=0.02). We did a subgroup analysis by the difference between the doses used for the treatments and significant differences were found among subgroups, presented a dose dependent effect (5mg: MD: -6.87, 95%CI: -10.29 to -3.45, P<0.0001; 10 mg: MD: -9.62, 95%CI: -13.11 to -6.13, P<0.000 01; 15mg: MD: -11.00, 95%CI: -14.29 to -7.70, P<0.000 01) (Figure 2).

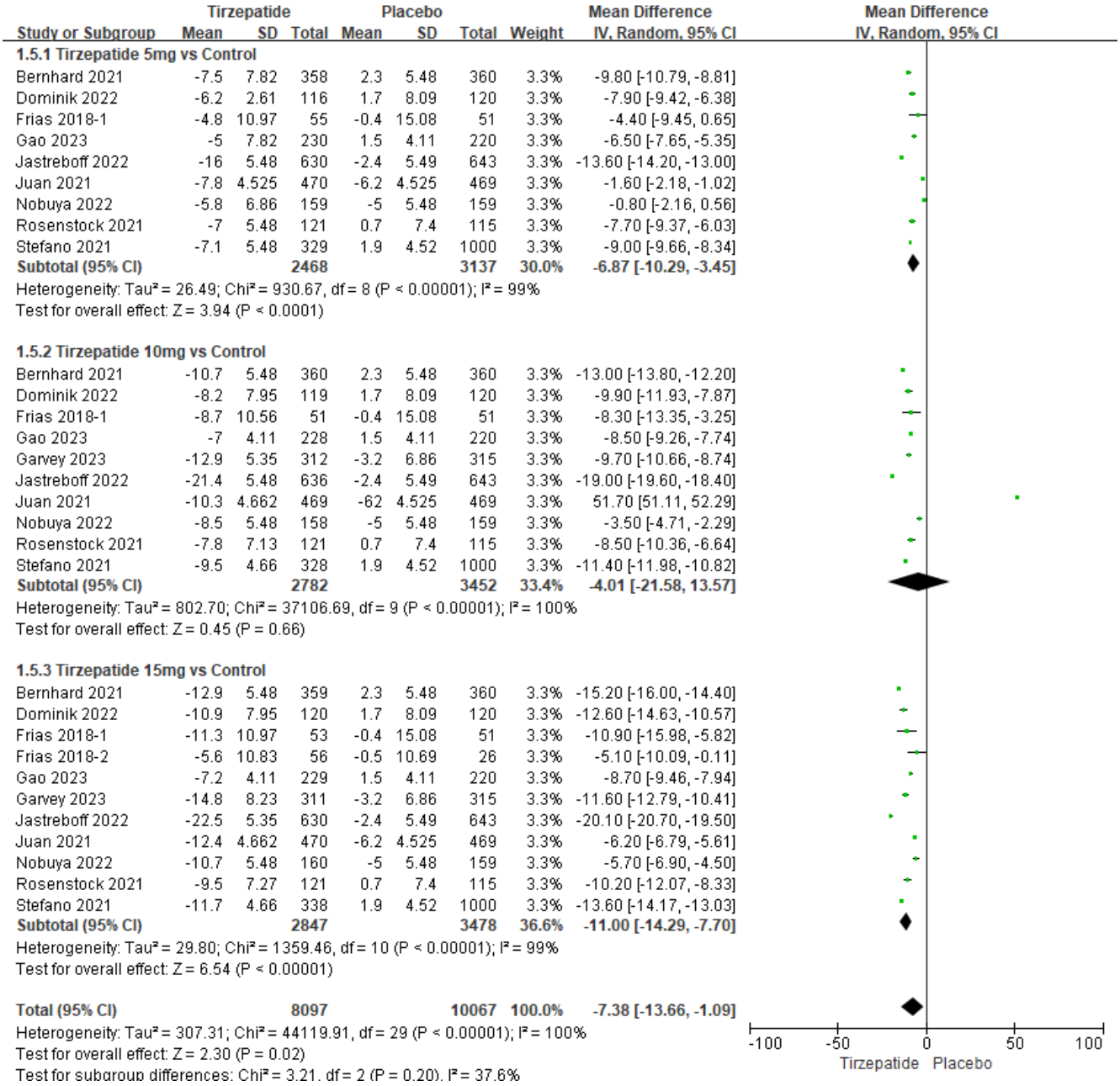

Figure 2 Forest plot of the meta-analysis for bodyweight, Tirzepatide vs Control

3.3.2 HbA1c

Nine studies [10, 11, 13-19] reported the comparison of the changes in HbA1c about Tirzepatide vs. control group, significant heterogeneity among studies (P<0.000 01, I^2=75%), a random-effects model was used for meta-analysis. Compared to control, the difference was statistically significant (MD: -1.38, 95%CI: -1.52 to -1.23, P<0.000 01). Sub-group analysis by the difference between the doses used for the treatments and significant differences were found among subgroups (5mg: MD: -1.17, 95%CI: -1.45 to -0.90, P<0.000 01; 10 mg: MD: -1.40, 95%CI: -1.66 to -1.15, P<0.000 01; 15mg: MD: -1.51, 95%CI: -1.72 to -1.29, P<0.000 01) (Figure 3).

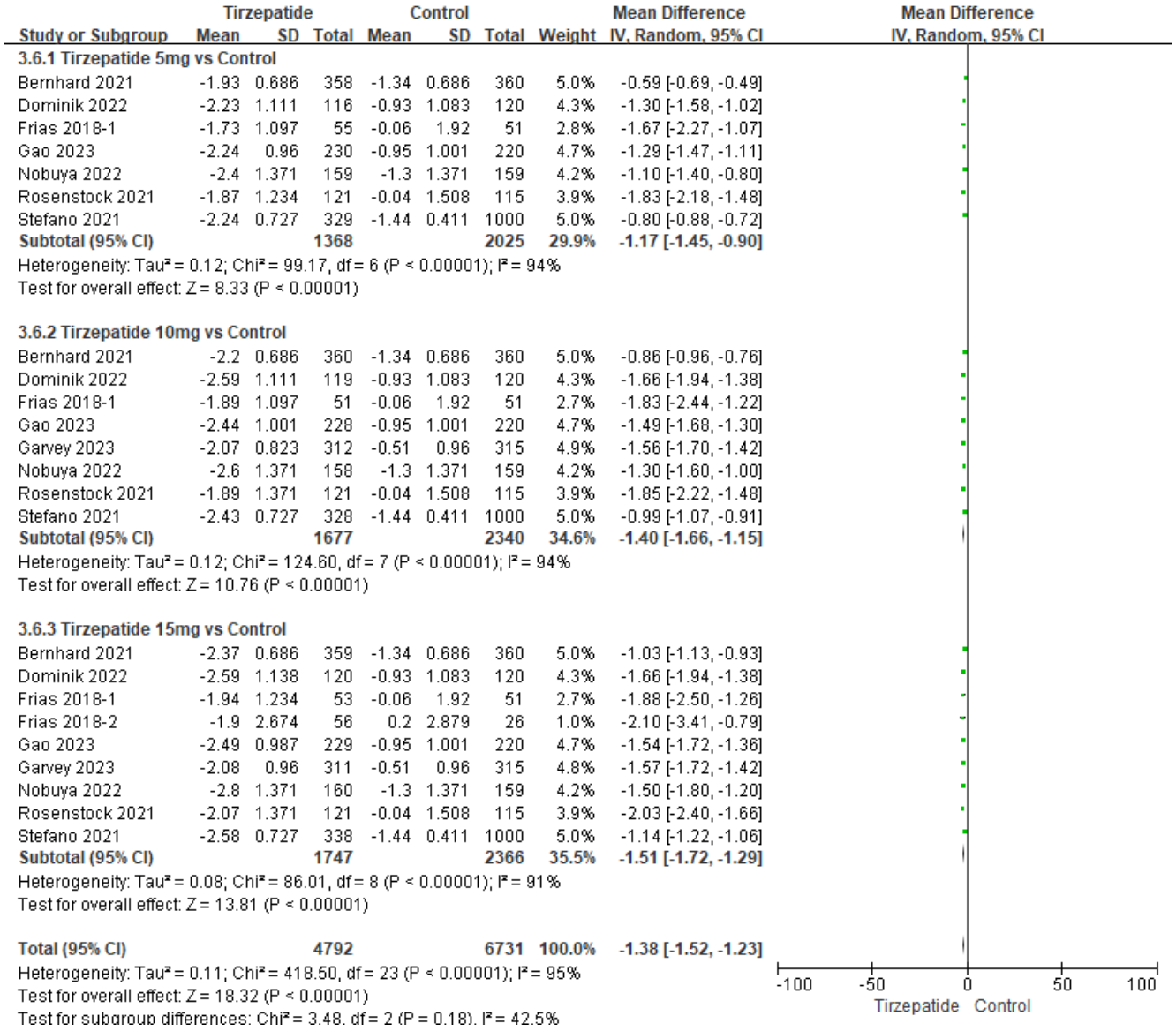

Figure 3 Forest plot of the meta-analysis for HbA1c, Tirzepatide vs Control

3.3.3 Meta-analysis of Safety Outcome

Eleven studies [6, 10-19] reported the comparison of the adverse reactions about Tir-zepatide vs. control group, significant heterogeneity among studies (P<0.000 01, I^2=75%), a random-effects model was used for meta-analysis. Compared to control, the difference was statistically significant (odds ratio (OR): 1.57, 95% CI: 1.35 to 1.81, P<0.000 01). We did a subgroup analysis by the difference between the doses used for the treatments and significant differences were found among subgroups, presented a dose dependent effect (5mg: OR: 1.40, 95%CI: 1.14 to 1.71, P=0.001; 10 mg: OR: 1.59, 95%CI: 1.23 to 2.07, P=0.000 5; 15mg: OR: 1.73, 95%CI: 1.29 to 2.31, P=0.000 2) (Figure 4). The results of the analysis of other outcomes are shown in Table 3.

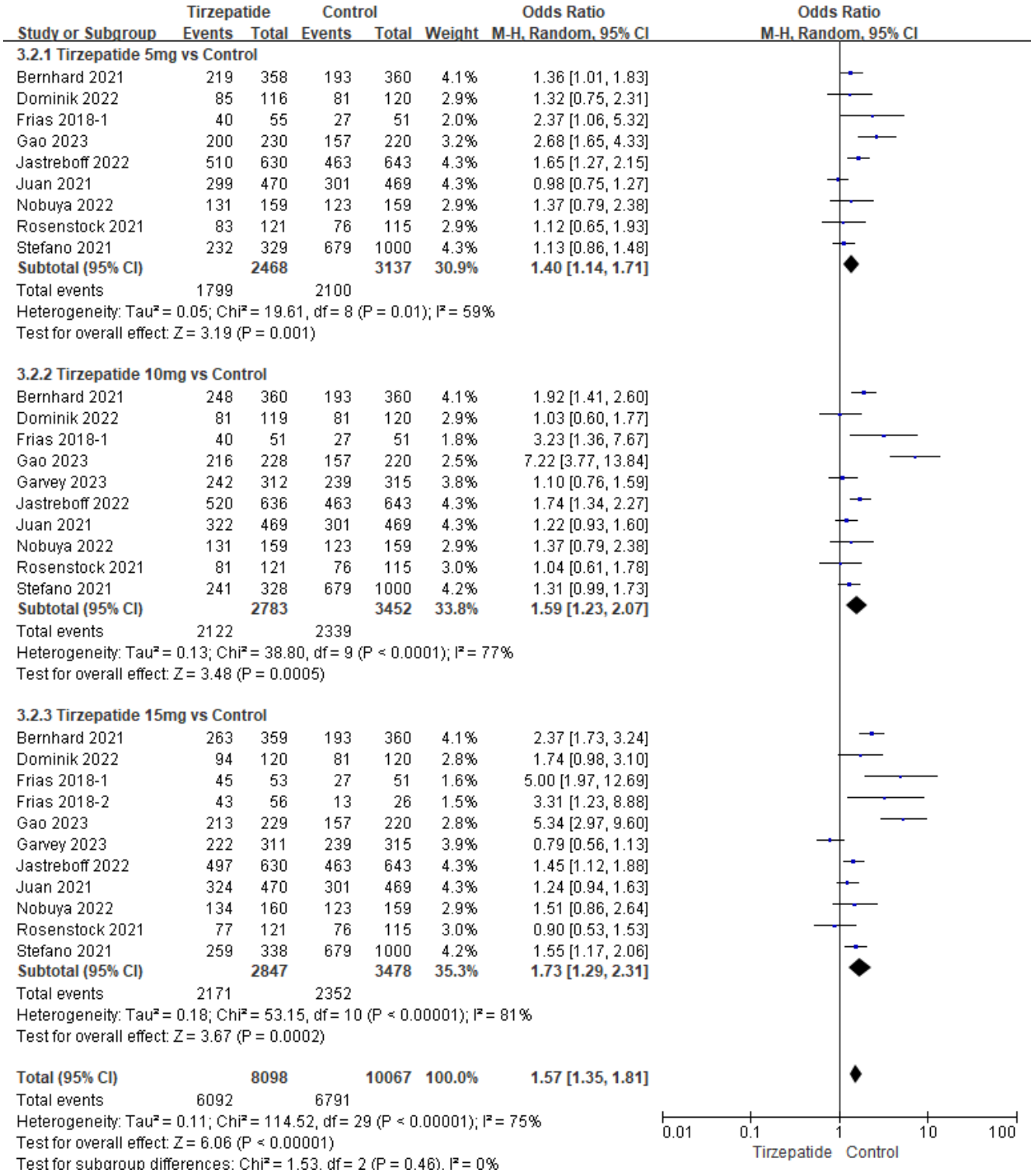

Figure 4 Forest plot of the meta-analysis for adverse event, Tirzepatide vs Control

Table 3 The results of the analysis of other outcomes

Outcomes	Interventions	Studies	0R	95%CI	*P*	I^2
serious adverse event	TZP 5 mg vs Control	9	0.90	(0.74, 1.09)	0.28	11%
	TZP 10 mg vs Control	10	0.94	(0.78, 1.13)	0.49	0%
	TZP 15 mg vs Control	11	0.70	(0.57, 0.85)	0.0004	63%

Outcomes	Interventions	Studies	0R	95%CI	*P*	I^2
	TZP 5 mg vs Control	9	2.62	(1.60, 4.28)	0.0001	7%
nausea	TZP 10 mg vs Control	10	3.41	(2.10, 5.54)	<0.000 01	0%
	TZP 15 mg vs Control	11	4.32	(2.75, 6.79)	<0.000 01	1%
	TZP 5 mg vs Control	9	6.61	(2.31, 18.99)	0.0004	59%
diarrhea	TZP 10 mg vs Control	10	6.14	(1.61, 23.38)	0.008	76%
	TZP 15 mg vs Control	11	8.51	(3.17, 22.82)	<0.0001	66%

3.3.4 Publication Bias Analysis

Publication bias was assessed for Tirzepatide vs. control meta-analyses. In the 11 litera-tures [6, 10-19] evaluated with body weight as outcome indicator, RR value was used to evaluate the publication bias of the included studies, and funnel plots were drawn. The funnel diagram showed that the points were roughly symmetrically distributed in an in-verted funnel shape, and there was no publication bias (Figure 5).

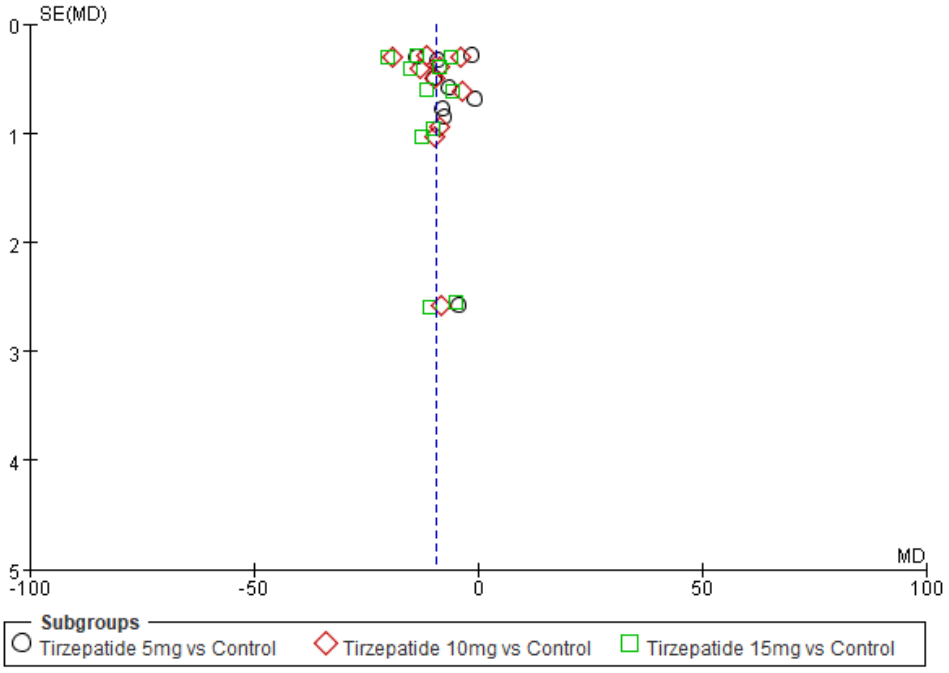

Figure 5 The funnel plots of Bodyweight, Tirzepatide vs Control

4 Discussion

Tirzepatide is a peptide modified with fatty acids that exhibits dual agonist activity for GIP/GLP-1 receptors. It has been approved by the FDA in May 2022 and by the EMA in November 2022 for the purpose of enhancing glycemic control in adults diagnosed with T2DM [6, 7]. TZP has demonstrated the ability to enhance insulin secretion, suppress glucagon secretion, reduce hepatic gluconeogenesis, enhance insulin sensitivity, delay gastric emptying, decrease food intake, and promote weight loss [6, 7, 9, 20]. A recom-mended initial dosage of Tirzepatide, administered through once-weekly subcutaneous injections, would be 2.5 mg. This dosage may be increased to 5 mg after a period of 2 to 4 weeks, with the maximum dosage being 15 mg, also administered once weekly via subcutaneous injections [6, 7]. Our research encompasses a total of 11 randomized controlled trials, involving approximately 11,710 patients with a BMI≥28kg/m^2 and obesity. In com-parison to the control group, statistically significant differences were observed. Further-more, a subgroup analysis was conducted based on variations in treatment dosages, re-vealing significant differences among subgroups and indicating a dose-dependent effect.

In the long term, the reduction of weight, blood lipid levels, and blood pressure has been found to be beneficial in delaying the development of microangiopathy and mac-

ro-angiopathy [21]. In recent years, there has been a significant increase in the global preva-lence of obesity, leading to an annual rise in the incidence of obesity-related T2DM. GLP-1 plays a crucial role in maintaining glucose homeostasis by increasing insulin secretion and suppressing glucagon secretion in response to changes in blood glucose levels. In ad-dition, insulin secretion is appropriately suppressed in response to hypoglycemia [8]. Furthermore, it has been observed that anorexic actions of GIP are potentially influenced by the direct stimulation of the GLP-1 receptor within the central nervous system. This stimulation results in heightened feelings of satiety and a diminished inclination to con-sume sweet and salty foods, thereby contributing to the anorexigenic effects of endotoxin and subsequent reduction in body weight [22]. Additionally, numerous studies have in-dicated that GIP functions as an insulin sensitizer in adipocytes, activating lipoprotein lipase and facilitating triglyceride hydrolysis. This process leads to a decrease in lipid overflow and the accumulation of fat in ectopic locations [20]. The findings of this study indicate that the treatment group exhibited a significantly superior effect compared to the control group. In this paper, a total of eleven studies [6, 10-19] reported on the comparison of changes in body weight between Tirzepatide and the control group, with statistically significant differences observed when compared to the control group. Additionally, nine studies [10, 11, 13-19] reported on the comparison of changes in HbA1c between Tir-zepatide and the control group, with statistically significant differences observed when compared to the control group. Additionally, a total of three studies [12, 14, 17] have re-ported on the comparison between Tirzepatide and duraglutide/semaglutide/insulin. The findings from these studies provide evidence that Tirzepatide is superior in terms of weight loss and reduction of HbA1c. Furthermore, we conducted a subgroup analysis based on the varying doses administered for the treatments, revealing significant differ-ences among the subgroups. This analysis demonstrated a dose-dependent effect, high-lighting the significance of our findings in guiding the design of clinical trials and in-forming clinical medication selection.

The findings of this study demonstrate statistically significant disparities in adverse reactions between the research groups and the control group when examining safety in-dicators. Additionally, the research group exhibited a notably higher occurrence of ad-verse reactions compared to the control group. Notably, new concerns regarding serious adverse effects were identified; however, there was no significant variance in the incidence of serious adverse reactions between the 5mg and 10mg groups and the control group, rendering these differences statistically insignificant. However, the 15mg group exhibited a notably higher incidence compared to the control group. Despite the elevated prevalence of adverse effects associated with this treatment, a majority of patients demonstrated tol-erance towards the medication.

5 Conclusions

In terms of weight loss and reduction of HbA1c, Tirzepatide demonstrates superior efficacy, with the inhibitory effect being contingent upon dosage. Although the occurrence of adverse reactions is more frequent, severe adverse reactions are infrequent. Nonetheless, Tirzepatide holds promise as a potential therapeutic avenue for diabetic patients grap-pling with obesity, particularly those who have not responded favorably to conventional systemic medications or require expeditious weight loss for life-sustaining purposes.

Acknowledgments

The authors acknowledge the support of the fund of the People's Hospital of Jianyang.

Author Contributions

Z. J. established the study and reviewed the manuscript. F. L. and F. J. drafted the manuscript, re-viewed the manuscript, and contributed equally to this work. Z. J. and Y. X. analyzed the data and edited the manuscript. X. X. and Y. S. contributed to literature searches, article selections. F. L., F. J., X. X., Y. S. did the quality assessment and revised the manuscript.

Data Availability Statement

Data sharing is not applicable to this study as no new data were created or analyzed. PROSPERO: CRD42024506165.

Conflicts of Interest

The authors declare no competing financial interest.

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