GLP-1RAs For the Treatment of Inadequate Weight Loss And Weight Regain After Bariatric Surgery: A Systematic Review And Meta-Analysis

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CONFLICT OF INTEREST DISCLOSURE

I have no potential conflict of interest to report.

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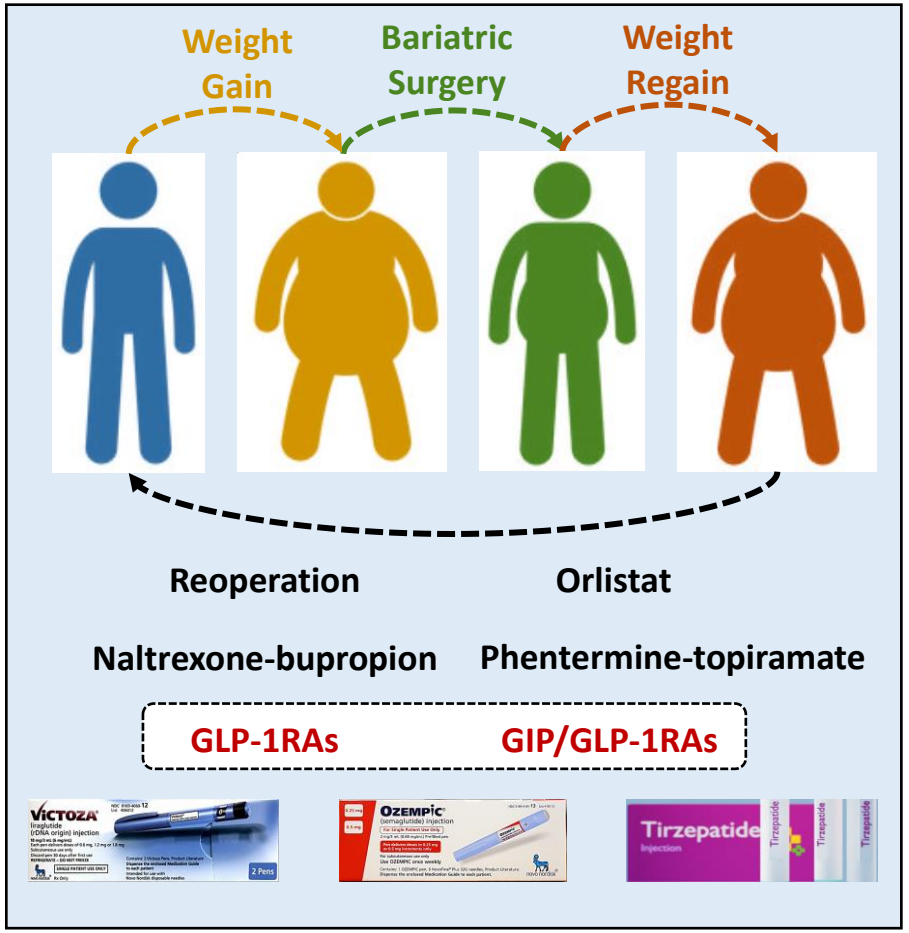
Background

- Bariatric surgery is an effective treatment for obesity and related comorbidities with a mean %TWL of 20-35%.

- **Inadequate weight loss (IWL)** and **weight regain (WR)** will occur in **15-40%** of patients, leading to the recurrence of obesity-related comorbidities, psychological health issues, failure of the initial surgery, and even the need for revisional surgery.

- Although revisional surgery has shown considerable efficacy in treating IWL or WR (%TWL: 7-24%), it imposes additional trauma and psychological barriers on patients, significantly increasing the rates of surgical complications and mortality.

- **GLP-1RAs** and **GIP/GLP-1RAs** are emerging weight loss medications that have demonstrated promising efficacy as adjunctive therapy following bariatric surgery.



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Question

What are the efficacy and safety of GLP-1RAs in treating IWL or WR after bariatric surgery?

Aim

To comprehensively summarize the effectiveness and adverse effects of GLP-1RAs in treating IWL or WR after bariatric surgery in patients with obesity by conducting a systematic review and meta-analysis.

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Methods

- **PROSPERO registration number:** CRD42024525608
- **Search Strategy**

  "bariatric surgery," "weight regain," "regain weight," "weight re-gain," "weight recidivism," "weight loss plateau," "post-bariatric weight regain," "post-operative weight regain," "insufficient weight loss," "inadequate weight loss," and "poor response" in Embase, Web of Science, Cochrane Library, and PubMed before **March 2024**
- **Eligibility Criteria**
  - ✓ **Inclusion**
    a. Studies must include **> 15 patients** who have undergone bariatric surgery
    b. Studies must report **IWL** or **WR** after bariatric surgery
    c. **GLP-1RAs** or **GIP/GLP-1RAs** must be used **> 3 months** for treatment of IWL or WR
    d. Study with the latest information would be included if multiple studies reported overlapping data
  - ✓ **Exclusion**

    Letters, comments, reviews, case reports, meeting abstracts, non-English articles, and non-human studies
- **Quality Assessment**
  a. Randomized controlled trial (RCT): the Cochrane risk of bias tool
  b. Nonrandomized studies: Newcastle-Ottawa Scale (NOS)

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Methods

Primary outcome

Weight loss outcome

a. %TWL

b. Weight loss (kg)

Secondary outcome 1

Biochemical markers

a. Triglycerides (mg/dL)

b. Total cholesterol (mg/dL)

c. LDL-C (mg/dL)

d. HDL-C (mg/dL)

e. HbA1c (%)

f. C-reactive protein (mg/L)

g. Alanine aminotransferase (U/L)

h. Aspartate aminotransferase (U/L)

Secondary outcome 2

Adverse events

a. Nausea

b. Vomiting

c. Diarrhea

d. Constipation

e. Headache

f. Fatigue

g. Abdominal pain

h. Abdominal bloating

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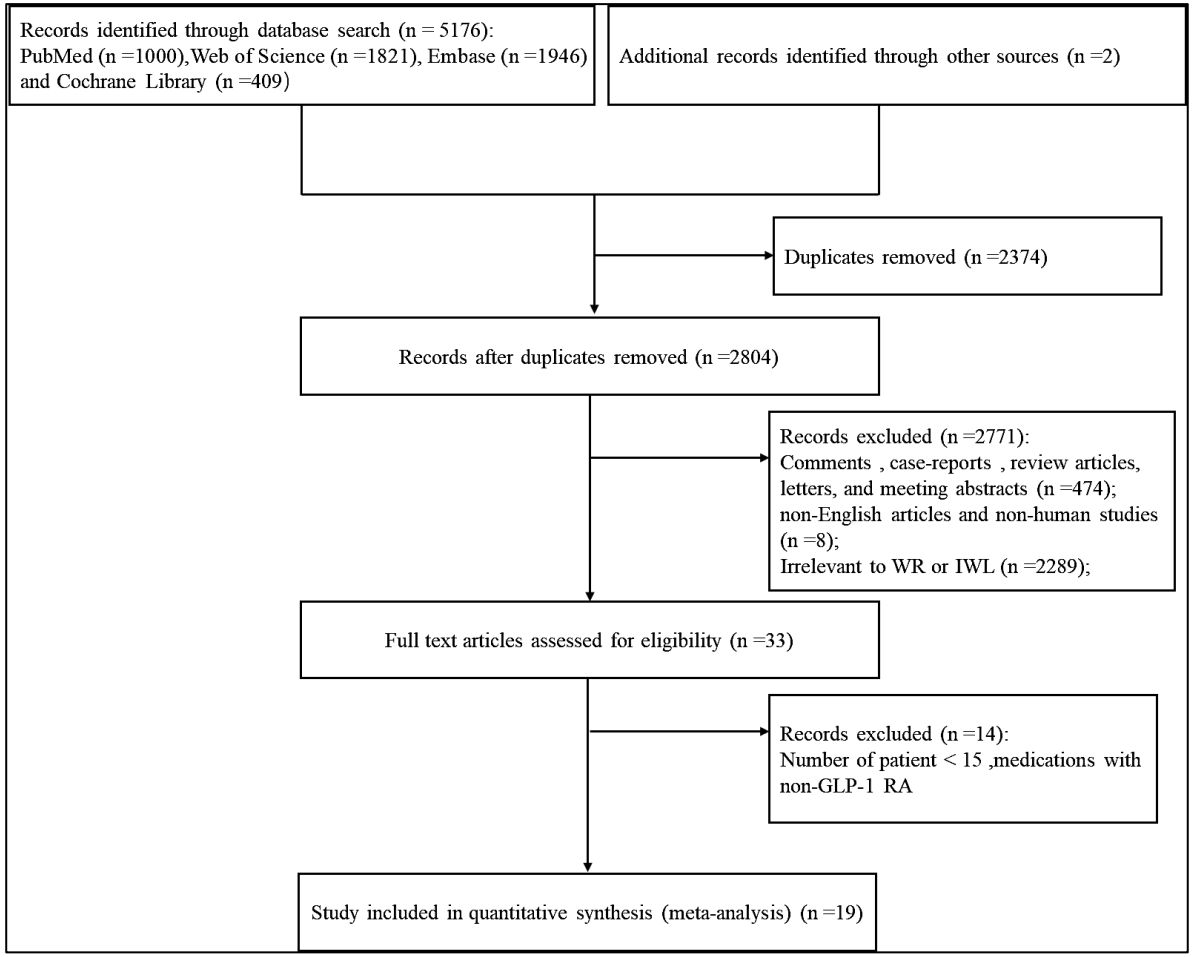
Results

Flow chart



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Results

Study characteristics

Study (Year)	Study Period	Region	Design	N	Center	Surgery Type	IWL or WR	Definition for IWL/WR
Pajecki (2012)	NR	Brazil	RCS	15	SC	RYGB/AGB/BPD/SG	IWL/WR	IWL: EWL < 50% after at least 2 years of follow-up WR: > 15% from weight nadir
Rye (2018)	2017-2018	Canada	RCS	20	SC	RYGB/SG/AGB	IWL/WR	IWL: < 20% weight loss from initial clinic assessment, or pre-operative weight WR: > 10% from weight nadir
Wharton (2019)	2009-2012	Canada	RCS	117	SC	RYGB	IWL/WR	NR
Horber (2020)	2016-2018	Switzerland	PCS	34	SC	RYGB	WR	WR: > 10% from weight nadir
Gazda (2021)	2014-2019	USA	RCS	84	SC	SG/RYGB	WR	NR
Rubio (2021)	NR	Spain	RCS	23	SC	NR	WR	WR: > 15% from weight nadir
Elhag (2022)	2016-2019	Qatar	RCS	119	SC	RYGB/SG/AGB	IWL/WR	IWL: EWL < 50% at 18 months after bariatric surgery WR: > 10 kg from weight nadir
Lautenbach (2022)	2020-2022	Germany	RCS	44	SC	RYGB/SG	IWL/WR	IWL: EWL < 50% at 18 months after bariatric surgery WR: continuous WR after an initial successful weight loss (EWL > 50%)
Muratori (2022)	2016-2021	Italy	RCS	62	SC	RYGB/SG	WR	WR: > 10% from weight nadir
Bonnet (2023)	2022	France	RCS	39	SC	SG/RYGB	IWL/WR	IWL: EWL < 50% at 18 months after bariatric surgery WR:NR
Colbourne (2023)	2020	Australia	PCS	68	SC	SG/RYGB	IWL	IWL: BMI > 35 kg/m^2 or self- identified as weight stable
Jensen (2023)	2016-2021	Switzerland	RCS	50	SC	RYGB/SG	WR	WR: Any weight gain following the weight nadir at least 12 months after bariatric surgery
Lautenbach (2023)	2020-2022	Germany	RCS	29	SC	SG/RYGB	IWL/WR	IWL: EWL < 50% at 18 months after bariatric surgery WR: continuous WR after an initial successful weight loss (EWL > 50%)
Mok (2023)	2018-2020	UK	RCT	32	SC	SG/RYGB	IWL	IWL: %TWL < 20%
Murvelashvili (2023)	2015-2021	USA	RCS	207	SC	RYGB/SG	WR	NR
Vinciguerra (2023)	2016-2022	Italy	RCS	59	SC	SG/OAGB	IWL/WR	IWL: EWL < 50% WR: > 15% of the weight lost
Jamal (2024)(1)	2009-2020	Kuwait	RCS	57	SC	SG	WR	WR: > 10% from weight nadir
Jamal (2024)(2)	2008-2022	Kuwait	RCS	115	SC	SG	WR	WR: > 10% from weight nadir
Vinciguerra (2024)	2018-2023	Italy	RCS	119	MC	RYGB/SG/OAGB	IWL/WR	IWL: EWL < 50% WR: > 15% of the weight lost

Abbreviations: AGB, adjusted gastric banding; BD, biliopancreatic diversion; EWL, excess weight loss (defined as percentage of excess weight loss, = preoperative weight - current weight x100% / preoperative weight - ideal weight (for BMI 25 kg/m2); MC, muti-center; NR, not reported; OAGB, one anastomosis gastric bypass; PCS, prospective cohort study; RCS, retrospective study; SC, single-center; SG, sleeve gastrectomy; RCT, randomized controlled trial; RYGB, Roux-e-Y gastric bypass.

- **Study design**: 16 retrospective, 2 prospective cohort studies and 1 RCT
- **Center**: 1 muti-center, 18 single-center
- **Number of patients**: 1290
- **Type of bariatric surgery**: sleeve gastrectomy, Roux-en-Y gastric bypass, one-anastomosis gastric bypass, adjustable gastric banding, and biliopancreatic diversion
- **Definitions of IWL and WR:**
  - ✓ IWL: excess weight loss (EWL) < 50% at 12 or 18 months after bariatric surgery
  - ✓ WR: >10-15% from weight nadir

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Results

Patient characteristics

Study (Year)	Age (Years)	Male	BMI (kg/m²)/ BW (kg) pre-operative	BMI (kg/m²)/ BW (kg) at nadir post-operative	BMI (kg/m²)/BW (kg) before treatment	Time from surgery to treatment (years)[a]	Medication (Dose)	Treatment duration (month)[a]
Pajecki (2012)	47	27%	47.2/120.8	NR/86.7	NR/100.9	5.3	Liraglutide (1.8 mg/d)	3.0
Rye (2018)	50	5%	NR/117.9	NR/101.2	NR/117.9	6.4	Liraglutide (3.0 mg/d)	7.0
Wharton (2019)	51	13%	49.7/NR	NR/NR	42.5/NR	7.8	Liraglutide (3.0 mg/d)	7.6
Horber (2020)	52	9%	45.0/120.0	25.5/NR	31.2/NR	9.0	Liraglutide (3.0 mg/d)	24.0
Gazda (2021)	48	23%	49.6/138.4	NR/93.7	42.3/117.9	7.3	Liraglutide, semaglutide, exenatide, dulaglutide, albiglutide, or lixisenatide (NR)	12.0
Rubio (2021)	55	30%	46.6/129.5	29.6/NR	36.6/NR	NR	Liraglutide (3.0 mg/d)	12.0
Elhag (2022)	43	16%	45.9/118.2	32.1/82.1	37.6/96.8	NR	Liraglutide (3.0 mg/d)	12.0
Lautenbach (2022)	46	27%	49.4/145.7	34.7/102.9	38.3/113.5	5.4	Semaglutide (0.5 mg/wk)	6.0
Muratori (2022)	44	3%	45.4/NR	29.5/NR	34.2/NR	5.9	Liraglutide (3.0 mg/d)	10.5
Bonnet (2023)	54	38%	45.7/125.2	NR/96.1	NR/NR	8.4	Semaglutide (2.4 mg/wk)	6.0
Colbourne (2023)	41	16%	44.8/117.4	34.6/89.1	35.2/95.8	NR	Liraglutide (3.0 mg/d)	3.0
Jensen (2023)	43	18%	41.8/112.4	29.2/78.3	34/90.5	6.0	Liraglutide (3.0 mg/d) or Semaglutide (1.0 mg/wk)	6.0
Lautenbach (2023)	48	17%	50.4/145.7	34.6/100.6	38.3/110.8	5.4	Semaglutide (1.0 mg/wk)	12.0
Mok (2023)	47	26%	NR/NR	NR/NR	41.6/116.1	4.6	Liraglutide (3.0 mg/d)	24.0
Murvelashvili (2023)(cohort1)	55	10%	50.3/136.8	NR/95.1	NR/114.4	8.2	Liraglutide (3.0 mg/d)	12.0
Murvelashvili (2023)(cohort2)	55	29%	48.5/134.1	NR/94.2	NR/110.7	7.8	Semaglutide (1.0 mg/wk)	12.0
Vinciguerra (2023)	39	29%	47.7/NR	33.4/NR	38.2/101.8	NR	Liraglutide (2.4 mg/d)	6.0
Jamal (2024)(1)	37	19%	NR/121.5	NR/77.8	NR/96.1	NR	Liraglutide (3.0 mg/d)	3.0
Jamal (2024)(2.cohort1)	38	20%	42.0/112.8	28.4/75.3	33.9/90.1	6.0	Semaglutide (2.5 mg/wk)	6.0
Jamal (2024)(2.cohort2)	40	18%	44.9/122.5	30.1/81.7	36.9/100.2	6.0	Tirzepetide (2.5 mg/wk)	6.0
Vinciguerra (2024)	41	29%	37.6/100.9	NR/NR	37.6/100.9	NR	Liraglutide (3.0 mg/d)	6.0

Abbreviations: BW, body weight; BMI, body mass index; NR, not reported.

- **Average age:** 46 years
- **Proportion of female:** 82%
- **BMI before bariatric surgery:** 46.3 kg/m²
- **Nadir BMI post-surgery:** 31.1 kg/m²
- **BMI before GLP-1RA:** 37.2 kg/m²
- **Interval between bariatric surgery and GLP-1RAs:** > 5 years
- **Type of GLP-1RAs:**
  - ✓ **Liraglutide:** 11 studies
  - ✓ **Semaglutide:** 5 studies
  - ✓ **Tirzeptide:** 1 study
  - ✓ **Other GLP-1 RAs modality:** 2 studies

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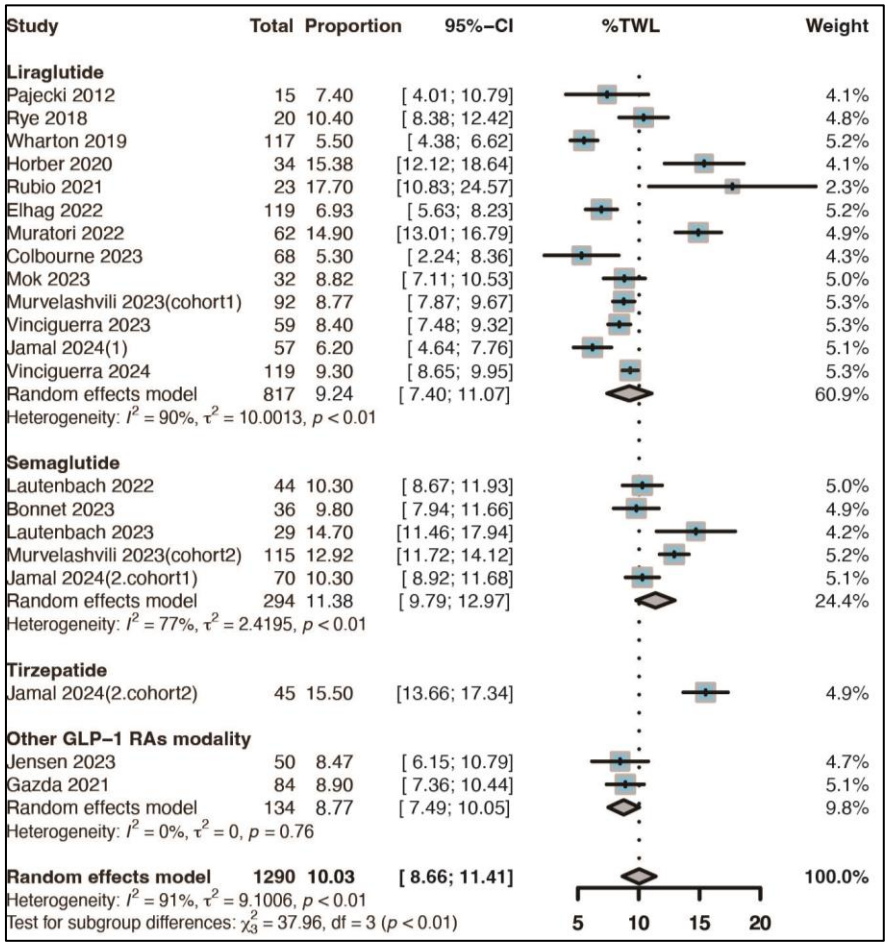
Results

Primary outcome——%TWL



Medication	%TWL (95% CI)
Liraglutide	9.24 (7.40-11.07)
Semaglutide	11.38 (9.79-12.97)
Tirzepatide	15.50 (13.66-17.34)
Total	10.03 (8.66-11.41)

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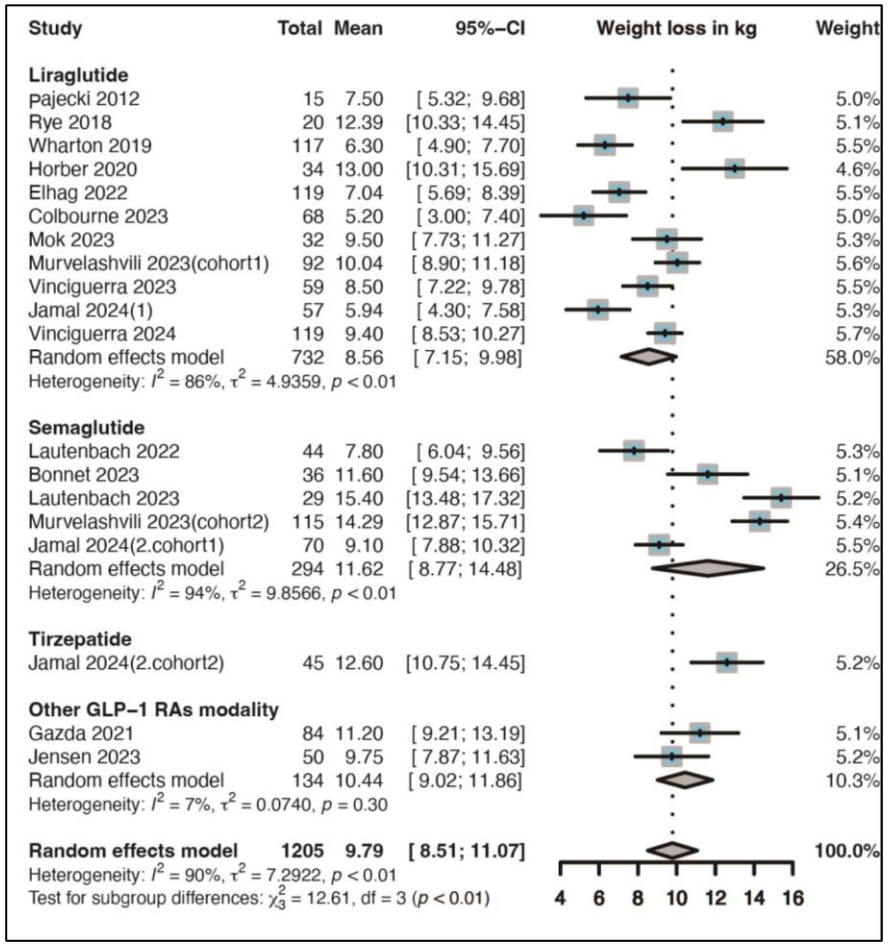
Results

Primary outcome——Weight loss (kg)



Medication	Weight loss (kg)
Liraglutide	8.56 (7.15-9.98)
Semaglutide	11.62 (8.77-14.48)
Tirzepatide	12.60 (10.75-14.45)
Total	9.79 (8.51-11.07)

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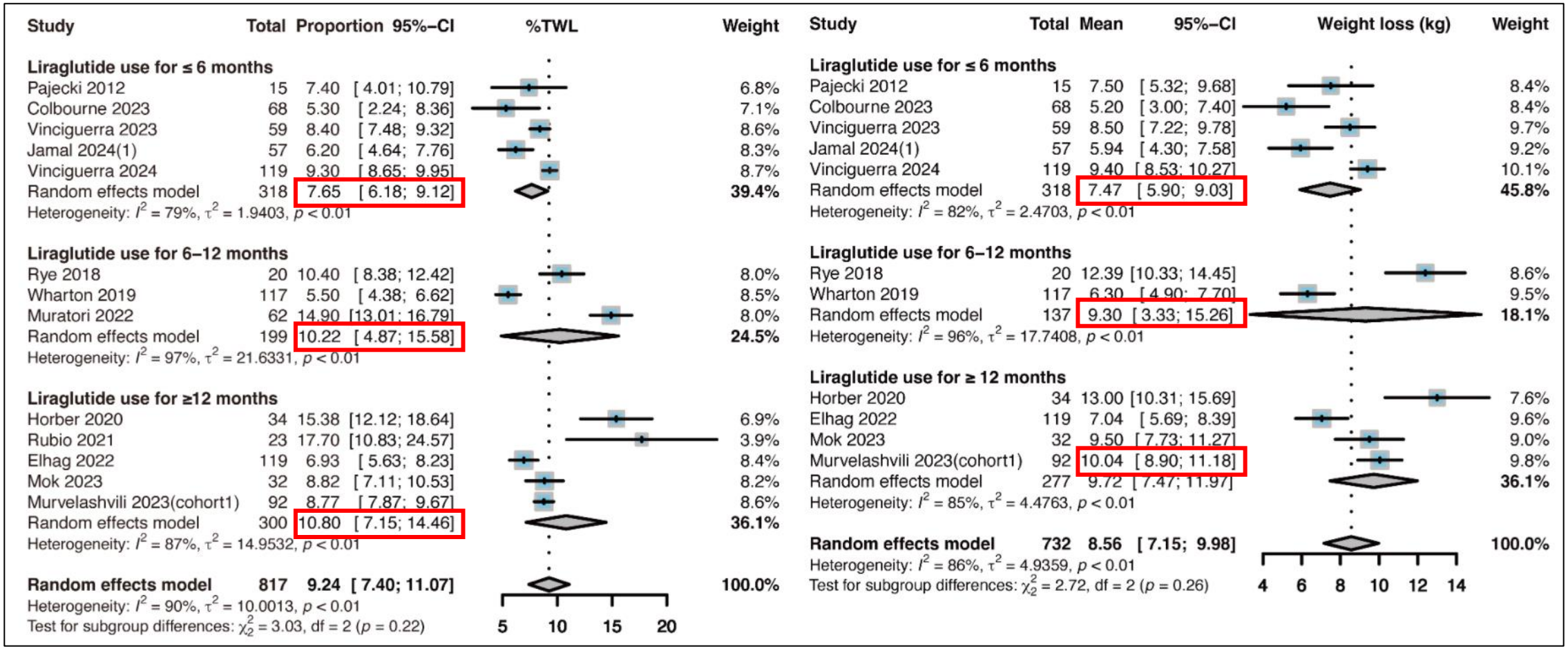
Results

Subgroup analysis——Liraglutide



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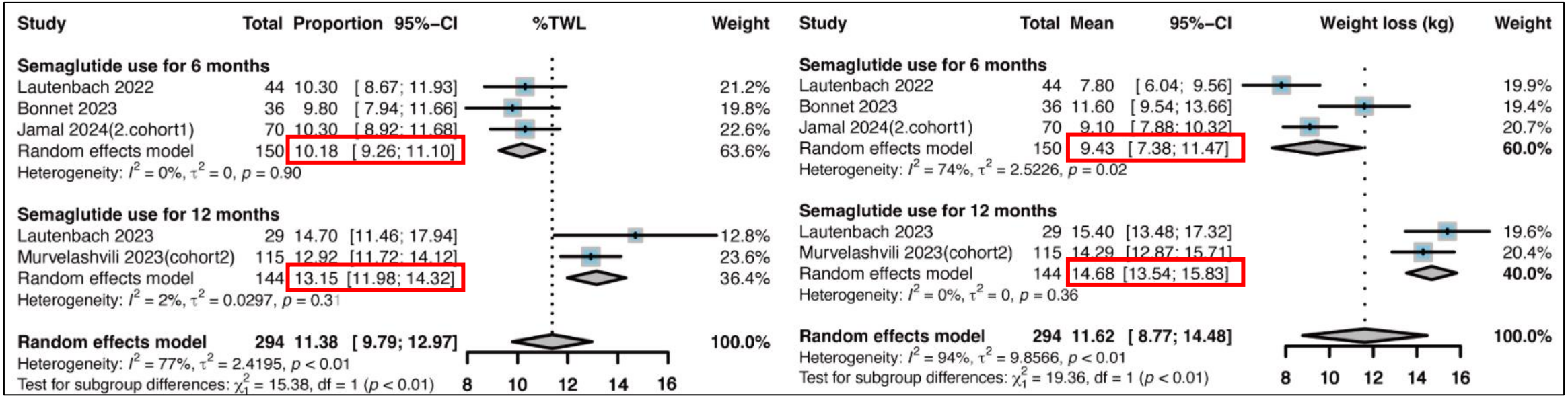
Results

Subgroup analysis——Semaglutide



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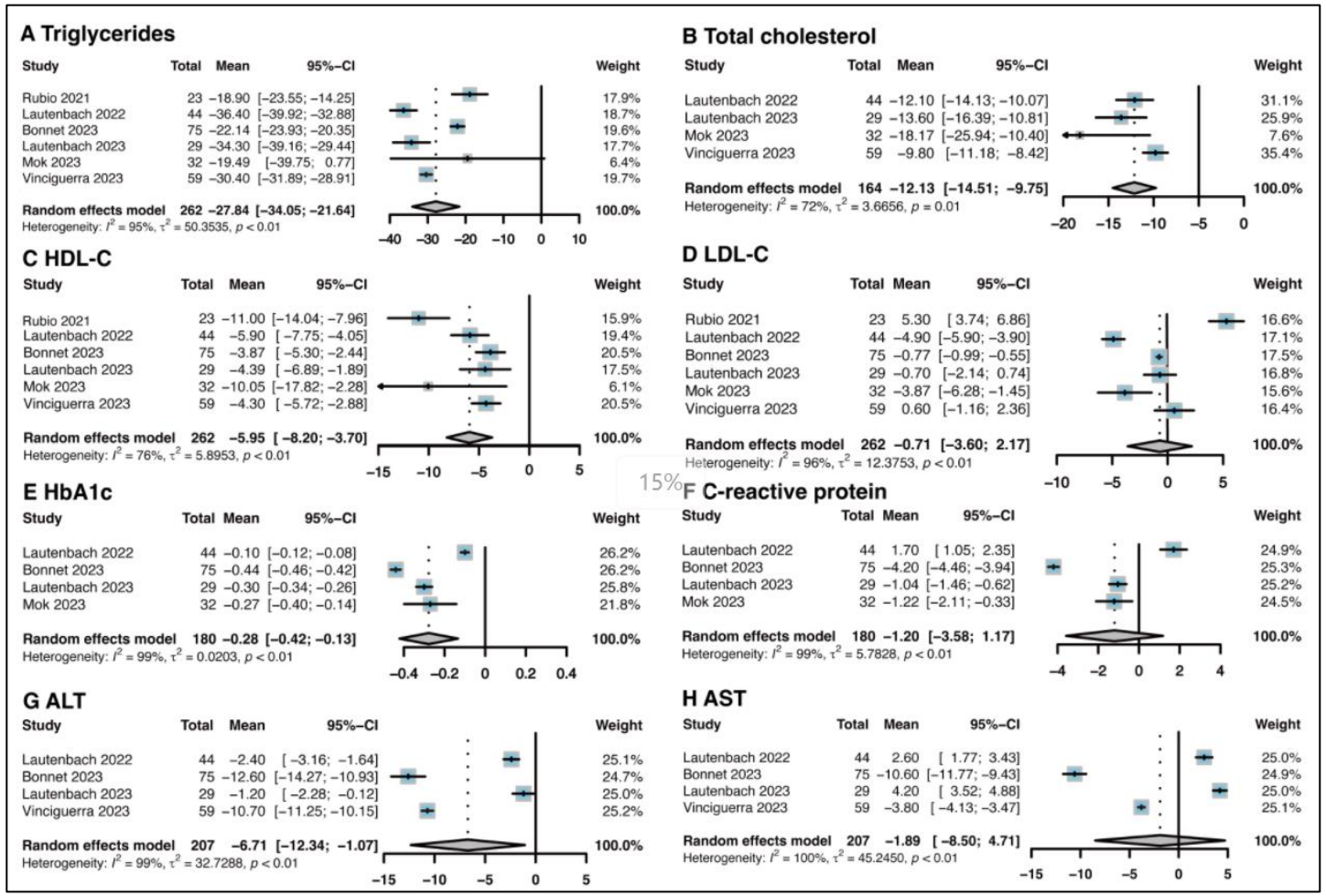
Results

Secondary outcome 1——Biochemical markers



Biochemical Markers	Outcomes (95% CI)	P-value
Triglycerides	**-27.84 mg/dL (-34.05, -21.64)**	**<0.001**
Total cholesterol	**-12.13 mg/dL (-14.51, -9.75)**	**<0.001**
LDL-C	**-5.95 mg/dL (-8.20, -3.70)**	**<0.001**
HDL-C	-0.71 mg/dL (-3.60, 2.17)	0.627
HbA1c	**-0.28% (-0.42, -0.13)**	**0.013**
C-reactive protein	-1.20 mg/L (-3.58, 1.17)	0.320
ALT	**-6.71 U/L (-12.34, -1.07)**	**0.043**
AST	-1.89 U/L (-8.50, 4.71)	0.728

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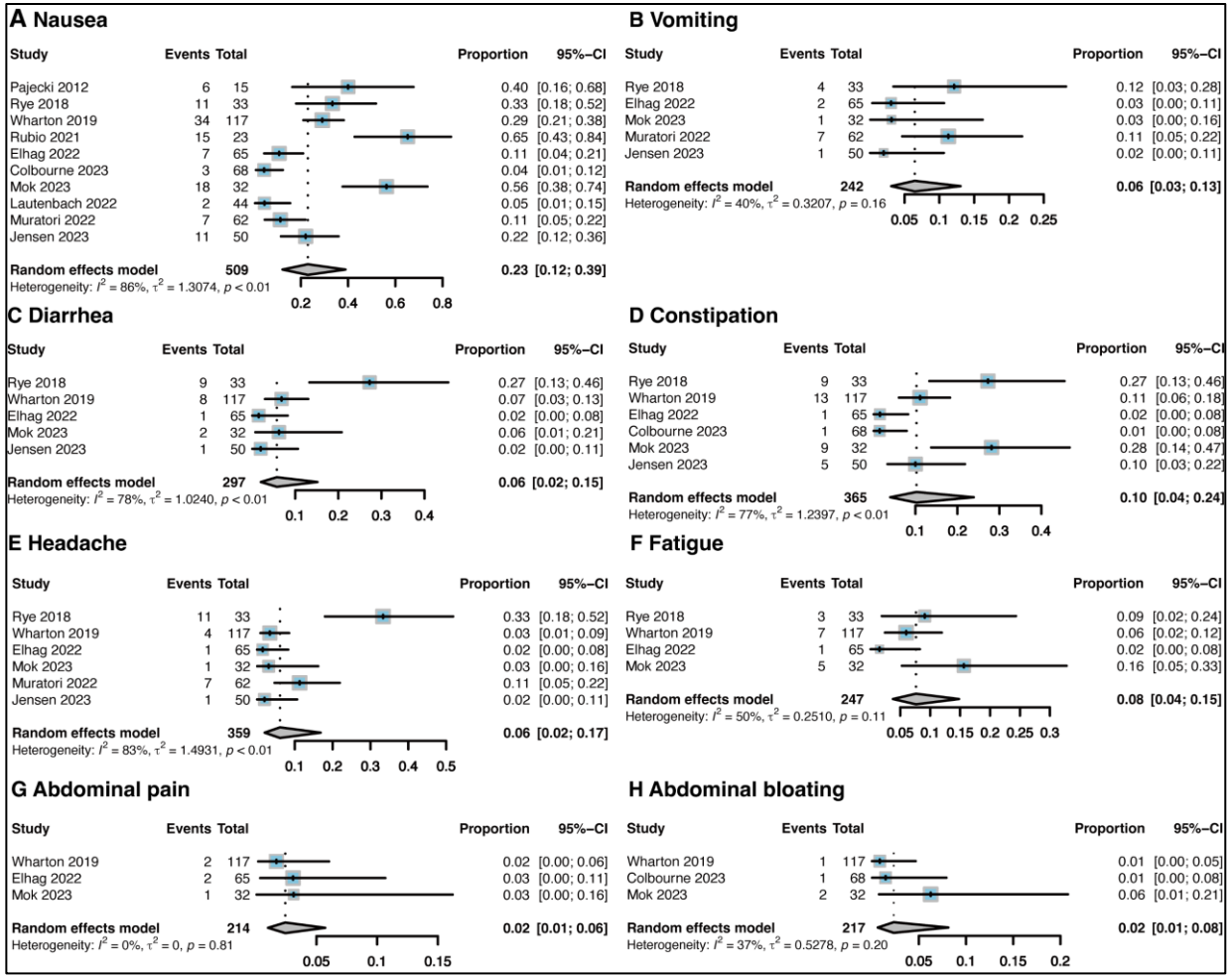
Results

Secondary outcome 2——Adverse events



Adverse events	Proportion (95% CI)
Nausea	23% (12-39)
Vomiting	6% (3-13)
Diarrhea	6% (2-15)
Constipation	10% (4-24)
Headache	6% (2-17)
Fatigue	8% (4-15)
Abdominal pain	2% (1-6)
Abdominal bloating	2% (1-8)

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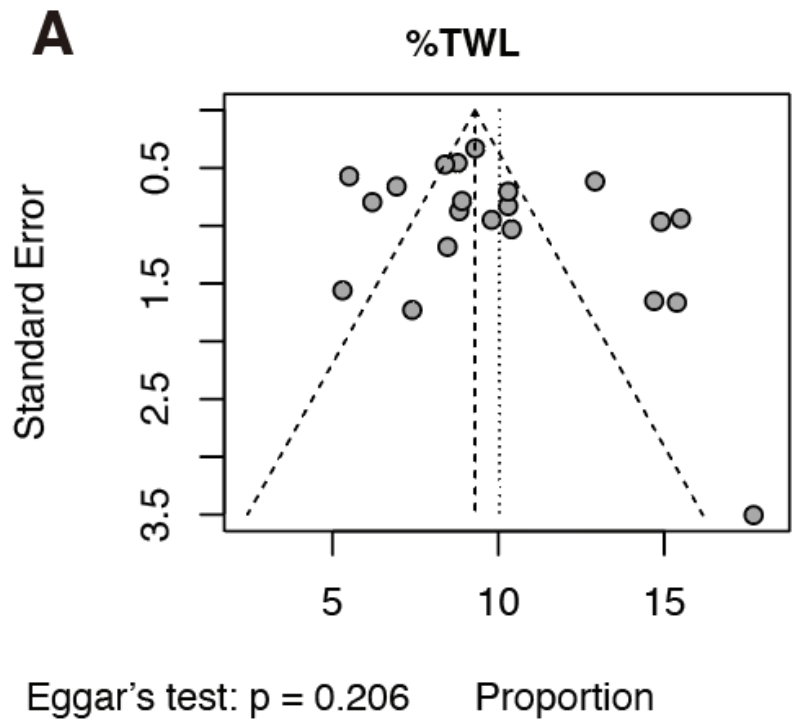
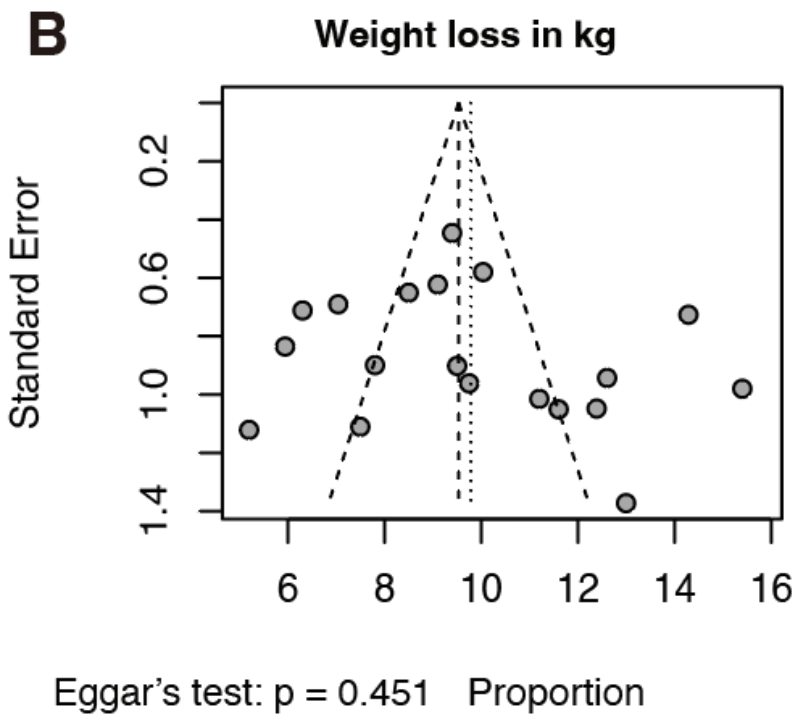
Results

Publication bias





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Conclusion

- Patients experiencing IWL or WR after bariatric surgery who were treated with GLP-1RAs achieved a pooled weight loss of 9.79 kg and a 10.03% TWL. Tirzeptide showed the greatest efficacy, followed by semaglutide, and then liraglutide.
- GLP-1RAs have been shown to reduce lipid profiles, glycemic profiles, and transaminase levels in patients with IWL or WR after bariatric surgery.
- Adverse effects occurring with GLP-1RAs treatment were predominantly gastrointestinal, with the highest incidence of nausea. However, the incidence of these adverse effects remains within an acceptable range.
- Future research should standardize the definition of IWL and WR after bariatric surgery to accurately determine the true efficacy of GLP-1RAs.

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