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Semaglutide 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. Semaglutide, a widely used glucagon-like peptide-1 receptor agonist (GLP-1RA), can aid in weight loss by reducing appetite. However, its efficacy remains unclear.

Objectives

To assess the effects of semaglutide on adults living with obesity.

Search methods

We searched CENTRAL, MEDLINE, Embase, LILACS, and two trials registries. The latest search date was 17 December 2024.

Eligibility criteria

We included randomised controlled trials (RCTs) that compared semaglutide with placebo, structured lifestyle modification programmes, other anti-obesity medications or other GLP-1RAs in adults living with obesity, with a minimum of six months' follow-up.

Outcomes

Critical outcomes were 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.

Risk of bias

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

Synthesis methods

We synthesised results for each outcome using meta-analysis with a random-effects model. Where this was not possible, we described the results narratively. We used GRADE to assess the certainty of evidence for each outcome. The main comparison of interest in the review is semaglutide versus placebo.

Included studies

We included 18 RCTs (27,949 participants), with a mean age ranging from 41.0 to 69.5 years, and an average BMI between 31.9 kg/m^2 and 40.3 kg/m^2. Seventeen RCTs reported that the drug manufacturer had a major role in their design, conduct, analysis, or writing. Seventeen RCTs compared semaglutide versus placebo, at medium- (16 RCTs) or long-term (2 RCTs) follow-up. Other comparators were liraglutide (2 RCTs) and tirzepatide (1 RCT).

Synthesis of results

Semaglutide versus placebo (medium term: 24 to 68 weeks)

At medium-term follow-up, semaglutide reduces percentage body weight (mean difference (MD) -10.73, 95% confidence interval (CI) -12.24 to -9.21; 15 studies, 8651 participants; high-certainty evidence) and increases the proportion of people achieving 5% weight loss (risk ratio (RR) 2.68, 95% CI 2.30 to 3.12; 12 studies, 7458 participants; high-certainty evidence).

Semaglutide may increase non-serious adverse events (RR 1.11, 95% CI 1.01 to 1.22; 13 studies, 8443 participants; low-certainty evidence), likely results in little to no absolute difference in adverse events leading to withdrawal (RR 1.84, 95% CI 1.53 to 2.21; 15 studies, 9054 participants; moderate-certainty evidence), and has very uncertain effects on serious adverse events (RR 1.01, 95% CI 0.78 to 1.29; 15 studies, 9054 participants; very low-certainty evidence).

Semaglutide likely results in little to no difference in quality of life (SF-36 physical functioning score: MD 2.12, 95% CI 0.95 to 3.28; 9 studies, 6083 participants; moderate-certainty evidence).

Semaglutide may result in little to no absolute difference in MACE (RR 0.63, 95% CI 0.44 to 0.90; 9 studies, 7647 participants; low-certainty evidence) and mortality (RR 0.69, 95% CI 0.48 to 0.98; 14 studies, 8953 participants; low-certainty evidence).

For most outcomes, the main reasons for downgrading certainty of evidence were related to imprecision and inconsistency.

Semaglutide versus placebo (long term: 104 weeks)

At long-term follow-up, semaglutide likely reduces percentage body weight (MD -11.11, 95% CI -16.47 to -5.75; 2 studies, 15124 participants; moderate-certainty evidence) and likely increases the proportion of people achieving 5% weight loss (RR 2.74, 95% CI 1.95 to 3.84; 2 studies, 17876 participants; moderate-certainty evidence).

Its effects on non-serious adverse events are very uncertain (RR 1.21, 95% CI 1.10 to 1.34; 1 study, 305 participants; very low-certainty evidence), with likely little to no difference in serious adverse events (RR 0.92, 95% CI 0.88 to 0.95; 2 studies, 17908 participants; moderate-certainty evidence), and a likely increase in adverse events leading to withdrawal (RR 2.03, 95% CI 1.86 to 2.20; 2 studies, 17908 participants; moderate-certainty evidence).

Semaglutide likely results in little to no clinically significant differences in quality of life (EQ-5D-5L: MD 0.02, 95% CI 0.02 to 0.02; moderate-certainty evidence), MACE (RR 0.81, 95% CI 0.73 to 0.90; moderate-certainty evidence), and mortality (RR 0.82, 95% CI 0.72 to 0.94; moderate-certainty evidence).

For most outcomes, the main reasons for downgrading certainty of evidence were related to risk of bias and imprecision.

Authors' conclusions

Semaglutide results in a clinically relevant weight loss at medium-term follow-up compared to placebo, which is likely to be sustained in the long term, while taking the drug. While semaglutide increases the risk of adverse events leading to withdrawal, it appears to be of limited clinical relevance in absolute terms at medium-term, and clinically relevant at long-term follow-up. The effects of semaglutide on quality of life, MACE, and mortality are likely limited or uncertain. Most studies were funded by the drug's manufacturer, raising important concerns about conflicts of interest. We identified 46 ongoing studies that may strengthen future evidence syntheses. Further independent studies are needed, particularly in underrepresented populations, to better understand the broader effects of semaglutide in the management of obesity.

Funding

This Cochrane review was funded by the World Health Organization (WHO).

Registration

Original protocol (10.1002/14651858.CD015092) published in September 2022. The modifications to the original protocol were prospectively registered in PROSPERO (CRD420250654193) in February 2025.

Plain language summary

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

Key messages

- Adults with obesity lose more weight with semaglutide than with placebo (a sham medication). However, the risk of unwanted events is probably higher with placebo after 24 months. Semaglutide makes little to no difference — or has uncertain effects — on quality of life, major cardiovascular events and death.
- Semaglutide's manufacturer was involved in 17 of the 18 included studies, raising concerns about the reliability of the results. More independent research is needed that focuses on people from different backgrounds and places.

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 large burden on healthcare systems. Managing obesity often 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 medication to support weight loss.

What is semaglutide?
Semaglutide is a medication that mimics a natural gut hormone. It reduces appetite, helping people to lose weight. It can be given as an injection or swallowed. Some people taking semaglutide experience unwanted effects, such as feeling or being sick, diarrhoea and indigestion. Similar medications include liraglutide and tirzepatide.

What did we want to find out?
We wanted to know how well semaglutide 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 loss, unwanted effects, health problems associated with obesity, quality of life, and risk of death.

We did not look at what happens after people stop taking semaglutide.

What did we do?
We searched for studies that compared semaglutide with a placebo (a sham medication), lifestyle changes or another weight-loss medication for people living with obesity. We compared and analysed the results, and assessed our confidence in the evidence.

What did we find?
We included 18 studies with 27,949 men and women, aged 41 to 69 years, who took semaglutide for between 6 months and 4 years or longer. The studies mainly took place in upper-middle- or high-income countries, and mostly included White and Asian people. They compared semaglutide with placebo, liraglutide and tirzepatide.

Semaglutide compared to placebo

- **In the medium term (16 studies, 10,041 people):** semaglutide leads to more weight loss as a percentage of body weight, and to more people losing 5% of their body weight than placebo. People may experience mild-to-moderate unwanted effects with semaglutide, but these unwanted effects probably make little or no

difference to people who decide to stop treatment. The effects of semaglutide on serious unwanted effects are unclear. Semaglutide likely makes little or no difference to quality of life and may not significantly reduce major cardiovascular events or deaths.

- **In the long term (2 studies, 17,908 people):** weight loss probably continues with semaglutide as a percentage of body weight and in the number of people who lose 5% of their body weight. Semaglutide probably makes little to no difference to serious unwanted effects, and we are unsure about its effects on mild-to-moderate unwanted effects. However, these unwanted effects probably make more people decide to stop treatment. Semaglutide likely makes little or no difference to quality of life, major cardiovascular events or death.

Semaglutide compared to liraglutide (medium term, 2 studies, x people)

- People taking semaglutide may lose more weight compared to those taking liraglutide. There may be little to no difference in quality of life. We are very uncertain about semaglutide's effects on unwanted events causing people to stop taking the medication, serious unwanted events, cardiovascular events and death.

Semaglutide compared to tirzepatide (medium term, 1 study, 750 people)

- People taking semaglutide may lose less weight than those taking tirzepatide. Semaglutide may make little to no difference to unwanted events causing people to stop taking the medication. We are very uncertain about its effects on serious unwanted events, cardiovascular events and death. The study did not report quality of life.

What are the limitations of the evidence?

We are very confident that people taking semaglutide lose more weight than those taking placebo. However, semaglutide’s manufacturer was involved in most of the studies, so our confidence in the results is limited. Study locations and participants were quite similar, so we don’t know how semaglutide works for people from different backgrounds and places.

How up-to-date is this review?
This evidence is up to date to 17 December 2024.

Summary of findings

Summary of findings 1

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

Patient or population: adults living with obesity
Setting: outpatient
Intervention: semaglutide
Comparison: placebo

Outcome domain	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 semaglutide				
Weight follow-up: range 24 to 68 weeks	% weight change from baseline	The mean % weight change from baseline - medium term was **−0.14**%	MD **10.73 % lower** (12.24 lower to 9.21 lower)	-	8651 (15 RCTs)	⊕⊕⊕⊕ High[a]	Semaglutide reduces weight (measured as percentage) at medium-term follow-up.
	People achieving a 5% weight reduction	319 per 1000	**855 per 1000** (734 to 996)	**RR 2.68** (2.30 to 3.12)	7458 (12 RCTs)	⊕⊕⊕⊕ High[b]	Semaglutide increases the proportion of people achieving a 5% weight reduction at medium-term follow-up.
Adverse events follow-up: range 24 to 68 weeks	Non-serious	643 per 1000	**714 per 1000** (650 to 785)	**RR 1.11** (1.01 to 1.22)	8443 (13 RCTs)	⊕⊕⊖⊖ Low[c,d,e]	Semaglutide may increase non-serious adverse events at medium-term follow-up.
	Serious	106 per 1000	**107 per 1000** (83 to 137)	**RR 1.01** (0.78 to 1.29)	9054 (15 RCTs)	⊕⊖⊖⊖ Very low[c,f,g]	The evidence is very uncertain about the effect of semaglutide on serious adverse events at medium-term follow-up.
	Leading to withdrawal	36 per 1000	**66 per 1000** (55 to 79)	**RR 1.84** (1.53 to 2.21)	9054 (15 RCTs)	⊕⊕⊕⊖ Moderate[c,e]	Semaglutide likely results in little to no clinically important difference in adverse events leading to withdrawal at medium-term follow-up.[h]
Major adverse cardiovascular event (MACE) follow-up: range 48 to 68 weeks		92 per 1000	**58 per 1000** (41 to 83)	**RR 0.63** (0.44 to 0.90)	7647 (9 RCTs)	⊕⊕⊖⊖ Low[e,i]	Semaglutide may result in little to no clinically important difference in MACE at medium-term follow-up.[j]
Quality of life: follow-up: range 44 to 68 weeks	SF-36 physical functioning score	The mean quality of life: SF-36 physical functioning score - medium term was **0.09.**	MD **2.12 higher** (0.95 higher to 3.28 higher)	-	6083 (9 RCTs)	⊕⊕⊕⊖ Moderate[k,l]	Semaglutide likely results in little to no clinically important difference in quality of life: SF-36 physical functioning score at medium-term follow-up.
Mortality follow-up: range 32 to 68 weeks		5 per 1000	**4 per 1000** (3 to 5)	**RR 0.69** (0.48 to 0.98)	8953 (14 RCTs)	⊕⊕⊖⊖ Low[m]	Semaglutide may result in little to no clinically important difference in mortality at medium-term follow-up.[n]

*__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; **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]Inconsistency: considering our prespecified minimal clinically important differences, we did not downgrade due to inconsistency even though I^2 statistic > 90%, as the point estimates and confidence intervals were consistently above the minimally important difference.

[b]Inconsistency: considering our prespecified minimal clinically important differences, we did not downgrade due to inconsistency even though I^2 statistic is between 60% and 90%, as the point estimates and confidence intervals were consistently above the minimally important difference.

[c]Risk of bias: we did not downgrade due to risk of bias. Despite some analyses including studies with unclear data about randomisation process (Eckard 2024 [1], SMART [2]). or not being adequately blinded (STEP 8 [3]), a sensitivity analysis excluding these studies did not significantly change the estimate for the following outcomes: any adverse events (RR 1.08, 95% CI 1.01 to 1.15, I^2 = 71%); only non-serious adverse events (RR 1.08, 95% CI 0.99 to 1.18, I^2 = 81%); serious adverse events (RR 1.00, 95% CI 0.75 to 1.34, I^2 = 68%); adverse events leading to withdrawal (RR 1.86, 95% CI 1.53 to 2.27, I^2 = 0%); systolic blood pressure (MD −5.21 mmHg, 95% CI −6.24 to −4.18, I^2 = 43%); diastolic blood pressure (MD −1.72 mmHg, 95% CI −2.26 to −1.18, I^2 = 15%); and increased need for antihypertensive drugs (RR 0.71, 95% CI 0.45 to 1.11, I^2 = 31%).

[d]Inconsistency: we downgraded one level due to inconsistency, with I^2 statistic between 60% and 90%, and estimates on both sides of the minimally important difference. Sensitivity analysis did not successfully explain the inconsistency.

[e]Imprecision: we downgraded one level, since the confidence interval crosses the minimally important difference.

[f]Inconsistency: we downgraded one level due to inconsistency, with I^2 statistic between 60% and 90%, and estimates on both sides of the minimally important difference. Sensitivity analysis solved the inconsistency when excluding the studies that considered patients with heart failure (STEP-HFpEF [4]; STEP-HFpEF DM [5]). This sensitivity analysis provides a result of RR 1.20 (95% CI 0.99 to 1.45, I^2 = 9%).

[g]Imprecision: we downgraded two levels, as the confidence interval crosses the minimally important difference both in favour and against semaglutide.

[h]Interpretation: RR = 1.84, meaning that with semaglutide there is 84% more risk of having an adverse event leading to withdrawal, as compared to placebo. Due to the baseline risk of the placebo group (3.6%), this translates into an absolute risk of 6.6% for the semaglutide group (absolute risk difference = 3.0%), which is below our minimally important threshold of 5% absolute risk difference. In populations with a higher baseline risk (from 6% baseline risk in the control group), the absolute difference would be clinically significant.

[i]Indirectness: we downgraded one level due to indirectness. Some studies included events not typically considered MACE (e.g. arrhythmia), or reported 'cardiovascular disorders' with no further explanation.

[j]Interpretation: RR = 0.63, meaning that with semaglutide there is 37% less risk of having a MACE compared to placebo. Due to the baseline risk of the placebo group (9.2%), this translates into an absolute risk of 5.8% for the semaglutide group (absolute risk difference = 3.4%), which is below our minimally important threshold of 5% absolute risk difference. In populations with a higher baseline risk (from 13.5% baseline risk in the control group), the absolute difference would be clinically significant.

[k]Imprecision: we did not downgrade due to imprecision, since both the upper and lower bound of the confidence interval show a non-important effect, as defined by the minimally important difference.

[l]Inconsistency: we downgraded one level due to inconsistency, with I^2 statistic between 60% and 90%. Sensitivity analysis showed that STEP 9 accounted for more than half of the inconsistency.

[m]Imprecision: we downgraded two levels due to imprecision, due to the few total events per arm.

[n]Interpretation: RR = 0.69, meaning that with semaglutide there is 31% less risk of mortality, as compared to placebo. Due to the baseline risk of the placebo group (0.5%), this translates into an absolute risk of 0.4% for the semaglutide group (absolute risk difference = 0.1%), which is below our minimally important threshold of 1% absolute risk difference. In populations with a higher baseline risk (from 1.7% baseline risk in the control group), the absolute difference would be clinically significant.

Summary of findings 2

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

Patient or population: adults living with obesity
Setting: outpatient
Intervention: semaglutide
Comparison: placebo

Outcome domain	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 semaglutide				
Weight follow-up: mean 104 weeks	% weight change from baseline	The mean % weight change from baseline - long term was **−0.68**%	MD **11.11 % lower** (16.47 lower to 5.75 lower)	-	15,124 (2 RCTs)	⊕⊕⊕⊖ Moderate[a,b]	Semaglutide likely reduces weight (measured as percentage) at long-term follow-up.
	People achieving a 5% weight reduction	215 per 1000	**589 per 1000** (419 to 825)	**RR 2.74** (1.95 to 3.84)	17,876 (2 RCTs)	⊕⊕⊕⊖ Moderate[a,c]	Semaglutide likely increases the proportion of people achieving a 5% weight reduction at long-term follow-up.
Adverse events follow-up: range 104 weeks to 240 weeks	Non-serious	765 per 1000	**925 per 1000** (841 to 1000)	**RR 1.21** (1.10 to 1.34)	305 (1 RCT)	⊕⊖⊖⊖ Very low[d]	The evidence is very uncertain about the effect of semaglutide on non-serious adverse events at long-term follow-up.

	Serious	360 per 1000	**331 per 1000** (317 to 342)	**RR 0.92** (0.88 to 0.95)	17,908 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	Semaglutide likely results in little to no clinically important difference in serious adverse events at long-term follow-up.[e]
	Leading to withdrawal	81 per 1000	**164 per 1000** (151 to 178)	**RR 2.03** (1.86 to 2.20)	17,908 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	Semaglutide likely increases adverse events leading to withdrawal at long-term follow-up.
Major adverse cardiovascular event (MACE) follow-up: range 104 weeks to 240 weeks		78 per 1000	**64 per 1000** (57 to 71)	**RR 0.81** (0.73 to 0.90)	17,908 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	Semaglutide likely results in little to no clinically important difference in MACE at long-term follow-up.[f]
Quality of life: follow-up: mean 104 weeks	EQ-5D-5L	The mean quality of life: EQ-5D-5L - long term was **−0.01**	MD **0.02 higher** (0.02 higher to 0.02 higher)	-	13,426 (1 RCT)	⊕⊕⊕⊖ Moderate[g,h,]	Semaglutide likely results in little to no clinically important difference in quality of life: EQ-5D-5L at long-term follow-up.
Mortality follow-up: range 104 weeks to 240 weeks		51 per 1000	**42 per 1000** (37 to 48)	**RR 0.82** (0.72 to 0.94)	17,908 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	Semaglutide likely results in little to no clinically important difference in mortality at long-term follow-up.[i]

*__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; **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]Risk of bias: we downgraded one level, since in the SELECT study [6], the number of individuals with data attending long-term visits is not clear (probably > 10%).

[b]Inconsistency: considering our prespecified minimal clinically important differences, we did not downgrade due to inconsistency even though I^2 statistic is > 90%, as the point estimates and confidence intervals were consistently above the minimally important difference.

[c]Inconsistency: considering our prespecified minimal clinically important differences, we did not downgrade due to inconsistency even though I^2 statistic is between 60% and 90%, as the point estimates and confidence intervals were consistently at one side relative to the minimally important difference.

[d]Imprecision: we downgraded three levels, since the confidence interval crosses the minimally important difference and optimal information size is not met (which was calculated according to the GRADE guidelines 6).

[e]Interpretation: RR = 0.92, meaning that with semaglutide there is 8% less risk of having a serious adverse event, compared to placebo. Due to the baseline risk of the placebo group (3.6%), this translates into an absolute risk of 3.3% for the semaglutide group (absolute risk difference = 0.3%), which is below our minimally important threshold of 1% absolute risk difference. In populations with a higher baseline risk (from 12.5% baseline risk in the control group), the absolute difference would be clinically significant.

[f]Interpretation: RR = 0.81, meaning that with semaglutide there is 19% less risk of having a MACE compared to placebo. Due to the baseline risk of the placebo group (7.8%), this translates into an absolute risk of 6.4% for the semaglutide group (absolute risk difference = 1.4%), which is below our minimally important threshold of 5% absolute risk difference. In populations with a higher baseline risk (from 26.3% baseline risk in the control group), the absolute difference would be clinically significant.

[g]Risk of bias: we downgraded one level, since approximately 25% of individuals had no data for this outcome.

[h]Imprecision: we did not downgrade due to imprecision, since both the upper and lower bound of the confidence interval show a non-important effect, as defined by the minimally important difference.

[i]Interpretation: RR = 0.82, meaning that with semaglutide there is 18% less risk of mortality compared to placebo. Due to the baseline risk of the placebo group (5.1%), this translates into an absolute risk of 4.2% for the semaglutide group (absolute risk difference = 0.9%), which is below our minimally important threshold of 1% absolute risk difference. In populations with a higher baseline risk (from 5.6% baseline risk in the control group), the absolute difference would be clinically significant.

Summary of findings 3

Semaglutide compared to liraglutide for adults living with obesity (medium-term follow-up)

Patient or population: adults living with obesity
Setting: outpatient
Intervention: semaglutide
Comparison: liraglutide

Outcome domain	Outcome measure	Anticipated absolute effects* (95% CI)	Relative effect	№ of participant	Certainty of the evidenc	Comments

		Risk with liraglutide	Risk with semaglutide	(95% CI)	s (studies)	e (GRADE)	
Weight follow-up: range 52 weeks to 68 weeks	% weight change from baseline	The mean % weight change from baseline - medium term was **−3.54**%	MD **6.75 % lower** (13.03 lower to 0.46 lower)	-	1002 (2 RCTs)	⊕⊕⊝⊝ Low[a,b,c]	Semaglutide may reduce weight (measured as percentage) at medium-term follow-up, compared to liraglutide.
	People achieving a 5% weight reduction	615 per 1000	**800 per 1000** (609 to 1000)	**RR 1.30** (0.99 to 1.71)	1002 (2 RCTs)	⊕⊕⊝⊝ Low[a,b,c]	Semaglutide may increase the proportion of people achieving a 5% weight reduction at medium-term follow-up, compared to liraglutide.
Adverse events follow-up: range 52 weeks to 68 weeks	Non-serious	835 per 1000	**860 per 1000** (810 to 927)	**RR 1.03** (0.97 to 1.11)	1074 (2 RCTs)	⊕⊕⊝⊝ Low[c,f]	Semaglutide may result in little to no clinically important difference in non-serious adverse events at medium-term follow-up, compared to liraglutide.
	Serious	78 per 1000	**92 per 1000** (32 to 257)	**RR 1.17** (0.41 to 3.29)	1074 (2 RCTs)	⊕⊝⊝⊝ Very low[a,b,g]	The evidence is very uncertain about the effect of semaglutide on serious adverse events at medium-term follow-up, compared to liraglutide.
	Leading to withdrawal	109 per 1000	**59 per 1000** (15 to 230)	**RR 0.54** (0.14 to 2.12)	1074 (2 RCTs)	⊕⊝⊝⊝ Very low[a,b,g]	The evidence is very uncertain about the effect of semaglutide on adverse events leading to withdrawal at medium-term follow-up, compared to liraglutide.
Major adverse cardiovascular event (MACE) follow-up: mean 52 weeks		0 per 1000	**0 per 1000** (0 to 0)	**RR 1.30** (0.07 to 24.00)	821 (1 RCT)	⊕⊝⊝⊝ Very low[h]	The evidence is very uncertain about the effect of semaglutide on MACE at medium-term follow-up, compared to liraglutide.
Quality of life: follow-up: mean 52 weeks	SF-36 physical functioning score	The mean quality of life: SF-36 physical functioning score - medium term (higher is better) was **6.79**	MD **0.29 lower** (2.74 lower to 2.16 higher)	-	211 (1 RCT)	⊕⊕⊝⊝ Low[i,j]	Semaglutide may result in little to no clinically important difference in quality of life: SF-36 physical functioning score at medium-term follow-up, compared to liraglutide.
Mortality follow-up: range 52 weeks to 68 weeks		0 per 1000	**0 per 1000** (0 to 0)	**RR 0.43** (0.02 to 10.58)	1074 (2 RCTs)	⊕⊝⊝⊝ Very low[a,k]	The evidence is very uncertain about the effect of semaglutide on mortality at medium-term follow-up, compared to liraglutide.

*__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; **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]Risk of bias: STEP 8 was open-label for the comparison semaglutide versus liraglutide [3]. However, we did not downgrade certainty of evidence for this outcome, since we considered it to be objectively measurable.

[b]Inconsistency: We downgraded one level due to inconsistency, with I^2 statistic between 60% and 90%, and estimates on both sides of the minimally important difference.

[c]Imprecision: We downgraded one level, since the confidence interval crosses the minimally important difference.

[d]Imprecision: We downgraded two levels, since the confidence interval crosses the minimally important difference, and optimal information size is not met for the liraglutide arm (which was calculated according to GRADE guideline 6).

[e]Inconsistency: Considering our prespecified minimal clinically important differences, we did not downgrade due to inconsistency even though I^2 is between 60% and 90%, as the point estimates and confidence intervals were consistently on the same side of the minimally important difference.

dRisk of bias: We downgrade one level, since STEP 8 was open-label for this comparison[3]. These outcomes (any adverse events or non-serious adverse events) were considered subjective for analysis purposes, as they were not adjudicated by an independent external committee.

[g]Imprecision: We downgraded two levels, as the confidence interval crosses the minimally important difference both in favour of semaglutide and in favour of liraglutide.

[h]Imprecision: We downgraded three levels, since the confidence interval crosses the minimally important difference both in favour of semaglutide and in favour of liraglutide, and optimal information was not met (which was calculated according to GRADE guideline 6).

[i]Imprecision: We downgraded two levels due to imprecision, since optimal information size is not met for any arm (which was calculated according to GRADE guideline 6).

[j]Both the upper and lower bound of the confidence interval show a non-important effect, as defined by the minimally important difference.

[k]Imprecision: We downgraded three levels due to extreme imprecision, since there is only one event for this outcome between the two studies, therefore, confidence intervals are very wide.

Summary of findings 4

Semaglutide compared to tirzepatide for adults living with obesity (medium-term follow-up)

Patient or population: adults living with obesity

Setting: outpatient
Intervention: semaglutide
Comparison: tirzepatide

Outcome domain	Outcome measure	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with tirzepatide	Risk with semaglutide				
Weight follow-up: 72 weeks	% weight change from baseline	The mean % weight change from baseline - medium term was **−20.2**%	MD **6.5 % higher** (4.87 higher to 8.13 higher)	-	750 (1 RCT)	⊕⊕⊖⊖ Low[a,b]	Semaglutide may result in a lower weight loss (measured as percentage), compared to tirzepatide.
	People achieving a 5% weight reduction	-	-	-	-	-	None of the included studies provided data for this outcome.
	People achieving a 10% weight reduction	813 per 1000	**601 per 1000** (553 to 667)	**RR 0.74** (0.68 to 0.82)	750 (1 RCT)	⊕⊕⊖⊖ Low[a,b]	Semaglutide may reduce the proportion of people achieving a 10% weight reduction at medium-term follow-up, compared to tirzepatide.
Adverse events follow-up: 72 weeks	Non-serious	719 per 1000	**755 per 1000** (690 to 820)	**RR 1.05** (0.96 to 1.14)	750 (1 RCT)	⊕⊕⊖⊖ Low[a,b]	Semaglutide may result in little to no clinically important difference in non-serious adverse events at medium-term follow-up, compared to tirzepatide.
	Serious	48 per 1000	**35 per 1000** (17 to 70)	**RR 0.72** (0.36 to 1.45)	750 (1 RCT)	⊕⊖⊖⊖ Very low[a,c]	The evidence is very uncertain about the effect of semaglutide on serious adverse events at medium-term follow-up, compared to tirzepatide.
	Leading to withdrawal	61 per 1000	**80 per 1000** (47 to 135)	**RR 1.30** (0.77 to 2.19)	750 (1 RCT)	⊕⊕⊖⊖ Low[a,b]	Semaglutide may result in little to no clinically important difference in adverse events leading to withdrawal at medium-term follow-up, compared to tirzepatide.
Major adverse cardiovascular event (MACE) follow-up: 72 weeks		Not pooled	Not pooled	Not pooled	750 (1 RCT)	⊕⊖⊖⊖ Very low[a,d]	The evidence is very uncertain about the effect of semaglutide on MACE at medium-term follow-up, compared to tirzepatide.
Quality of life		-	-	-	-	-	None of the included studies provided data for this outcome.
Mortality follow-up: 72 weeks		Not pooled	Not pooled	Not pooled	750 (1 RCT)	⊕⊖⊖⊖ Very low[a,d]	The evidence is very uncertain about the effect of semaglutide on mortality at medium-term follow-up, compared to tirzepatide.

*__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; **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.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_459514593765226506.

[a]Risk of bias: we downgraded one level due to a high risk of bias as the study had an unclear risk due to > 10% attrition and, in the case of subjective outcomes, high risk due to unblinding.
[b]Imprecision: we downgraded one level, since the confidence interval crosses the minimally important difference.
[c]Imprecision: we downgraded two levels, since the confidence interval crosses the minimally important difference both in favour and against semaglutide.
[d]Imprecision: we downgraded three levels due to extreme imprecision. There were no events for this outcome.

Background

Description of the condition

Obesity is a complex chronic disease, characterised by an abnormal or excessive accumulation of fat, which alters the anatomy and physiology and may result in metabolic, biomechanical, and psychosocial health consequences [7]. This condition is associated with hypertension, stroke, type 2 diabetes mellitus, dyslipidaemia, obstructive sleep apnoea, and certain types of cancer [8, 9]. Additionally, obesity increases the cardiovascular risk for those who suffer from these diseases [8, 9].

To determine if a person between 18 and 64 years old has overweight or obesity, we use the body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of his or her height in metres (kg/m^2). Overweight is defined as a BMI ranging from 25 kg/m^2 to 29.9 kg/m^2, and obesity is defined as a BMI of 30 kg/m^2 or more [9], although there may be some exceptions depending on context.

The global prevalence of obesity has tripled since 1975. In 2016, 39% of adults were overweight, and 13% were obese [9]. It is estimated that currently, at least 2.8 million people die each year worldwide due to conditions linked to overweight or obesity and that by 2050, 45% of the world's population will be overweight and 16% will be living with obesity [9, 10, 11]. Beyond individual-level factors, obesity — alongside undernutrition and climate change — has been conceptualised as part of a global 'syndemic' that threatens human health and survival on a large scale. This syndemic is driven by systemic forces, particularly those related to food and agriculture (e.g. widespread availability of ultra-processed foods), transportation (e.g. car-dependent infrastructure), urban design, and land-use patterns [12].

Obesity is a chronic condition with known complications, whose management has clear benefits. Treating obesity and its related conditions imposes a large economic burden on the individual, families, and nations [13]. In 2014, the global economic impact of obesity was estimated to be United States dollars (USD) 2.0 trillion [13]. Many investigations have evaluated the cost of obesity, estimating that per capita medical spending is 42% to 150% higher in individuals with obesity compared to individuals without obesity [14, 15]. Besides excess healthcare expenditure, obesity also has costs in the form of lost productivity and foregone economic growth as a result of lower productivity at work, lost workdays, permanent disability, and mortality [13].

Description of the intervention and how it might work

Semaglutide is a glucagon-like peptide-1 receptor agonist (GLP-1RA) used to achieve adequate glycaemic control for people with type 2 diabetes mellitus. Several studies that focused on glycaemic improvement in these people also reported a secondary benefit in terms of bodyweight reduction and cardiovascular improvements [16].

Glucagon-like peptide-1 (GLP-1) is a hormone produced in the intestinal enteroendocrine L-cells in response to meal ingestion, and it is rapidly inactivated by the enzyme dipeptidyl peptidase IV (DPP-IV). The main actions of GLP-1 are to stimulate insulin secretion and inhibit glucagon secretion in a glucose-dependent manner, thereby contributing to lowering glycaemic levels, without causing hypoglycaemia [17, 18]. The mechanism of action of GLP-1RAs for weight loss is not completely understood. Physiologically, endogenous GLP-1 is degraded by DPP-IV into inactive metabolites and has a half-life of less than 10 minutes [19]. It is thought that GLP-1 primarily stimulates GLP-1 receptors, slowing gastric emptying through a vagal pathway, and maximising nutrient absorption while limiting weight gain [17, 18, 20]. GLP-1RAs are drugs that imitate the actions of GLP-1 and have been modified so as not to be degraded by DPP-IV, achieving supraphysiological plasma concentrations [21]. It is proposed that this allows GLP-1RAs to target the homeostatic control of energy balance, leading to weight loss [22]. Preclinical studies have shown that GLP-1RAs injected peripherally target GLP-1 receptors located in the hypothalamic arcuate nucleus and that their stimulation produces an anorexigenic effect that ultimately induces weight loss [19, 22, 23]. In addition to the percentage of weight reduction, a decrease in visceral-abdominal fat mass is expected. These goals may be associated with a decrease in cardiovascular risk [24, 25].

In 2005, exenatide was the first GLP-1RA to be approved by the US Food and Drug Administration (FDA) and introduced to the market to treat type 2 diabetes [26]. Later, the SCALE study investigated the potential of liraglutide 3.0 mg to induce and maintain weight loss as well as its efficacy in delaying the onset of type 2 diabetes [27], which was fundamental for the FDA approval of this drug in 2015 for use in adults without diabetes but with overweight or obesity [28]. Semaglutide was also approved by the FDA and the European Medicines Agency (EMA) for the treatment of type 2 diabetes, especially in people with high cardiovascular risk [29, 30]. Besides semaglutide, the GLP-1RAs that are currently used in clinical settings are lixisenatide, albiglutide, dulaglutide, exenatide, and liraglutide. Additionally, newer drugs such as tirzepatide, a dual glucose-dependent insulinotropic polypeptide/GLP-1RA, have shown promising effects [31]. However, the only drugs approved by both the FDA and the EMA for weight loss are liraglutide and semaglutide [29, 30]. The prescription of these drugs for weight loss is considered in the case of:

- failure of diet, exercise, and behavioural management;
- a BMI above 30 kg/m^2 or above 27 kg/m^2 in the presence of comorbidities [32];
- a waist circumference above 88 cm in women and above 102 in men [33].

In studies that investigated glycaemic control for people with type 2 diabetes, both oral and subcutaneous semaglutide showed secondary weight loss benefits against placebo and other drugs [34, 35].

Adverse effects of the intervention

Gastrointestinal side effects are the most frequently reported adverse events caused by GLP-1RAs, including semaglutide [36, 37]. These gastrointestinal events include nausea, vomiting, diarrhoea, constipation, dyspepsia, and abdominal discomfort, of which nausea is the most common. Usually, the symptoms are mild to moderate in severity and occur within the first few weeks of treatment during the titration period. They also tend to be transient [36, 38]. Other possible but less frequent adverse effects described are injection site reactions (rash, erythema, or itching at the injection site), hyperhidrosis, and hypoglycaemia when in combination with sulphonylureas or insulin [39]. Systematic reviews have found no association between use of GLP-1RAs and the occurrence of thyroid cancer, pancreatic cancer, or pancreatitis [37, 39, 40, 41, 42].

Why it is important to do this review

Obesity is an important public health problem with an increasing need and demand for non-invasive treatments. Weight loss is associated with lower healthcare costs and clinical improvement of risk factors and comorbid conditions. A slight weight loss (2% to 5%) may improve menstrual irregularities and fertility in women with polycystic ovarian syndrome and infertility, while modest weight losses (5% to 10%) may be associated with improvement in cardiovascular risk factors, such as lower systolic and diastolic blood pressure, improvements in lipid profile, and lower rates of progression to type 2 diabetes. Even greater weight losses may produce clinical benefits in other comorbid conditions, such as obstructive sleep apnoea and non-alcoholic steatotic hepatitis, and could ultimately reduce mortality [24, 43].

Semaglutide has been proposed as an effective and safe option for the management of obesity in adults. Current systematic reviews have focused on the effects of GLP-1RAs in the prevention or treatment of type 2 diabetes [44, 45, 46]. So far, no comprehensive evidence syntheses have been conducted to assess the effects of semaglutide in adults with overweight or obesity, exhaustively assessing weight outcomes, quality of life, safety measures, major cardiovascular events, mortality, and other important outcomes. We have generated a common protocol to assess the effects of GLP-1RAs in adults with obesity. In this systematic review, we will assess the effects of semaglutide for this population, considering that it has been approved by both EMA and FDA for weight loss, and that it has preliminarily shown a more significant effect in weight loss than liraglutide for people with obesity [47].

Objectives

To assess the effects of semaglutide on adults living with obesity.

Methods

We followed standard Cochrane methodology, including the *Cochrane Handbook for Systematic Reviews of Interventions*, the Methodological Expectations of Cochrane Intervention Reviews (MECIR), and PRISMA 2020 for conducting and reporting this review [48, 49, 50].

Our protocol was initially published in 2022 [51]. We based parts of the Methods, as well as Supplementary material 1 of this Cochrane review, on a standard template established by the Cochrane Metabolic and Endocrine Disorders Group. In 2024, we were commissioned by the World Health Organization (WHO) to conduct a series of reviews to support their guidelines on the use of GLP-1RA 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 comorbidities. People with co-morbid obesity and diabetes were retained in the review, but the review was 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 focuses on one of them, semaglutide. 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' and added BMI changes for weight measurements, major adverse cardiovascular events (MACE), 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 steatolic liver disease, metabolic dysfunction-associated steatohepatitis, cirrhosis), obstructive sleep apnoea, and lipid metabolism-related outcomes (including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, need for lipid-lowering treatment).
- We added equity considerations to subgroup analysis and the presence of comorbidities.

We registered these modifications prospectively as a new protocol in PROSPERO [52]. This common protocol includes tirzepatide, liraglutide, and semaglutide as interventions and comparators; however, this review reports the findings of semaglutide only.

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) that assessed the effects of semaglutide for 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 when data were limited. 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 and overweight 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 about adults aged 18 years or older living with obesity as defined by the 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.

Types of interventions

Interventions

We considered semaglutide, prescribed at any dose or route of administration, for a minimum of six months.

Controls and comparisons

We considered studies that compared semaglutide to:

- placebo or no treatment;
- structured programmes targeting 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.

Summary of specific exclusion criteria

We excluded the following types of participants and studies.

- Pregnant women, due to expected variability in weight and BMI, and the safety profile of GLP1-RAs.
- 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.

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 they did not measure any of the outcomes relevant to this review, provided there was supporting evidence (e.g. contact with study authors, access to the original protocol, etc.). We classified the outcomes into 'critical' and 'important' based on the guidance of the WHO international Guideline Developing Group.

Critical outcomes

- Weight change, measured as:
    - percentage, BMI change or absolute change in kg from baseline;
    - people achieving 5% or 10% weight loss.

- Adverse events, including:
  - any adverse event;
  - non-serious adverse events;
  - serious adverse events;
  - adverse events leading to discontinuation.
- Major adverse cardiovascular events (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, measured with any validated scale, including:
  - Short Form 36 Health Survey (SF-36);
  - Impact of Weight on Quality of Life (IWQoL);
  - EuroQol 5 Dimensions (EQ-5D).
- Mortality, considered as death from any cause.

Important outcomes

- Waist circumference
- Heart failure
- Diabetes–related outcomes
- Blood pressure–related outcomes
- Liver disease–related outcomes
- Obstructive sleep apnoea
- Lipid metabolism–related outcomes

Supplementary material 7 provides further details about outcome measurements and minimal clinically important differences (MCIDs).

Time frames for outcome assessment

We analysed outcome data as medium-term (6 to 24 months) and long-term (24 months or more) follow-up, according to suggestions by experts as adequate thresholds for follow-up time points [53]. 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 the search, with no restrictions on the language of publication. We included post-publication amendments and retractions 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) [54].

The search strategy details are available in Supplementary material 1.

Searching other resources

We checked the reference lists of relevant articles to find additional studies [55, 56, 57, 58, 59, 60]. We contacted experts in the field to identify additional unpublished data to obtain additional information about the retrieved studies and to determine if we had omitted other studies.

Data collection and analysis

Researchers and authors who took part in making study selection, data extraction, risk of bias assessment or GRADE assessments were not involved in the conduct, analysis, and publication of the studies included in this review.

Selection of studies

Two independent researchers (see Acknowledgements) screened the abstract, title, or both, of every record retrieved by the literature searches. We obtained the full text of all potentially relevant records. We resolved disagreements through consensus or by recourse to a third review author (among JB, NM, JF and EM). We used Covidence to perform all the screening process [61], and summarised the selection process in a PRISMA flow diagram [50].

Data extraction and management

Two review authors (among JB, MOV, SM, DP, FRL, GL, EM) independently extracted data from the included studies, with a third review author (JB, EM) solving any discrepancies. We extracted the following data from the included studies.

- Methods
    - Study design
- Participants
    - Inclusion and exclusion criteria
    - Participant details and baseline characteristics, including age, sex, ethnicity, and baseline weight measurements, blood pressure, and lipid profile measurements
    - The number of participants by study and by study arm
- Interventions and comparisons according to the 'Template for Intervention Description and Replication' (TIDieR) checklist [62; 63]. We presented a summary in the Characteristics of included studies (Supplementary material 2). The detailed information on the TIDieR checklist will be published in a separate manuscript.
- Outcomes
    - Definitions, methods and timing of outcome measurement, including any relevant subgroups
- Dates (if dates were not available, then we reported it).
- Study setting, country, language of publication, and study identifier.

These data were reported in the 'Characteristics of included studies' (Supplementary material 2), and in summary tables in the main text (see Table 1; Table 2).

We characterised the conflicts of interest (COI) in the included studies and discussed how they might have impacted the effect estimates. We also collected, processed, and used information on conflicts of interest in two ways.

- We extracted information from the authors' COI disclosures regarding their relationship to the 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 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 — elements considered by the Tool for Addressing Conflicts of Interest in Trials (TACIT), which was under development at the time [64].

These data are reported in Supplementary material 8 and Supplementary material 9.

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 yield 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 primary study, and study documents of included studies (such as trial registry information) as secondary references under the study ID of the included study. We listed duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded studies (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trials registers

If data from included studies were available as study results in clinical trials registers, such as ClinicalTrials.gov or similar sources, we made full use of this information and extracted the data. If there was also a full publication of the

study, we collated and critically appraised all available data. If an included study had been marked as completed in a clinical trials register but no additional information (study results, publication, or both) was available, we added it to the 'Studies awaiting classification' table.

Risk of bias assessment in included studies

Two review authors (among JB, MOV, SM, DP, FRL, GL, EM) independently assessed the risk of bias of each included study, solving discrepancies by consensus or with a third review author (JB, EM). We used the Cochrane risk of bias tool, RoB 1, to assess each included RCT according to the following domains [65].

- 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 bias

We judged the risk of bias domains as 'low risk', 'high risk', or 'unclear risk' according to guidance in the *Cochrane Handbook for Systematic Reviews of Interventions,* summarising the judgements in figures and detailing them in the description of each included study [65]. To assess attrition bias, we examined both the proportion of participants lost to follow-up and whether attrition was balanced between arms. We considered studies at low risk when losses were minimal (< 5%). We judged unclear risk when attrition was 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. We rated studies at high risk if overall attrition exceeded 20%, or if attrition between 10% and 20% was unbalanced in magnitude or across groups.

We assessed the domains 'random sequence generation', 'allocation concealment' and 'selective reporting' across outcomes (at the study level). We distinguished between self-reported and investigator-assessed and adjudicated outcome measures. We considered health-related quality of life as a self-reported outcome, and weight loss, adverse events, and all secondary outcomes as investigator-assessed and adjudicated outcomes.

Then, we assessed the risk of bias for each specific outcome measure by including all entries relevant to that outcome (i.e. both study-level entries and outcome-specific entries). To facilitate the certainty of evidence assessment, we assessed the risk of bias across studies and domains for the outcomes included in the summary of findings tables. 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 a sufficient proportion of information came from studies at high risk of bias [66]. 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.

Measures of treatment effect

We analysed dichotomous data as risk ratio (RR), with 95% confidence intervals (CIs). We estimated the intervention effect using the mean difference (MD) with 95% CIs for continuous outcomes measured on the same scale (e.g. weight loss in kg), and standardised mean differences (SMDs) with 95% CIs if pooled data were reported using different measures for the same outcome.

Unit of analysis issues

We considered 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 (e.g. multiple doses of the same drug), we planned to either combine groups to create a single pairwise comparison, or appropriately reduce 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 offers some solutions for adjusting the precision of the comparison, it does not account for correlation arising from the inclusion of the same set of participants in multiple comparisons [67].

Dealing with missing data

We asked the authors of the included studies for missing data. We carefully evaluated important numerical data such as screened, randomly assigned participants, as well as intention-to-treat and 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. We conducted available case analyses for our primary analyses.

For studies that reported outcomes without SD, we imputed it from SE or CI using the Review Manager (RevMan) calculator [68], or, if not possible, by standardising by the mean of the pooled baseline SD from studies that

reported this information [67].

Reporting bias assessment

If an outcome included 10 or more studies, we used funnel plots to assess small-study effects. We planned to interpret these results carefully, since several explanations may account for funnel plot asymmetry, including the true heterogeneity of the effect with respect to study size, poor methodological design (and hence bias of small studies), and publication bias [67, 69]. In case of suspicion of publication bias, we stated it in our certainty of evidence assessment.

Synthesis methods

We conducted meta-analysis whenever two or more studies reported an outcome, without having substantial important clinical and methodological heterogeneity [70]. We meta-analysed data using a random-effects model [71]. We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* [70]. If meta-analysis was not possible for a certain outcome, we planned to conduct 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* [72].

Investigation of heterogeneity and subgroup analysis

We used the I^2 statistic to measure statistical heterogeneity among the studies in each analysis [73]. We reported substantial, unexplained heterogeneity, and explored possible causes by prespecified subgroup analysis. We guided our interpretation of the I^2 statistic as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* [67]:

- 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 considered examining visually 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 strength of evidence for heterogeneity (e.g. the P value from the Chi^2 test or CI for I^2 statistic).

In case of substantial heterogeneity, we planned to carry out the following subgroup analyses [74].

- Age (people younger than 60 versus those aged 60 years and older)
- Sex
- Dose within a drug
- Presence of comorbidities (e.g. diabetes)
- Baseline BMI
- Equity considerations (see below)

Whenever appropriate, we incorporated the results of subgroup analyses in the certainty of evidence assessments for each outcome.

Equity-related assessment

We planned to conduct subgroup analysis between genders and age groups in case there were studies that assessed the effect of semaglutide as disaggregated data. Although there might be differences in baseline characteristics or conduct of the studies between high-income and low-income settings, we did not conduct a specific assessment addressing these potential differences, but we considered this in our discussion. We did not assess the effect of semaglutide in men and women separately, since no data were available.

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.
- Excluding studies that included a subgroup of people with diabetes or prediabetes.

We stated any differences between the main analyses and the sensitivity analyses in the main text, figures or certainty of evidence assessments, whenever relevant.

Certainty of the evidence assessment

We present certainty of the evidence assessments according to the GRADE approach for each outcome. Given that we included only RCTs, we initially rated the certainty of evidence as high. Then, two review authors (JB, EM)

evaluated the domains of risk of bias, indirectness, inconsistency, imprecision, and publication bias to potentially downgrade the certainty, resolving any discrepancy by discussion. We defined the target certainty using two explicit thresholds, based on minimal clinically important differences (MCIDs) for benefit and harm (Supplementary material 7) [75].

We present the certainty of evidence assessments in the summary of findings tables according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* [76], along with Review Manager [68] and the GRADEpro software [77]. The summary of findings tables compile the total number of included studies, a detailed assessment of each key domain to assess certainty, the relative and absolute effect estimates, and the overall confidence in the estimates for each outcome. Whenever a meta-analysis was not possible, we presented the results in a narrative format in the summary of findings table. We justified all decisions to downgrade the certainty of the evidence by using informative footnotes, and using GRADE guidelines for informative statements [78, 79]. Supplementary material 7 provides additional comments regarding the outcomes' interpretation.

We created a summary of findings table for each comparison, and for each of the prespecified time points. The data available allowed us to create four summary of findings tables.

- Semaglutide versus placebo at medium-term follow-up
- Semaglutide versus placebo at long-term follow-up
- Semaglutide versus liraglutide at medium-term follow-up
- Semaglutide versus tirzepatide at medium-term follow-up

We created main summary of findings tables including the critical outcomes, weight, adverse events, MACE, quality of life, and mortality. We also prepared extended summary of findings tables, including all critical and important outcome measurements, as supplementary material.

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

Supplementary material 6 is the full data package for all the comparisons in this review. Summary of findings table 1; Summary of findings table 2; Summary of findings table 3; Summary of findings table 4 provide a summary of the main critical outcome measurements for each comparison. Supplementary material 10; Supplementary material 11; Supplementary material 12; Supplementary material 13 provide the extended versions of the summary of findings tables for each comparison, including all critical and important outcomes.

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 semaglutide [52]. 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.

Semaglutide

We included a total of 502 records. Of these, 18 RCTs (198 records) provided useful data for this review (Eckard 2024 [1, 80, 81]; O'Neil 2018 [82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96]; OASIS 1 [97, 98, 99, 100]; SELECT [6, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124]; SMART [2, 125, 126, 127]; STEP 1 [128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 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, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179]; STEP 10 [180, 181, 182, 183]; STEP 2 [184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202]; STEP 3 [203, 204, 205, 206]; STEP 4 [207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218]; STEP 5 [219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230]; STEP 6 [231, 232, 233]; STEP 7 [234, 235, 236]; STEP 8 [3, 237, 238, 239, 240, 241, 242]; STEP 9 [243, 244, 245, 246, 247]; STEP-HFpEF [4, 248, 249,

250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263]; STEP-HFpEF DM [5, 264, 265, 266, 267]; SURMOUNT-5 [268, 269]). The current version of this review has no studies awaiting assessment and 46 ongoing studies.

Figure 1 provides the PRISMA flowchart summarising the selection process.

Included studies

Characteristics of studies

The 18 included RCTs were published between 2018 and 2025, and enrolled a total of 27,949 participants. Supplementary material 2 provides further details of each individual study.

Participants

Table 1 summarises the main characteristics of the participants in each study. All studies included adult participants aged 18 years or older, who lived with obesity, according to World Health Organization (WHO) criteria [9], or using the study authors' description of obesity.

Most studies included North American (Eckard 2024; O'Neil 2018; OASIS 1; SELECT; SMART; STEP 1; STEP 10; STEP 2; STEP 3; STEP 4; STEP 5; STEP 8; STEP 9; STEP-HFpEF; STEP-HFpEF DM; SURMOUNT-5), Asian (O'Neil 2018; OASIS 1; SELECT; STEP 1; STEP 2; STEP 4; STEP 6; STEP 7; STEP 9; STEP-HFpEF; STEP-HFpEF DM) or European countries (O'Neil 2018; OASIS 1; SELECT; SMART; STEP 1; STEP 10; STEP 2; STEP 4; STEP 5; STEP 9; STEP-HFpEF; STEP-HFpEF DM). Eight studies included at least one Latin American country (SELECT; STEP 1; STEP 2; STEP 7; STEP 9; STEP-HFpEF; STEP-HFpEF DM; SURMOUNT-5); four included at least one African country (SELECT; STEP 2; STEP 4; STEP 9); and two included Australia (O'Neil 2018; SELECT). All studies were international, except for three studies conducted exclusively in the USA (Eckard 2024; STEP 3; STEP 8). Most studies included a predominantly White population (O'Neil 2018; OASIS 1; SELECT; SMART; STEP 1; STEP 2; STEP 3; STEP 4; STEP 5; STEP 8; STEP 9; STEP 10; STEP-HFpEF; STEP-HFpEF DM; SURMOUNT-5), with the exception of two that included predominantly Asian individuals (STEP 6; STEP 7), and one that considered mainly a Black or African American population (Eckard 2024).

Mean BMI ranged from 31.9 kg/m^2 to 40.3 kg/m^2, with a mean age of 41.0 to 69.5 years. No study disaggregated data by baseline BMI or age group, and no study was conducted exclusively in men or women. For these reasons, we were unable to conduct these subgroup analyses as planned.

Regarding comorbidities, 14 studies included exclusively people without diabetes (Eckard 2024; O'Neil 2018; OASIS 1; SELECT; SMART; STEP 1; STEP 10; STEP 3; STEP 4; STEP 5; STEP 8; STEP 9; STEP-HFpEF; SURMOUNT-5), two included only people with diabetes (STEP 2; STEP-HFpEF DM), and two considered people with and without diabetes (STEP 6; STEP 7). Additionally, one study considered HIV-associated lipohypertrophy as inclusion criterion (Eckard 2024), one was conducted in people living with chronic kidney disease (SMART), and one considered adults with established cardiovascular disease (SELECT). Two studies were conducted in people with heart failure with preserved ejection fraction (STEP-HFpEF; STEP-HFpEF DM), and were the only ones with a median participants' age above 65 years.

Interventions and comparisons

Table 2 summarises the interventions and comparisons for each study. The most common scheme used was semaglutide 2.4 mg weekly via subcutaneous injections. One study assessed semaglutide 1 mg weekly, one used daily subcutaneous semaglutide in different doses, and one administered daily oral semaglutide. The following specific schemes were used as interventions.

- Subcutaneous semaglutide
    - 2.4 mg weekly (SELECT; SMART; STEP 1; STEP 10; STEP 2; STEP 3; STEP 4; STEP 5; STEP 6; STEP 7; STEP 8; STEP 9; STEP-HFpEF; STEP-HFpEF DM; SURMOUNT-5)
    - 1.7 mg weekly (STEP 6; SURMOUNT-5)
    - 1 mg weekly (Eckard 2024; STEP 2)
    - Daily at different doses (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg (O'Neil 2018)
- Oral semaglutide
    - 50 mg daily (OASIS 1)

All studies included a matching placebo arm as comparator, except for one study that compared semaglutide versus tirzepatide (SURMOUNT-5). Most provided data for medium-term follow-up (Eckard 2024; O'Neil 2018; OASIS 1; SMART; STEP 1; STEP 10; STEP 2; STEP 3; STEP 4; STEP 5; STEP 6; STEP 7; STEP 8; STEP 9; STEP-HFpEF; STEP-HFpEF DM; SURMOUNT-5); only two informed long-term outcomes (SELECT; STEP 5). Two studies with a medium-term follow-up also included a liraglutide arm, both subcutaneously at a dose of 3 mg daily (O'Neil 2018; STEP 8). Therefore, we were able to analyse the following comparisons.

1. Semaglutide versus placebo: medium-term follow-up
2. Semaglutide versus placebo: long-term follow-up
3. Semaglutide versus liraglutide:medium-term follow-up

4. Semaglutide versus tirzepatide: medium-term follow-up

Outcomes

All studies contributed quantitative data for at least one measurement of weight and adverse events. For the comparisons of semaglutide versus placebo or liraglutide at medium-term follow-up, quality of life was mostly reported using the SF-36 scale. For the comparison of semaglutide versus placebo at long-term follow-up, only one study reported quality-of-life data, using EQ-5D-5L. Twelve studies reported MACE, although with some heterogeneity in terms of outcome definition (stated in each meta-analysis). Most studies reported data regarding mortality, with very few events. Supplementary material 2 provides further details of the outcomes.

Funding sources

Sixteen studies (27,841 participants) reported that their funding source was the manufacturer of semaglutide, Novo Nordisk (O'Neil 2018; OASIS 1; SELECT; SMART; STEP 1; STEP 10; STEP 2; STEP 3; STEP 4; STEP 5; STEP 6; STEP 7; STEP 8; STEP 9; STEP-HFpEF; STEP-HFpEF DM). One study (750 participants), which assessed semaglutide versus tirzepatide, reported funding by Eli-Lilly (SURMOUNT-5). The funder had a major role in the design and conduct, data analysis, and writing of these studies, as detailed in Supplementary material 8. Moreover, several study authors report direct financial ties to the company, as specified in Supplementary material 9. Only one small study (104 participants) had non-commercial funding (Eckard 2024).

Ongoing studies

We have also identified 46 ongoing, potentially eligible RCTs (see Supplementary material 4). We reviewed the registers of each study near the date of publication to ensure we did not miss any newly published results. Among the ongoing studies, 16 explicitly declare funding by the drug manufacturer.

Excluded studies

We excluded 154 studies (231 references). The main reasons for exclusions are as follows: 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). Some studies had more than one reason for exclusion.

The full details of the 154 excluded studies are in the Supplementary material 3.

Risk of bias in included studies

We assessed the risk of bias using the Cochrane RoB1 tool. We judged most domains as low risk of bias for the majority of studies. One study had a high risk of performance and detection bias (STEP 8), since the placebo group mimicked two different dose schemes, one weekly for semaglutide and one daily for liraglutide, and the results for this arm were provided as a pooled group. We considered one study to be at high risk of selective reporting bias, since it did not provide data for quality of life using the IWQoL scale, as stated in its protocol (O'Neil 2018). Two studies were at unclear risk of selection bias (Eckard 2024; SMART), and we also considered one of these studies to be at high risk of other bias, since some data were incorrectly reported (e.g. median outside interquartile ranges; Eckard 2024).

Figure 2 summarises the risk of bias assessments. The support for judgements across all domains is available in Supplementary material 2 and Supplementary material 6.

Synthesis of results

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

Sixteen studies provided data for this comparison (Eckard 2024; O'Neil 2018; OASIS 1; SMART; STEP 1; STEP 10; STEP 2; STEP 3; STEP 4; STEP 5; STEP 6; STEP 7; STEP 8; STEP 9; STEP-HFpEF; STEP-HFpEF DM). Main estimates of effects and certainty of evidence assessments for the critical outcomes are compiled in Summary of findings table 1. An extended version of the summary of findings table, including all outcome measurements for all critical and important outcomes, is available in Supplementary material 10.

Critical outcomes

Weight change

Compared to placebo, semaglutide results in a reduction of the percentage of body weight (MD -10.73, 95% CI -12.24 to -9.21; 15 studies, 8651 participants; high-certainty evidence; Analysis 1.1), total kg (MD -10.87, 95% CI -12.54 to -9.21; 13 studies, 7291 participants; high-certainty evidence; Analysis 1.2), and change in BMI (MD -3.73, 95% CI -4.48 to -2.99; 10 studies, 6803 participants; high-certainty evidence; Analysis 1.3) at medium-term follow-up. Semaglutide increases the proportion of people achieving 5% weight loss (RR 2.68, 95% CI 2.30 to 3.12; 12 studies, 7458 participants; high-certainty evidence; Analysis 1.4) and 10% weight loss (RR 5.21, 95% CI 4.32 to 6.30; 14 studies, 8510 participants; high-certainty evidence; Analysis 1.5).

Adverse events

Compared to placebo, semaglutide may increase the risk of any adverse event (RR 1.06, 95% CI 1.02 to 1.10; 11 studies, 7298 participants; low-certainty evidence; Analysis 1.6) or non-serious adverse events (RR 1.11, 95% CI 1.01 to 1.22; 13 studies, 8443 participants; low-certainty evidence; Analysis 1.7) at medium-term follow-up. Semaglutide may result in little to no difference in serious adverse events, but the evidence is very uncertain (RR 1.01, 95% CI 0.78 to 1.29; 15 studies, 9054 participants; very low-certainty evidence; Analysis 1.8).

Semaglutide likely results in little to no absolute difference in adverse events leading to withdrawal at medium-term follow-up (RR 1.84, 95% CI 1.53 to 2.21; 15 studies, 9054 participants; moderate-certainty evidence; Analysis 1.9). Although the estimate of effect indicates an 84% higher risk of having an adverse event leading to withdrawal, due to the baseline risk of the placebo group (3.6%), this translates into an absolute risk difference of 3.0%, which is below our minimally important threshold of 5% absolute risk difference. In populations with a higher baseline risk (from 6% baseline risk in the control group), the absolute difference would be clinically significant.

Major adverse cardiovascular events

Compared to placebo, semaglutide may result in little to no absolute difference in MACE at medium-term follow-up (RR 0.63, 95% CI 0.44 to 0.90; 9 studies, 7647 participants; low-certainty evidence; Analysis 1.10). The estimate of effect suggests a 37% lower risk of having MACE with semaglutide. Due to the baseline risk of the placebo group in the included studies (9.2%), this translates into an absolute risk difference of 3.4%, which is below our minimally important threshold of 5%.

Quality of life

For this comparison, quality of life was measured using the SF-36 scale, IWQoL-Lite-CT, and EQ-5D-5L.

Compared to placebo, semaglutide likely results in little to no difference in quality of life, as measured with the SF-36 mental component score (MD 0.79, 95% CI -0.01 to 1.59; 8 studies, 5497 participants; moderate-certainty evidence; Analysis 1.11), SF-36 physical component score (MD 1.91, 95% CI 0.31 to 3.52; 8 studies, 5493 participants; moderate-certainty evidence; Analysis 1.12), and SF-36 physical functioning score (MD 2.12, 95% CI 0.95 to 3.28; 9 studies, 6083 participants; moderate-certainty evidence; Analysis 1.13) at medium-term follow-up.

Semaglutide may result in little to no difference in quality of life, as measured with the IWQoL-Lite-CT total score (MD 6.35, 95% CI 2.01 to 10.68; 4 studies, 3610 participants; low-certainty evidence; Analysis 1.14) and IWQoL-Lite-CT physical function (MD 6.86, 95% CI 3.29 to 10.43; 5 studies, 4200 participants; low-certainty evidence; Analysis 1.15) at medium-term follow-up. Measured with EQ-5D-5L, semaglutide may result in an increase in quality of life at medium-term follow-up (MD 0.08, 95% CI 0.03 to 0.13; 1 study, 207 participants; low-certainty evidence; Analysis 1.16).

Mortality

Compared to placebo, semaglutide may result in little to no difference in mortality at medium-term follow-up (RR 0.69, 95% CI 0.48 to 0.98; 14 studies, 8953 participants; low-certainty evidence; Analysis 1.17).

Important outcomes

The included studies provided data for all the important outcomes within this comparison. Briefly, compared to placebo at medium-term follow-up, semaglutide likely reduces waist circumference; likely results in little to no difference in heart failure events; has uncertain effects on fasting glycaemia and HbA1c; may result in a reduction in systolic blood pressure with little to no difference in diastolic blood pressure; and likely results in little to no difference in total cholesterol. A detailed assessment of all important outcomes is provided in Supplementary material 10.

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

Two studies provided data for this comparison (SELECT; STEP 5). Main estimates of effects and certainty of evidence assessments for the critical outcomes are compiled in Summary of findings table 2. An extended version of the summary of findings table, including all outcome measurements for all critical and important outcomes, is available in Supplementary material 11.

Critical outcomes

Weight change

Compared to placebo at long-term follow-up, semaglutide likely reduces percentage body weight (MD -11.11, 95% CI -16.47 to -5.75; 2 studies, 15124 participants; moderate-certainty evidence; Analysis 2.1) and may reduce weight measured in kg (MD -14.80, 95% CI -17.62 to -11.98; 1 study, 272 participants; low-certainty evidence; Analysis 2.2) or change in BMI (MD -5.50, 95% CI -6.56 to -4.44; 1 study, 272 participants; low-certainty evidence; Analysis 2.3). Semaglutide likely increases the proportion of people achieving 5% weight loss (RR 2.74, 95% CI 1.95 to 3.84; 2 studies, 17876 participants; moderate-certainty evidence; Analysis 2.4) or 10% weight loss (RR 5.94, 95% CI 4.55 to 7.76; 2 studies, 17876 participants; moderate-certainty evidence; Analysis 2.5).

Adverse events

At long-term follow-up, the effects of semaglutide compared to placebo are very uncertain on the risk of any adverse events (RR 1.07, 95% CI 1.01 to 1.14; 1 study, 304 participants; very low-certainty evidence; Analysis 2.6) or non-serious adverse events (RR 1.21, 95% CI 1.10 to 1.34; 1 study, 305 participants; very low-certainty

evidence; Analysis 2.7). Semaglutide likely results in little to no difference in serious adverse events (RR 0.92, 95% CI 0.88 to 0.95; 2 studies, 17908 participants; moderate-certainty evidence; Analysis 2.8), but likely increases adverse events leading to withdrawal (RR 2.03, 95% CI 1.86 to 2.20; 2 studies, 17908 participants; moderate-certainty evidence; Analysis 2.9) at long term.

Major adverse cardiovascular events

Semaglutide likely results in little to no difference in MACE at long-term follow-up (RR 0.81, 95% CI 0.73 to 0.90; 2 studies, 17908 participants; moderate-certainty evidence; Analysis 2.10). Although the effect estimate indicates a 19% relative reduction, considering the baseline risk of the placebo group (7.8%), this translates into an absolute risk difference of 1.4%, which is below our minimally important threshold of 5%.

Quality of life

For this comparison, quality of life was measured only by one study, using EQ-5D-5L. At long-term follow-up, semaglutide likely results in little to no difference in quality of life (MD 0.02, 95% CI 0.02 to 0.02; 1 study, 13426 participants; moderate-certainty evidence; Analysis 2.11).

Mortality

Compared to placebo, semaglutide likely results in little to no difference in mortality at long-term follow-up (RR 0.82, 95% CI 0.72 to 0.94; 2 studies, 17908 participants; moderate-certainty evidence; Analysis 2.12). The effect estimate suggests a relative reduction in mortality of 18%, however, due to the baseline risk of the control group (5.1%), this translates into an absolute risk difference of 0.9%, which is below our minimally important threshold of 1%. In populations with higher baseline risk (from 5.6%), the absolute difference would be clinically significant.

Important outcomes

The detailed results for the important outcomes within this comparison are provided in Supplementary material 11. Briefly, compared to placebo at long-term follow-up, semaglutide may reduce waist circumference; may result in little to no difference in heart failure events; may result in little to no difference in fasting glycaemia and likely results in little to no difference in HbA1c; likely results in little to no difference in systolic blood pressure, and has very uncertain effects on diastolic blood pressure; and likely results in little to no difference in total cholesterol.

3. Semaglutide versus liraglutide: medium-term follow-up

Two studies provided data for this comparison (O'Neil 2018; STEP 8). Main estimates of effects and certainty of evidence assessments for the critical outcomes are compiled in Summary of findings table 3. An extended version of the summary of findings table—including all outcome measurements for all critical and important outcomes—is available in Supplementary material 12.

Critical outcomes

Weight change

Compared to liraglutide, semaglutide may reduce percentage body weight (MD -6.75, 95% CI -13.03 to -0.46; 2 studies, 1002 participants; low-certainty evidence; Analysis 3.1) and absolute weight measured in kg (MD -6.37, 95% CI -11.40 to -1.34; 2 studies, 1002 participants; low-certainty evidence; Analysis 3.2), and may make little to no difference in change in BMI (MD -1.37, 95% CI -2.07 to -0.67; 1 study, 768 participants; low-certainty evidence; Analysis 3.3), which may be explained by the absence of reporting of this measurement by one of the studies. Semaglutide may increase the proportion of people achieving 5% weight reduction (RR 1.30, 95% CI 0.99 to 1.71; 2 studies, 1002 participants; low-certainty evidence; Analysis 3.4), and likely increases the proportion of people achieving 10% weight loss (RR 2.05, 95% CI 1.15 to 3.65; 2 studies, 1002 participants; moderate-certainty evidence; Analysis 3.5).

Adverse events

Compared to liraglutide, semaglutide may result in little to no difference in non-serious adverse events (RR 1.03, 95% CI 0.97 to 1.11; 2 studies, 1074 participants; low-certainty evidence; Analysis 3.7), with very uncertain effects on any adverse event (RR 1.03, 95% CI 0.94 to 1.13; 2 studies, 1074 participants; very low-certainty evidence; Analysis 3.6), serious adverse events (RR 1.17, 95% CI 0.41 to 3.29; 2 studies, 1074 participants; very low-certainty evidence; Analysis 3.8), and adverse events leading to withdrawal (RR 0.54, 95% CI 0.14 to 2.12; 2 studies, 1074 participants; very low-certainty evidence; Analysis 3.9).

Major adverse cardiovascular events

Semaglutide has very uncertain effects on MACE at medium-term follow-up, compared to liraglutide (RR 1.30, 95% CI 0.07 to 24.00; 1 study, 821 participants; very low-certainty evidence; Analysis 3.10).

Quality of life

For this comparison, quality of life was measured using the SF-36 instrument. Compared to liraglutide at medium-term follow-up, semaglutide may result in little to no difference in quality of life according to the SF-36 mental component score (MD 0.45, 95% CI -1.82 to 2.71; 1 study, 215 participants; low-certainty evidence; Analysis 3.11), SF-36 physical component score (MD 0.02, 95% CI -2.24 to 2.28; 1 study, 211 participants; low-certainty evidence;

Analysis 3.12) and SF-36 physical functioning score (MD -0.29, 95% CI -2.74 to 2.16; 1 study, 211 participants; low-certainty evidence; Analysis 3.13).

Mortality

The evidence is very uncertain about the effects of semaglutide on mortality at medium-term follow-up, compared to liraglutide (RR 0.43, 95% CI 0.02 to 10.58; 2 studies, 1074 participants; very low-certainty evidence; Analysis 3.14).

Important outcomes

The detailed results for the important outcomes within this comparison are provided in Supplementary material 12. Briefly, compared to liraglutide at medium-term follow-up, semaglutide has very uncertain effects on waist circumference and heart failure events; likely results in little to no difference in fasting glycaemia, with very uncertain effects on HbA1c; likely results in little to no difference in systolic blood pressure, with very uncertain effects on diastolic blood pressure; and may result in little to no difference in total cholesterol levels.

4. Semaglutide versus tirzepatide: medium-term follow-up

One study provided data for this comparison (SURMOUNT-5). Main estimates of effects and certainty of evidence assessments for the critical outcomes are compiled in Summary of findings table 4. An extended version of the summary of findings table, including all outcome measurements for all critical and important outcomes, is available in Supplementary material 13.

Critical outcomes

Weight change

Compared to tirzepatide, semaglutide may result in a lower percentage of weight loss (MD 6.50, 95% CI 4.87 to 8.13; 1 study, 750 participants; low-certainty evidence; Analysis 4.1), and probably in lower weight loss measured as kg (MD 7.80, 95% CI 5.96 to 9.64; 1 study, 750 participants; moderate-certainty evidence; Analysis 4.2) and BMI (MD 2.70, 95% CI 1.99 to 3.41; 1 study, 750 participants; moderate-certainty evidence; Analysis 4.3). Semaglutide may also reduce the proportion of people achieving a 10% weight reduction at medium-term follow-up, compared to tirzepatide (RR 0.74, 95% CI 0.68 to 0.82; 1 study, 750 participants; low-certainty evidence; Analysis 4.4). The included study did not report the proportion of people achieving 5% weight loss.

Adverse events

Compared to tirzepatide, semaglutide may result in little to no difference in any adverse event (RR 1.03, 95% CI 0.95 to 1.11; 1 study, 750 participants; low-certainty evidence; Analysis 4.5), non-serious adverse events (RR 1.05, 95% CI 0.96 to 1.14; 1 study, 750 participants; low-certainty evidence; Figure 4; Analysis 4.6), and adverse events leading to withdrawal (RR 1.30, 95% CI 0.77 to 2.19; 1 study, 750 participants; low-certainty evidence; Analysis 4.8), with very uncertain effects regarding serious adverse events (RR 0.72, 95% CI 0.36 to 1.45; 1 study, 750 participants; very low-certainty evidence; Analysis 4.7).

Major adverse cardiovascular events

None of the study participants had a MACE event. Therefore, semaglutide has very uncertain effects on MACE at medium-term follow-up compared to tirzepatide.

Quality of life

Although mentioned in the protocol, the currently available reports of the included study for this comparison did not provide data about quality of life.

Mortality

None of the study participants died. Therefore, semaglutide has very uncertain effects on mortality at medium-term follow-up compared to tirzepatide.

Important outcomes

The detailed results for the important outcomes within this comparison are provided in Supplementary material 13. Briefly, compared to tirzepatide at medium-term follow-up, semaglutide may result in a lower decrease in waist circumference; and likely results in little to no difference in fasting glycaemia, HbA1c, systolic blood pressure, and levels of HDL, LDL and triyglycerides; and may result in little to no difference in diastolic blood pressure.

Equity assessment

The available data prevented us from assessing equity-related characteristics by exploring potential differences in the effects of semaglutide between low-income versus high-income settings, between genders, or among people with special needs. None of the studies reported disaggregated data to appraise potential differences in women's and men's vulnerability to adverse events.

We should note that most individuals were recruited from high-income countries, with an underrepresentation of people from the Global South, and races other than White and Asian (especially Black or African American).

Reporting biases

Some studies did not provide explicit data for any adverse event, but only for serious adverse events or adverse events leading to withdrawal (SELECT; STEP 9; STEP 10; STEP-HFpEF), although this does not constitute a reporting bias by itself, since this specific measurement was not mentioned in the studies' protocols. Six studies did not provide any of our prespecified quality-of-life measurements (Eckard 2024; SMART; STEP 5; STEP 8; STEP-HFpEF; STEP-HFpEF DM), and although this outcome was also not prespecified in their protocols, it should be a considered a critical outcome for this population. Also, one study did not report full data for all outcome measurements of quality of life, as prespecified in its protocol (O'Neil 2018). Among the studies that assessed blood pressure, three studies reported only systolic blood pressure change (STEP 10; STEP-HFpEF; STEP-HFpEF DM), since diastolic blood pressure was not included among their prespecified outcomes. The study that provided data for the comparison of semaglutide versus tirzepatide did not report quality of life (SURMOUNT-5). Due to the recent publication of this study, we hypothesise this could be due to time lag bias. We did not identify evidence of publication bias in those comparisons with 10 or more studies.

Discussion

Summary of main results

This review includes 18 RCTs, summarising data for 27,949 adults living with obesity.

Compared to placebo at medium-term follow-up, semaglutide reduces weight; likely has little to no absolute difference in adverse events leading to withdrawal and has very uncertain effects on serious adverse events; likely has little to no difference in quality of life; and may result in little to no difference in MACE and mortality.

Compared to placebo at long-term follow-up, semaglutide likely reduces weight; likely increases adverse events leading to withdrawal and likely results in little to no clinically important difference in serious adverse events; and likely results in little to no clinically significant differences in quality of life, MACE and mortality.

Compared to liraglutide at medium-term follow-up, semaglutide may result in a reduction of weight; may have little to no difference in quality of life; and has very uncertain effects on adverse events leading to withdrawal, serious adverse events, MACE and mortality.

Compared to tirzepatide at medium-term follow-up, semaglutide may result in a lower percentage of weight loss; may result in little to no difference in adverse events leading to withdrawal; has very uncertain effects on serious adverse events, MACE and mortality. No data are currently available for quality of life.

None of the included studies reported data for the other prespecified comparisons.

Limitations of the evidence included in the review

The included studies defined obesity primarily using BMI as the main inclusion criterion. While BMI is a practical and widely used measure, it may not consistently reflect total body fat, particularly across different ethnicities, sexes, and degrees of obesity. Moreover, the diagnosis of obesity should also take into account associated comorbidities and functional status [270; 271; 272].

Despite the included studies reporting most of our predefined outcomes, we could not conduct most of the prespecified subgroup analyses due to the lack of disaggregated data. Additionally, although we judged only one study at high risk of selective reporting for a specific outcome (O'Neil 2018 for a specific measurement of quality of life), some studies did not report outcomes that, despite not being prespecified, probably were collected or at least available to investigate. For example, SELECT, SMART, STEP 8, STEP 9 and STEP 10 had available data for change in weight percentage or total kg, but not for BMI; and STEP 10, STEP-HFpEF and STEP-HFpEF DM provided data for systolic but not for diastolic blood pressure. The available reports of SURMOUNT-5 also did not include data on quality of life, a prespecified outcome, which could be due to time lag bias.

Sixteen studies were funded by Novo Nordisk (O'Neil 2018; OASIS 1; SELECT; SMART; STEP 1; STEP 10; STEP 2; STEP 3; STEP 4; STEP 5; STEP 6; STEP 7; STEP 8; STEP 9; STEP-HFpEF; STEP-HFpEF DM), and one by Eli-Lilly (SURMOUNT-5). Previous meta-epidemiological studies have described a positive association between sponsorship and more favourable results. A Cochrane review by Lundh and colleagues showed that industry-sponsored studies are probably more likely to show favourable efficacy results [273], while a meta-epidemiological study by Hansen Nejstgaard and colleagues described an "important association between commercial funder influence and estimated intervention effects", with an estimation of exaggeration of the effects of interventions by 12% [274]. Novo Nordisk had a major influence in the design, conduct, analysis, and writing of the funded studies. Furthermore, several authors declared major conflicts of interest, such as patents or shareholdings, as detailed in Supplementary material 9.

Although the current risk of bias tools do not consider financial conflict of interest as a bias in itself, the high level of involvement of the funder may have influenced the results through mechanisms other than those described under the Cochrane risk of bias tools. We believe there is an important need for structured approaches to assess studies with conflicts of interest. To the best of our knowledge, the 'Tool for Addressing Conflicts of Interest in Trials' (TACIT) [64], that aims to address the potential influence of conflicts of interest in studies included in systematic

reviews, is currently under development. In the future, we expect this tool to serve as a complement to aid interpretation of review findings such as ours.

All our analyses and conclusions were based on studies about which we have concerns about conflicts of interest between the authors and the drug manufacturer. We believe that independent investigations to make clinical and public policy decisions would better establish the role of semaglutide in weight management; however, current decisions continue to be based, at least in part, on compromised evidence.

Limitations of the review processes

Although we measured the effects of using semaglutide, we did not assess outcomes after the discontinuation of semaglutide. We included the STEP 4 study, which randomised patients to continue semaglutide or switch to placebo after a 20-week run-in period of semaglutide (we only analysed the period after randomisation, since it was the period that provided comparative data between the two interventions of interest). During the run-in period, the study authors reported a weight reduction of 10.6% for the whole cohort receiving semaglutide. After randomisation, the group that switched to placebo gained 6.9% of body weight at week 68. The STEP 1 study extension study included a subset of interested patients from five selected countries, who completed treatment with either semaglutide 2.4 mg or placebo at week 68, following them for an additional 52 weeks without semaglutide [275]. In this period, the patients who had previously received semaglutide regained 11.6% of body weight, compared to 1.9% in the patients who had previously received a placebo. These results can be interpreted as a possible important weight regain after suspending semaglutide, although this specific conclusion is outside the scope of our methods.

We considered two studies as having a long-term follow-up (SELECT; STEP 5), defined for the purposes of our review as 24 months or more. The STEP 5 study had a follow-up of two years, and SELECT has a recent publication informing outcomes up to four years. However, in the latter case, we were unsure about the rate of attrition for weight-related outcomes, so we decided to use data for the two-year follow-up (see Analysis 2.1 for further comments). Our results should not be directly extrapolated to follow-up periods longer than those considered by the included studies.

Agreements and disagreements with other studies or reviews

Other reviews assessing the effects of semaglutide for weight loss in the same population have found similar results. A recent meta-analysis by Qin and colleagues estimated a weight change of −11.80% (95% CI −12.93 to −10.68) favouring semaglutide 2.4 mg weekly versus placebo, but with a higher risk of adverse events leading to discontinuation (RR 1.77, 95% CI 1.25 to 2.49, moderate-certainty evidence) and gastrointestinal adverse events (RR 1.49, 95% CI 1.38 to 1.60, moderate-certainty evidence) [56]. Dorneles and colleagues reported similar findings in terms of body weight change (MD −11.80%, 95% CI −13.53 to −10.07, high-certainty evidence), with small effects in terms of adverse events (RR 1.03, 95% CI 1 to 1.06, high-certainty evidence) and serious adverse events (RR 1.07, 95% CI 0.70 to 1.62, low-certainty evidence), but with an increased risk of discontinuation of treatment (RR 2.03, 95% CI 1.87 to 2.20, high-certainty evidence) and gastrointestinal adverse events (RR 3.26, 95% CI 1.99 to 5.34, moderate-certainty evidence) [57]. Another systematic review of four RCTs conducted by Zhong and colleagues estimated a weight change of −12.57% (95% CI −14.80 to −10.35), favouring semaglutide once-weekly [55]. They reported gastrointestinal adverse events disaggregately, estimating a higher risk of nausea, vomiting, diarrhoea and constipation in the semaglutide group, similar to what other reviews found [276, 277]. The review by Moiz and colleagues reported similar results [58]. Another review suggested no increased risk of thyroid cancer with semaglutide in people with type 2 diabetes or obesity [278]. The review by Patoulias and colleagues assessed the effects of semaglutide versus other GLP-1RAs in people with type 2 diabetes, showing better weight loss with semaglutide compared with dulaglutide, exenatide and liraglutide (pooled MD -0.91 kg/m^2, 95% CI -1.18 to -0.63) [279], while Li and colleagues estimated an overall weight reduction of −1.78 kg (95% CI −2.64 to −0.93) of oral semaglutide 14 mg compared to empaglifozin, sitagliptin, liraglutide or dulaglutide [280]. The review by Stretton and colleagues shows similar results in people with diabetes, although they state that tirzepatide may result in a greater weight reduction than semaglutide [281].

Overall, the efficacy of semaglutide seen in our review seems consistent with the findings reported in other reviews. Our analyses included total adverse events of any severity, serious and non-serious adverse events, and adverse events leading to discontinuation. These other reviews complement our findings in terms of further detailing gastrointestinal adverse events and other specific adverse events.

Authors' conclusions

Implications for practice

In people living with obesity, semaglutide compared to placebo results in weight loss at medium-term follow-up, and the initial weight loss is likely sustained at longer-term follow-up, although its effects on quality of life, major adverse cardiovascular events (MACE), and mortality are likely limited or uncertain. While it likely increases the risk of adverse events leading to withdrawal, this appears to be of limited clinical relevance in absolute terms. Compared with liraglutide, semaglutide may offer superior weight reduction and little to no clinically important difference in quality of life, with uncertain effects on other patient-important outcomes. Compared to tirzepatide, semaglutide

may result in a lower weight loss and little to no clinically important difference in adverse events, with uncertain effects on other critical outcomes. The majority of studies were funded by the drug's manufacturer, raising important concerns about potential conflicts of interest. 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

Most of our included studies declare that they were conducted predominantly in White (O'Neil 2018; OASIS 1; SELECT; SMART; STEP 1; STEP 10; STEP 2; STEP 3; STEP 4; STEP 5; STEP 8; STEP 9; STEP-HFpEF; STEP-HFpEF DM; SURMOUNT-5) or Asian (STEP 6; STEP 7) populations. No studies were conducted exclusively on women or men, and we did not find any studies that disaggregated results by gender, which prevented us from investigating the effect of semaglutide on women or men separately.

Differences in access to care or the quality of care across countries may affect the implementation of this intervention. The implications of implementing this intervention in different scenarios are very important because the decisions to allocate public resources in this case should consider factors other than effectiveness results. Implementing any intervention intended to improve health should consider that only providing a pharmacological intervention in low-resource settings, without appropriate lifestyle interventions or access to healthy foods, might both guarantee access to the intervention and increase health inequalities simultaneously.

Another topic related to equity, especially in vulnerable settings, is drug pricing, cost-effectiveness and affordability, considering that the costs of the treatment are estimated at GBP 175.80 per month in the UK and up to USD 1,349.02 in the USA [282, 283].

Decision-makers may need to carefully consider the differential impacts of providing this intervention on different subgroups within the population to benefit those who need it, with the necessary support for the co-interventions needed to help maintain weight loss and promote equity in those populations.

Implications for research

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. In this case, the drug manufacturer played a major role in the design, conduction, analysis and reporting of 17 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 promising, it would be advisable to count on independent research that might reaffirm these categorical findings. Especially for resource-constrained settings, 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 46 ongoing, potentially eligible studies, of which 16 explicitly report funding by the drug manufacturer (Supplementary material 4). The high number of ongoing studies reflects a very active research pipeline, which will impact upcoming evidence syntheses. In a future update of this systematic review, we plan to re-assess the status of all these ongoing studies, aiming to refine our results further, trying to assess the consistency of the results shown here with those published by independent authors, and estimating the potential risk for publication bias.

Weight loss helps reduce chronic disease risk, but unfortunately, people may regain much of 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 until independent studies are available to assess weight regain after drug discontinuation and after a sufficient period of pharmacovigilance to ensure its safety profile has been completed.

Equity-related implications for research

Despite overweight and obesity being a global problem, current research has been mainly conducted in upper-middle or high-income countries, and mostly considering White and Asian populations. Future research should also consider populations from low-income and lower-middle-income countries and people from other ethnic backgrounds.

Supplementary materials

[For display in the published PDF only] Supplementary materials are available with the online version of this article: 10.1002/14651858.CD015092.pub2.

[For display on the Cochrane Library only] Supplementary materials are published alongside the article and contain additional data and information that support or enhance the article. Supplementary materials may not be subject to the same editorial scrutiny as the content of the article and Cochrane has not copyedited, typeset or proofread these materials. The material in these sections has been supplied by the author(s) for publication under a Licence for Publication and the author(s) are solely responsible for the material. Cochrane accordingly gives no representations or warranties of any kind in relation to, and accepts no liability for any reliance on or use of, such material.

Supplementary material 1

CD015092-SUP-01-searchStrategy.html

Search strategies

Supplementary material 2

CD015092-SUP-02-characteristicsOfIncludedStudies.html

Characteristics of included studies

Supplementary material 3

CD015092-SUP-03-characteristicsOfExcludedStudies.html

Characteristics of excluded studies

Supplementary material 4

CD015092-SUP-04-characteristicsOfOngoingStudies.html

Characteristics of ongoing studies

Supplementary material 5

CD015092-SUP-05-analyses.html

Analyses

Supplementary material 6

CD015092-SUP-06-dataPackage.zip

Data package

Supplementary material 7

CD015092-SUP-07-other.html

Detailed outcome domains, measures and thresholds for minimal clinically important difference.

Supplementary material 8

CD015092-SUP-08-other.html

Funder involvement in each included study

Supplementary material 9

CD015092-SUP-09-other.html

Summary of authors' conflict of interests, as reported by each included study

Supplementary material 10

CD015092-SUP-10-other.html

Summary of findings table: Semaglutide versus placebo - medium term follow-up

Supplementary material 11

CD015092-SUP-11-other.html

Summary of findings table: Semaglutide versus placebo - long term follow-up

Supplementary material 12

CD015092-SUP-12-other.html

Summary of findings table: Semaglutide versus liraglutide - medium term follow-up

Supplementary material 13

CD015092-SUP-13-other.html

Summary of findings table: Semaglutide versus tirzepatide - medium term follow-up

Additional information

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Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Tari Turner, Cochrane Australia
- Managing Editor (provided editorial guidance to authors, edited the article): Jenny Bellorini, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments and supported editorial team): Cynthia Stafford, Cochrane Central Editorial Service;
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- Peer-reviewers (provided comments and recommended an editorial decision): Joel Lexchin MD, Professor Emeritus, Faculty of Health, York University, Toronto Ontario Canada (clinical/content review)*, Brian Duncan (patient and public review), Andreas Lundh, Cochrane Denmark & Centre for Evidence-Based Medicine Odense, University of Southern Denmark (special methods review), Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review), Jo Platt, Central Editorial Information Specialist (search review).

Contributions of authors

- Javier Bracchiglione: conceptualisation; methodology; investigation; formal analysis; writing - original draft
- Nicolás Meza: conceptualisation; methodology; investigation; writing - review, and editing
- Juan Franco: conceptualisation; methodology; investigation; writing - review, and editing
- Camila Micaela Escobar Liquitay: conceptualisation; methodology; investigation; writing - review, and editing
- Victoria Novik A: conceptualisation; methodology; writing - review, and editing
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- Eva Madrid: conceptualisation; methodology; investigation; formal analysis; writing - original draft

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Registration and protocol

The original protocol (10.1002/14651858.CD015092) was published in September 2022 [51]. The modifications to the original protocol were prospectively registered in PROSPERO (CRD420250654193; via www.crd.york.ac.uk/PROSPERO/view/CRD420250654193) on 25 February 2025.

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); 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 5; Supplementary material 6). 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 [68].

History

Protocol first published: Issue 9, 2022

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Tables

Table 1

Overview of synthesis and included studies: general characteristics

Study ID	Country/setting	Intervention: semaglutide	Comparison	n (randomised)	Age	Sex (% male)	Weight (kg)	BMI	Subpopulation	Follow-up: weeks
Eckard 2024	USA	SC, 1 mg, weekly	Placebo weekly	108 (1:1)	53	60%	97.7	33.35	HIV-associated lipohypertrophy	32
O'Neil 2018	Australia, Belgium, Canada, Germany, Israel, Russia, UK, USA	SC, 0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, daily	Liraglutide, SC, 3 mg daily Placebo, daily	957 (1:1:1:1:1:1)	47	35%	111.5	39.3	-	52
OASIS 1	Canada, Denmark, Finland, France, Germany, Japan, Poland, Russia, USA	Oral, 50 mg, daily	Placebo, daily	667 (1:1)	50	27%	105.4	37.5	-	68
SELECT	Algeria, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Columbia, Croatia, Czechia, Denmark, Finland, France, Germany, Greece, Hungary, India, Ireland, Israel, Italy, Japan, Latvia, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Puerto Rico, Romania, Russian Federation, Serbia, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, Ukraine, UK, USA	SC, 2.4 mg, weekly	Placebo, weekly	17,604 (1:1)	61.6	72.3%	96.65	33.35	Established CVD (MI, stroke, PAD or other)	Up to 240
SMART	Netherlands, Germany, Spain, Canada	SC, 2.4 mg, weekly	Placebo, weekly	101 (1:1)	55.8	60.4%	105	36.2	People living with CKD	24
STEP 1	Argentina, Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, India, Japan, Mexico, Poland, Russia, Taiwan, UK, USA	SC, 2.4 mg, weekly	Placebo, weekly	1961 (1:1)	46	25.9%	105.3	37.9	-	68
STEP 2	Argentina, Canada, Germany, Greece, India, Japan, Puerto Rico, Russian Federation, South Africa, Spain, United Arab Emirates, UK, USA	SC 2.4 mg, 1.0 mg, weekly	Placebo, weekly	1210 (1:1:1)	55	49.1%	99.8	35.7	T2DM	68
STEP 3	USA	SC, 2.4 mg, weekly	Placebo, weekly	611 (1:1)	46	19.0%	105.83	38.0	-	68
STEP 4	Denmark, Israel, Netherlands, Portugal, South Africa, Spain, Sweden, Switzerland, Ukraine, USA	SC, 2.4 mg, weekly	Placebo, weekly	803 (1:1)	46	21.0%	96.1	34.4	20-week run-in phase with semaglutide 2.4 mg weekly. Randomised to continuing semaglutide, or discontinuation (placebo)	68
STEP 5	Canada, Hungary, Italy, Spain, USA	SC, 2.4 mg, weekly	Placebo, weekly	304 (1:1)	47.35	22.36%	106.05	38.55	-	104
STEP 6	Japan, Korea	SC	Placebo, weekly	401 (1:1)	51	63.1%	87.5	31.9	East Asian population. Participants with and without diabetes	68

		2.4 mg, 1.7 mg, weekly								
STEP 7	China, Hong Kong, Brazil, South Korea	SC2.4 mg, weekly	Placebo, weekly	375 (1:1)	41	54.7%	96.4	34	Mostly East Asian population. Participants with and without diabetes	44
STEP 8	USA	SC, 2.4 mg, weekly	Liraglutide, SC, 3 mg, daily Placebo, weekly or daily	338 (1:1:1)	49	21.6%	104.54	37.53	-	68
STEP 9	Canada, Colombia, Denmark, France, Norway, Russia, Saudi Arabia, South Africa, Spain, Sweden, USA	SC, 2.4 mg, weekly	Placebo, weekly	407 (1:1)	58	18.4%	108.6	40.3	Knee OA	68 + 7
STEP 10	Canada, Denmark, Finland, Spain, UK	SC, 2.4 mg, weekly	Placebo, weekly	207 (1:1)	53	29%	111.6	40.1	Prediabetes	52
STEP-HFpEF	Argentina, Austria, Canada, Czechia, Germany, Hungary, India, Israel, Italy, Japan, Netherlands, Poland, Spain, Sweden, UK, USA	SC, 2.4 mg, weekly	Placebo, weekly	529 (1:1)	68.50	43.85%	105.1	37	HFpEF	52
STEP-HFpEF DM	Argentina, Austria, Canada, Czechia, Germany, Hungary, India, Israel, Italy, Japan, Netherlands, Poland, Spain, Sweden, UK, USA	SC, 2.4 mg, weekly	Placebo, weekly	616 (1:1)	69.50	55.68%	-	36.9	HFpEF and diabetes	52
SURMOUNT-5	Puerto Rico, USA	1.7 mg, 2.4 mg, weekly	Tirzepatide, 10 mg, 15 mg, weekly	750 (1:1)	44.7	64.7%	113	39.4	-	72

CKD: chronic kidney disease; **CVD:** cardiovascular disease; **HFpEF:** heart failure with preserved ejection fraction; **MI:** myocardial infarction; **OA:** osteoarthritis; **PAD:** peripheral arterial disease; **SC:** subcutaneous; **T2DM:** type 2 diabetes mellitus

Table 2

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

Study ID (Study period)	Intervention and comparison	SBP/DBP (mmHg)	TC/LDL/HDL (mmol/L)	TG (mmol/L)	Ethnicity	Race	Comorbidites
Eckard 2024	SC semaglutide 1 mg vs placebo (weekly)	126/80	185.5/106/44.96 (mg/dL)	118.25 (mg/dL)	8% Hispanic 92% non-Hispanic	62% Black or African American 35% White 2% more than once race 1% Native American	100% people living with HIV
O'Neil 2018	SC semaglutide at different doses (0.05 mg, 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg) vs SC liraglutide 3 mg vs placebo (daily)	128/81	5.1/3/1.2	-	-	73.14% White 17.86% unknown or NR 6.37% Black or African American 0.94% Asian	-

						0.41% American Indian or Alaska Native 0.31% Native Hawaiian or Pacific Islander	
OASIS 1	Oral semaglutide 50 mg vs placebo (daily)	129/82	5/2.9/1.3	1.4	-	74% White 10.79% Asian 8.69% unknown or NR 6.44% Black or African American	45.72% hypertension 40.02% dyslipidaemia 13.94% OSA 11.39% knee or hip OA 10.49% asthma or COPD 9.89% thyroid disorder 7.94% glucose metabolism disorder 5.99% liver disease 4.04% gout 1.94% reproductive system disorders 1.34% coronary artery disease 1.04% kidney disease 0.59% cerebrovascular disease
SELECT	SC semaglutide 2.4 mg vs placebo (weekly)	130.95/79.30	-/-/-	-	88.67% not Hispanic or Latino 10.34% Hispanic or Latino 0.97% unknown or NR	84.02% White 8.21% Asian 3.81% Black or African American 3.65% unknown or NR 0.24% American Indian or Alaska Native 0.045% Native Hawaiian or Pacific Islander	CVD: • 67.63% MI • 17.80% stroke • 8.16% ≥ 2 • 4.41% PAD • 1.98% other
SMART	SC semaglutide 2.4 mg vs placebo (weekly)	131.7/81.1	-/2.7/-	-	-	91.08% White 6.93% unknown or NR 1.98% Asian	-
STEP 1	SC semaglutide 2.4 mg vs placebo (weekly)	126.33/80.0	190.44/111.03/49.43 (mg/dL)	-	85.10% not Hispanic or Latino 12.03% Hispanic or Latino 2.85% unknown or NR	75.06% White 13.30% Asian 5.66% Black or African American 2.80% unknown or NR 1.68% other 1.37% American Indian or Alaska Native 0.10% Native Hawaiian or Pacific Islander	-
STEP 2	SC semaglutide at different doses (2.4 mg, 1.0 mg) vs placebo (weekly)	130/80	4.4/2.3/1.1	1.8		62.06% White	70.1% hypertension

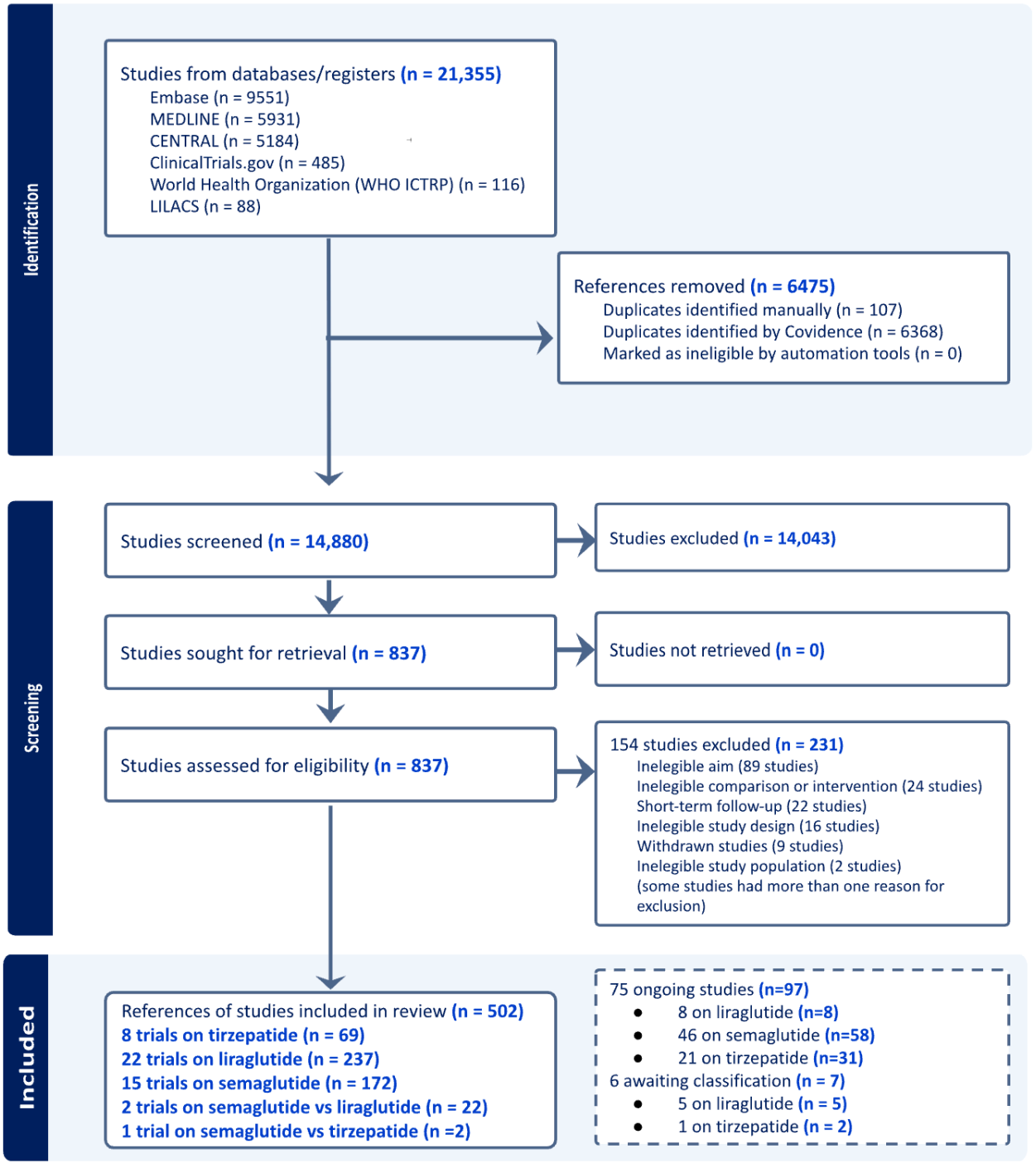
					87.19% not Hispanic or Latino 12.80% Hispanic or Latino	26.19% Asian 8.26% Black or African American 2.89% unknown or NR 0.49% American Indian or Alaska Native 0.08% Native Hawaiian or Pacific Islander	68.3% dyslipidaemia 21.6% NAFLD 16.2% knee OA 14.5% OSA 9.5% asthma or COPD 8.2% coronary artery disease 2.06% polycystic ovary syndrome
STEP 3	SC semaglutide 2.4 mg vs placebo (weekly)	124/80.33	186.50/109.07/51.37 (mg/dL)	-	80.19% not Hispanic or Latino 19.80% Hispanic or Latino	76.10% White 18.98% Black or African American 2.45% unknown or NR 1.80% Asian 0.49% Native Hawaiian or Pacific Islander 0.16% American Indian or Alaska Native	-
STEP 4	SC semaglutide 2.4 mg vs placebo (weekly)	121/78	-/-/-	-	92.15% not Hispanic or Latino 7.84% Hispanic or Latino	83.68% White 12.95% Black or African American 2.36% Asian 0.99% unknown or NR	-
STEP 5	SC semaglutide 2.4 mg vs placebo (weekly)	125.5/80	4.85/2.9/1.2	1.25	16.11% Hispanic or Latino	93.09% White 3.94% Black or African American 0.98% American Indian or Alaska Native 0.65% Asian	-
STEP 6	SC semaglutide at different doses (2.4 mg, 1.7 mg) vs placebo (weekly)	134/84	5.2/3.1/13	-	-	100% Asian	25% diabetes
STEP 7	SC semaglutide 2.4 mg vs placebo (weekly)	-/-	-/-/-	-	90.13% not Hispanic or Latino 9.86% Hispanic or Latino	90.66% Asian 8.26% White 1.06% Black or African American	25.6% diabetes
STEP 8	Weekly SC semaglutide 2.4 mg vs daily SC liraglutide 3 mg vs weekly or daily placebo (matching semaglutide and liraglutide)	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 NR	-
STEP 9	SC semaglutide 2.4 mg vs placebo (weekly)	132/82	-/-/-	-	80.58% not Hispanic or Latino 13.75% Hispanic or Latino 5.65% unknown or NR	60.93% White 14.25% unknown or NR 11.79% American Indian or Alaska Native 7.61% Black or African American 5.40% Asian	48.15% hypertension 30.46% dyslipidaemia 5.15% CVD
STEP 10	SC semaglutide 2.4 mg vs placebo (weekly)	131/-	4.7/2.7/1.2	1.6	96.61% not Hispanic or Latino	88.40% White 4.34% Asian 4.34% Black or African Am	46.37% hypertension 41.06% dyslipidaemia

					3.38% Hispanic or Latino	erican 2.41% other 0.48% American Indian or Alaska Native	12.56% knee OA 10.62% OSA 8.69% CVD
STEP-HFpEF	SC semaglutide 2.4 mg vs placebo (weekly)	133/-	-/-/-	-	93.19% not Hispanic or Latino 6.8% Hispanic or Latino	95.84% White 3.96% Black or African American 0.18% other	81.85% hypertension 51.98% atrial fibrillation 34.02% coronary artery disease 12.47% OSA
STEP-HFpEF DM	SC semaglutide 2.4 mg vs placebo (weekly)	-/-	-/-/-	-	-	84.25% White 12.33% Asian 2.92% Black or African American 0.48% other	85.38% hypertension 39.44% atrial fibrillation 24.02% coronary artery disease 8.60% OSA
SURMOUNT-5	Tirzepatide (10 mg or 15 mg) vs semaglutide (1.7 mg or 2.4 mg) (weekly)	125.7/81.3	4.91/2.95/1.29	1.47	26.13% Hispanic 73.87% non-Hispanic	76.1% White, 19.2% Black or African American, 0.8% American Indian or Alaska Native, 2.4% Asian, 1.5% more than one race	39.6% hypertension 24.3% dyslipidaemia 19.1% impaired glucose metabolism 18.3% anxiety 14.7% OSA 12.9% back pain 12.1% depression 9.7% asthma 10.8% gallbladder disease 8.9% OA 3.6% NAFLD/NASH 2.4% gout/ hyperuricaemia

COPD: chronic obstructive pulmonary disease; **CVD:** cardiovascular disease; **DBP:** diastolic blood pressure; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein; **MI:** myocardial infarction; **NAFLD:** nonalcoholic fatty liver disease; **NASH**: non-alcoholic steatohepatitis; **NR:** not reported; **OA:** osteoarthritis; **OSA:** obstructive sleep apnoea; **PAD:** peripheral arterial disease; **SBP:** systolic blood pressure; **TC:** total cholesterol; **TG:** triglyceride

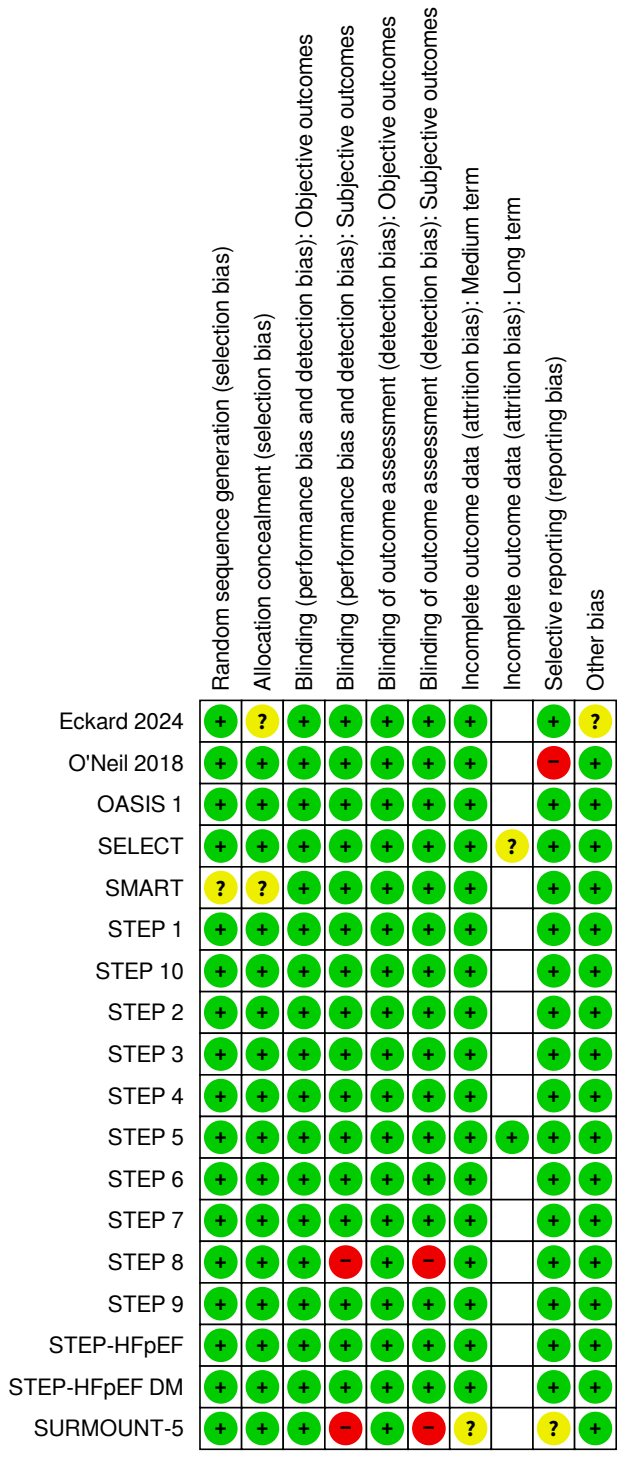
Figures

Figure 1



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

Figure 2



Risk of bias summary