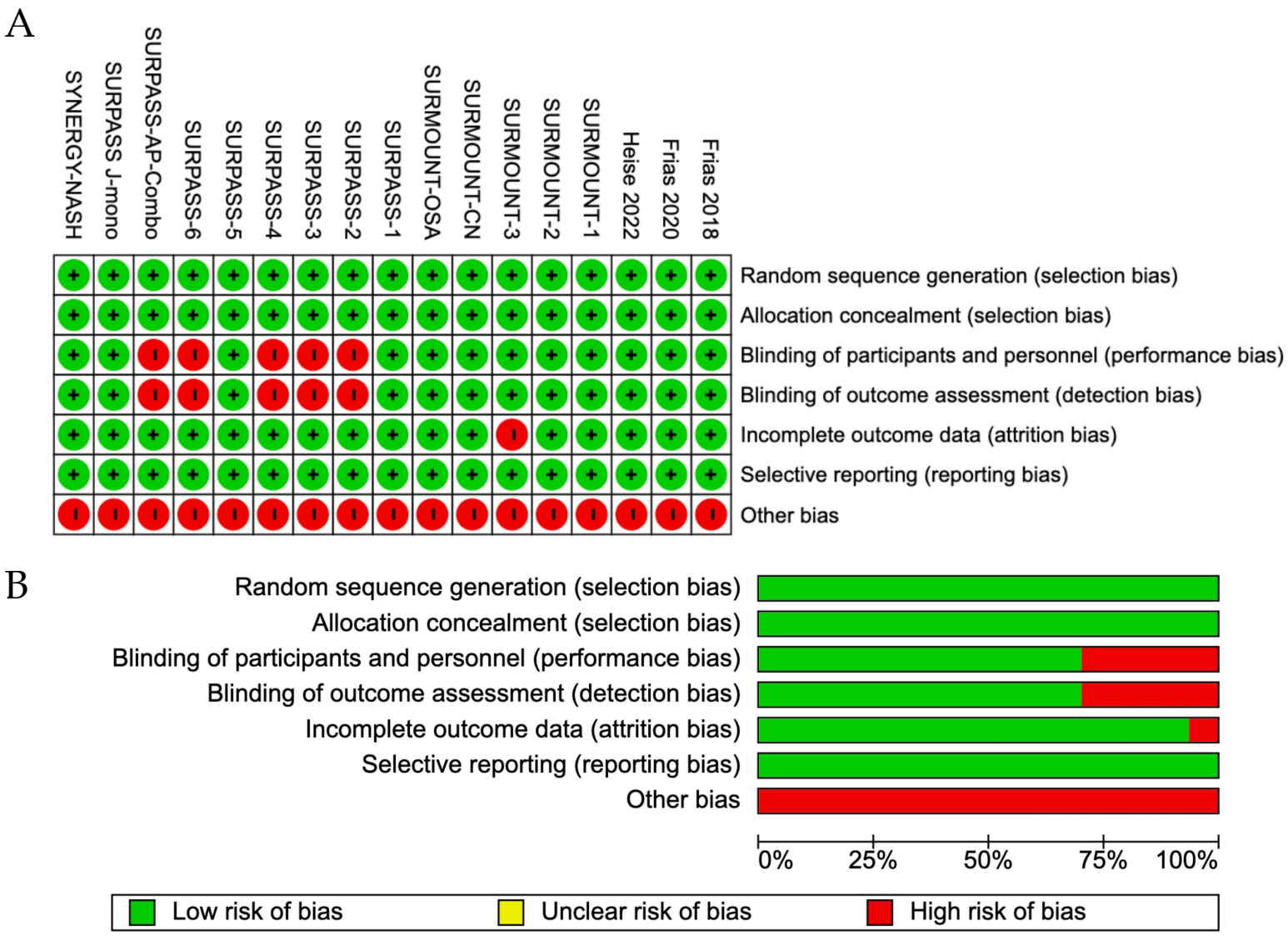
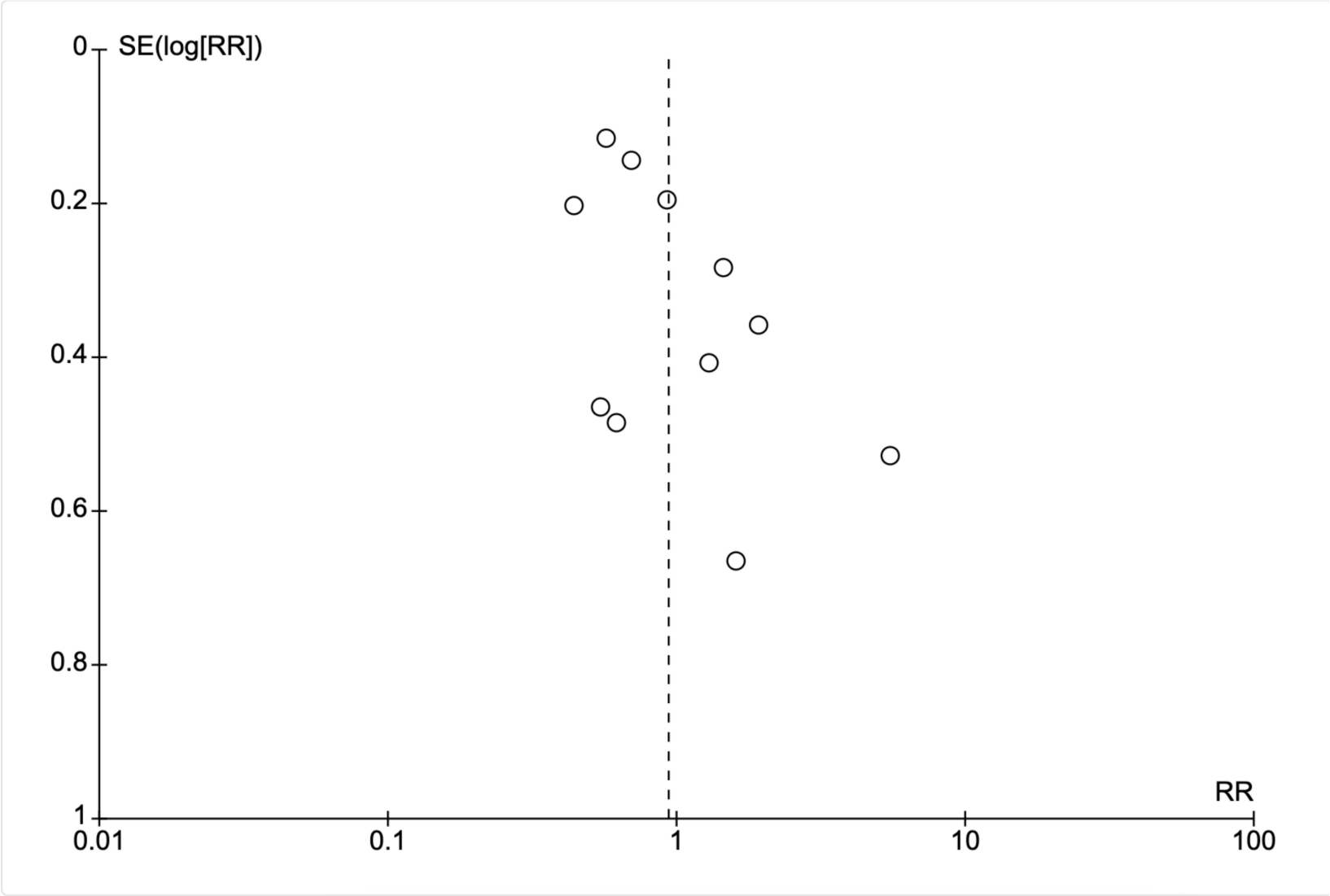
Supplementary Figure 1. A. Risk of bias summary: Review authors' judgments about each risk of bias item for each included study; B. Risk of bias graph: Review authors' judgments about each risk of bias item presented as percentages across all included studies



Supplementary Figure 2. Funnel plot for the studies that included the proportion of study subjects with permanent discontinuation of the study drug in tirzepatide 15 mg vs. placebo groups.



Supplementary Table 1 The basic and baseline characteristics of the included randomized controlled trials and participants

Registration no., Phase, Place of the Trial	Trial ID (name), Authors (publication year) of included studies	Major characteristics of the study subjects	Study arms	N	Age (y), mean (SD)	Female (%)	Duration
NCT03131687, Phase 2, Multicenter in Poland, Puerto Rico, Slovakia, and USA	Frias 2018, Frias et al. (2018) [16]	Adults with T2D on diet and exercise (± metformin), HbA1c 7–10.5%, BMI 23–50 kg/m^2	Tirzepatide 1 mg	52	57.4 (8.9)	44	26 weeks
			Tirzepatide 5 mg	55	57.9 (8.2)	38	
			Tirzepatide 10 mg	51	56.5 (9.9)	41	
			Tirzepatide 15 mg	53	56.0 (7.6)	59	
			Placebo	51	56.6 (8.9)	56	
			Dulaglutide 1.5 mg	54	58.7 (7.8)	43	
NCT03311724, Phase 2, Multicenter in USA	Frias 2020, Frias et al. (2020) [17]	Adults with T2D on diet and exercise (± metformin), HbA1c 7–10.5%, BMI 23–45 kg/m^2	Tirzepatide 12 mg*	29	61.2 (7.56)	48.3	12 weeks
			Tirzepatide 15 mg-1†	28	55.5 (8.54)	42.9	
			Tirzepatide 15 mg-2†	28	56.6 (9.21)	17.9	
			Placebo	26	56.0 (10.13)	53.8	

NCT03951753, Phase 1, Two centers in Germany	Heise 2022, Heise et al. (2022) [18]	Adults, aged 20–74 years, with T2D inadequately controlled with lifestyle advice and metformin exercise (± one OHA), HbA1c 7.0–9.5%, BMI 25–45 kg/m²	Tirzepatide 15 mg	45	61.1 (7.1)	31	28 weeks
			Semaglutide 1 mg	44	63.7 (5.9)	23	
			Placebo	28	60.4 (7.6)	25	
NCT04184622, Phase 3, Multicenter in multiple countries	SURMOUNT-1, Jastreboff et al. (2022) [19]	Adults with BMI ≥30, or ≥27 kg/m² and at least one weight-related complication, excluding diabetes	Tirzepatide 5 mg	630	45.6 (12.7)	67.6	72 weeks
			Tirzepatide 10 mg	636	44.7 (12.4)	67.1	
			Tirzepatide 15 mg	630	44.9 (12.3)	67.5	
			Placebo	642	44.4 (12.5)	67.8	
NCT04657003, Phase 3, Multicenter in multiple countries	SURMOUNT-2, Garvey et al. (2023) [20]	Adults with T2D, BMI ≥27 kg/m², HbA1c 7–10%	Tirzepatide 10 mg	312	54.3 (10.7)	51	72 weeks
			Tirzepatide 15 mg	311	53.6 (10.6)	51	
			Placebo	315	54.7 (10.5)	50	
NCT04657016, Phase 3, Multicenter in USA,	SURMOUNT-3, Wadden et al. (2023) [21]	Adults with BMI ≥30, or ≥27 kg/m² and at least one weight-related complication, excluding diabetes	Tirzepatide MTD (10 or 15 mg) ‡	287	45.4 (12.6)	63.1	72 weeks
			Placebo	292	45.7 (11.8)	62.7	

Argentina and Brazil							
NCT05024032, Phase 3, Multicenter in China	SURMOUNT-CN, Zhao et al. (2024) [22]	Adults with BMI ≥28, or ≥24 kg/m^2 and at least one weight-related comorbidity, excluding diabetes	Tirzepatide 10 mg	70	34.7 (7.2)	50	52 weeks
			Tirzepatide 15 mg	71	35.8 (9.3)	49.3	
			Placebo	69	37.8 (10.2)	47.8	
NCT05412004, Phase 3, Multicenter in multiple countries	SURMOUNT-OSA, Malhotra et al. (2024) [23]	Adults with moderate-to-severe obstructive sleep apnea and obesity (BMI ≥30 kg/m^2), excluding diabetes	Trial 1§:				52 weeks
			Tirzepatide MTD‡	114	47.3 (11.0)	31.6	
			Placebo	120	48.4 (11.9)	34.2	
			Trial 2§:				
			Tirzepatide MTD‡	120	50.8 (10.7)	27.5	
			Placebo	115	52.7 (11.3)	27.8	
NCT03954834, Phase 3, Multicenter in India, Japan, Mexico, and USA	SURPASS-1, Rosenstock et al. (2021) [24]	Adults with T2D inadequately controlled with diet and exercise alone and who were naive to injectable diabetes therapy, HbA1c 7–9.5%, BMI ≥23 kg/m^2	Tirzepatide 5 mg	121	54.1 (11.9)	54	40 weeks
			Tirzepatide 10 mg	121	55.8 (10.4)	40	
			Tirzepatide 15 mg	121	52.9 (12.3)	48	
			Placebo	115	53.6 (12.8)	51	

NCT03987919, Phase 3, Multicenter in multiple countries	SURPASS-2, Frías et al. (2021) [25]	Adults with T2D inadequately controlled with metformin, HbA1c 7–10.5%, BMI ≥25 kg/m^2	Tirzepatide 5 mg	470	56.3 (10.0)	56.4	40 weeks
			Tirzepatide 10 mg	469	57.2 (10.5)	49.3	
			Tirzepatide 15 mg	470	55.9 (10.4)	54.5	
			Semaglutide	469	56.9 (10.8)	52.0	
NCT03882970, Phase 3, Multicenter in multiple countries	SURPASS-3, Ludvik et al. (2021) [26]	Adults with T2D treated with any combination of metformin, SU, or SGLT2i, HbA1c 7–10.5%, BMI ≥25 kg/m^2	Tirzepatide 5 mg	358	57.2 (10.1)	44	52 weeks
			Tirzepatide 10 mg	360	57.4 (9.7)	46	
			Tirzepatide 15 mg	359	57.5 (10.2)	46	
			Insulin degludec	360	57.5 (10.1)	41	
NCT03730662, Phase 3, Multicenter in multiple countries	SURPASS-4, Del Prato et al. (2021) [27]	Adults with T2D inadequately controlled with metformin ± an SGLT2i, HbA1c 7–10.5%, BMI ≥25 kg/m^2	Tirzepatide 5 mg	329	62.9 (8.6)	40	52 weeks
			Tirzepatide 10 mg	328	63.7 (8.7)	36	
			Tirzepatide 15 mg	338	63.7 (8.6)	40	
			Insulin glargine	1000	63.8 (8.5)	36	
NCT04039503, Phase 3,	SURPASS-5, Dahl et al. (2022) [28]	Adults with T2D receiving stable doses of once daily insulin glargine ± metformin,	Tirzepatide 5 mg	116	62 (10)	47	40 weeks
			Tirzepatide 10 mg	119	60 (10)	39	
			Tirzepatide 15 mg	120	61 (10)	46	
			Placebo	120	60 (10)	45	

Multicenter in multiple countries		HbA1c 7–10.5%, BMI ≥23 kg/m^2					
NCT04537923, Phase 3b, Multicenter in multiple countries	SURPASS-6, Rosenstock et al. (2023) [29]	Adults with T2D inadequately controlled with basal insulin ± up to two OADs, HbA1c 7.5–11%, BMI 23–45 kg/m^2	Tirzepatide 5 mg	243	58.0 (10.2)	56.4	52 weeks
			Tirzepatide 10 mg	238	59.6 (9.4)	62.6	
			Tirzepatide 15 mg	236	58.2 (9.6)	59.3	
			Insulin lispro	708	59.0 (9.7)	55.9	
NCT04093752, Phase 3, Multicenter in China, South Korea, Australia and India	SURPASS-AP-Combo, Gao et al. (2023) [30]	Adults with T2D inadequately controlled with metformin ± SU, HbA1c 7.5–11%, BMI ≥23 kg/m^2	Tirzepatide 5 mg	230	53.1 (11.2)	41.7	40 weeks
			Tirzepatide 10 mg	228	53.5 (11.1)	44.7	
			Tirzepatide 15 mg	229	54.3 (11.6)	43.7	
			Insulin glargine	220	55.6 (11.4)	46.4	
NCT03861052, NCT04093752, Phase 3,	SURPASS J-mono, Inagaki et al. (2022) [31]	Age ≥20 years with T2D on diet and exercise or discontinued OAD	Tirzepatide 5 mg	159	56.8 (10.1)	29	52 weeks
			Tirzepatide 10 mg	158	56.2 (10.3)	25	
			Tirzepatide 15 mg	160	56.0 (10.7)	18	

Multicenter in Japan		monotherapy, HbA1c 7–10%, BMI ≥23 kg/m^2	Dulaglutide 0.75 mg	159	57.5 (10.2)	26	
NCT04166773, Phase 2, Multicenter in multiple countries	SYNERGY-NASH, Loomba et al. (2024) [32]	Adults with biopsy-confirmed MASH and stage F2 or F3 fibrosis, with or without T2D, BMI 27–50 kg/m^2	Tirzepatide 5 mg	47	55.0 (11.6)	57	52 weeks
			Tirzepatide 10 mg	47	54.3 (12.1)	55	
			Tirzepatide 15 mg	48	54.9 (10.0)	60	
			Placebo	48	53.5 (11.6)	56	

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; BMI, Body mass index; HbA1c, Glycated hemoglobin, MASLD, Metabolic dysfunction-associated steatotic liver disease; MASH, Metabolic dysfunction–associated steatohepatitis; MTD, Maximum tolerated dose; NAFLD, Nonalcoholic fatty liver disease; OHA, Oral anti-diabetic drugs; SD, Standard deviation; SE, Standard error; SGLT2i, Sodium-glucose cotransporter-2 inhibitors; SU, Sulphonylureas, T2D, Type 2 diabetes

*Analyzed in the subgroup Tirzepatide 10 mg

†Outcome results were polled to analyze in a single subgroup of Tirzepatide 15 mg

‡Tirzepatide MTD was analyzed as Tirzepatide 15 mg

§Outcome results of Tirzepatide MTD and placebo groups in Trials 1 and 2 were pooled into single groups of Tirzepatide MTD and placebo.

Supplementary Table 2 The basic characteristics of the excluded randomized controlled trials and participants

Trial reg. no.	Authors (publication year)	Reason of exclusion
NCT03882970	Battelino et al. (2022) [33]	Substudy of the SURPASS-3 trial
NCT03882970	Cariou et al. (2023) [34]	Substudy of the SURPASS-3 trial
NCT03882970	Gastaldelli et al. (2022) [35]	Substudy of the SURPASS-3 trial
NCT03730662	Heerspink et al. (2022) [36]	Post hoc analysis of SURPASS-4 trial
NCT03131687	Hartman et al. (2018) [37]	Post hoc analysis of included study by Frias et al. (2018)
NCT03131687	Pirro et al. (2022) [38]	Post hoc analysis of included study by Frias et al. (2018)
NCT03131687	Thomas et al. (2021) [39]	Post hoc analysis of included study by Frias et al. (2018)
NCT03131687	Wilson et al. (2020) [40]	Post hoc analysis of included study by Frias et al. (2018)
NCT03131687	Wilson et al. (2022) [41]	Post hoc analysis of included study by Frias et al. (2018)
NCT04235959	Feng et al. (2023) [42]	Not reported the outcome(s) of interest
NCT03322631	Furihata et al. (2021) [43]	Not reported the outcome(s) of interest
NCT03861039	Kadowaki et a. (2022) [44]	Not reported the outcome(s) of interest
NCT04143802	Urva et al. (2022) [45]	Not reported the outcome(s) of interest

Supplementary Table S3. Summary of Findings Table

Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**No. of participants (studies)**	**Certainty of the evidence (GRADE)**
	Risk with Placebo	**Risk with Tirzepatide**			
Permanent discontinuation from study treatment - Tirzepatide 05 mg	42 per 1,000	**31 per 1,000** (20 to 49)	**RR 0.74** (0.47 to 1.17)	1946 (5 RCTs)	⊕⊕⊕◯ Moderate[a]
Permanent discontinuation from study treatment - Tirzepatide 10 mg	34 per 1,000	**23 per 1,000** (17 to 32)	**RR 0.69** (0.51 to 0.93)	2773 (8 RCTs)	⊕⊕⊕⊕ High
Permanent discontinuation from study treatment - Tirzepatide 15 mg	60 per 1,000	**56 per 1,000** (41 to 78)	**RR 0.94** (0.68 to 1.31)	3918 (11 RCTs)	⊕⊕◯◯ Low[b]
	Risk with Insulin	**Risk with Tirzepatide**			
Permanent discontinuation from study treatment - Tirzepatide 05 mg	124 per 1,000	**119 per 1,000** (93 to 153)	**RR 0.96** (0.75 to 1.24)	3466 (4 RCTs)	⊕⊕⊕⊕ High
Permanent discontinuation from study treatment - Tirzepatide 10 mg	124 per 1,000	**147 per 1,000** (95 to 225)	**RR 1.19** (0.77 to 1.82)	3462 (4 RCTs)	⊕⊕◯◯ Low[b]
Permanent discontinuation from study treatment - Tirzepatide 15 mg	124 per 1,000	**162 per 1,000** (127 to 206)	**RR 1.31** (1.03 to 1.67)	3468 (4 RCTs)	⊕⊕⊕⊕ High

	Risk with GLP-1RA	Risk with Tirzepatide			
Permanent discontinuation from study treatment - Tirzepatide 05 mg	92 per 1,000	**91 per 1,000** (65 to 127)	**RR 0.98** (0.70 to 1.37)	1367 (3 RCTs)	⊕⊕⊕⊕ High
Permanent discontinuation from study treatment - Tirzepatide 10 mg	92 per 1,000	**129 per 1,000** (95 to 176)	**RR 1.40** (1.03 to 1.90)	1361 (3 RCTs)	⊕⊕⊕⊕ High
Permanent discontinuation from study treatment - Tirzepatide 15 mg	88 per 1,000	**150 per 1,000** (112 to 200)	**RR 1.70** (1.27 to 2.27)	1437 (4 RCTs)	⊕⊕⊕⊕ High

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations

a. Moderate heterogeneity among the studies present.

b. High heterogeneity among the studies present.