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Liraglutide for adults living with obesity

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Abstract

Rationale

Obesity is a complex chronic condition linked to various comorbidities, such as hypertension, diabetes, and dyslipidaemia, with a significant global burden. Standard treatments, such as diet modifications and physical activity, often have limited effects and poor compliance. Pharmacological options, including glucagon-like peptide-1 receptor agonists (GLP-1RAs), show promise for individuals with obesity. This is one of three reviews investigating GLP-1RAs for adults living with obesity.

Objectives

To assess the effects of liraglutide, a GLP-1RA, for adults living with obesity.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS, and two trials registries on 17 December 2024.

Eligibility criteria

We included randomised controlled trials (RCTs) that compared liraglutide at any dose with placebo or no treatment, structured lifestyle-modification programmes, other anti-obesity medications, or other GLP-1RAs, in adults with obesity, with a minimum follow-up of six months.

Outcomes

Critical outcomes were body weight, adverse events, major adverse cardiovascular events (MACE), quality of life, and mortality. Important outcomes were waist circumference, heart failure, diabetes-related outcomes, blood pressure-related outcomes, liver disease-related outcomes, obstructive sleep apnoea, and lipid metabolism-related outcomes. We prioritised critical outcomes for the main comparison of interest, liraglutide versus placebo, for the Abstract and key summary of findings tables.

Risk of bias

We used the original Cochrane tool for assessing risk of bias (RoB 1).

Synthesis methods

We synthesised results for each outcome using meta-analysis, where possible, with a random-effects model. We assessed the certainty of evidence for each outcome using GRADE.

Included studies

We included 24 RCTs involving 9937 participants, aged 31.3 to 64.7 years, primarily from middle- and high-income countries. Most studies compared liraglutide to placebo, alone or within multi-arm designs (two studies included semaglutide as an active comparator, one included orlistat); two studies compared liraglutide versus structured lifestyle-modification programmes. Studies included participants with weight-related comorbidities; 17 focused on specific subgroups, including people with diabetes, non-alcoholic fatty liver disease, polycystic ovary syndrome, and obstructive sleep apnoea. All studies had medium-term follow-ups, and three also provided data at long-term follow-up. Twenty-two studies were funded by the drug manufacturer, with major involvement in design, conduct, analysis, or reporting in 13 studies.

Synthesis of results

Liraglutide versus placebo (medium-term: 26 to 68 weeks)

The evidence is very uncertain about the effect of liraglutide on percentage weight change from baseline (mean difference (MD) −4.72, 95% confidence interval (CI) −5.32 to −4.12; I^2 = 57%; 16 studies, 6050 participants; very low-certainty evidence), but likely increases the number of people achieving 5% weight reduction (risk ratio (RR) 2.10, 95% CI 1.80 to 2.45; I^2 = 78%; 18 studies, 6651 participants; moderate-certainty evidence).

Liraglutide may increase any adverse events (RR 1.07, 95% CI 1.04 to 1.11; I^2 = 28%; 16 studies, 8147 participants; low-certainty evidence) and serious adverse events (RR 1.20, 95% CI 1.00 to 1.43; I^2 = 0%; 20 studies, 8487 participants; low-certainty evidence). The evidence is very uncertain about the effects of liraglutide on non-serious adverse events (RR 1.14, 95% CI 1.05 to 1.24; I^2 = 76%; 17 studies, 7440 participants; very low-certainty evidence) and on adverse events leading to withdrawal (RR 1.98, 95% CI 1.30 to 3.02; I^2 = 47%; 19 studies, 8628 participants; very low-certainty evidence).

Liraglutide likely results in little to no clinically meaningful difference in MACE (RR 0.86, 95% CI 0.66 to 1.10; I^2 = 0%; 6 studies, 5762 participants; moderate-certainty evidence).

Liraglutide likely results in little to no difference in quality of life measured by the IWQOL-Lite-CT physical function (MD 2.90, 95% CI -0.08 to 5.89; I^2 = 58%; 6 studies, 3733 participants; moderate-certainty evidence).

The evidence is very uncertain about the effect of liraglutide on mortality (RR 0.44, 95% CI 0.08 to 2.25; I^2 = 0%; 18 studies, 8224 participants; very low-certainty evidence).

Liraglutide versus placebo (long-term: 104 to 162 weeks)

Liraglutide may result in little to no clinically meaningful difference in percentage weight change from baseline (MD −4.34, 95% CI −5.26 to −3.43; I^2 = 0%; 2 studies, 1262 participants; low-certainty evidence), and likely increases the number of participants achieving 5% weight reduction (RR 1.78, 95% CI 1.51 to 2.09; I^2 = 0%; 2 studies, 1262 participants; moderate-certainty evidence).

The evidence is very uncertain about the effect of liraglutide on any adverse events (RR 1.19, 95% CI 0.93 to 1.52; I^2 = 93%; 2 studies, 2640 participants; very low-certainty evidence) and on non-serious adverse events (RR 1.19, 95% CI 0.94 to 1.51; I^2 = 93%; 2 studies, 2640 participants; very low-certainty evidence). Liraglutide may increase serious adverse events (RR 1.20, 95% CI 0.98 to 1.48; I^2 = 0%; 2 studies, 2640 participants; low-certainty evidence) and adverse events leading to withdrawal (RR 2.16, 95% CI 1.59 to 2.93; I^2 = 0%; 2 studies, 2640 participants; low-certainty evidence).

The evidence is very uncertain about the effect of liraglutide on MACE (RR 0.83, 95% CI 0.20 to 3.46; I^2 not applicable; 1 study, 2248 participants; very low-certainty evidence).

Liraglutide likely results in little to no clinically meaningful difference in quality of life measured by the IWQoL-Lite-CT physical function (MD 3.81, 95% CI 1.03 to 6.59; I^2 not applicable; 1 study, 863 participants; moderate-certainty evidence).

The evidence is very uncertain about the effect of liraglutide on mortality (RR 0.81, 95% CI 0.16 to 4.17; I^2 = 0%; 2 studies, 2640 participants; very low-certainty evidence).

Authors' conclusions

Liraglutide likely increases the proportion of people achieving at least 5% weight loss at medium-term follow-up; this effect is likely to be sustained at longer-term follow-up. Medium- or long-term impact on percentage weight change, MACE, quality of life, and mortality may be limited or uncertain. Liraglutide may lead to an increase in adverse events, including serious adverse events in both the medium and long term, which might further limit the sustainability of the initial effects.

The drug manufacturer funded 22 studies, raising concerns about potential conflicts of interest. Further independent and long-term studies are needed to better understand the broader effects of liraglutide in the management of obesity.

Funding

World Health Organization (WHO)

Registration

Original protocol (2022): DOI 10.1002/14651858.CD015092

Updated protocol (2025): PROSPERO CRD420250654193

Plain language summary

Is liraglutide an effective weight-loss treatment for adults living with obesity and does it cause unwanted effects?

Key messages

- Liraglutide compared with placebo (a sham medication) likely increases the number of people who lose at least 5% of their body weight, but its impact on unwanted effects, quality of life, and major cardiovascular events appears small or uncertain over both the medium term (6 to 24 months) and long term (more than 24 months).
- Our confidence in the evidence is limited due to how the studies were done and missing information. The manufacturers of liraglutide were involved in 22 of the 24 included studies, which raises concerns about the reliability of the results.
- Future studies should look at long-term results in diverse types of people and be independent of liraglutide manufacturers.

What is obesity?

Obesity is a long-term condition in which a person has too much body fat. It can increase the risk of health problems like type 2 diabetes, diseases of the heart and blood vessels (cardiovascular disease), and some types of cancer. Obesity levels are increasing worldwide, placing a significant burden on healthcare systems. Managing obesity usually involves lifestyle changes such as eating a healthier diet and being more physically active. However, many people find these changes difficult to maintain, and doctors may prescribe medications to support weight loss.

What is liraglutide?

Liraglutide is a type of medication that helps people feel full sooner, and so eat less. It was originally developed to treat type 2 diabetes but has been approved in many countries to help people lose weight. It is given as a daily injection. Some people taking liraglutide experience unwanted effects, such as feeling or being sick, diarrhoea and constipation. Liraglutide is a 'GLP-1 receptor agonist' (GLP-1RA). Similar medications include semaglutide and tirzepatide.

What did we want to find out?

We wanted to know how well liraglutide works in adults with obesity in the medium term (6 to 24 months) and long term (24 months or more). We examined its effects on weight, unwanted effects, obesity-related health problems, quality of life and risk of death. We did not look at what happens after people stop taking tirzepatide.

What did we do?

We searched for studies that investigated liraglutide for adults living with obesity. Studies could investigate any dose of liraglutide compared with placebo (sham medication), no treatment, lifestyle changes or another weight-loss medication. We included studies in which people took liraglutide for at least 6 months. We compared and analysed the results and assessed our confidence in the evidence.

What did we find?

We found 24 studies with 9937 men and women with obesity, aged between 31 and 64 years. Some people had weight-related conditions like diabetes or liver disease. Most studies compared liraglutide with placebo. They mainly took place in high- and middle-income countries.

Liraglutide compared to placebo

- **Weight loss:** people who took liraglutide were more likely to lose at least 5% of their body weight than those who took a placebo in the medium (18 studies, 6651 people) and long term (2 studies, 1262 people). However, we are uncertain about liraglutide's effects on people's overall percentage weight change from the beginning of the study to the medium term (16 studies, 6050 people) and there may be little to no difference in percentage weight change in the long term (2 studies, 1262 people).
- **Unwanted effects:** in the medium term, people taking liraglutide might experience more unwanted effects of any kind (16 studies, 8147 people) and more serious unwanted effects (20 studies, 8487 people) than those taking placebo. We are unsure about mild-to-moderate unwanted effects (17 studies, 7440 people) or whether unwanted effects caused people to stop treatment (19 studies, 8628 people). In the long term (2 studies, 2640 participants), liraglutide may increase unwanted effects and people may be more likely to stop treatment because of them. We are unsure about unwanted events overall and mild-to-moderate unwanted effects.
- **Quality of life**: liraglutide probably makes little or no difference to quality of life both in the medium term (6 studies, 3733 people) and in the long term (1 study, 863 people)
- **Other results:** liraglutide probably makes little or no difference to major cardiovascular events in the medium term (6 studies, 5762 people). We are unsure about its effects on major cardiovascular events in the long term and on deaths in the medium and long term.

What are the limitations of the evidence?

We are moderately confident that people taking liraglutide lose more weight than those taking placebo. However, our confidence in the other evidence is limited because of how the studies were conducted and information that was missing. Few studies looked at long-term effects or included different people from different places, so the results may not apply to everyone. The manufacturers of liraglutide were involved in the design, conduct or analysis of 22 of the 24 studies, which limits our confidence in the results. More independent studies are needed.

How up to date is this evidence?

The evidence is up to date to December 2024.

Summary of findings

Summary of findings 1

Liraglutide compared to placebo for adults living with obesity (medium-term follow-up)

Patient or population: adults living with obesity

Setting: outpatient; studies conducted in North America, Europe, Asia, Oceania, and Latin America

Intervention: liraglutide

Comparison: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with liraglutide				
Weight Follow-up: 26 to 68 weeks	% weight change	The mean % weight change was –**2.2 2%**	MD **4.72 lower** (5.32 lower to 4.12 lower)	-	6050 (16 RCTs)	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of liraglutide on % weight change in the medium term.
	People achieving a 5% weight reduction	303 per 1000	**636 per 1000** (545 to 742)	**RR 2.10** (1.80 to 2.45)	6651 (18 RCTs)	⨁⨁⨁◯ Moderate[a,d]	Liraglutide likely increases the number of people achieving a 5% weight reduction in the medium term.
Adverse events Follow-up: 26 to 68 weeks	Any	816 per 1000	**873 per 1000** (849 to 906)	**RR 1.07** (1.04 to 1.11)	8147 (16 RCTs)	⨁⨁◯◯ Low[a,c]	Liraglutide may increase any adverse events in the medium term.
	Non-serious	751 per 1000	**856 per 1000** (788 to 931)	**RR 1.14** (1.05 to 1.24)	7440 (17 RCTs)	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of liraglutide on non-serious adverse events in the medium term.
	Serious	50 per 1000	**61 per 1000** (50 to 72)	**RR 1.20** (1.00 to 1.43)	8487 (20 RCTs)	⨁⨁◯◯ Low[a,c]	Liraglutide may increase serious adverse events in the medium term.
	Leading to withdrawal	41 per 1000	**80 per 1000** (53 to 123)	**RR 1.98** (1.30 to 3.02)	8628 (19 RCTs)	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of liraglutide on adverse events leading to withdrawal in the medium term.
Major adverse cardiovascular events (MACE) Follow-up: 26 to 58 weeks		14 per 1000	**12 per 1000** (9 to 16)	**RR 0.86** (0.66 to 1.10)	5762 (6 RCTs)	⨁⨁⨁◯ Moderate[a]	Liraglutide likely results in little to no clinically meaningful difference in MACE in the medium term.[e]
Quality of life Follow-up: 52 to 56 weeks	IWQoL-Lite-CT physical function Ranges from 0 to 100 points Higher is better	The mean quality of life: IWQoL-Lite-CT physical function was **10.7 points**	MD **2.9 higher** (0.08 lower to 5.89 higher)	-	3733 (6 RCTs)	⨁⨁⨁◯ Moderate[a,d]	Liraglutide likely results in little to no clinically meaningful difference in quality of life (IWQoL-Lite-CT physical function) in the medium term.[f]
Mortality Follow-up: 26 to 68 weeks		1 per 1000	**0 per 1000** (0 to 2)	**RR 0.44** (0.08 to 2.25)	8224 (19 RCTs)	⨁◯◯◯ Very low[a,g]	The evidence is very uncertain about the effect of liraglutide on mortality in the medium term.

*__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; **MACE:** Major adverse cardiovascular events; **MD:** mean difference; **RCT:** randomised controlled trial; **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.

[a]Downgraded one level due to risk of bias as most of the studies had an unclear (5% to 10% attritions or moderate discontinuations (10% to 20%) but balanced) or high risk of bias (10% to 20% unbalanced attritions or discontinuation rates > 20%) due to attrition.

[b]Downgraded one level due to inconsistency because, in addition to I^2 statistic being > 50%, the point estimates of individual studies were distributed on different sides of the minimally important difference threshold.

[c]Downgraded one level due to imprecision as the 95% CI crossed the minimally important difference threshold.

[d]Following a minimally contextualised approach, we did not downgrade due to inconsistency even though I^2 statistic is > 50%, as the point estimates and confidence intervals were consistently not crossing the minimally important difference threshold.

[e]RR 0.86, meaning that with liraglutide there is a 14% lower risk of having a major adverse cardiovascular event compared to placebo. Given the baseline risk of the placebo group (1.4%), this corresponds to an absolute risk of 1.2% in the liraglutide group (absolute risk difference = 0.2%), which is well below our minimally important threshold of 5% absolute risk difference. Even in populations with a higher baseline risk, the absolute difference would remain far from the clinically significant threshold.

[f]Analyses of other QoL scales/measures are presented in Supplementary material 11.

[g]Downgraded two levels due to imprecision as the number of events did not meet the optimal information size.

Summary of findings 2

Liraglutide compared to placebo for adults living with obesity (long-term follow-up)

Patient or population: adults living with obesity

Setting: outpatient; studies conducted in North America, Europe, Asia, Oceania, Latin America, and Africa

Intervention: liraglutide

Comparison: placebo

Outcomes	Outcome measure	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with liraglutide				
Weight Follow-up: 104 to 160 weeks	% weight change from baseline	The mean % weight change from baseline was –**1.95%**	MD **4.34 lower** (5.26 lower to 3.43 lower)	-	1262 (2 RCTs)	⨁⨁◯◯ Low[a,b]	Liraglutide may result in little to no clinically meaningful difference in % weight change in the long term.[c]
	People achieving a 5% weight reduction	311 per 1000	**553 per 1000** (469 to 649)	**RR 1.78** (1.51 to 2.09)	1262 (2 RCTs)	⨁⨁⨁◯ Moderate[a]	Liraglutide likely increases the number of people achieving a 5% weight reduction in the long term.
Adverse events Follow-up: 104 to 162 weeks	Any	861 per 1000	**1000 per 1000** (801 to 1000)	**RR 1.19** (0.93 to 1.52)	2640 (2 RCTs)	⨁◯◯◯ Very low[a,d,e]	The evidence is very uncertain about the effect of liraglutide on any adverse events in the long term.
	Non-serious	856 per 1000	**1000 per 1000** (804 to 1000)	**RR 1.19** (0.94 to 1.51)	2640 (2 RCTs)	⨁◯◯◯ Very low[a,d,e]	The evidence is very uncertain about the effect of liraglutide on non-serious adverse events in the long term.
	Serious	127 per 1000	**153 per 1000** (125 to 189)	**RR 1.20** (0.98 to 1.48)	2640 (2 RCTs)	⨁⨁◯◯ Low[a,b]	Liraglutide may increase serious adverse events in the long term.
	Leading to withdrawal	52 per 1000	**113 per 1000** (83 to 153)	**RR 2.16** (1.59 to 2.93)	2640 (2 RCTs)	⨁⨁◯◯ Low[a,b]	Liraglutide may increase adverse events leading to withdrawal in the long term.

Major adverse cardiovascular events (MACE) Follow-up: 162 weeks		4 per 1000	**3 per 1000** (1 to 14)	**RR 0.83** (0.20 to 3.46)	2248 (1 RCT)	⨁◯◯◯ Very low[a,f]	The evidence is very uncertain about the effect of liraglutide on MACE in the long term.
Quality of life Follow-up: 160 weeks	IWQoL-Lite-CT physical function	The mean quality of life: IWQoL-Lite-CT physical function was **10.94 points**	MD **3.81 higher** (1.03 higher to 6.59 higher)	-	863 (1 RCT)	⨁⨁⨁◯ Moderate[a]	Liraglutide likely results in little to no clinically meaningful effect in quality of life as measured by the IWQoL-Lite-CT physical function score in the long term.[g]
Mortality Follow-up: 104 to 162 weeks		2 per 1000	**2 per 1000** (0 to 9)	**RR 0.81** (0.16 to 4.17)	2640 (2 RCTs)	⨁◯◯◯ Very low[a,f]	The evidence is very uncertain about the effect of liraglutide on mortality in the long term.

*__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; **MD:** mean difference; **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.

[a]Downgraded one level due to risk of bias as most of the studies had an unclear (5 to 10% attritions or moderate discontinuations (10 to 20%) but balanced) or high risk of bias (10 to 20% unbalanced attritions or discontinuation rates >20%) due to attrition.

[b]Downgraded one level due to imprecision as the 95% CI crossed the minimally important difference threshold.

[c]The MD = −4.34 indicates that, on average, participants treated with liraglutide experienced an additional 4.34% reduction in body weight compared to placebo. Since the mean percentage weight change in the placebo group was −1.95%, this corresponds to an average percentage weight change of −6.29% with liraglutide. Although this represents a greater reduction than in controls, the incremental benefit of liraglutide remains below our minimally important threshold (an additional reduction in body weight of 5%).

[d]Following a minimally contextualised approach, we downgraded one level due to inconsistency because, in addition to I^2 being >90%, the point estimates of individual studies were distributed in different sides of the minimally important difference threshold.

[e]Downgraded two levels due to imprecision as the confidence interval crosses the minimally important difference for both benefit and harm.

[f]Downgraded two levels due to imprecision as the number of events does not meet the optimal information size.

[g]Analyses of other QoL measures/scales are illustrated in Supplementary material 12.

Background

Description of the condition

Since 1975, the global prevalence of obesity has surged, with rates tripling over the past decades. In 2016, it was reported that 39% of adults worldwide were overweight and 13% were living with obesity [1]. Forecasts predict that by 2050, nearly 45% of the global population will be overweight and 16% will be living with obesity [1, 2]. Additionally, overweight and obesity contributed to approximately five million deaths, representing 12% of all non-communicable disease deaths globally [3]; and 160 million disability-adjusted life years in 2019, reflecting the global health burden [4].

Obesity is a chronic and complex health condition that arises from a significant accumulation of fat tissue, impairing the structure and function of the body [5]. Yet its multifactorial aetiology is not limited only to a simple imbalance between metabolism and energy expenditure and food intake, as it also involves environmental factors as well as the genetic composition of each individual [6], and can be influenced by clinical, socioeconomic, and behavioural factors [7, 8]. This condition is associated with significant metabolic, biomechanical, and psychosocial consequences, increasing the risk of hypertension, type 2 diabetes mellitus, stroke, dyslipidaemia, obstructive sleep apnoea, and cancer [1, 9]. Furthermore, among individuals who already have these illnesses, obesity intensifies the overall cardiovascular risk [1, 9]. Besides its traditional metabolic impact, waist circumference has emerged as a critical clinical measure, being a surrogate for visceral adiposity and an independent predictor of metabolic syndrome and cardiovascular disease risk, beyond body mass index (BMI) alone [10, 11].

Although being overweight also carries health risks, the severity and frequency of complications are generally lower compared to those associated with obesity. Given the chronic nature of obesity and the well-established benefits of its management, early and effective intervention remains a critical health priority.

The economic implications of obesity are substantial, affecting not only individuals but also families and national economies [12]. Obesity also deepens social and economic inequalities worldwide, with projected costs reaching USD (US dollars) 3 trillion annually by 2030 and consuming up to 18% of national health budgets in countries with high obesity prevalence [3]. Healthcare expenditure per capita for individuals with obesity is estimated to be between 42% and 150% higher compared to those without obesity [13, 14]. Additionally, obesity imposes indirect costs, including loss of productivity, increased absenteeism, disability, and premature mortality, all contributing to significant economic losses [12].

Description of the intervention and how it might work

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted primarily by intestinal L-cells in response to nutrient intake, which plays a central role in glucose regulation by enhancing glucose-dependent insulin secretion, inhibiting glucagon release, delaying gastric emptying, and promoting satiety [15]. Liraglutide is one of several GLP-1 receptor agonists (GLP-1RAs), which are pharmacological agents that replicate these physiological effects by activating the GLP-1 receptor, leading to improved glycaemic control and weight reduction [15]. Specifically, liraglutide has been modified with a fatty acid side chain to enable albumin binding, resulting in a 97% sequence homology to native GLP-1, and also extending its half-life to approximately 13 hours, allowing once-daily subcutaneous administration [15].

Several studies that primarily focused on glycaemic improvement reported a secondary benefit in terms of bodyweight reduction and cardiovascular benefits [16]. However, concerns regarding the safety and tolerability of GLP-1RAs have been reported. Gastrointestinal adverse events, including nausea, vomiting, diarrhoea, and constipation, are common, affecting 80% to 97% of users compared with 63% to 100% in placebo groups [15, 17]. Although most of these events are mild to moderate, adverse events leading to treatment discontinuation have been observed in up to 26% of patients [17]. Serious adverse events were rare but included gastrointestinal complications, biliary disorders, and psychiatric events [17]. The tolerability profile, particularly the high rate of gastrointestinal side effects and discontinuations, remains an important consideration in clinical practice and may impact the long-term adherence and effectiveness of GLP-1RA therapies [17]. Comparative analyses suggest that newer agents, such as semaglutide and tirzepatide, while highly effective, may present greater challenges in tolerability compared to liraglutide, especially at higher doses, which may further influence treatment adherence and patient selection [18].

The SCALE study evaluated the use of liraglutide 3.0 mg for inducing and maintaining weight loss and delaying the onset of type 2 diabetes mellitus, leading to its approval by the US Food and Drug Administration (FDA) in 2015 for adults with overweight or obesity without diabetes [19, 20]. Since then, the therapeutic landscape for people living with obesity has rapidly advanced. Comparative studies have shown that newer agents, such as semaglutide and the dual agonist tirzepatide, achieve significantly greater weight loss than liraglutide, and both have been approved by the FDA and the European Medicines Agency (EMA) for obesity management [17, 18]. However, persistent issues such as limited availability and high costs have restricted the widespread adoption of these newer therapies, particularly in low-resource settings, exacerbating existing inequities in obesity care [21]. Recognising these challenges, the FDA recently approved the first generic version of liraglutide, aiming to improve affordability and access amid global supply constraints [22].

Why it is important to do this review

Obesity is a chronic, relapsing condition that has reached pandemic proportions. The global burden of obesity contributes significantly to morbidity, mortality, and economic strain. Despite substantial efforts to address obesity, global rates continue to rise, underscoring the need for effective, integrated management strategies [23].

GLP-1RAs, including liraglutide, have emerged as promising pharmacological treatments for individuals living with obesity, showing clinically meaningful reductions in body weight and improvements in cardiometabolic risk factors. However, as highlighted by the World Health Organization (WHO), pharmacological interventions must be integrated into broader chronic disease management models that emphasise accessibility, affordability, and sustainability [23].

Existing systematic reviews have primarily evaluated GLP-1RAs in populations with type 2 diabetes mellitus or for glycaemic control [24, 25, 26], and those aiming to elucidate the effects of GLP-1RAs in the treatment of overweight and obesity are not comprehensive enough [17, 18, 27]. This systematic review on liraglutide is part of a wider suite of systematic reviews on GLP-1RAs for adults living with obesity, which aims to address this gap by providing evidence that supports clinical decision making and public health priorities, contributing to ongoing efforts led by the WHO to integrate pharmacological treatment into equitable, sustainable models of obesity care [23].

Objectives

To assess the effects of liraglutide, a GLP-1RA, for adults living with obesity.

Methods

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) [28], and the PRISMA 2020 guidelines for reporting [29].

Our protocol was initially published in 2022 [30]. We based parts of the Methods, as well as Supplementary material 1 of this Cochrane protocol, on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group. In 2024, we were commissioned by the WHO to conduct a series of reviews to support their guidelines on the use of GLP-1RAs and dual GLP-1/GIP agonists. Therefore, we had to apply the following modifications to our initial protocol to adequately inform the guidelines.

- We expanded our inclusion criteria to support multiple definitions of obesity based on different BMI thresholds or the combination of BMI and co-morbidities. People with co-morbid obesity and diabetes were retained in the reviews, but the reviews were limited to studies in which obesity was a primary inclusion criterion. We investigated only three GLP-1 analogues (liraglutide, semaglutide, and tirzepatide) at any route of administration - this review focused on liraglutide.
- We added structured lifestyle programmes as comparators and expanded the minimal duration of intervention and follow-up to at least six months.
- Based on the prioritisation of the WHO Guideline Panel Group, we defined primary outcomes as critical outcomes. We added:
    - changes in BMI (alongside other weight-related measures);
    - major adverse cardiovascular events (MACE; a composite of nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death); and
    - mortality.
- We defined secondary outcomes as important outcomes and added:
    - waist circumference;
    - heart failure;
    - diabetes-related outcomes (including fasting glycaemia, HbA1c, need for glucose-lowering therapy);
    - blood pressure-related outcomes (including need for antihypertensive, systolic blood pressure, diastolic blood pressure)
    - liver disease-related outcomes (including metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated steatohepatitis, cirrhosis);
    - obstructive sleep apnoea; and
    - lipid metabolism-related outcomes (including total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, need for lipid-lowering treatment).
- We incorporated equity considerations into subgroup analysis and the presence of co-morbidities.

We prospectively registered these modifications as a new protocol in PROSPERO on 24 February 2025 [31]. This common protocol includes tirzepatide, liraglutide, and semaglutide as interventions and comparators; however, this review investigated the effects of liraglutide only.

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that assessed the effects of GLP-1 analogues or GIP/GLP-1 dual agonists in adults with obesity. We included studies only if they reported outcomes based on the completion of the intended treatment period for efficacy analysis. We excluded studies that focused on outcomes following discontinuation or withdrawal of these agents.

We included studies reported as full text, those published as abstracts only, and unpublished data where it was possible to establish their eligibility for inclusion. There were no language restrictions.

We excluded cluster-RCTs, as they might have biased results due to identification or recruitment bias, and overestimation of the precision of the results. We also excluded cross-over trials because obesity can evolve over time, and the washout itself might induce a rebound effect in the second period of the study.

Types of participants

We included studies of adults aged 18 years or older living with obesity, as defined by each study. The definition of obesity used here is not made in reference to a specific BMI threshold, to ensure maximal inclusivity of all populations. People with co-morbid obesity and diabetes are retained in the review, but the review is limited to studies in which obesity is a primary inclusion criterion. We did not include studies that exclusively recruited participants with secondary causes of obesity. We also excluded the following participants.

- Pregnant women: due to expected variability in weight and BMI, and the safety profile of GLP1-RAs [32]
- Studies in which diabetes or a condition other than obesity was the primary inclusion criterion or aim of treatment, irrespective of obesity status
- Studies that included strategies with bariatric surgery

Types of interventions

Intervention

We considered liraglutide at any dosage and route of administration as an intervention.

Comparators

We considered studies that compared liraglutide with:

- placebo or no treatment;
- structured programmes that targeted lifestyle modification;
- any other pharmacological intervention for obesity;
- any other GLP-1RA or GLP-1 dual agonist for managing obesity.

Concomitant interventions had to be identical in both the intervention and comparator groups to establish fair comparisons. If a study included multiple arms, we included any arm that met the inclusion criteria for this review.

Minimum duration of intervention and follow-up

We considered interventions prescribed for at least six months after randomisation, regardless of the follow-up period.

Outcome measures

We did not exclude a study if it failed to report one or several of our critical or important outcome measures. We excluded studies only if none of the outcomes relevant to this review were measured, provided there was supporting evidence (e.g. contact with study authors, access to the original protocol, etc.). We classified outcomes as critical and important based on the guidance of the WHO international Guideline Developing Group.

Critical outcomes

- Weight
    - Percentage weight change from baseline
    - Change in kg
    - Change in BMI
    - People achieving a 5% weight reduction
    - People achieving a 10% reduction
- Adverse events
    - Mild to moderate

    - Serious adverse events
- Major adverse cardiovascular event (MACE): defined as a composite outcome including the occurrence of coronary artery disease, stroke, peripheral arterial disease, heart failure, or cardiovascular-related mortality, as reported by the study authors.
- Quality of life: evaluated by validated instruments such as EQ-5D [33], the World Health Organization-Five Well-Being Index (WHO-5) [34], the Short-Form Health Survey (SF-36) [35], or the 12-item Short-Form Health Survey (SF-12) [36].
- Mortality: defined as death from any cause.

Important outcomes

- Waist circumference (cm)
- Heart failure
- Diabetes-related outcomes
    - Fasting glycaemia
    - HbA1C
    - Need for glucose-lowering therapy
- Blood pressure-related outcomes
    - Need for antihypertensives
    - Systolic blood pressure
    - Diastolic blood pressure
- Liver disease-related outcomes
    - Metabolic dysfunction-associated steatotic liver disease
    - Metabolic dysfunction-associated steatohepatitis
    - Cirrhosis
- Obstructive sleep apnoea
- Lipid metabolism-related outcomes
    - Total cholesterol
    - High-density lipoprotein (HDL) cholesterol
    - Low-density lipoprotein (LDL) cholesterol
    - Triglycerides
    - Need for lipid-lowering treatment

Time frame of follow-up

We analysed outcome data as medium-term (6 to 24 months) and long-term (24 months or more) follow-up, as suggested by experts, as adequate thresholds for follow-up time points [37]. Whenever a study reported multiple assessments within our time frame, we analysed the outcome measurement at the time closest to the end of the time frame. We considered intermediate time points (e.g. 10 or 9 months) for critical outcomes to inform temporal trends or fluctuations within each time frame.

Search methods for identification of studies

Electronic searches

We searched the following sources from the inception of each database to the date of search, with no restrictions on the language of publication. Postpublication amendments and retractions were included in the comprehensive search:

- the Cochrane Central Register of Controlled Trials (CENTRAL; 2024, Issue 12) in the Cochrane Library (searched 17 December 2024);
- MEDLINE Ovid (MEDLINE ALL 1946 to 17 December 2024);
- Embase Ovid (1974 to 17 December 2024);
- LILACS (Latin American and Caribbean Health Science Information database; 1982 to 17 December 2024);
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch/).

We used the Cochrane Highly Sensitive Search Strategy for identifying RCTs in Embase (2023 revision; Ovid format) and the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity-

maximising version (2023 revision; Ovid format) [38].

The details of the search strategies can be found in Supplementary material 1.

Searching other resources

We examined the reference list of included studies, systematic reviews, meta-analyses, and health technology assessment reports to identify studies not retrieved by the database searches.

Data collection and analysis

Selection of studies

Two researchers (from the review team, see Acknowledgements) independently screened the titles and abstracts of every record retrieved by the broad literature search. We obtained the full texts of all potentially relevant records for comprehensive eligibility assessment. We resolved disagreements through consensus or by consulting an independent author (from JB, NM, JF, EM), who was not involved with study selection. If we could not resolve a disagreement, we categorised the study as 'awaiting classification' and contacted the study authors for clarification. We presented an adapted PRISMA flow diagram to show the study selection process [29].

We used Covidence for the entire screening process [39].

Data extraction and management

For studies that fulfilled our inclusion criteria, two researchers (from the review team, see Acknowledgements) independently extracted key information on participants, interventions, comparators, outcomes and other study-level characteristics. We resolved disagreements by consensus or by involving an additional author (from NM, EM, JVAF, YG, LVB) not involved with data extraction.

We extracted the following data from study reports.

- Methods
    - Study design
- Participants
    - Inclusion and exclusion criteria
    - Participant details, baseline demographics, including age, sex, ethnicity, and baseline measurements of weight, blood pressure, and lipid profile
    - The number of participants by study and by study arm
- Interventions and comparisons, according to the Template for Intervention Description and Replication (TIDieR) [40, 41].
    - Data extracted based on TIDieR will be published in a separate article.
- Outcomes
    - Definitions of relevant outcomes, method and timing of outcome measurement, as well as any relevant subgroups to the review
- Dates (we also reported whether dates were not available).
- Study settings and country, the language of publication, and the study identifier
- Funding sources
- Conflicts of interest as declared by study authors

We characterised the conflicts of interest in the included studies, according to the *Cochrane Handbook for Systematic Reviews of Interventions* [42]. We also collected, processed, and used information on conflicts of interest in two ways.

- We extracted information from the study authors' disclosures regarding their relationship to the study funder (e.g. consultant, employee, stockholder, patent holder, independent researcher) or any circumstances that created a risk that professional judgement or actions regarding their primary interest might have been unduly influenced by a secondary interest. We presented the proportion of study authors in each condition as supplementary material.
- We also assessed whether the funder had any involvement in the design, conduct, data analysis, or dissemination of the study.

We had planned to email the authors of the included studies to enquire whether they would be willing to answer questions about their studies. However, given that we did not have pressing or critical queries during the review process, and due to the commissioning status and the restricted timeline for conducting this review, we will address this in future updates.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximised the information yielded by collating all available data, and we used the most complete data set aggregated across all known publications. We listed duplicate publications, companion documents, multiple reports of a study, and study documents of included studies (such as trial registry information) as secondary references under the study ID of both the included and excluded studies.

Data from clinical trials registers

We collated and critically appraised all available data from fully published studies. We also extracted results data for included studies from clinical trials registers, such as ClinicalTrials.gov or similar sources, if available. If an included study was marked as completed in a clinical trials register but no additional information was available (e.g. study results, publication details), we added it to 'Studies awaiting classification'.

Risk of bias assessment in included studies

Two independent researchers (from the review team, see Acknowledgements) assessed the risk of bias in included studies using the original version of the Cochrane tool for assessing risk of bias (RoB 1) [43]. We resolved disagreements by consensus or through consultation with a third review author (from NM, EM, JVAF, YG, LVB).

We assessed the following domains.

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other potential sources of bias

When assessing risk of bias in included studies, we distinguished between outcome measures that had been self-reported (quality of life, any adverse events, and non-serious adverse events) and investigator-assessed or adjudicated outcome measures (all other critical outcomes and important outcomes (see also Critical outcomes; Important outcomes)).

We judged the risk of bias domains as 'low risk', 'high risk', or 'unclear risk'. We further summarised the risk of bias across domains for each outcome in each included study, as well as across studies and domains, for each outcome described according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* [43].

For the domain 'Incomplete outcome data' (attrition bias), we examined both the proportion of participants lost to follow-up and whether attrition was balanced between arms. We considered studies as follows.

- Low risk of attrition bias when losses to follow-up were minimal (< 5%)
- Unclear risk when attrition rates were between 5% and 10%, or when discontinuation rates were moderate (10% to 20%) but balanced between groups, with no evidence of differential reasons for missing data.
- High risk when overall attrition exceeded 20%, or if attrition between 10% and 20% was unbalanced across groups, potentially introducing systematic differences.

We presented a risk of bias summary figure to illustrate these findings.

We assessed the risk of bias across studies and domains for the key outcomes included in the summary of findings tables (see Certainty of the evidence assessment). As per the *Cochrane Handbook for Systematic Reviews of Interventions,* we defined the evidence as being at low risk of bias when most information came from studies at low risk of bias, unclear risk of bias when most information came from studies at low or unclear risk of bias, and high risk of bias when sufficient information came from studies at high risk of bias [43]. For across-study judgements of risk of bias, we considered the overall within-study assessments. We did not downgrade when all studies were at low risk; we downgraded one level when most information came from studies at unclear or high risk. When a study at high risk contributed sufficient weight to influence the pooled result, we examined its impact in sensitivity analyses and downgraded if necessary [44].

Measures of treatment effect

We expressed dichotomous data as risk ratio (RR), with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. weight loss in kg), we estimated the intervention effect using the mean difference (MD) with 95% CIs. When we pooled data from studies that used different instruments to measure the same outcome, we planned to calculate standardised mean differences (SMDs) with 95% CIs, entering data presented as a scale with a consistent direction of effect and to multiply the SMD by a standard deviation (SD) representative of the pooled studies, for example, the SD from a well-known scale used by several of the studies included in the analysis on which the result was based. When studies reported continuous outcome data as medians and interquartile ranges, we approximated means and SDs using the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* [45], assuming a normal distribution. For data reported as means and

standard errors (SEs), we converted SEs to SDs according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* [45]. We planned to express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We took into account the level at which randomisation occurred, such as multiple observations for the same outcome. If more than one comparison from the same study was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison, or we appropriately reduced the sample size so that the same participants did not contribute data to the meta-analysis more than once (splitting the 'shared' group into two or more groups). Although the latter approach offered some solutions for adjusting the precision of the comparison, it did not account for correlation arising from the inclusion of the same set of participants in multiple comparisons [45].

Dealing with missing data

If possible, we obtained missing data from the authors of the included studies. We carefully evaluated important numerical data such as screened, randomly assigned participants, as well as intention-to-treat (ITT), as-treated, and per-protocol populations in our risk of bias assessments. For this, we investigated attrition rates (e.g. dropouts, losses to follow-up and withdrawals) and we critically appraised issues concerning missing data and the use of imputation methods (e.g. last observation carried forward). For our primary analyses, we conducted available case analyses, taking these issues into account when assessing the risk of bias and the certainty of the evidence.

For studies in which the SD of the outcome was not available at follow-up, or we could not recreate it, we standardised by the mean of the pooled baseline SD from studies that reported this information.

Reporting bias assessment

If we included 10 or more studies that investigated a particular outcome, we used funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including the true heterogeneity of the effect concerning study size, poor methodological design (and hence bias of small studies), and publication bias [46]. Therefore, we interpreted the results carefully [47].

Synthesis methods

We undertook a meta-analysis only when participants, interventions, comparisons, and outcomes were sufficiently similar to yield a clinically meaningful result. Given the anticipated clinical and methodological diversity across studies, we used a random-effects model to account for expected variability in true effects. We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects and presented a confidence interval. We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* [48]. When meta-analysis was not possible, we conducted alternative forms of synthesis, including the summary of effect estimates, the combination of P values, and vote counting based on the direction of effects, as described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* [49].

In cases of substantial clinical or methodological heterogeneity, we did not report the study results as a pooled effect estimate in a meta-analysis.

We used the I^2 statistic to measure heterogeneity among the studies in each analysis [50]. If we identified substantial unexplained heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis. We used the rough guide to interpretation as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions*, as follows [48].

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

We also took into account a visual examination of the variability in point estimates and the overlap in CIs. We avoided using absolute cutoff values, but interpreted the I^2 statistic in relation to the size and direction of effects and the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test, or CI for I^2 statistic).

Investigation of heterogeneity and subgroup analysis

We expected the following characteristics to introduce clinical heterogeneity, and we had planned to carry out the following subgroup analyses for these, including an investigation of interactions [51].

- Age (people younger than 60 versus those aged 60 years and older)
- Sex
- Dose
- Presence of comorbidities (e.g. diabetes)

- Baseline BMI
- Equity considerations (see below)

Equity-related assessment

We examined whether study populations included underrepresented groups, such as individuals from low-income settings, vulnerable populations, or populations with limited access to obesity management services. Where possible, we assessed whether equity-related factors influence the effectiveness or accessibility of interventions. This included exploring subgroup data and evaluating study contexts for equity considerations.

Sensitivity analysis

We performed sensitivity analyses to explore the influence of the following factors, when applicable, on effect sizes.

- Restricting the analysis to studies at an overall low risk of bias.

Certainty of the evidence assessment

We presented the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which took into account issues related to internal validity (overall risk of bias, inconsistency, imprecision, publication bias) and external validity (such as the directness of the results).

Two review authors (NM, JB) independently rated the certainty of the evidence for each outcome. We resolved any differences in assessment by discussion or by consultation with a third review author (EM, JVAF).

We used an approach based on three target ratings to rate down imprecision and inconsistency [52, 53, 54], and we established predefined minimally important differences (see Supplementary material 8).

We presented a summary of the evidence in summary of findings tables, which provided key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences for each relevant comparison of alternative management strategies, the number of participants and studies addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the summary of findings tables using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* [55], along with Review Manager [56] and GRADEpro GDT software [57].

If a meta-analysis was not possible, we presented the results in a narrative format in the summary of findings tables. We justified all decisions to downgrade the certainty of the evidence by using informative footnotes, and we followed the GRADE guidelines for making informative statements [58, 59].

We created two main summary of findings tables for the critical outcomes at medium- and long-term follow-up for the comparison of liraglutide versus placebo.

- Weight (% weight change from baseline, people achieving 5% weight reduction)
- Adverse events (any, non-serious, serious and leading to withdrawal)
- Major adverse cardiovascular events
- Quality of life
- Mortality

We also prepared additional summary of findings tables with all critical and important outcomes in the supplementary materials.

Whenever a study reported multiple assessments within our time frame, we included the outcome measurement at the time point that was closest to the end of the time frame.

Consumer involvement

We consulted the following stakeholders via a 'Public Notice and Comment' to prioritise questions and outcomes for the WHO guideline development: advocacy groups, professional and scientific associations, non-governmental organisations working on obesity management, health providers, health insurance companies, researchers, academic organisations, and the general public.

Results

Description of studies

Results of the search

All GLP-1RAs

Our updated protocol illustrated methods for synthesising evidence for all types of GLP-1RAs, and thus we conducted a broad literature search for eligible studies that investigated any GLP-1RAs, rather than exclusively

liraglutide [31]. Subsequently, we screened the search results and selected studies that were eligible for a specific GLP-1RA for each of the three Cochrane reviews.

We identified 21,355 records from this broad literature search. After duplicates were removed, 14,880 records remained for title-and-abstract screening. We excluded 14,043 irrelevant records and obtained full-text reports of 837 records for comprehensive eligibility assessment. Of these, we excluded 231 full-text articles with reasons. Of the remaining 606 references, 502 were references to included studies, 97 were references to ongoing studies, and seven were references to studies awaiting classification.

Liraglutide

Of the 502 references to included studies, 24 studies (259 references) were on liraglutide (Alba 2021 [60, 61, 62]; Altintas Dogan 2022 [63, 64]; Astrup 2009 [65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77]; Elkind-Hirsch 2022 [78, 79]; Khoo 2019 [80, 81, 82, 83, 84]; Lau 2021 [85, 86, 87]; LOSEIT [88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98]; McElroy 2024 [99, 100]; MODEL [101, 102, 103, 104, 105, 106, 107]; Nahra 2021 [108, 109, 110, 111, 112]; Neeland 2021 [113, 114, 115, 116, 117]; O'Donnell 2024 [118, 119, 120, 121, 122]; O'Neil 2018 [123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137]; ROMANCE [138, 139, 140]; S-LITE [141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166]; SCALE Diabetes [167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208]; SCALE IBT [209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220]; SCALE Insulin [221, 222, 223, 224, 225, 226, 227]; SCALE Maintenance [228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239]; SCALE Obesity and Prediabetes [240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297]; SCALE Sleep Apnoea [298, 299, 300, 301, 302, 303, 304, 305]; STEP 8 [306, 307, 308, 309, 310, 311, 312]; STRIVE [313, 314, 315, 316, 317]; Sun 2023 [318]). We also categorised five studies as awaiting classification and identified eight ongoing studies.

Figure 1 illustrates our study selection process. See also Supplementary material 2; Supplementary material 3; Supplementary material 4; Supplementary material 5.

Included studies

See Table 1, Table 2 and Supplementary material 2.

We included 24 studies on liraglutide (259 references) with a total of 9937 randomised participants.

Study design and settings

All the included studies were parallel-group RCTs. The median sample size was 189.5 (interquartile range 116.5 to 393).

Most studies were multicentre studies conducted across several countries and regions. Seven studies were large international multicentre studies conducted in Europe, North America, and other global regions, including Japan, Hong Kong, India, Turkey, Israel, Brazil, Argentina, and South Africa (Alba 2021; Lau 2021; Nahra 2021; O'Neil 2018; SCALE Diabetes; SCALE Insulin; SCALE Obesity and Prediabetes). Four studies were multicentre but limited to specific regions, mainly Europe (Astrup 2009; STRIVE) and North America (SCALE Maintenance; SCALE Sleep Apnoea). Thirteen studies were conducted in a single country. Six were based in the USA (Elkind-Hirsch 2022; McElroy 2024; MODEL; Neeland 2021; SCALE IBT; STEP 8), three in Denmark (Altintas Dogan 2022; S-LITE; LOSEIT), one in the UK (ROMANCE), one in Singapore (Khoo 2019), one in Ireland (O'Donnell 2024), and one in China (Sun 2023).

Participants

The mean age of participants ranged from 31.3 years (Elkind-Hirsch 2022), to 64.7 years (Altintas Dogan 2022). The percentage of male participants varied widely, from 8.6% (Neeland 2021) to 93.3% (Khoo 2019). Only one study included exclusively female participants (Elkind-Hirsch 2022), while several studies included predominantly male populations, such as Khoo 2019 (93.3% male), Altintas Dogan 2022 (60% male), and O'Donnell 2024 (80% male).

Mean weight ranged from 93.6 kg (LOSEIT), to 127.1 kg (STRIVE), while BMI ranged from 26.5 kg/m^2 (Sun 2023), to 45.5 kg/m^2 (STRIVE). Some studies targeted specific subgroups. For instance, STRIVE enrolled participants with a BMI of 35 kg/m^2 or higher, and either prediabetes, type 2 diabetes, hypertension or sleep apnoea. SCALE Insulin, SCALE Diabetes, and Nahra 2021 focused on participants with type 2 diabetes, while SCALE Sleep Apnoea, ROMANCE, and O'Donnell 2024 recruited participants with moderate-to-severe obstructive sleep apnoea. Elkind-Hirsch 2022 was limited to women with polycystic ovary syndrome, LOSEIT recruited patients with knee osteoarthritis, and Khoo 2019 included participants with non-alcoholic fatty liver disease. McElroy 2024 focused on people with stable bipolar disorder. Sun 2023 included participants with impaired glucose tolerance, and SCALE Maintenance included participants who had already lost 5% or more of their weight through a low-calorie diet prior to randomisation. In addition, SCALE Obesity and Prediabetes stratified participants by prediabetes status; Altintas Dogan 2022 targeted individuals with chronic obstructive pulmonary disease; Neeland 2021 focused on participants with metabolic syndrome; and Lau 2021 included individuals with hypertension and dyslipidaemia.

The populations of the included studies were diverse in terms of ethnicity and race. Several studies included over 80% white participants (Alba 2021, Astrup 2009; McElroy 2024; Nahra 2021; ROMANCE; SCALE Diabetes; SCALE IBT; SCALE Maintenance; SCALE Insulin, SCALE Obesity and Prediabetes, STRIVE). In contrast, others, such as Elkind-Hirsch 2022; Neeland 2021, MODEL, SCALE Sleep Apnoea, and STEP 8 included more racially diverse populations, with a large proportion of Black or African American participants. The proportion of Hispanic or Latino participants ranged widely from 4.5% (Lau 2021), to over 88% (SCALE IBT).

Interventions and comparisons

Liraglutide was administered once daily by subcutaneous injection. Most studies tested the 3.0 mg dose, although some also evaluated lower doses (e.g. 1.2 mg or 1.8 mg) for specific populations or comparisons (Astrup 2009; Nahra 2021; SCALE Diabetes; ROMANCE; Sun 2023).

All studies considered co-interventions or co-medications aligned with local standards and participant comorbidities. Some studies included structured lifestyle or weight management programmes as co-interventions, such as diet, physical activity, behavioural counselling, or intensive behavioural therapy (MODEL; SCALE IBT; S-LITE), while O'Donnell 2024 and ROMANCE included CPAP as a co-intervention for obstructive sleep apnoea.

Studies that targeted specific conditions often included additional treatments: for instance, SCALE Insulin and SCALE Diabetes allowed for concurrent antihyperglycaemic medications in participants with type 2 diabetes; McElroy 2024 included participants with stable bipolar disorder under ongoing psychiatric treatment. Elkind-Hirsch 2022 adapted lifestyle interventions for women with polycystic ovary syndrome, and Khoo 2019 compared liraglutide with a structured diet and exercise programme in non-alcoholic fatty liver disease.

The majority of the 24 included studies compared liraglutide to placebo, either alone or within multi-arm designs. Two studies included semaglutide as an active comparator (O'Neil 2018; STEP 8), and one included orlistat (Astrup 2009). Two studies compared liraglutide versus structured lifestyle interventions as a standalone comparator (Khoo 2019; Sun 2023).

Outcomes and follow-up periods

Supplementary material 2 details all the important characteristics of the included studies, including which outcomes (and measurements) were reported and contributed to data synthesis.

All the included studies contributed medium-term data (ranging from 26 to 68 weeks). Three studies provided data for long-term follow-up, with outcomes assessed at 104 and 162 weeks (Astrup 2009; SCALE Obesity and Prediabetes; STRIVE).

Funding sources

Twenty of the 24 included studies reported that the manufacturer of liraglutide, Novo Nordisk, funded the study (Altintas Dogan 2022; Astrup 2009; Elkind-Hirsch 2022; Lau 2021; LOSEIT; McElroy 2024; MODEL; Neeland 2021; O'Donnell 2024; O'Neil 2018; ROMANCE; S-LITE; SCALE Diabetes; SCALE IBT; SCALE Insulin; SCALE Maintenance; SCALE Obesity and Prediabetes; SCALE Sleep Apnoea; STEP 8; STRIVE), while one study was funded by Janssen (Alba 2021), and one was funded by AstraZeneca (Nahra 2021). Only two smaller studies, with a total of 69 participants, were funded by independent government grants (Khoo 2019; Sun 2023). Thirteen of the 22 industry-funded included studies declared that the funder had a substantial involvement in the planning, conduct, analysis or dissemination of the results (Alba 2021; Astrup 2009; Lau 2021; Nahra 2021; O'Neil 2018; S-LITE; SCALE Diabetes; SCALE IBT; SCALE Insulin; SCALE Maintenance; SCALE Obesity and Prediabetes; SCALE Sleep Apnoea; STEP 8), with many of the study investigators and authors having direct financial ties to the company (see Supplementary material 9 and Supplementary material 10 for a detailed analysis of these aspects).

Ongoing studies and studies awaiting classification

We identified eight ongoing studies (ACTRN12622000703707 [319]; ChiCTR2000035091 [320]; ChiCTR2200064261 [321]; EUCTR2013-005395-18-NL [322]; ISRCTN76189107 [323]; NCT05952882 [324]; NL-OMON20833 [325]; NL-OMON24018 [326]), and five studies are awaiting classification (NCT02503943 [327]; NCT04487743 [328]; NCT04525300 [329]; NCT04605861 [330]; NCT05111912 [331]).

Full details are presented in Supplementary material 4 and Supplementary material 5. We last verified the status of these studies on 16 April 2025.

Excluded studies

We excluded 154 studies (231 references) across the suite of reviews on GLP-1RA. The main reasons for exclusions are as follows (noting that some studies were excluded due to more than one reason): ineligible aim (89 studies), ineligible comparison or intervention (24 studies), short-term follow-up (22 studies), ineligible study design (16 studies), withdrawn studies (9 studies), and ineligible population (2 studies).

See Supplementary material 3.

Risk of bias in included studies

Most studies were at low risk of bias for random sequence generation and allocation concealment, suggesting that randomisation procedures were generally adequate. However, we judged three studies to have an unclear risk of

selection bias due to insufficient details on random sequence generation or allocation concealment, or both (Altintas Dogan 2022; O'Donnell 2024; Sun 2023), and we rated one study at high risk because the random sequence was generated by the funder and implemented by an unblinded study nurse (S-LITE).

We judged all studies at low risk for both performance and detection bias for objective outcomes.

We rated performance bias for subjective outcomes as high risk in nine studies due to their open-label design (Alba 2021; Astrup 2009; Khoo 2019; MODEL; Nahra 2021; O'Donnell 2024; ROMANCE; STEP 8; STRIVE). We considered two studies at unclear risk, as blinding procedures were described but not clearly justified (SCALE Obesity and Prediabetes; S-LITE).

We judged detection bias for subjective outcomes as high risk in eight studies due to lack of blinding in open-label settings (Alba 2021; Astrup 2009; MODEL; Nahra 2021; O'Donnell 2024; ROMANCE; STEP 8; STRIVE). In addition, we rated seven studies at unclear risk due to insufficient information on the blinding of outcome assessors (Altintas Dogan 2022; Khoo 2019; McElroy 2024; SCALE IBT; SCALE Insulin; S-LITE; Sun 2023).

We judged attrition bias for outcomes in the medium term as high risk in fourteen studies, mainly due to high discontinuation rates (> 20%) or 10% to 20% unbalanced attritions (Alba 2021; Altintas Dogan 2022; Astrup 2009; Elkind-Hirsch 2022; Khoo 2019; McElroy 2024; Neeland 2021; O'Donnell 2024; SCALE Diabetes; SCALE IBT; SCALE Maintenance; SCALE Obesity and Prediabetes; SCALE Sleep Apnoea; STRIVE). We judged six studies at unclear risk due to 5% to 10% attrition or moderate discontinuation rates (10% to 20%) but balanced among arms (LOSEIT; MODEL; Nahra 2021; ROMANCE; S-LITE; Sun 2023). Regarding outcomes in the long term, we assessed and judged three studies at high risk of attrition bias due to high discontinuation rates (> 20%) or 10% to 20% unbalanced attritions (Astrup 2009; SCALE Obesity and Prediabetes; STRIVE).

Generally, we judged most studies to be at low risk of selective reporting. However, we considered five studies at unclear or high risk due to incomplete or unpublished protocols, or discrepancies between registered and reported outcomes (Astrup 2009; Khoo 2019; O'Neil 2018; ROMANCE, Sun 2023).

We identified other sources of bias in two studies, which we rated at high risk due to baseline imbalances or inconsistencies in reported outcomes (ROMANCE; Sun 2023).

Of the remaining studies, we judged most to be at low risk of bias across all domains. Notably, we assessed one study as being at low risk of bias in all domains (Lau 2021).

Figure 2 summarises the risk of bias in the included studies.

Synthesis of results

1. Liraglutide versus placebo: medium-term follow-up

See Summary of findings table 1 and Supplementary material 6 for the analyses.

Weight

The evidence is very uncertain about the effects of liraglutide on percentage weight change from baseline (MD −4.72, 95% CI −5.32 to −4.12; I^2 = 57%; 16 studies, 6050 participants; very low-certainty evidence; Analysis 1.1), change in weight in kg (MD −4.88, 95% CI −5.48 to −4.27; I^2 = 56%; 22 studies, 6925 participants; very low-certainty evidence; Analysis 1.2), and change in BMI from baseline (MD −1.92, 95% CI −2.27 to −1.57; I^2 = 62%; 11 studies, 4794 participants; very low-certainty evidence; Analysis 1.3) in the medium term.

Liraglutide likely increases the number of people achieving 5% weight reduction (RR 2.10, 95% CI 1.80 to 2.45; I^2 = 78%; 18 studies, 6651 participants; moderate-certainty evidence; Analysis 1.4) and 10% weight reduction (RR 2.69, 95% CI 2.16 to 3.35; I^2 = 63%; 18 studies, 6651 participants; moderate-certainty evidence; Analysis 1.5) in the medium term.

Adverse events

Liraglutide may result in an increase in any adverse events (RR 1.07, 95% CI 1.04 to 1.11; I^2 = 28%; 16 studies, 8147 participants; low-certainty evidence; Analysis 1.6) and serious adverse events (RR 1.20, 95% CI 1.00 to 1.43; I^2 = 0%; 20 studies, 8487 participants; low-certainty evidence; Analysis 1.8) in the medium term.

The evidence is very uncertain about the effects of liraglutide on non-serious adverse events (RR 1.14, 95% CI 1.05 to 1.24; I^2 = 76%; 17 studies, 7440 participants; very low-certainty evidence; Analysis 1.7) and on adverse events leading to withdrawal (RR 1.98, 95% CI 1.30 to 3.02; I^2 = 47%; 19 studies, 8628 participants; very low-certainty evidence; Analysis 1.9) in the medium term.

Major adverse cardiovascular event (MACE)

Liraglutide likely results in little to no clinically meaningful difference in MACE in the medium term (RR 0.86, 95% CI 0.66 to 1.10; I^2 = 0%; 6 studies, 5762 participants; moderate-certainty evidence; Analysis 1.10).

Quality of life

Liraglutide likely results in little to no clinically meaningful difference in quality of life as measured by the SF-36 mental component (MD 0.66, 95% CI 0.15 to 1.47; I^2 = 14%; 7 studies, 3425 participants; moderate-certainty evidence; Analysis 1.11), physical component (MD 0.94, 95% CI 0.49 to 2.37; I^2 = 60%; 7 studies, 3425

participants; moderate-certainty evidence; Analysis 1.12) and physical functioning component (MD 0.86, 95% CI 0.72 to 2.43; I^2 = 54%; 6 studies, 3201 participants; moderate-certainty evidence; Analysis 1.13); and the IWQOL-Lite-CT total score (MD 2.87, 95% CI 1.83 to 3.91; I^2 = 0%; 7 studies, 3944 participants; moderate-certainty evidence; Analysis 1.14) and physical function (MD 2.90, 95% CI 0.08 to 5.89; I^2 = 58%; 6 studies, 3733 participants; moderate-certainty evidence; Analysis 1.15) in the medium term.

Mortality

The evidence is very uncertain about the effect of liraglutide on mortality in the medium term (RR 0.44, 95% CI 0.08 to 2.25; I^2 = 0%; 18 studies, 8224 participants; very low-certainty evidence; Analysis 1.16).

Other critical and important outcomes

Findings are presented in Supplementary material 11 and Supplementary material 17 (Analysis 1.17; Analysis 1.18; Analysis 1.19; Analysis 1.20; Analysis 1.21; Analysis 1.22; Analysis 1.23; Analysis 1.24; Analysis 1.25; Analysis 1.26; Analysis 1.27; Analysis 1.28; Analysis 1.29; Analysis 1.30; Analysis 1.31; Analysis 1.32; Analysis 1.33; Analysis 1.34; Analysis 1.35; Analysis 1.36; Analysis 1.37; Analysis 1.38; Analysis 1.39; Analysis 1.40; Analysis 1.41; Analysis 1.42; Analysis 1.43; Analysis 1.44; Analysis 1.45; Analysis 1.46; Analysis 1.47; Analysis 1.48).

2. Liraglutide versus placebo: long-term follow-up

See Summary of findings table 2 and Supplementary material 6 for the analyses.

Weight

Liraglutide may result in little to no clinically meaningful difference in a reduction in percentage weight change (MD −4.34, 95% CI −5.26 to −3.43; I^2 = 0%; 2 studies, 1262 participants; low-certainty evidence; Analysis 2.1) and change in kg from baseline (MD −4.76, 95% CI −5.82 to −3.70; I^2 = 0%; 2 studies, 1262 participants; low-certainty evidence; Analysis 2.2) and may reduce change in BMI from baseline (MD −1.71, 95% CI −2.08 to −1.34; I^2 = 0%; 2 studies, 1269 participants; low-certainty evidence; Analysis 2.3) in the long term.

Liraglutide likely increases the number of people achieving a 5% (RR 1.78, 95% CI 1.51 to 2.09; I^2 = 0%; 2 studies, 1262 participants; moderate-certainty evidence; Analysis 2.4) and a 10% weight reduction (RR 2.03, 95% CI 1.57 to 2.63; I^2 = 0%; 2 studies, 1262 participants; moderate-certainty evidence; Analysis 2.5) in the long term.

Adverse events

The evidence is very uncertain about the effect of liraglutide on any adverse events (RR 1.19, 95% CI 0.93 to 1.52; I^2 = 93%; 2 studies, 2640 participants; very low-certainty evidence; Analysis 2.6) and non-serious adverse events (RR 1.19, 95% CI 0.94 to 1.51; I^2 = 93%; 2 studies, 2640 participants; very low-certainty evidence; Analysis 2.7) in the long term.

Liraglutide may result in an increase in serious adverse events (RR 1.20, 95% CI 0.98 to 1.48; I^2 = 0%; 2 studies, 2640 participants; low-certainty evidence; Analysis 2.8) and adverse events leading to withdrawal (RR 2.16, 95% CI 1.59 to 2.93; I^2 = 0%; 2 studies, 2640 participants; low-certainty evidence; Analysis 2.9) in the long term.

Major adverse cardiovascular event (MACE)

The evidence is very uncertain about the effect of liraglutide on MACE (RR 0.83, 95% CI 0.20 to 3.46; I^2 not applicable; 1 study, 2248 participants; very low-certainty evidence; Analysis 2.10) in the long term.

Quality of life

Liraglutide likely results in little to no clinically meaningful difference in quality of life as measured by the SF-36 mental component (MD 1.16, 95% CI 0.13 to 2.45; I^2 not applicable; 1 study, 829 participants; moderate-certainty evidence; Analysis 2.11), physical component (MD 0.59, 95% CI 0.57 to 1.75; I^2 not applicable; 1 study, 829 participants; moderate-certainty evidence; Analysis 2.12), and physical functioning component (MD 0.93, 95% CI 0.22 to 2.08; I^2 not applicable; 1 study, 831 participants; moderate-certainty evidence; Analysis 2.13); and the IWQoL-Lite-CT total score (MD 2.54, 95% CI 0.56 to 4.53; I^2 = 0%; 2 studies, 1021 participants; moderate-certainty evidence; Analysis 2.14) and physical function (MD 3.81, 95% CI 1.03 to 6.59; I^2 not applicable; 1 study, 863 participants; moderate-certainty evidence; Analysis 2.15) in the long term.

Mortality

The evidence is very uncertain about the effect of liraglutide on mortality in the long term (RR 0.81, 95% CI 0.16 to 4.17; I^2 = 0%; 2 studies, 2640 participants; very low-certainty evidence; Analysis 2.16).

Other critical and important outcomes

Findings are presented in Supplementary material 12 and Supplementary material 18 (Analysis 2.17; Analysis 2.18; Analysis 2.19; Analysis 2.20; Analysis 2.21; Analysis 2.22; Analysis 2.23; Analysis 2.24; Analysis 2.25; Analysis 2.26; Analysis 2.27; Analysis 2.28; Analysis 2.29; Analysis 2.30; Analysis 2.31; Analysis 2.32; Analysis 2.33; Analysis 2.34; Analysis 2.35; Analysis 2.36; Analysis 2.37; Analysis 2.38; Analysis 2.39; Analysis 2.40; Analysis 2.41).

3. Liraglutide versus another pharmacological intervention (orlistat): medium-term follow-up

See Supplementary material 13 for the Summary of findings table and Supplementary material 6 for the analyses.

Weight

Compared to orlistat, the evidence is very uncertain about the effect of liraglutide on weight change in kg in the medium term (MD −1.40, 95% CI −3.27 to 0.47; I^2 not applicable; 1 study, 294 participants; very low-certainty evidence; Analysis 3.1).

None of the studies reported data for percentage weight change or change in BMI.

The evidence is very uncertain about the effect of liraglutide on the number of participants achieving 5% (RR 1.10, 95% CI 0.88 to 1.38; I^2 not applicable; 1 study, 294 participants; very low-certainty evidence; Analysis 3.2) and 10% weight reduction in the medium term (RR 1.37, 95% CI 0.82 to 2.28; I^2 not applicable; 1 study, 284 participants; very low-certainty evidence; Analysis 3.3).

Adverse events

Compared to orlistat, the evidence is very uncertain about the effects of liraglutide on any adverse events (RR 0.93, 95% CI 0.88 to 0.99; I^2 not applicable; 1 study, 466 participants; very low-certainty evidence; Analysis 3.4), serious adverse events (RR 4.39, 95% CI 0.26 to 75.34; I^2 not applicable; 1 study, 466 participants; very low-certainty evidence; Analysis 3.5) and adverse events leading to withdrawal in the medium term (RR 1.96, 95% CI 0.60 to 6.40; I^2 not applicable; 1 study, 466 participants; very low-certainty evidence; Analysis 3.6).

None of the studies reported data for non-serious adverse events.

Major adverse cardiovascular event (MACE)

None of the studies reported data for MACE.

Quality of life

Compared to orlistat, the evidence is very uncertain about the effect of liraglutide on quality of life as measured by the IWQOL-Lite-CT total score (MD 0.14, 95% CI −3.07 to 3.35; I^2 not applicable; 1 study, 286 participants; very low-certainty evidence; Analysis 3.7) and the IWQOL-Lite-CT physical function score (MD 0.30, 95% CI −4.11 to 3.51; I^2 not applicable; 1 study, 293 participants; very low-certainty evidence; Analysis 3.8) in the medium term.

Mortality

One study provided data on mortality, yet no events were reported (Not estimable; 1 study, 466 participants; Analysis 3.9).

Other critical and important outcomes

Findings are presented in Supplementary material 19 (Analysis 3.10; Analysis 3.11; Analysis 3.12; Analysis 3.13; Analysis 3.14; Analysis 3.15; Analysis 3.16; Analysis 3.17; Analysis 3.18).

4. Liraglutide versus another pharmacological intervention (orlistat): long-term follow-up

See Supplementary material 14 for the Summary of findings table and Supplementary material 6 for the analyses.

Weight

Compared to orlistat, the evidence is very uncertain about the effect of liraglutide on weight change in kg in the long term (MD −2.24, 95% CI −4.76 to 0.28; I^2 not applicable; 1 study, 221 participants; very low-certainty evidence; Analysis 4.1).

None of the studies reported percentage weight change from baseline or BMI.

The evidence is very uncertain about the effect of liraglutide on the number of participants achieving 5% (RR 1.31, 95% CI 0.93 to 1.85; I^2 not applicable; 1 study, 204 participants; very low-certainty evidence; Analysis 4.2) and 10% weight reduction (RR 1.18, 95% CI 0.71 to 1.95; I^2 not applicable; 1 study, 221 participants; very low-certainty evidence; Analysis 4.3) in the long term.

Adverse events

Compared to orlistat, liraglutide may result in little to no clinically meaningful difference in any adverse events in the long term (RR 1.02, 95% CI 0.97 to 1.08; I^2 not applicable; 1 study, 466 participants; low-certainty evidence; Analysis 4.4); however, it may increase adverse events leading to withdrawal (RR 3.58, 95% CI 1.14 to 11.32; I^2 not applicable; 1 study, 466 participants; low-certainty evidence; Analysis 4.6).

The evidence is very uncertain about the effect of liraglutide on serious adverse events in the long term (RR 1.54, 95% CI 0.67 to 3.54; I^2 not applicable; 1 study, 466 participants; very low-certainty evidence; Analysis 4.5).

None of the studies reported data for non-serious adverse events.

Major adverse cardiovascular event (MACE)

None of the studies reported data for MACE.

Quality of life

Compared to orlistat, the evidence is very uncertain about the effect of liraglutide on quality of life as measured by the IWQOL-Lite-CT total score (MD −2.36, 95% CI −6.26 to 1.54; I^2 not applicable; 1 study, 275 participants; very low-certainty evidence; Analysis 4.7) and physical function score (MD −2.04, 95% CI −6.44 to 2.36; I^2 not applicable; 1 study, 283 participants; very low-certainty evidence; Analysis 4.8) in the long term.

Mortality

One study provided data on mortality, yet no events were reported (Not estimable; 1 study, 466 participants; not specified; Analysis 4.9).

Other critical and important outcomes

Findings are presented in Supplementary material 20 (Analysis 4.10; Analysis 4.11; Analysis 4.12; Analysis 4.13; Analysis 4.14; Analysis 4.15; Analysis 4.16; Analysis 4.17; Analysis 4.18; Analysis 4.19).

5. Liraglutide versus structured programmes targeting lifestyle modification: medium-term follow-up

See Supplementary material 15 for the Summary of findings table and Supplementary material 6 for the analyses.

Weight

The evidence is very uncertain about the effect of liraglutide on percentage weight change (MD 0.98, 95% CI −1.30 to 3.26; I^2 not applicable; 1 study, 30 participants; very low-certainty evidence; Analysis 5.1), change in kg (MD 0.50, 95% CI −1.51 to 2.51; I^2 not applicable; 1 study, 30 participants; very low-certainty evidence; Analysis 5.2) and BMI from baseline (MD −1.56, 95% CI −5.19 to 2.06; I^2 = 99%; 2 studies, 69 participants; very low-certainty evidence; Analysis 5.3) in the long term.

None of the studies reported data on participants who achieved a 5% or 10% weight reduction.

Adverse events

The evidence is very uncertain about the effect of liraglutide on any adverse events in the medium term (RR 1.00, 95% CI 0.88 to 1.13; I^2 not applicable; 1 study, 30 participants; very low-certainty evidence; Analysis 5.4).

We found no studies reporting data on MACE, quality of life, or mortality.

Other critical and important outcomes

Findings are presented in Supplementary material 21; Analysis 5.10; Analysis 5.11; Analysis 5.12; Analysis 5.13; Analysis 5.14; Analysis 5.15; Analysis 5.16; Analysis 5.5; Analysis 5.6; Analysis 5.7; Analysis 5.8; Analysis 5.9.

6. Liraglutide versus another GLP-1RA (semaglutide): medium-term follow-up

See Supplementary material 16 for the Summary of findings table and Supplementary material 6 for the analyses.

Weight

People on liraglutide may lose less weight than those on semaglutide, measured as percentage change (MD 6.75, 95% CI 0.47 to 13.03; I^2 = 94%; 2 studies, 1002 participants; low-certainty evidence; Analysis 6.1) and change in kg (MD 6.37, 95% CI 1.35 to 11.40; I^2 = 90%; 2 studies, 1002 participants; low-certainty evidence; Analysis 6.2), but likely results in little to no clinically meaningful difference in change in BMI (MD 1.37, 95% CI 0.67 to 2.07; I^2 not applicable; 1 study, 768 participants; moderate-certainty evidence; Analysis 6.3) from baseline in the medium term.

The evidence is very uncertain about the effect of liraglutide on the number of participants who achieve a 5% weight reduction in the medium term (RR 0.77, 95% CI 0.58 to 1.01; I^2 = 83%; 2 studies, 1002 participants; very low-certainty evidence; Analysis 6.4). Liraglutide likely reduces the number of participants who achieve 10% weight reduction (RR 0.49, 95% CI 0.27 to 0.87; I^2 = 86%; 2 studies, 1002 participants; moderate-certainty evidence; Analysis 6.5) in the medium term when compared to semaglutide.

Adverse events

Compared to semaglutide, the evidence is very uncertain about the effect of liraglutide on any adverse events (RR 0.97, 95% CI 0.88 to 1.06; I^2 = 72%; 2 studies, 1074 participants; very low-certainty evidence; Analysis 6.6), serious adverse events (RR 0.86, 95% CI 0.30 to 2.41; I^2 = 63%; 2 studies, 1074 participants; very low-certainty evidence; Analysis 6.8) and on adverse events leading to withdrawal (RR 1.85, 95% CI 0.47 to 7.23; I^2 = 79%; 2 studies, 1074 participants; very low-certainty evidence; Analysis 6.9) in the medium term.

Liraglutide may result in little to no clinically meaningful difference in non-serious adverse events in the medium term when compared to semaglutide (RR 0.97, 95% CI 0.90 to 1.04; I^2 = 0%; 2 studies, 1074 participants; low-certainty evidence; Analysis 6.7).

Major adverse cardiovascular event (MACE)

The evidence is very uncertain about the effect of liraglutide on MACE when compared to semaglutide in the medium term (RR 0.77, 95% CI 0.04 to 14.16; I^2 not applicable; 1 study, 821 participants; very low-certainty

evidence; Analysis 6.10).

Quality of life

The evidence is very uncertain about the effect of liraglutide on quality of life as measured by the SF-36 mental component (MD 0.44, 95% CI −2.71 to 1.83; I^2 not applicable; 1 study, 215 participants; very low-certainty evidence; Analysis 6.11), physical component (MD 0.02, 95% CI −2.28 to 2.24; I^2 not applicable; 1 study, 211 participants; very low-certainty evidence; Analysis 6.12), and physical functioning component (MD 0.29, 95% CI −2.16 to 2.74; I^2 not applicable; 1 study, 211 participants; very low-certainty evidence; Analysis 6.13) compared to semaglutide in the medium term.

Mortality

The evidence is very uncertain about the effect of liraglutide compared to semaglutide on mortality in the medium term (RR 2.30, 95% CI 0.09 to 56.20; I^2 not applicable; 2 studies, 1074 participants; very low-certainty evidence; Analysis 6.14).

Subgroup analyses

We investigated potential sources of heterogeneity for critical outcomes by conducting subgroup analyses based on dose, presence of comorbidities, baseline BMI, and equity-related factors. These analyses were restricted to the comparison of liraglutide versus placebo in the medium term, for which data were available. Subgroup analyses by age and sex were not conducted because the available data were insufficient.

Doses

A higher dose of liraglutide (3 mg) compared to lower doses (1.2 mg to 1.8 mg), led to a greater reduction in weight measured as percentage weight change (Analysis 7.1, $P < 0.00001$) and change in BMI (Analysis 7.3, $P < 0.0001$), while no other important differences were observed for other critical outcomes. See Supplementary material 6 (Analysis 7.2; Analysis 7.10; Analysis 7.11; Analysis 7.12; Analysis 7.13; Analysis 7.14; Analysis 7.15; Analysis 7.16; Analysis 7.4; Analysis 7.5; Analysis 7.6; Analysis 7.7; Analysis 7.8; Analysis 7.9).

Comorbidities

We observed a greater reduction in weight as measured by percentage weight change (Analysis 8.1, $P = 0.02$), change in kg (Analysis 8.2, $P = 0.0009$) and change in BMI (Analysis 8.3, $P < 0.00001$) for participants recruited in studies without predefined comorbidities as part of the inclusion criteria. No significant differences were observed for other critical outcomes. See Supplementary material 6 (Analysis 8.10; Analysis 8.11; Analysis 8.12; Analysis 8.13; Analysis 8.14; Analysis 8.15; Analysis 8.16; Analysis 8.4; Analysis 8.5; Analysis 8.6; Analysis 8.7; Analysis 8.8; Analysis 8.9).

Baseline BMI

Among participants with a baseline BMI of 40 kg/m^2 or more, we observed a greater reduction in weight as measured by change in kg (Analysis 9.2, $P = 0.003$), and there were fewer adverse events leading to withdrawal (Analysis 9.9, $P = 0.008$), while no significant differences were observed for other critical outcomes. See Supplementary material 6.

Equity considerations

Subgroup analyses indicated no significant differences between studies with less than 25% minority racial groups and those with more than 25% minority racial groups (substantial representation of Black, Asian, etc.) across critical outcomes. See Supplementary material 6 (Analysis 10.1 to Analysis 10.16).

Due to insufficient data, we were unable to conduct additional subgroup analyses based on other PROGRESS-Plus characteristics, such as socioeconomic status, education level, place of residence, or social capital. (PROGRESS-PLUS is an acronym that covers many characteristics that may lead to potential health inequities [332].)

Sensitivity analyses

We conducted sensitivity analyses restricted to studies rated as having an overall low risk of bias across the critical outcomes for the comparison of liraglutide versus placebo in the medium term, as sufficient data were available. The results were consistent with the main analyses, and no relevant changes in effect estimates or conclusions were observed.

Equity assessment

Distribution of effects across PROGRESS-PLUS characteristics

We could not identify possible effect modification related to race or other PROGRESS-PLUS characteristics (see Subgroup analyses above).

Interventions focusing on disadvantaged or at-risk populations

Only one study explicitly recruited participants from public specialist weight management services within the UK National Health Service, potentially involving underserved populations (STRIVE). Several studies focused on individuals with specific comorbidities such as chronic obstructive pulmonary disease (Altintas Dogan 2022), polycystic ovary syndrome (Elkind-Hirsch 2022), non-alcoholic fatty liver disease (Khoo 2019), metabolic syndrome (Neeland 2021), and stable bipolar disorder (McElroy 2024). However, they were not framed as equity-focused interventions.

Race and ethnicity were variably reported. Some studies conducted in the USA and UK included diverse populations, such as MODEL (44.7% Black participants) and SCALE IBT (88.3% Hispanic or Latino participants), but most studies were predominantly composed of White participants (Table 2). No studies were explicitly designed to address racial or ethnic disparities, nor were subgroup analyses by race or ethnicity reported.

None of the included studies were conducted in low-income countries. Most were conducted in high-income settings, with a few studies based in middle-income countries (e.g. China, Mexico, Argentina, South Africa). Several studies were multicentre and included sites across both high- and middle-income countries (Lau 2021; Nahra 2021; SCALE Obesity and Prediabetes; SCALE Diabetes; SCALE Insulin), reflecting broad geographic coverage but limited focus on equity.

Reporting biases

We did not identify evidence of publication bias in those comparisons with 10 or more studies.

Discussion

Summary of main results

We included 24 RCTs, with 9937 participants, that assessed the effects of liraglutide for adults living with obesity, with follow-up periods ranging from 26 weeks to 162 weeks, which constitute the main findings of this review.

The synthesised evidence indicates that liraglutide likely increases the proportion of people who achieve at least 5% weight loss in the medium term, and this effect is sustained in the long term. Liraglutide may increase the risk of serious adverse events in the medium term, and it may also increase the risk of serious adverse events and adverse events leading to withdrawal in the long term. The evidence is very uncertain about the effect of liraglutide on percentage weight change from baseline in the medium term, but it may result in little to no clinically meaningful difference in the long term. Liraglutide likely results in little to no clinically meaningful difference in quality of life in both the medium and long term. It also likely results in little to no clinically meaningful difference in MACE in the medium term, while the evidence for the long term remains very uncertain. The evidence is very uncertain about the effect of liraglutide on mortality in both the medium and long term.

Limitations of the evidence included in the review

The main limitation in the evidence was the generally low- to very low-certainty evidence for many outcomes, mainly due to imprecision and risk of bias across studies. Attrition bias was common, with several studies reporting high or unbalanced dropout rates. We based our analysis on complete-case data rather than on imputed datasets (i.e. ITT or modified ITT approaches). Although high attrition represents a limitation, we considered complete-case analysis to be more appropriate in this context. Ideally, imputation techniques such as multiple imputation would be preferred when missing data are moderate and handled appropriately [333]. However, in the included studies, imputation methods were either not applied or relied on approaches such as last observation carried forward, which are prone to introducing additional bias [333].

There was also limited reporting of long-term outcomes, especially for MACE and mortality. Most studies had follow-up periods of less than 68 weeks, with only three extending from 104 to 162 weeks. Furthermore, the diversity of patient populations was not always reflected in subgroup analyses, and no studies were explicitly designed to examine equity-relevant populations. In addition, there was scarce data for comparisons against active interventions other than placebo or other GLP-1RAs, limiting the ability to evaluate the relative effectiveness of liraglutide compared to other anti-obesity medications or structured lifestyle-modification programmes.

Although the RoB 1 tool does not consider financial conflict of interest as a bias domain in itself, the high level of involvement of the funder may have influenced the results through mechanisms other than those considered by RoB 1. We believe there is a pressing need for structured approaches to assess studies involving conflicts of interest. To the best of our knowledge, the 'Tool for Addressing Conflicts of Interest in Trials' (TACIT), that aims to address the potential influence of conflicts of interest in studies included in systematic reviews, is currently under development [334]. In the future, we expect this tool to serve as a complementary checklist for robust interpretation of review findings.

All our analyses and conclusions were driven by evidence originating from industry-funded studies, with concerns regarding the conflicts of interest between the study authors and the manufacturer. We believe that independent practice and policy decision making are crucial in understanding and establishing the benefits and harms of liraglutide in the management of obesity, since current decisions would be based, at least in part, on compromised evidence from clinical trials with conflicts of interest [335].

Limitations of the review processes

Although we conducted a comprehensive search and followed a rigorous review process, we faced some challenges. Some included studies did not report outcomes consistently or used different descriptive statistics to assess the same outcome (e.g. blood lipids), which limited our ability to pool the results.

Another challenge we faced concerned how to operationalise minimally important difference (MID) thresholds for weight loss. Although the '5% or more' weight loss threshold was originally defined as within-group change from baseline, we applied it to between-group mean differences, following regulatory guidance and precedent in high-quality systematic reviews. This choice has conceptual limitations, and it may result in seemingly contradictory findings. For instance, when the proportion of participants who achieve clinically meaningful weight loss (≥ 5%) is significantly higher with the intervention, but the mean between-group difference in percentage weight loss remains less than 5%. Still, we considered this framing appropriate for two reasons. First, applying the MID to between-group effects avoids overstating clinical benefit in contexts where control groups also achieve substantial weight loss through diet, behavioural support, or other non-pharmacological components. Second, because participants in control groups may also lose weight, what ultimately matters is the added benefit attributable to the intervention itself. From this perspective, the '5% or more' threshold can be reasonably adapted as a benchmark for comparative benefit. Future work, however, may benefit from more nuanced MID frameworks that distinguish explicitly between within-group and between-group interpretations.

In some cases, we made post hoc decisions that constituted deviations from the protocol, such as combining data from multiple groups (i.e. different doses) or defining outcomes to preserve analytical power. These decisions were guided by clinical reasoning and methodological consistency and not based on the outcome values, but they introduced an element of discretion that should be acknowledged.

Another limitation was the lack of individual patient data, which restricted our ability to explore subgroup effects.

Agreements and disagreements with other studies or reviews

Our findings align with previous systematic reviews and meta-analyses, which suggest that liraglutide may lead to slight reductions in body weight and is associated with an increased incidence of adverse events when compared to placebo.

A recent comprehensive systematic review, which focused on individuals without diabetes, found that liraglutide 3.0 mg showed up to 5.8% weight loss after 26 weeks [17]. Similarly, another recent systematic review reported consistent reductions in body weight (–4.57 kg), BMI (–2.07 kg/m^2), and waist circumference (–4.55 cm), which reinforce the notion that liraglutide leads to weight loss, but also highlight considerable heterogeneity in treatment effects depending on baseline characteristics such as glycaemic status, age, sex, and treatment duration [27].

Two systematic reviews showed that the effect of liraglutide on reducing body weight and waist circumference was relatively modest [336, 337]. In contrast to our findings, one of these systematic reviews reported high-certainty evidence that liraglutide reduced the risk of MACE [336]. In our review, the certainty of the evidence for MACE ranged from moderate to very low. These differences may reflect methodological approaches, as we relied on an approach based on three target ratings (formerly defined as minimally contextualised approach) according to the GRADE Working Group [52, 53], which required the optimal information size (OIS) to be met and is more stringent in assessing imprecision by applying MID thresholds.

Our review found very low-certainty evidence suggesting that liraglutide may increase the number of participants achieving clinically relevant weight loss, both in the medium and long term, in comparison to orlistat. This is consistent with another systematic review, which reported that orlistat had a small effect among the weight-lowering drugs evaluated, and was less effective than GLP-1RAs overall [338]. However, in their network meta-analysis, GLP-1RAs (including liraglutide) showed superior efficacy compared to orlistat, albeit with increased risk of adverse events leading to withdrawal. This apparent discrepancy with our results may reflect the limited direct comparative data available between liraglutide and orlistat, as well as the very low certainty of the evidence in our review [338].

Regarding comparisons with structured lifestyle-modification programmes alone, we found very low-certainty evidence and were uncertain whether liraglutide is more effective than lifestyle intervention without co-intervention. This finding contrasts with broader impressions from other systematic reviews, which generally favoured pharmacotherapy over lifestyle interventions [336, 337]. However, most external analyses either combined lifestyle interventions with pharmacological treatments or compared pharmacotherapy to placebo controls, where lifestyle modification was provided equally to both groups as a balanced co-intervention, or where participants were recruited after participation in a structured lifestyle programme. This limits the direct comparability with our findings.

Overall, our findings align with the broader body of evidence, which supports the modest efficacy of liraglutide in promoting weight loss, while emphasising less favourable tolerability compared to newer agents, and highlighting the need for shared decision making based on individual risk profiles and treatment goals. However, our systematic review provides a more comprehensive GRADE-based assessment, including a broad spectrum of outcomes relevant to decision making and generating recommendations. In addition, our review applied more stringent inclusion criteria, focusing exclusively on studies that recruited participants living with obesity for the primary purpose of weight management, and excluding studies primarily aimed at glycaemic control, treatment of non-alcoholic fatty liver disease, or other indications. We also restricted inclusion to studies that assessed medium- and long-term outcomes, excluding studies limited to short-term follow-up, better to reflect clinically meaningful

treatment effects. We made these methodological and clinical decisions in collaboration with the WHO to ensure alignment with public health priorities and global guideline development processes.

Authors' conclusions

Implications for practice

Compared to placebo, liraglutide likely increases the proportion of people who achieve at least 5% weight loss at medium-term follow-up, and this effect is likely sustained at longer-term follow-up. The impact on other critical outcomes, such as percentage weight change, major adverse cardiovascular events, quality of life, and mortality, may be limited or uncertain. Liraglutide may increase the risk of adverse events, including serious adverse events, which might further limit the sustainability of the initial effects. Furthermore, the health effects of withdrawal or discontinuation of liraglutide, while outside the scope of this review, should be considered when implementing it in practice.

Both clinical and public policy decision-making should interpret this evidence with caution, given the predominance of conflicts of interest. Decisions should therefore be considered provisional, with explicit recognition of this limitation.

Equity-related implications for practice

Obesity is often diagnosed based on weight status in adults, making weight loss a standard measure of treatment effectiveness. While weight loss may be the desirable goal for many, it might not be the main goal of all adults living with obesity. Considering the diversity in body composition, eating habits and overall health behaviours, it might be necessary to consider additional contextual factors when using these drugs in a target population. Obesity as a heterogeneously defined condition indicates that treatment needs differ for individuals with non-comorbid overweight versus severe obesity with complications. Moreover, considering the high prevalence of obesity, the implementation of these drugs may raise important questions about cost-effectiveness and affordability. This is particularly important in the case of liraglutide, which is the only glucagon-like peptide-1 receptor agonist (GLP-1RA) whose patent has expired, allowing for cheaper generic versions to be available. In summary, without considering the social and commercial determinants of health for obesity, the widespread implementation of these drugs taken in isolation may increase existing inequities in people living with obesity.

Implications for research

There are several areas in which further research is urgently needed. First, we need high-quality randomised trials with longer follow-up periods that report on cardiovascular outcomes, mortality, and sustained weight loss, particularly in real-world clinical settings. These studies should also aim to include diverse populations, especially those underrepresented in the current evidence, such as people from low-income and middle-income countries, individuals from racial and ethnic minority groups, or those living with obesity accompanied by complex clinical presentations, including multiple comorbidities, who are not always the primary focus of inclusion criteria.

Second, we encourage future studies to report outcomes more consistently and transparently, using validated patient-reported outcome measures and predefined time points. Researchers should also address the high attrition rates and ensure blinding whenever possible, especially for subjective outcomes such as quality of life.

We also see value in studies that directly compare liraglutide with other active pharmacological agents (e.g. semaglutide, orlistat) and structured lifestyle interventions, as current evidence in these comparisons is scarce and uncertain.

The research work necessary to test the effectiveness of any intervention on the human population should ideally be conducted by independent researchers, without any interest other than generating knowledge, and free from commercial conflicts of interest. As declared in the included studies, the drug manufacturer had a major role in the design, conduct, analysis, or reporting of 13 of the 22 industry-funded studies. Several publications were written not by the researchers but by external writers who were paid by the drug manufacturer. Considering that the results seem to be promising, it would be very advisable to rely on independent research that can reaffirm these categorical findings. For resource-constrained settings, in particular, where the acquisition of high-priced medications requires careful justification, having more independent research is particularly important to guide practice and policy.

We have identified eight ongoing, potentially eligible studies, one of which reports funding from the drug manufacturer (Supplementary material 5). This very active research pipeline will impact upcoming evidence syntheses. In a future update of this review, we plan to reassess the status of all these ongoing studies, aiming to refine our results further, and trying to assess the consistency of the results shown here with those published by independent authors.

Weight loss helps reduce chronic disease risk, but unfortunately, people may regain this lost weight, which may negatively impact metabolic disease risk parameters by reversing or worsening the achieved benefit. Therefore, our findings should be taken cautiously while we await independent studies to assess weight regain after the drug discontinuation and until a sufficient period of pharmacovigilance has been completed to ensure its safety.

Finally, we advocate for future research to incorporate equity-focused analyses and ensure accessibility of anonymised individual participant data (IPD) to facilitate more granular and meaningful meta-analyses across

subgroups.

Equity-related implications for research

Obesity is a significant public health concern that necessitates interventions aimed at improving health outcomes and addressing underlying health inequities. Although the included studies were conducted in various regions, the majority originated from high-income countries, with limited or no representation from regions such as Africa, Central America, and Southeast Asia. Additionally, few studies provided disaggregated data on equity-relevant factors, such as socioeconomic status, educational attainment, or geographic setting, thereby limiting the ability to assess differential intervention effects across socially stratified groups. Future research should adopt and transparently report equity-related variables in accordance with the PROGRESS-Plus framework. Furthermore, there is a pressing need to evaluate interventions that incorporate GLP-1RAs within care models tailored to the needs of structurally marginalised populations and adapted for use in resource-limited settings.

Supplementary materials

[For display in the published PDF only] Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016017.

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Supplementary material 1
CD016017-SUP-01-searchStrategy.html
Search strategies

Supplementary material 2
CD016017-SUP-02-characteristicsOfIncludedStudies.html
Characteristics of included studies

Supplementary material 3
CD016017-SUP-03-characteristicsOfExcludedStudies.html
Characteristics of excluded studies

Supplementary material 4
CD016017-SUP-04-characteristicsOfAwaitingStudies.html
Characteristics of studies awaiting classification

Supplementary material 5
CD016017-SUP-05-characteristicsOfOngoingStudies.html
Characteristics of ongoing studies

Supplementary material 6
CD016017-SUP-06-analyses.html
Analyses

Supplementary material 7
CD016017-SUP-07-dataPackage.zip
Data package

Supplementary material 8
CD016017-SUP-08-other.html
Threshold for minimally important differences

Supplementary material 9
CD016017-SUP-09-other.html

Funder involvement in the included studies

Supplementary material 10

CD016017-SUP-10-other.html

Conflicts of interest declared by study investigators/authors in included studies

Supplementary material 11

CD016017-SUP-11-other.html

Summary of findings table - Liraglutide compared to placebo for adults living with obesity (medium term) - Critical outcomes

Supplementary material 12

CD016017-SUP-12-other.html

Summary of findings table - Liraglutide compared to placebo for adults living with obesity (long term) - Critical outcomes

Supplementary material 13

CD016017-SUP-13-other.html

Summary of findings table - Liraglutide compared to orlistat for adults living with obesity (medium term) - Critical outcomes

Supplementary material 14

CD016017-SUP-14-other.html

Summary of findings table - Liraglutide compared to orlistat for adults living with obesity (long term) - Critical outcomes

Supplementary material 15

CD016017-SUP-15-other.html

Summary of findings table - Liraglutide compared to Structured programmes targeting lifestyle modification for adults living with obesity (medium term) - Critical outcomes

Supplementary material 16

CD016017-SUP-16-other.html

Summary of findings table - Liraglutide compared to other GLP-1 RAs (semaglutide) for adults living with obesity (medium term) - Critical outcomes

Supplementary material 17

CD016017-SUP-17-other.html

Summary of findings table - Liraglutide compared to placebo for adults living with obesity (medium term) - Important outcomes

Supplementary material 18

CD016017-SUP-18-other.html

Summary of findings table - Liraglutide compared to placebo for adults living with obesity (long term) - Important outcomes

Supplementary material 19

CD016017-SUP-19-other.html

Summary of findings table - Liraglutide compared to any other pharmacological intervention for obesity (orlistat) for adults living with obesity (medium term) - Important outcomes

Supplementary material 20

CD016017-SUP-20-other.html

Summary of findings table - Liraglutide compared to any other pharmacological intervention for obesity (orlistat) for adults living with obesity (long term) - Important outcomes

Supplementary material 21

CD016017-SUP-21-other.html

Summary of findings table - Liraglutide compared to structured programmes targeting lifestyle modification for adults living with obesity (medium term) - Important outcomes

Additional information

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The following people conducted the editorial process for this review.

- Sign-off Editor (final editorial decision): Jamie Hartmann-Boyce, UMass Amherst, USA
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- Camila Micaela Escobar Liquitay: Information Specialist; writing
- Eva Madrid: conceptualisation; methodology; writing, review and editing
- Lucía Varela: methodology; writing
- Yang Guo: methodology; writing
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- Daniel Poloni: methodology; writing
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All authors approved the final version to be published and agree to be accountable for all aspects of the review.

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Registration and protocol

The methods for this review were prospectively registered in PROSPERO (CRD420250654193; available in www.crd.york.ac.uk/PROSPERO/view/CRD420250654193) on 24 February 2025 [31]. An earlier version of this protocol was registered in the *Cochrane Database of Systematic Reviews* (DOI: 10.1002/14651858.CD015092) [30]. The protocol covers three systematic reviews, on liraglutide, semaglutide and tirzepatide.

Data, code and other materials

As part of the published Cochrane review, the following is made available for download for users of the Cochrane Library: full search strategies for each database (Supplementary material 1); full citations of each unique report for all included (Supplementary material 2), excluded, awaiting assessment and ongoing studies (Supplementary material 3; Supplementary material 4; Supplementary material 5); study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows (Supplementary material 6; Supplementary material 7). Appropriate permissions have been obtained for such use. Analyses and data management were conducted using Cochrane's authoring tool, Review Manager, which utilises built-in computational methods.

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Tables

Table 1

Overview of included studies and syntheses: general characteristics

Study ID	Country/setting	Intervention and comparison	n (randomised)	Age[a]	Sex[b]	Weight (kg)[a]	BMI[a]	Subpopulation	Follow-up
Alba 2021	US, UK, Belgium, Canada, Poland, Sweden	Liraglutide 3 mg/d vs placebo weekly	179 (1:1)	46.0	23.46%	114.3	40.73	-	26 weeks (plus 4-week non-treatment follow-up)
Altintas Dogan 2022	Denmark	Liraglutide 3 mg/d vs placebo	40 (1:1)	64.7	60%	103.45	35.85	COPD (former smokers)	44 weeks
Astrup 2009	Denmark, Sweden, Finland, UK, Netherlands, Belgium, Spain, Czech Republic	Liraglutide 1.2 mg vs 1.8 mg versus 2.4 vs 3 mg/d vs orlistat 120 mg 3 times/d vs placebo	564 (1:1:1:1:1:1)	45.91	23.9%	97.2	34.8	-	52 weeks (with extension period up to 104 weeks)
Elkind-Hirsch 2022	USA	Liraglutide 3 mg vs placebo (daily)	82 (1:1)	31.3	-	120.7	42.4	Women with PCOS	32 weeks
Khoo 2019	Singapore	Liraglutide 3 mg/d vs structured diet and exercise programme	30 (1:1)	41.1	93.3%	96.2	33.3	NAFLD	26 weeks (plus 26-week non-treatment follow-up)
Lau 2021	Canada, Denmark, Finland, Ireland, Japan, Poland, Serbia, South Africa, UK, USA	Liraglutide 3 mg/d vs placebo	200 (1:1)	51.44	38%	106.99	37.90	Hypertension Dyslipidaemia	26 weeks (plus 6-week non-treatment follow-up)
LOSEIT	Denmark	Liraglutide 3 mg/d vs placebo	156 (1:1)	59.2	35%	93.6	32.1	KOA	52 weeks
McElroy 2024	USA	Liraglutide 3 mg/d vs placebo	60 (1:1)	42.6	20%	106.1	38.07	Stable bipolar disorder	40 weeks
MODEL	USA	IBT vs IBT plus liraglutide 3 mg/d vs IBT plus liraglutide 3 mg/d plus diet therapy	100 (1:1:1)	47.6	20.7%	108.4	38.4	-	52 weeks
Nahra 2021	Bulgaria, Canada, Czech Republic, Germany, Mexico, Russia, Slovakia, USA	Liraglutide 1.8 mg/d vs placebo	222 (1:1)	56.4	48.2%	100.08	34.79	T2DM	54 weeks (plus 4-week non-treatment follow-up)
Neeland 2021	USA	Liraglutide 3 mg/d vs placebo	185 (1:1)	50.15	8.59%	101.55	37.58	Metabolic syndrome	40 weeks (plus 2-week non-treatment follow-up)
O'Donnell 2024	Ireland	Liraglutide 3 mg/d vs CPAP vs liraglutide plus CPAP	30 (1:1:1)	50	80%	-	35	OSA	24 weeks
O'Neil 2018	Australia, Belgium, Canada, Germany, Israel , Russia, UK, USA	Semaglutide 0.05 mg vs 0.1 mg vs 0.2 mg vs 0.3 mg vs 0.4 mg vs liraglutide 3 mg vs placebo (daily)	957	47	35%	111.5	39.3	-	52 weeks (plus a 7-week non-treatment follow-up)
ROMANCE	UK						-	OSA and T2DM	26 weeks

		Liraglutide 1.8 mg/d vs CPAP vs liraglutide plus CPAP vs conventional care	132 (1:1:1:1)	54.5	49.24%	106.87			
S-LITE	Denmark	Liraglutide 3 mg/d vs exercise vs exercise plus liraglutide vs placebo	195 (1:1:1:1)	42.7	36.73%	96.7	32.6	-	52 weeks
SCALE Diabetes	France, Germany, Israel, South Africa, Spain, Sweden, Turkey, UK, USA	Liraglutide 3 mg/d vs 1.8 mg/d vs placebo	846 (1:1:1)	54.90	50.23%	105.92	37.15	T2DM	56 weeks (plus 12-week non-treatment follow-up)
SCALE IBT	USA	Liraglutide 3.0 mg/d vs placebo, both combined with IBT	282 (1:1)	47.2	16.7%	107.6	39.00	-	56 weeks (plus 4-week non-treatment follow-up)
SCALE Insulin	USA, Canada, Germany, Israel, Italy, Mexico, Turkey	Liraglutide 3 mg/d vs placebo	396 (1:1)	56.8	47.7%	99.8	35.6	T2DM treated with basal insulin	56 weeks (plus 4-week non-treatment follow-up)
SCALE Maintenance	USA and Canada	Liraglutide 3 mg/d vs placebo	422 (1:1)	46.2	18.7%	99.6	35.6	After ≥ 5% weight reduction with low-calorie diet	56 weeks (plus 12-week non-treatment follow-up)
SCALE Obesity and Prediabetes	Australia, Austria, Belgium, Brazil, Canada, Denmark, Finland, France, Germany, Hong Kong, Hungary, India, Ireland, Israel, Italy, Mexico, Netherlands, Norway, Poland, Russian Federation, Serbia, South Africa, Spain, Switzerland, Turkey, UK, USA	Liraglutide 3 mg/d vs placebo	3731 (1:1)	45.1	21.5%	106.2	38.3	Stratified by the presence of prediabetes	No prediabetes: 56 weeks, followed by 12-week period of re-randomisation (plus 2-week non-treatment follow-up) Prediabetes: 160 weeks (plus 12-week non-treatment follow-up)
SCALE Sleep Apnoea	Canada and USA	Liraglutide 3 mg/day vs placebo	359 (1:1)	48.5	71.9%	117.6	39.1	OSA	32 weeks (plus 2-week non-treatment follow-up)
STEP 8	USA	Semaglutide 2.4 mg/week vs liraglutide 3 mg/d vs placebo	338 (1:1:1)	49	21.6%	104.54	37.53	-	68 weeks (plus 7-week non-treatment follow-up).
STRIVE	Ireland, UK	Liraglutide 3 mg/d plus SWMS vs standard SWMS care alone	392 (1:1)	51.8	40.2%	127.1	45.5	BMI ≥ 35 plus prediabetes, T2DM, hypertension or sleep apnoea	52 weeks (with extension period up to 104 weeks)
Sun 2023	China	Liraglutide 1.2 mg/d vs lifestyle intervention	39 (1:1)	47.16	66.6%	-	26.48	Impaired glucose tolerance	24 weeks

COPD: chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure; **IBT:** intensive behavioural therapy; **KOA:** knee osteoarthritis; **NAFLD:** non-alcoholic fatty liver disease; **OSA:** obstructive sleep apnoea; **PCOS:** polycystic ovary syndrome; **SWMS:** specialist weight management services; **T2DM:** type 2 diabetes mellitus

[a]Mean or median.

[b]% male.

Table 2

Overview of included studies and syntheses: additional details on population and interventions

Study ID	Intervention and comparison	SBP/DBP (mmHg)	TC/LDL/HDL (mmol/L)	TG (mmol/L)	Ethnicity	Race	Comorbidites
Alba 2021	Liraglutide 3 mg /d vs placebo weekly	126.6/79.1	-	-	-	87% White	Fasting insulin pmol/L FPG mmol/L

						8.37% Black or African American 2.23% Asian 2.23% unknown or not reported	HbA1C
Altintas Dogan 2022	Liraglutide 3 mg/d vs placebo	-	-	-	-	-	100% COPD 100% former smokers
Astrup 2009	Liraglutide 1.2 mg vs 1.8 mg versus 2.4 vs 3 mg/d vs orlistat 120 mg 3 times/d vs placebo	124.5/77.9	4.97/3.47/1.31	1.43	-	98.4% White 1.06% Black or African American 0.35% > 1 race 0.17% American Indian or Alaska Native	Prediabetes T2DM
Elkind-Hirsch 2022	Liraglutide 3 mg/d vs placebo	124.0/81.8	4.1/2.9/1.1	1.5	-	73.1% White 26.8% Black or African American	100% PCOS
Khoo 2019	Liraglutide 3 mg/d vs a structured diet and exercise programme	-	-	-	-	-	100% NAFLD
Lau 2021	Liraglutide 3 mg/d vs placebo	131.85/83.64	-/-/-	-	95.5% not Hispanic or Latino 4.5% Hispanic or Latino	76.5% White 15% Asian 4% unknown or not reported	-
LOSEIT	Liraglutide 3 mg/d vs placebo	-	-	-	-	-	-
McElroy 2024	Liraglutide 3 mg/d vs placebo	120.26/70.97	197.19/116.45/54.02	157.57	100% not Hispanic or Latino	95% White 3% Black or African American 2% unknown or not reported	23.3% dyslipidaemia 18.3% hypertension 6.6% T2DM
MODEL	IBT vs IBT plus liraglutide 3 mg/d vs IBT plus liraglutide plus diet therapy	137.7/76.6	4.99/1.49/2.95	1.19	93.3% not Hispanic or Latino 6.6% Hispanic or Latino	54% White 44.66% Black or African American 1.3% > 1 race	-
Nahra 2021	Liraglutide 1.8 mg/d vs placebo	134.28/81.04	5.02/2.69/1.19	2.57	-	94.59% White 2.7% American Indian or Alaska Native 0.45% unknown or not reported 1.35% Black or African American 0.90% Asian	-
Neeland 2021	Liraglutide 3 mg/d vs placebo	128.36/79.86	-/-/1.47	113.22	23.43% Hispanic or Latino	60.93% White 36.71% Black or African American 2.34% > 1 race	39.06% hypertension 24.21% hyperlipidaemia 3.90% prediabetes
O'Donnell 2024	Liraglutide 3 mg/d vs CPAP vs liraglutide plus CPAP	121/74	4.8/2.85/1.09	1.88			23.3% hypertension

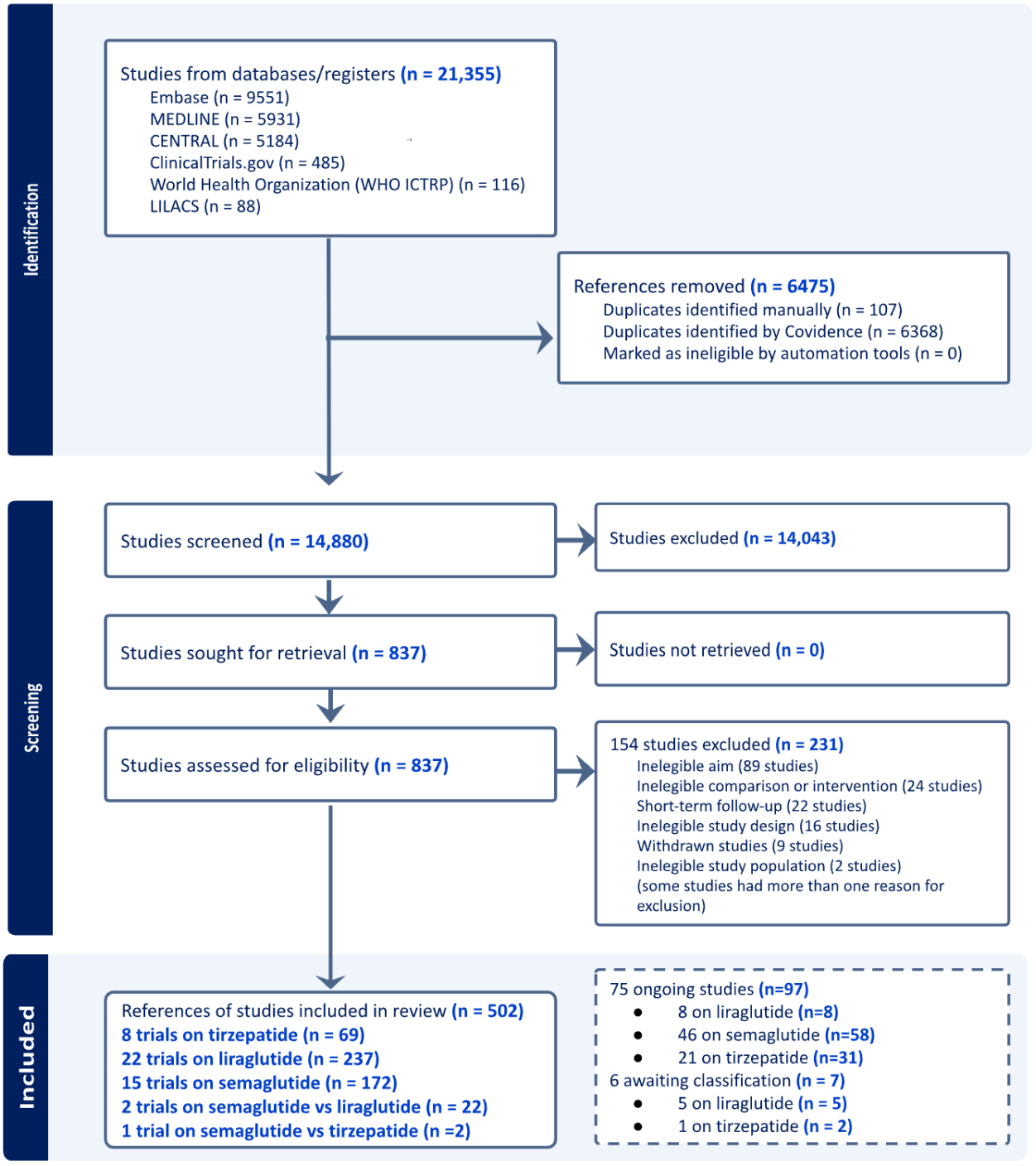
					100% unknown or not reported	100% unknown or not reported	6.67% ischaemic heart disease
O'Neil 2018	Semaglutide 0.05 mg vs 0.1 mg vs 0.2 mg vs 0.3 mg vs 0.4 mg vs liraglutide 3 mg vs placebo (daily)	128/81	5.1/3/1.2	-	-	73.14% White 17.86% unknown or not reported 6.37% Black or African American 0.94% Asian 0.41% American Indian or Alaska Native 0.31% Native Hawaiian or Pacific Islander	-
ROMANCE	Liraglutide 1.8 mg/d vs CPAP vs liraglutide plus CPAP	-	-	-	-	97.72% White 2.27% unknown or not reported	100% moderate-severe OSA and T2DM
S-LITE	Liraglutide 3 mg/d vs exercise vs exercise plus liraglutide vs placebo	122/79	4.07/2.5/1.13	1.07	-	-	-
SCALE Diabetes	Liraglutide 3 mg/d vs 1.8 mg/d vs placebo	79.35/-	-	-	89.36% not Hispanic or Latino 10.28% Hispanic or Latino 0.35% unknown or not reported	83.33% White 11.58% Black or African American 2.36% unknown or not reported 2.24% Asian 0.47% American Indian or Alaska Native	69.26% hypertension 66.66% dyslipidaemia
SCALE IBT	Liraglutide 3.0 mg/d vs placebo, both combined with IBT	125.99/80.49	4.99/2.94/1.34	1.45	88.29% Hispanic or Latino	80.49 % White 17.37 % Black or African American 1.77 % Asian	-
SCALE Insulin	Liraglutide 3 mg/d vs placebo	130.5/78	4.45/2.4/1.2	1.95	81.82% not Hispanic or Latino 18.18 % Hispanic or Latino	89.39% White 7.07% Black or African American 2.02 % Asian 0.51% American Indian or Alaska Native 0.51% Native Hawaiian or Pacific Islander 0.51% Unknown or not reported	100 % T2DM 13.63% current smoker
SCALE Maintenance	Liraglutide 3 mg/d vs placebo	117.2/75	4.6/2.65/1.2	1.25	93.36% not Hispanic or Latino 6.63% Hispanic or Latino	84.12% White 13.27% Black or African American 1.89% unknown or not reported 0.47% Native Hawaiian or Pacific Islander	45% hypertension 31.27% dyslipidaemia

						0.23% Asian	
SCALE Obesity and Prediabetes	Liraglutide 3 mg/d vs placebo	123.09/78.75	5.01/2.89/1.32	1.43	89.46% unknown or not reported 10.53% Hispanic or Latino	84.91% White 9.54% Black or African American 3.65% Asian 1.55% unknown or not reported 0.24% American Indian or Alaska Native 0.10% Native Hawaiian or Pacific Islander	61.24% prediabetes 34.73% hypertension 29.37% dyslipidaemia 13.72% gallbladder disease 8.60% cardiovascular disease
SCALE Sleep Apnoea	Liraglutide 3 mg/d vs placebo	126.44/81.69	-	-	88.02% not Hispanic or Latino 11.98% Hispanic or Latino	73% White 19% Black or AfricanAmerican 4.5% Asian 1.67% Unknown or not reported 0.84% Native Hawaiian or Pacific Islander	63.2% prediabetes 43.7% history of cardiovascular disease 42.3% hypertension 33.4% dyslipidaemia 10.5% history of gall bladder disease
STEP 8	Liraglutide 3 mg/d vs semaglutide 2.4 mg/week vs placebo	124.87/87.99	185.61/106.74/122.99 (mg/dL)	-	-	73.66% White 18.93% Black or African American 3.84% Asian 3.55% unknown or not reported	-
STRIVE	SWMS with or without liraglutide 3 mg/d	136.6/81.6	4.8/2.7/1.2	1.9	-	6% Black 86% White	16% prediabetes 35% T2DM 49% sleep apnoea 64% hypertension
Sun 2023	Liraglutide 1.2 mg/d vs lifestyle intervention	119.79/66.53	5.56/5.61/1.49	1.28	-	-	-

COPD: chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure; **DBP:** diastolic blood pressure; **IBT:** intensive behavioural therapy; **LDL:** low-density lipoprotein; **NAFLD:** non-alcoholic fatty liver disease; **OSA:** obstructive sleep apnoea; **PCOS:** polycystic ovary syndrome; **SBP:** systolic blood pressure; **SWMS:** specialist weight management services; **T2DM:** type 2 diabetes mellitus; **TC:** total cholesterol

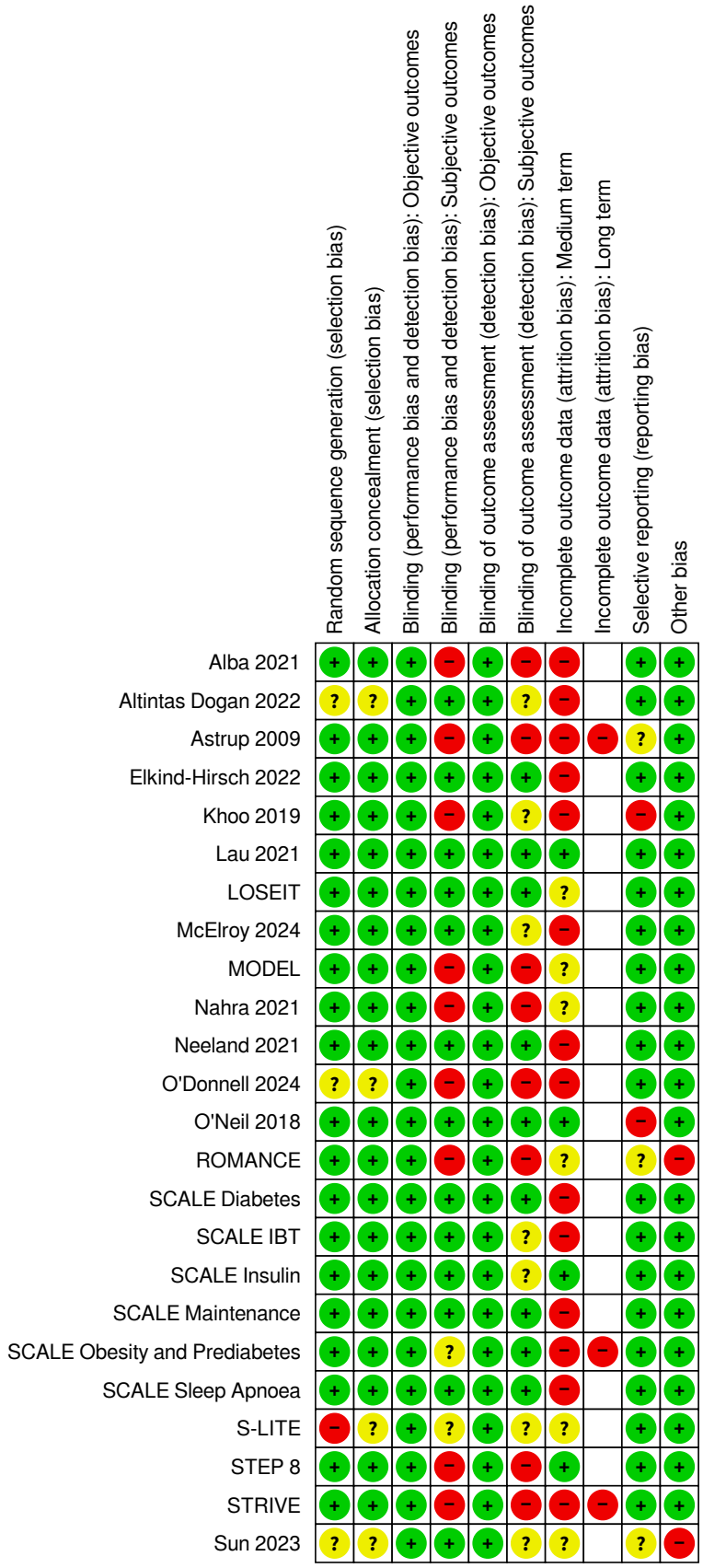
Figures

Figure 1



PRISMA flow diagram for the suite of reviews on liraglutide, semaglutide and tirzepatide

Figure 2



A 'risk of bias summary' figure illustrating all of the judgements in a cross-tabulation of included studies