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# Tirzepatide for adults living with obesity

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# Abstract

## Rationale

Obesity is a complex chronic condition linked to various comorbidities, such as hypertension, diabetes, and dyslipidaemia, with a significant global burden. Standard treatments, such as diet, exercise and behavioural changes, often have limited effects and poor compliance. Pharmacological options, including glucagon-like peptide receptor agonists (GLP-1RAs) and glucose-dependent insulinotropic polypeptide (GIP) dual agonists, show promise for individuals with obesity. This is one of three reviews investigating different GIP/GLP1-RAs for adults living with obesity.

## Objectives

To assess the effects of the dual GIP/GLP-1 receptor agonist, tirzepatide, for adults living with obesity.

## Search methods

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

## Eligibility criteria

We included randomised controlled trials (RCTs) on adults with obesity that compared tirzepatide at any dose with placebo, structured lifestyle modification programmes, another anti-obesity medication or other GLP-1RAs or GIP/GLP-1RAs, with a minimum follow-up of six months.

## Outcomes

Critical outcomes were weight, adverse events, major adverse cardiovascular events (MACE), quality of life, and mortality. Important outcomes included waist circumference and other obesity-related comorbidities.

## Risk of bias

We used the original version of the Cochrane tool for assessing risk of bias (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 tirzepatide versus placebo.

## Included studies

We included nine RCTs with 7111 participants, aged 36.1 to 65.25 years, primarily from middle- and high-income countries. The main comparison, tirzepatide versus placebo, is based on eight studies; one study compared tirzepatide with semaglutide. Studies included participants with weight-related comorbidities. Seven studies focused on specific subgroups, including type 2 diabetes, prediabetes, chronic heart failure, obstructive sleep apnoea (after a long pretreatment phase), and different racial populations. Tirzepatide was injected once a week, with dosing ranging from 5 mg to 15 mg. All the studies had medium-term follow-ups, and one had a long-term follow-up. All nine studies reported a major role of the drug manufacturer in their design, conduct, analysis, or writing.

## Synthesis of results

#### Tirzepatide versus placebo (medium-term: 12 to 18 months)

Tirzepatide likely results in a greater percentage reduction in body weight from baseline (mean difference (MD) -16.03, 95% confidence interval (CI) -18.91 to -13.14; 8 studies, 6317 participants; moderate-certainty evidence), and an increase in the number of people achieving a 5% weight reduction (risk ratio (RR) 3.60, 95% CI 2.44 to 5.30; I2 = 86%; 5 studies, 4455 participants; moderate-certainty evidence).

Tirzepatide may result in an increase in non-serious adverse events (RR 1.33, 95% CI 1.03 to 1.71; 5 studies, 4582 participants; low-certainty evidence). The evidence is very uncertain about the effect on serious adverse events (RR 0.99, 95% CI 0.88 to 1.12; 8 studies, 6359 participants; very low-certainty evidence). Tirzepatide may result in little to no difference in adverse events leading to withdrawal (RR 2.06, 95% CI 1.21 to 3.52; 8 studies, 6359 participants; low-certainty evidence).

Tirzepatide likely results in little to no difference in MACE (RR 0.75, 95% CI 0.34 to 1.66; $I^2$ = 0%; 7 studies, 5628 participants; moderate-certainty evidence).

Tirzepatide likely results in little to no clinically important difference in quality of life as measured by the IWQOL-Lite-CT physical function domain (MD 9.91, 95% CI 7.81 to 12.02; 6 studies, 5020 participants; moderate-certainty evidence).

Tirzepatide likely results in little to no difference in mortality (RR 0.79, 95% CI 0.34 to 1.83; 7 studies, 5628 participants; moderate-certainty evidence).

#### Tirzepatide versus placebo (long-term: 3.5 years)

Tirzepatide likely results in a greater percentage reduction in body weight from baseline (MD -15.66, 95% CI -19.14 to -12.18; 1 study, 1032 participants; moderate-certainty evidence), and an increase in the number of people achieving a 5% weight reduction (RR 2.81, 95% CI 2.33 to 3.38; 1 study, 1032 participants; moderate-certainty evidence).

Tirzepatide may result in an increase in non-serious adverse events (RR 1.05, 95% CI 0.98 to 1.11; 1 study, 1032 participants; low-certainty evidence). The evidence is very uncertain about the effect on serious adverse events (RR 1.14, 95% CI 0.79 to 1.65; 1 study, 1032 participants; very low-certainty evidence). Tirzepatide may result in little to no difference in adverse events leading to withdrawal (RR 1.64, 95% CI 0.97 to 2.76; 1 study, 1032 participants; low-certainty evidence).

Tirzepatide likely results in little to no difference in MACE (RR 0.56, 95% CI 0.22 to 1.42; 1 study, 1032 participants; moderate-certainty evidence).

Tirzepatide may result in little to no clinically important difference in quality of life as measured by SF-36 physical component score (MD 2.70, 95% CI 0.00 to 5.40; 1 study, 1032 participants; low-certainty evidence).

Tirzepatide may result in little to no difference in mortality (RR 0.83, 95% CI 0.22 to 3.17; 1 study, 1032 participants; low-certainty evidence).

## Authors' conclusions

Tirzepatide likely results in weight loss at medium-term follow-up, and this initial weight loss is likely to be sustained at longer-term follow-up. The long-term impact on other patient-important outcomes may be limited or uncertain. The certainty of the evidence on events leading to withdrawal at medium- and long-term follow-up is low, which might further limit our understanding of the sustainability of the initial effects.

All the included studies were funded by the drug manufacturer, raising concerns about potential conflicts of interest. Further independent studies are needed, particularly in underrepresented populations, to better understand the broader effects of tirzepatide in the management of obesity.


## Funding

World Health Organization (WHO)


## Registration


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# Plain language summary

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

**Key messages**

- Compared to placebo (a sham medication), tirzepatide likely helps adults with obesity lose weight in the medium term (up to 2 years), and this weight reduction is likely to be maintained over the long term (more than 2 years). Tirzepatide may increase the risk of non-serious unwanted effects in the medium and long term, but may have little to no effect on serious unwanted effects, including those that cause people to stop taking tirzepatide. It may have little to no effect on quality of life, major cardiovascular events, and mortality.
- The manufacturer of tirzepatide was involved in the funding, design, running and reporting of all nine included studies. This raises concerns about conflicts of interest that might affect the results. More independent research is needed.

**What is obesity?**

Obesity is a condition in which a person has too much body fat, which can increase the risk of health problems like type 2 diabetes, heart disease, and some types of cancer. Managing obesity often involves lifestyle changes such as eating a healthier diet and being more physically active. In some cases, doctors may prescribe medications to support weight loss.

**What is tirzepatide?**

Tirzepatide is a medication developed to treat people living with obesity or weight-related health problems. It works by mimicking two hormones that help to regulate appetite, stomach emptying, feeling full, blood sugar, and metabolism. It is given as a weekly injection. Some people taking tirzepatide experience unwanted effects, such as indigestion, feeling sick, diarrhoea, and constipation. Other similar medications are liraglutide and semaglutide.

**What did we want to find out?**

We wanted to know how well tirzepatide works in adults with obesity in the medium term (up to 2 years) and long term (2 or more years). We examined its effects on weight loss, health problems associated with obesity, unwanted effects, quality of life, and risk of death. We did not look at what happens after people stop taking tirzepatide.

**What did we do?**

We searched for studies that compared tirzepatide with placebo (a sham treatment), no treatment, lifestyle changes or another weight-loss medication. We focused on studies that compared tirzepatide with placebo. We included studies that followed participants for at least six months. We analysed the results and rated our confidence in the evidence.

**What did we find?**

We included nine studies involving 7111 adults with obesity, aged 36 to 65 years, mainly from middle- and high-income countries. Eight studies compared tirzepatide with placebo, and 1 study compared tirzepatide with semaglutide. Tirzepatide was given as a weekly injection in doses ranging from 5 mg to 15 mg. The main comparison with placebo (8 studies, 6361 people) has the following findings.

- Tirzepatide likely results in significant weight loss in the medium term (up to about 1.5 years) and probably maintains this effect in the long term (around 3.5 years).
- People taking tirzepatide may experience non-serious unwanted effects, but may be no more or less likely to discontinue treatment because of these effects than people taking a placebo. There may be little or no difference in serious unwanted effects.
- Tirzepatide may result in little to no difference in cardiovascular events, but it might not improve quality of life or decrease mortality.

**What are the limitations of the evidence?**

Our confidence in the evidence is limited because of concerns about how some of the studies were conducted. The long-term findings are based on only one study. The manufacturer of tirzepatide funded all the studies, which raises concerns about the reliability of the results. More independent research is needed.

**How up to date is this evidence?**

The evidence is up to date as of December 2024.

# Summary of findings

**Summary of findings 1**

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

**Population:** adults living with obesity
**Setting:** outpatient
**Intervention:** tirzepatide
**Comparator:** 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 tirzepatide | | | | |
| **Weight**<br>Follow-up: range 52 weeks to 72 weeks | % weight change from baseline | The median % weight change from baseline was **−2.2** % | MD **16.03 % lower** (18.91 lower to 13.14 lower) | - | 6317 (8 RCTs) | ⨁⨁⨁◯ Moderate[a,b] | Tirzepatide likely results in a greater % reduction in weight from baseline in the medium term. |
| | People achieving a 5% weight reduction | 261 per 1000 | **941 per 1000** (638 to 1000) | **RR 3.60** (2.44 to 5.30) | 4455 (5 RCTs) | ⨁⨁⨁◯ Moderate[a,c] | Tirzepatide likely results in an increase in the number of people achieving a 5% weight reduction in the medium term. |
| **Adverse events**<br>Follow-up: range 52 weeks to 72 weeks | Non-serious | 407 per 1000 | **541 per 1000** (419 to 696) | **RR 1.33** (1.03 to 1.71) | 4582 (5 RCTs) | ⨁⨁◯◯ Low[a,c,d] | Tirzepatide may result in an increase in non-serious adverse events in the medium term. |
| | Serious | 92 per 1000 | **91 per 1000** (81 to 103) | **RR 0.99** (0.88 to 1.12) | 6359 (8 RCTs) | ⨁◯◯◯ Very low[a,e] | Tirzepatide may have little to no effect on serious adverse events in the medium term but the evidence is very uncertain. |
| | Leading to withdrawal | 27 per 1000 | **56 per 1000** (33 to 95) | **RR 2.06** (1.21 to 3.52) | 6359 (8 RCTs) | ⨁⨁⨁◯ Low[a,d] | Tirzepatide may result in little to no difference in adverse events leading to withdrawal in the medium term. |
| **Major adverse cardiovascular events (MACE)**<br>Follow-up: range 52 weeks to 72 weeks | | 6 per 1000 | **5 per 1000** (2 to 10) | **RR 0.75** (0.34 to 1.66) | 5628 (7 RCTs) | ⨁⨁⨁◯ Moderate[a] | Tirzepatide likely results in little to no difference in MACE in the medium term. |
| **Quality of life**<br>Follow-up: range 52 weeks to 72 weeks | IWQoL-Lite-CT physical function score | The median quality of life assessed by IWQoL-Lite-CT physical function was **2.35** change from baseline | MD **9.91 change from baseline higher** (7.81 higher to 12.02 higher) | - | 5020 (6 RCTs) | ⨁⨁⨁◯ Moderate[a] | Tirzepatide likely results in little to no clinically important difference in quality of life as measured by IWQoL-Lite-CT physical function in the medium term. |
| **Mortality**<br>Follow-up: range 52 weeks to 72 weeks | | 3 per 1000 | **2 per 1000** (1 to 6) | **RR 0.79** (0.34 to 1.83) | 5628 (7 RCTs) | ⨁⨁⨁◯ Moderate[a] | Tirzepatide likely results in little to no difference in mortality in the medium term. |

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

**CI:** confidence interval; **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: downgraded one level due to a high risk of bias as all studies had an unclear (> 10% attrition or unbalanced attrition) or high risk of bias (> 20% attrition) due to attrition.

[b]Inconsistency: following a minimally contextualised approach, we did not downgrade for inconsistency even though $I^2$ statistic > 90%, as the point estimates and confidence intervals were consistently below the minimally important difference.

[c]Inconsistency: following a minimally contextualised approach, we did not downgrade for inconsistency even though $I^2$ statistic is between 60% and 90%, as the point estimates and confidence intervals were consistently below the minimally important difference.

[d]Imprecision: downgraded one level because the confidence interval crosses the minimally important difference.

[e]Serious imprecision: downgraded two levels as the confidence interval crosses the minimally important difference for both benefit and harm.

**Summary of findings 2**

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

**Population:** adults living with obesity
**Setting:** outpatient
**Intervention:** tirzepatide
**Comparator:** 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 tirzepatide | | | | |
| **Weight**<br>Follow-up: mean 176 weeks | % weight change from baseline | The median % weight change from baseline (lower indicates benefit) was **−1.3** | MD **15.66 lower** (19.14 lower to 12.18 lower) | - | 1032 (1 RCT) | ⨁⨁⨁◯ Moderate[a,b] | Tirzepatide likely results in a greater % reduction in weight from baseline in the long term. |
| | People achieving a 5% weight reduction | 296 per 1000 | **833 per 1000** (690 to 1000) | **RR 2.81** (2.33 to 3.38) | 1032 (1 RCT) | ⨁⨁⨁◯ Moderate[a,b] | Tirzepatide likely results in an increase in the number of people achieving a 5% weight reduction in the long term. |
| **Adverse events**<br>Follow-up: mean 176 weeks | Non-serious | 826 per 1000 | **867 per 1000** (809 to 917) | **RR 1.05** (0.98 to 1.11) | 1032 (1 RCT) | ⨁⨁◯◯ Low[a,b,c] | Tirzepatide may result in an increase in non-serious adverse events in the long term. |
| | Serious | 119 per 1000 | **135 per 1000** (94 to 196) | **RR 1.14** (0.79 to 1.65) | 1032 (1 RCT) | ⨁◯◯◯ Very low[a,b,d] | Tirzepatide may have little to no effect on serious adverse events in the long term, but the evidence is very uncertain. |
| | Leading to withdrawal | 59 per 1000 | **97 per 1000** (57 to 164) | **RR 1.64** (0.97 to 2.76) | 1032 (1 RCT) | ⨁⨁◯◯ Low[a,b,c] | Tirzepatide may result in little to no difference in adverse events leading to withdrawal in the long term. |
| **Major adverse cardiovascular events (MACE)**<br>Follow-up: mean 176 weeks | | 26 per 1000 | **15 per 1000** (6 to 37) | **RR 0.56** (0.22 to 1.42) | 1032 (1 RCT) | ⨁⨁⨁◯ Moderate[a,b] | Tirzepatide likely results in little to no difference in MACE in the long term. |
| **Quality of life**<br>Follow-up: mean 176 weeks | SF-36 physical component score | The median quality of life assessed by SF-36 physical component score (higher indicates benefit) was **1.7** | MD **2.7 higher** (0 to 5.4 higher) | - | 1032 (1 RCT) | ⨁⨁◯◯ Low[a,b,c] | Tirzepatide may result in little to no clinically important difference in quality of life as measured by SF-36 physical component score in the long term. |
| **Mortality**<br>Follow-up: mean 176 weeks | | 11 per 1000 | **9 per 1000** (2 to 35) | **RR 0.83** (0.22 to 3.17) | 1032 (1 RCT) | ⨁⨁◯◯ Low[a,b,c] | Tirzepatide may result in little to no difference in mortality in the long term. |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; MD: mean difference; 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: downgraded one level due to a high risk of bias as all studies had an unclear (> 10% attrition or unbalanced attrition) or high risk of bias (> 20% attrition) due to attrition.
[b]Inconsistency could not be evaluated (single study).
[c]Imprecision: downgraded one level as the confidence interval crosses the minimally important difference.
[d]Serious imprecision: downgraded two levels as the confidence interval crosses the minimally important difference for both benefit and harm.

**Summary of findings 3**

## Tirzepatide compared to semaglutide for adults living with obesity (medium-term follow-up)

**Population:** adults living with obesity
**Setting:** outpatient
**Intervention:** tirzepatide
**Comparator:** semaglutide

| Outcome domain | Outcome measure | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Certainty of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|---|
| | | Risk with semaglutide | Risk with tirzepatide | | | | |
| **Weight**<br>Follow-up: 72 weeks | % weight change from baseline | The median % weight change from baseline was **−13.7** % | MD **6.5 % lower** (8.13 lower to 4.87 lower) | - | 750 (1 RCT) | ⨁⨁◯◯ Low[a,b,c] | Tirzepatide may result in a greater % reduction in weight from baseline in the medium term. |
| | Number of people achieving a 5% weight reduction - not reported | | | | | | |
| **Adverse events**<br>Follow-up: 72 weeks | Non-serious | 790 per 1000 | **766 per 1000** (711 to 829) | **RR 0.97** (0.90 to 1.05) | 750 (1 RCT) | ⨁⨁◯◯ Low[a,b,c] | Tirzepatide may result in little to no difference in non-serious adverse events in the medium term. |
| | Serious | 35 per 1000 | **48 per 1000** (24 to 97) | **RR 1.39** (0.69 to 2.80) | 750 (1 RCT) | ⨁◯◯◯ Very low[a,b,d] | Tirzepatide may have little to no effect on serious adverse events in the medium term but the evidence is very uncertain. |
| | Leading to withdrawal | 80 per 1000 | **61 per 1000** (37 to 104) | **RR 0.77** (0.46 to 1.30) | 750 (1 RCT) | ⨁⨁⨁◯ Moderate[a,b] | Tirzepatide likely results in little to no difference in adverse events leading to withdrawal in the medium term. |
| **Major adverse cardiovascular event (MACE)**<br>Follow-up: 72 weeks | No events in either group. | | | | 750 (1 RCT) | ⨁◯◯◯ Very low[a,b,e] | The evidence is very uncertain on the effect of tirzepatide on MACE in the medium term. |
| **Quality of life** - not reported | | | | | | | |
| **Mortality**<br>Follow-up: 72 weeks | No events in either group | | | | 750 (1 RCT) | ⨁◯◯◯ Very low[a,b,e] | The evidence is very uncertain on the effect of tirzepatide on mortality in the medium term. |

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

**CI**: confidence interval; **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: downgraded one level due to a high risk of bias as the study had an unclear risk due to >10% attrition or high risk due to unblinding (on subjective outcomes).
[b]Inconsistency could not be assessed (single study).
[c]Imprecision: downgraded one level as the confidence interval crosses the minimally important difference.
[d]Serious imprecision: downgraded two levels as the confidence interval crosses the minimally important difference for both benefit and harm.
[e]Serious imprecision: downgraded two levels due to zero events in all study arms.

# Background

## Description of the condition

Obesity is a complex chronic condition 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. Its aetiology has been regarded as multifactorially driven, such as increasing consumption of ultra-processed food [1, 2]. Obesity is associated with hypertension, stroke, type 2 diabetes mellitus, dyslipidaemia, obstructive sleep apnoea, and certain types of cancer [3, 4]. Additionally, obesity increases the cardiovascular risk for those with underlying conditions [3, 4].

To determine the presence of obesity, the body mass index (BMI) is commonly used, which is calculated by dividing a person's weight in kilograms by the square of their height in metres ($kg/m^2$). Overweight is usually defined as having a BMI ranging from 25 $kg/m^2$ to 29.9 $kg/m^2$, and obesity as having a BMI of 30 $kg/m^2$or higher [4]. Diagnostic criteria of overweight and obesity reliant exclusively on the assessment of BMI in adults, including WHO definitions [5], may not adequately consider the nuances of differences in body composition among ethnic groups and other factors related to health inequalities [6].

The global prevalence of obesity has been increasing. The number of adults with obesity has more than doubled and reached approximately 890 million adults in 2022 [5]. It is estimated that currently, at least 2.8 million people die each year worldwide due to conditions linked to living with overweight or obesity [7], and that in 2050, 45% of the world population will be living with overweight and 16% with obesity [4, 8].

Treating obesity and its related conditions imposes a large economic burden on individuals, families, and nations [9]. In 2014, the global economic impact of obesity was estimated to be USD 2 trillion [9]. Many investigations have evaluated the cost of obesity per capita, estimating that per capita medical spending is 42% to 150% higher in individuals with obesity compared with individuals without obesity [10, 11]. 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 [9].

## Description of the intervention and how it might work

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 [12, 13].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) were initially introduced for patients with type 2 diabetes to achieve adequate glycaemic control. Several studies that focused on glycaemic improvement in these patients also reported a secondary benefit in terms of body weight reduction and cardiovascular benefits [14]. In 2005, exenatide was the first GLP-1RA to be approved by the US Food and Drug Administration (FDA) and introduced to the market for the treatment of type 2 diabetes [15]. 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 [16]. This study was fundamental for the FDA approval of this drug in 2015 for use in overweight adults and adults living with obesity who do not have diabetes [17]. The GLP-1RAs that are currently used in clinical settings are lixisenatide, albiglutide, dulaglutide, exenatide, liraglutide, and semaglutide.

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 [18]. It is thought that GLP-1 primarily stimulates GLP receptors (GLP-1Rs) within the intestine to reduce food intake, and slows gastric emptying through a vagal pathway, maximising nutrient absorption while limiting weight gain [12, 13, 19]. GLP-1RAs are drugs that mimic the actions of GLP-1 and have been modified to resist degradation by DPP-IV, achieving supraphysiological plasma concentrations [20]. It is proposed that this allows GLP-1RAs to target the homeostatic control of energy balance, leading to weight loss [21]. Preclinical studies have shown that GLP-1RAs injected peripherally target GLP-1 receptors (GLP-1Rs) located in the hypothalamic arcuate nucleus and that their stimulation produces an anorexigenic effect that ultimately induces weight loss [18, 21, 22]. 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 [23].

As a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, tirzepatide showed favourable treatment efficacy in glucose control in patients with type 2 diabetes, along with weight loss (24). Furthermore, a phase 3 RCT confirmed its long-term treatment potential in individuals with obesity and prediabetes (SURMOUNT-1) [25]. Both the FDA and European Medicines Agency (EMA) have approved tirzepatide, alongside other weight-loss GLP-1RA, liraglutide and semaglutide, for adults with obesity [26, 27].

### Adverse effects of the intervention

Gastrointestinal side effects are the most frequently reported adverse events caused by GLP-1RAs [28]. 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 [28, 29]. 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 [30]. Systematic reviews have found no strong association between GLP-1RA usage and the occurrence of thyroid cancer, pancreatic cancer, or pancreatitis [30, 31, 32, 33].

### Why it is important to do this review

People living with obesity need management options that provide effective, safe and sustainable effects. Weight loss is associated with an improvement in risk factors and comorbid conditions. For instance, a slight weight loss (2% to 5%) may improve menstrual irregularities and fertility in women with polycystic ovarian syndrome and infertility. In comparison, 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 steatohepatitis, and could potentially reduce mortality [23, 34].

GLP-1RAs have been proposed as an effective and safe option for the management of adults living with obesity. Existing systematic reviews have primarily focused on the effects of GLP-1RAs in the prevention or treatment of type 2 diabetes [35, 36, 37], and reviews focusing on the effects of tirzepatide in the management of obesity have indicated potential therapeutic efficacy in weight-loss parameters, but other important clinical parameters and patient-reported outcomes are yet to be thoroughly explored [24, 38, 39].

## Objectives

To assess the effects of the dual GIP/GLP-1 receptor agonist, tirzepatide, for adults living with obesity.

## Methods

We followed the Methodological Expectations of Cochrane Intervention Reviews (MECIR) when conducting the review [40], and PRISMA 2020 for the reporting [41].

Our Cochrane protocol was published in 2022 [42]. We based parts of the Methods, as well as Supplementary material 1 of the protocol for this 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 Cochrane reviews to support their guidelines on the use of GLP-1RAs and dual GLP-1/GIP agonists. Consequently, we applied the following modifications to our published protocol to inform these WHO guidelines adequately [43].

- We expanded our inclusion criteria to support multiple definitions of obesity based on different BMI thresholds or the combination of BMI and co-morbidities, which also includes people within the BMI range of 'overweight' [44]. This is reflected in the change of the title, focusing on people living with obesity.
- 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 tirzepatide. 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 'change in BMI' as a measure for weight measurements, as well as major adverse cardiovascular events (MACE) and mortality. We also defined secondary outcomes as 'important outcomes', and added waist circumference, heart failure, diabetes-related outcomes (including fasting glycaemic, 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, lipid metabolism-related outcomes (including total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, need for lipid-lowering treatment).
- We incorporated equity considerations into subgroup analysis and the assessment of comorbidities.
- We clarified that we did not include post-discontinuation extension studies, which were not explicitly excluded in the previous protocol but were beyond the scope of our review.
- We clarified that we excluded studies related to bariatric surgery, as this subpopulation is significantly different and would require a separate review focusing solely on the use of these medicines before, during, and after bariatric surgery procedures.

These modifications were prospectively registered as a new protocol in PROSPERO [43]. This generic protocol includes tirzepatide, liraglutide, and semaglutide as interventions and comparators; however, this review investigated the effects of tirzepatide only.

# Criteria for considering studies for this review

## Types of studies

We included randomised controlled trials (RCTs) that assessed the effects of tirzepatide in adults living with obesity. Studies were included only if they reported outcomes based on the completion of the intended treatment period for efficacy analysis. Studies that focused on outcomes following discontinuation or withdrawal of these agents were excluded.

We included studies reported as full texts, 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 can evolve over time, and the washout itself might induce a rebound effect in the second period of the study.

## Types of participants

We included studies of adults aged 18 years or older living with obesity, as defined by each study. The definition of obesity, for the purpose of this review, 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 RCTs in which obesity is a primary inclusion criterion. We excluded studies that exclusively recruited participants with secondary causes of obesity.

We also excluded the following types of participants:

- pregnant women, due to expected variability in weight and BMI, and the safety profile of GLP1-RAs [45, 46];
- studies in which diabetes or a condition other than obesity was the primary inclusion criterion or aim of treatment, irrespective of obesity status; and
- studies that included strategies for bariatric surgery.

## Types of interventions

### Interventions

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

### Comparisons

We considered studies that compared tirzepatide with:

- placebo or no treatment;
- structured programmes targeting lifestyle modification;
- any pharmacological intervention for obesity;
- any GLP-1RA or GIP/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.

# Outcome measures

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

## Critical outcomes

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

    - Non-serious adverse events
    - Serious adverse events
- 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: evaluated by validated instruments such as EQ-5D [47], the World Health Organization-Five Well-Being Index (WHO-5) [48], the Short-Form Health Survey (SF-36) [49], or the 12-item Short-Form Health Survey (SF-12) [50].
- Mortality: defined as death from any cause.

### Important outcomes

- Waist circumference (cm)
- Heart failure
- Diabetes-related outcomes
    - Fasting glycaemia
    - HbA1C
    - Need for glucose-lowering therapy
- Blood pressure-related outcomes
    - Need for antihypertensives
    - Systolic blood pressure
    - Diastolic blood pressure
- Liver disease-related outcomes
    - Metabolic dysfunction-associated steatotic liver disease (MASLD): formerly known as non-alcoholic fatty liver disease (NAFLD)
    - Metabolic dysfunction-associated steatohepatitis
    - Cirrhosis
- Obstructive sleep apnoea
- Lipid metabolism-related outcomes
    - Total cholesterol
    - HDL cholesterol
    - LDL cholesterol
    - Triglycerides
    - Need for lipid-lowering treatment

#### Time frame of follow-up

We analysed outcome data as medium-term (6 to 24 months) and long-term (24 months or more) follow-up, according to suggestions by experts as adequate thresholds for follow-up time points [51]. Whenever a study reported multiple assessments within our time frame, we analysed the outcome measurement at the time closest to the end of the time frame. We considered intermediate time points (e.g. 10 or 9 months) for critical outcomes to inform temporal trends or fluctuations within each time frame.

## Search methods for identification of studies

### Electronic searches

We searched the following sources from the inception of each database to the date of search, with no restrictions on the language of publication. 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) [52].

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

### Searching other resources

We screened the reference lists of included studies, systematic reviews, meta-analyses, and health technology assessment reports for studies not identified by the database searches.

## Data collection and analysis

### Selection of studies

Two independent researchers (from the review team, 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 (from JB, NM, JF, EM). If we could not resolve a disagreement, we categorised the study as 'awaiting classification' and contacted the study authors for clarification. We presented an adapted PRISMA flow diagram to illustrate the study selection process [41]. We listed all articles excluded after full-text assessment in the 'Characteristics of excluded studies' table and provided the reasons for exclusion.

We used Covidence for the entire screening process [53]. We showed our selection process using a PRISMA flow diagram, specifying the total number of included references and included studies [41].

### Data extraction and management

For studies that fulfilled our inclusion criteria, two researchers (from the review team, see Acknowledgements) independently extracted key information on participants, interventions, and comparators. We resolved disagreements through consensus or by consulting a third review author (from YG, EM, JF).

We extracted the following data from reports.

- Methods
    - Study design
- Participants
    - Inclusion and exclusion criteria
    - Participant details, baseline demographics, including age, sex, ethnicity, and baseline measurements of weight, blood pressure, and lipid profile
    - The number of participants by study and by study arm
- Interventions and comparisons according to the 'template for intervention description and replication' (TIDieR) checklist [54, 55]. The detailed information on the types of interventions and comparators as per TIDieR will be published separately.
- Outcomes
    - Definitions of relevant outcomes, method and timing of outcome measurement as well as any relevant subgroups to the review
- Dates (if dates were not available, then we reported it as such).
- Study settings and country, the language of publication, and study identifier
- Funding sources
- Conflicts of interest declared by study investigators/authors

We characterised the conflicts of interest in the included studies and discussed how they might have impacted the effect estimates [56]. We also collected, processed, and used information on conflicts of interest in two ways.

- We extracted information from the study investigators' disclosures regarding their relationship to the funder (e.g. consultant, employee, stockholder, patent holder, independent researcher) or any circumstances that created a risk that a secondary interest might have unduly influenced professional judgement or actions regarding their primary 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.

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

### Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximised the information 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. Furthermore, we listed duplicate publications, companion documents, multiple reports of a study, and study documents of excluded studies (such as study registry information) as secondary references under the study ID of the excluded study.

### Data from clinical trial 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 (NM, YG) independently assessed the risk of bias of each included study. We resolved disagreements by consensus or through consultation with a third review author (EM or JF). We assessed the following domains as per the original version of the Cochrane Collaboration's tool for assessing risk of bias (RoB 1) [57].

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

We distinguished between self-reported outcome measures and those assessed or adjudicated by the study authors. We considered quality of life and non-serious adverse events as self-reported outcomes. We considered all other critical outcomes and important outcomes as investigator-assessed or adjudicated (see also Critical outcomes; Important outcomes).

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

- we considered studies at low risk of attrition bias when loss to follow-up was minimal (< 5%);
- we judged risk of attrition bias to be unclear when the rate of loss to follow-up was 5% to 10% or when the rate was 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 the attrition rate was 10% to 20% but was unbalanced in magnitude or reasons across groups.

We judged the risk of bias domains as 'low risk', 'high risk', or 'unclear risk'. We further summarised the risk of bias across domains for each outcome in each included study according to the *Cochrane Handbook for Systematic Reviews of Interventions* [57].

To facilitate our assessment of the certainty of the evidence, we assessed the risk of bias across studies and domains for the outcomes included in a summary of findings table (see Certainty of the evidence assessment). As per the *Cochrane Handbook for Systematic Reviews of Interventions* [57], we defined the evidence across studies as being at low risk of bias when most information came from studies at low risk of bias, unclear risk of bias when most information came from studies at low or unclear risk of bias, and high risk of bias when sufficient information came from studies at high risk of bias [58]. 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 [58].

## Measures of treatment effect

We expressed dichotomous data as risk ratio (RR), with 95% confidence intervals (CIs). For continuous outcomes measured on the same scale (e.g. weight loss in kg), we estimated the intervention effect using the mean difference (MD) with 95% CIs. When data were pooled in studies that used different instruments to measure the same outcome, we planned to calculate standardised mean differences (SMDs) with 95% CIs, entering data presented as a scale with a consistent direction of effect, and to multiply the SMD by a standard deviation (SD) that is representative of the pooled studies, for example, the SD from a well-known scale used by several of the studies

included in the analysis on which the result was based. We planned to express time-to-event data as a hazard ratio (HR) with 95% CIs.

### Unit of analysis issues

We took into account the level at which randomisation occurred, such as multiple observations for the same outcome. If more than one comparison from the same study was eligible for inclusion in the same meta-analysis, we either combined groups to create a single pair-wise comparison, or we appropriately reduced the sample size so that the same participants did not contribute data to the meta-analysis more than once (splitting the 'shared' group into two or more groups). Although the latter approach offered some solutions for adjusting the precision of the comparison, it did not account for correlation arising from the inclusion of the same set of participants in multiple comparisons [59].

### Dealing with missing data

If possible, we aimed to obtain missing data from the authors of the included studies; however, the missing data were due to study discontinuation. We carefully evaluated important numerical data, including screened, randomly assigned participants, as well as intention-to-treat, 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 critically appraised issues concerning missing data and the use of imputation methods (e.g. last observation carried forward). For our primary analyses, we conducted available case analyses, taking these issues into account when assessing the risk of bias and the certainty of the evidence.

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

### Reporting bias assessment

If we had included 10 or more studies that investigated a particular outcome, we would have used funnel plots to assess small-study effects. 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 [59]. Therefore, we would have interpreted the results carefully [60].

### Synthesis methods

We undertook a meta-analysis only if we judged the participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure a result that is clinically meaningful. Unless good evidence showed homogeneous effects across studies of different methodological quality, we primarily summarised data using a random-effects model [61]. We interpreted random-effects meta-analyses with due consideration for the whole distribution of effects and presented a confidence interval. We performed statistical analyses according to the statistical guidelines presented in the *Cochrane Handbook for Systematic Reviews of Interventions* [62]. For future updates of this review, if meta-analysis is not possible, we plan 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* [63].

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

We used the $I^2$ statistic to measure heterogeneity among the studies in each analysis [64]. If we identified substantial unexplained heterogeneity, we reported it and explored possible causes by prespecified subgroup analysis. We used the rough guide to interpretation as outlined in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* [59], as follows:

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

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

### Investigation of heterogeneity and subgroup analysis

We expected the following characteristics to introduce clinical heterogeneity, and we had planned to carry out the following subgroup analyses for them, including an investigation of interactions [65].

- Age (people younger than 60 versus those aged 60 years and older)
- Sex
- Dose within a drug
- Presence of co-morbidities (e.g. diabetes)

- Baseline BMI
- Equity considerations (see below)

#### Equity-related assessment

We examined whether study populations included underrepresented groups, such as individuals from low-income settings, vulnerable populations, or populations with limited access to obesity management services. Where possible, we assessed whether equity-related factors influence the effectiveness or accessibility of interventions following the PROGRESS-PLUS Framework, which is an acronym that covers many characteristics that may lead to potential health inequities [66]. This included exploring subgroup data and evaluating study contexts for equity considerations.

### Sensitivity analysis

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

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

### Certainty of the evidence assessment

We presented the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which took into account issues related to internal validity (overall risk of bias and study limitations, inconsistency of results, imprecision, publication bias) and external validity (indirectness of evidence). Two review authors (NM, YG) independently rated the certainty of the evidence for each outcome. We resolved any differences in assessment through discussion or consultation with a third review author (JF). We used an approach based on three target ratings to rate down imprecision, by establishing predefined, symmetrical minimally important differences for benefits and harms (see Supplementary material 8) [67, 68].

We created summary of findings tables, which provide key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies, the number of participants and studies addressing each important outcome, and a rating of overall confidence in effect estimates for each outcome. We created the summary of findings tables as per the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* [69], using Review Manager [70] and GRADEpro GDT [71].

If 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 we followed the GRADE guidelines for making informative statements [72, 73].

We created two main summary of findings tables for the following critical outcomes (see also Critical outcomes), at medium- and long-term follow-up, for the comparison of tirzepatide versus placebo, and a third for tirzepatide versus semaglutide.

- Weight (% weight change, people achieving 5%)
- Adverse events (non-serious, serious, or leading to withdrawal)
- MACE
- Quality of life
- Mortality

We also prepared additional summary of findings tables for all critical and important outcomes (see Critical outcomes; Important outcomes) in the supplementary materials.

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

## Consumer involvement

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

# Results

## Description of studies

### Results of the search

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

exclusively [43]. 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 (154 studies) with reasons, and included 606 references. Of these, 502 were references to included studies, 97 were references to ongoing studies, and seven were references to studies awaiting classification.

Of these 505 references to included studies, nine studies (71 references) were on tirzepatide (SUMMIT [74, 75, 76, 77, 78]; SURMOUNT-1 [25, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114]; SURMOUNT-2 [115, 116, 117, 118]; SURMOUNT-3 [119, 120, 121, 122, 123, 124]; SURMOUNT-4 [125, 126, 127, 128, 129, 130]; SURMOUNT-5 [131, 132]; SURMOUNT-CN [133, 134, 135, 136]; SURMOUNT-J [137, 138]; SURMOUNT-OSA [139, 140, 141, 142, 143]). We also categorised one study as awaiting classification (2 references) and identified 21 ongoing studies (31 references).

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

## Included studies

See also Table 1, Table 2, and Supplementary material 2.

### Study designs and settings

All nine included studies were RCTs with parallel-group randomisation. They included a total of 7111 participants. The median sample size was 670 (interquartile range 469 to 750).

All studies were conducted during the COVID-19 pandemic, starting from 2019 to 2025. The authors reported COVID-19-related adverse events that might have affected their original aims. Seven studies were launched in multicentre settings across various countries, including the USA, Argentina, Brazil, China, India, Israel, Mexico, Puerto Rico, Russia, Taiwan, the Czech Republic, Germany, and Japan. Two studies were conducted in a single country (SURMOUNT-CN; SURMOUNT-J).

### Participants

An overview of the characteristics of the included participants is given in Table 1 and Table 2.

The mean age of the participants varied from 36.1 years (SURMOUNT-CN) to 65.25 years (SUMMIT). The percentages of male participants ranged from 29.4% (SURMOUNT-4) to 64.7% (SURMOUNT-5).

Except for one study with missing data for mean weight and BMI (SURMOUNT-J), seven studies had participants with total mean weights from 85.2 kg to 115.09 kg. Three studies enrolled participants with a BMI over 35 kg/m$^2$. Participants in SURMOUNT-CN had a mean BMI of 32.3 kg/m$^2$, whereas those in the SURMOUNT-4 had a baseline BMI of 30.5 kg/m$^2$. The other seven studies had a mean BMI from 35.9 kg/m$^2$ to 38.9 kg/m$^2$ (SUMMIT; SURMOUNT-1; SURMOUNT-2; SURMOUNT-3; SURMOUNT-4; SURMOUNT-5; SURMOUNT-OSA).

Seven studies focused on various subgroups.

- SUMMIT enrolled people with heart failure with preserved ejection fraction.
- SURMOUNT-1 studied prediabetes in the extension phase until 176 weeks' follow-up.
- SURMOUNT-2 included participants with type 2 diabetes.
- SURMOUNT-4 randomised participants only after a 36-week lead-in phase; participants were treated with tirzepatide until they reached the maximal tolerated doses of 10 mg to 15 mg once weekly.
- SURMOUNT-CN recruited Chinese participants.
- SURMOUNT-J recruited Japanese participants.
- SURMOUNT-OSA included patients with moderate-to-severe obstructive sleep apnoea with an AHI (Apnea-Hypopnea Index) of 15 or more events per hour.

The populations of the included studies were diverse in terms of ethnicity and race. In terms of ethnicity, in five studies, approximately half of the participants were Hispanic or Latino (SUMMIT; SURMOUNT-1; SURMOUNT-2; SURMOUNT-3; SURMOUNT-4); as for reported race, seven studies enrolled primarily White participants (SUMMIT; SURMOUNT-1; SURMOUNT-2; SURMOUNT-3; SURMOUNT-4; SURMOUNT-5; SURMOUNT-OSA). Two studies enrolled only Asian participants (SURMOUNT-CN; SURMOUNT-J).

Studies included participants with weight-related comorbidities. The most common ones were obstructive sleep apnoea, prediabetes, hypertension, dyslipidaemia, atherosclerotic cardiovascular disease (ASCVD), polycystic ovary syndrome (PCOS), asthma or chronic obstructive pulmonary disease (COPD), MASLD, anxiety or depression, and osteoarthritis. In particular, SUMMIT included participants with chronic heart failure, SURMOUNT-2 type 2 diabetes, and SURMOUNT-OSA moderate-to-severe obstructive sleep apnoea. In SURMOUNT-1, the extension phase focused only on prediabetes.

## Interventions and comparisons

Tirzepatide was injected once weekly in all included studies. The dosage of tirzepatide was escalated to maximum tolerated doses from 10 mg to 15 mg except in one arm of SURMOUNT-1 where the dose was escalated to 5 mg. Each study assessed the gastrointestinal tolerability of tirzepatide.

All studies had noted co-interventions or co-medications dependent on local standards and comorbidities. Except for SUMMIT, most studies used lifestyle or weight management programmes as a co-intervention, including regular diet, physical activity, and lifestyle counselling sessions (SURMOUNT-1; SURMOUNT-2; SURMOUNT-3; SURMOUNT-4; SURMOUNT-5; SURMOUNT-CN; SURMOUNT-J; SURMOUNT-OSA). Additionally, SUMMIT had concomitant medications for chronic heart failure. In SURMOUNT-1, participants with prediabetes at baseline were included in the extension phase and treated with lifestyle interventions with a focus on balanced meals and physical activity. SURMOUNT-2 had antihyperglycaemic medications for type 2 diabetes, which should not interfere with tirzepatide. SURMOUNT-OSA treated two subgroups with continuous positive airway pressure (CPAP) due to moderate-to-severe obstructive sleep apnoea.

Eight studies compared tirzepatide to a placebo (SUMMIT; SURMOUNT-1; SURMOUNT-2; SURMOUNT-3; SURMOUNT-4; SURMOUNT-CN; SURMOUNT-J; SURMOUNT-OSA); one compared tirzepatide with semaglutide (SURMOUNT-5).

## Outcomes

### Medium-term outcomes

For critical outcomes, all studies reported percentage weight change from baseline, serious adverse events, adverse events leading to withdrawal, and MACE. Most studies reported weight change in kg, weight change in BMI, the number of participants achieving 5% and 10% weight reduction, non-serious adverse events, quality of life measured by IWQoL-Lite-CT scoring, and mortality. The least reported critical outcomes were non-serious adverse events and quality of life, as measured by the SF-36 scoring. One of the studies, SURMOUNT-5, collected SF-36 scores but did not report them with the main findings.

Regarding important outcomes, all studies reported changes in systolic and diastolic blood pressure from baseline. Most reported changes in waist circumference (cm), the number of participants with heart failure, changes in fasting glycaemia and HbA1C, and changes in lipid profiles. The least reported important outcomes were assessments of heart failure, the number of participants who achieved an HbA1c less than 7%, the number of participants needing glucose-lowering therapy or incidence of diabetes, the number of participants with metabolic dysfunction-associated steatotic liver disease, and assessment of obstructive sleep apnoea. The numbers of participants with cirrhosis and requiring lipid-lowering treatment were not reported.

### Long-term outcomes

Only SURMOUNT-1 reported percentage weight change from baseline, weight change in kg, the number of participants achieving 5% and 10% weight reduction, non-serious adverse events, serious adverse events, adverse events leading to withdrawal, major adverse cardiovascular events, quality of life as measured by SF-36 scoring, and mortality in the long term. Other critical outcomes were not reported.

### Follow-up

Eight studies had medium-term follow-up between 52 and 94 weeks (SUMMIT; SURMOUNT-2; SURMOUNT-3; SURMOUNT-4; SURMOUNT-5; SURMOUNT-CN; SURMOUNT-J; SURMOUNT-OSA), and one study had both medium-term (72 weeks) and long-term (176 weeks) follow-up (SURMOUNT-1).

## Funding and conflicts of interest

All nine included studies were funded by Eli Lilly, the drug manufacturer. The funder was substantially involved in the planning, conduct, analysis and dissemination of the results. Many of the study investigators and authors had direct financial ties to the company – all the included studies had more than one study author with conflicts of interest. Moreover, the study authors of industry-funded studies had financial conflicts of interest in relation to the study drug. See Supplementary material 10 and Supplementary material 9 for a detailed analysis of these aspects.

## Ongoing studies and studies awaiting classification

We identified a total of 75 ongoing studies from our broad literature search (see Results of the search), of which 21 are exploring the effects of tirzepatide. The estimated completion dates of these studies are in 2025 (ISRCTN14812004 [144, 145]; NCT06297616 [146, 147]; NCT06326060 [148, 149]; NCT06605703 [150]), 2026 (NCT05536804 [151, 152, 153, 154]; NCT06037252 [155, 156]; NCT06143956 [157]; NCT06588283 [158]; NCT06588296 [159, 160]; NCT06603571 [161, 162]; NCT06737042 [163]; SURMOUNT-MAINTAIN [164]), 2027 (NCT06643728 [165, 166]; SURMOUNT-MMO [167]), 2028 (NCT06606821 [168, 169]), 2029 (ISRCTN10203365 [170]), 2037 (NCT06191848 [171]), or unknown (ACTRN12623001236684 [172]; ACTRN12624000270516 [173]; ACTRN12624001278527 [174]; ACTRN12624001369516 [175]).

Of these 21 ongoing studies, 12 are funded by Eli Lilly and Company (ACTRN12623001236684; NCT05536804; NCT06037252; NCT06143956; NCT06191848; NCT06297616; NCT06588283; NCT06588296; NCT06603571; NCT06643728; SURMOUNT-MAINTAIN; SURMOUNT-MMO).

Others are funded by: Baker Heart and Diabetes Institute (ACTRN12624000270516), Betty McGrath Seeding Grant (ACTRN12624001278527), Sydney Local health District (ACTRN12624001369516), National Institutes of Health (ISRCTN10203365), Eucalyptus (Juniper) UK (ISRCTN14812004), Royal North Shore Hospital (NCT06180616 [176]), WW International Inc. (NCT06605703), Steno Diabetes Centre Copenhagen (NCT06606821), Gan and Lee Pharmaceuticals (NCT06737042).

One study on tirzepatide is classified as awaiting classification due to unknown status (NCT06326060). It is funded by Novo Nordisk A/S.

See also Supplementary material 4 and Supplementary material 5.

### Excluded studies

We excluded 154 studies (231 references) across the suite of reviews on GLP-1RA. 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. See also Supplementary material 3.

## Risk of bias in included studies

See Figure 2 for a summary of the risk of bias across studies and domains.

Selection bias (random sequence generation and allocation concealment): we rated all nine included studies at low risk of bias.

Performance bias (blinding of participants and personnel)

- Subjective: we rated all but one of the included studies at low risk of performance bias; we rated SURMOUNT-5 at high risk.
- Objective: we rated all included studies at low risk of performance bias.

Detection bias (blinding of outcome assessment)

- Subjective: we rated all but one of the included studies at low risk of detection bias; we rated SURMOUNT-5 at high risk.
- Objective: we rated all included studies at low risk of detection bias.

Attrition bias (incomplete outcome data)

- Medium-term follow-up: we rated four studies at high risk of attrition bias due to 10% to 20% unbalanced attrition or high discontinuation rates (> 20%; SURMOUNT-1; SURMOUNT-3; SURMOUNT-J; SURMOUNT-OSA). The remaining five studies we judged to be at unclear risk of bias due to 5% to 10% attrition or moderate (10% to 20%) discontinuations but balanced among arms (SUMMIT; SURMOUNT-2; SURMOUNT-4; SURMOUNT-5; SURMOUNT-CN).
- Long-term follow-up: only one study had a long-term follow-up with 29% to 52% discontinuation rates in both arms, and we rated it at high risk of attrition bias (SURMOUNT-1).

Reporting bias (selective reporting)

- We judged four included studies to be at unclear risk of reporting bias due to not reporting long-term outcomes (SUMMIT), or lack of quality-of-life scores (SUMMIT; SURMOUNT-3; SURMOUNT-CN; SURMOUNT-5). We rated the remaining five studies at low risk of reporting bias.

We did not identify any other sources of bias.

### Overall risk of bias in included studies across domains

Based on the above, we concluded that four studies were at unclear risk of overall bias (SUMMIT; SURMOUNT-2; SURMOUNT-4; SURMOUNT-CN), and four others were at high risk of overall bias (SURMOUNT-1; SURMOUNT-3; SURMOUNT-J; SURMOUNT-OSA). One study was at overall unclear risk of bias for objective outcomes, but high risk of bias for subjective outcomes (SURMOUNT-5).

## Synthesis of results

See Summary of findings table 1, Summary of findings table 2, and Summary of findings table 3 for detailed descriptions of evidence synthesis. Additional results can be found in Supplementary material 11; Supplementary material 12; Supplementary material 13.

### 1. Tirzepatide versus placebo (medium-term follow-up)

#### Weight

Tirzepatide likely results in a greater percentage reduction in body weight (MD −16.03, 95% CI −18.91 to −13.14; $I^2$ = 95%; 8 studies, 6317 participants; moderate-certainty evidence; Analysis 1.1), change in kg (MD −16.63, 95% CI

−21.35 to −11.90; $I^2$ = 98%; 5 studies, 2583 participants; moderate-certainty evidence; Analysis 1.2), and change in BMI (MD −6.06, 95% CI −7.96 to −4.17; $I^2$ = 98%; 6 studies, 5099 participants; moderate-certainty evidence; Analysis 1.3) from baseline than placebo in the medium-term.

Tirzepatide likely results in an increase in the number of people achieving a 5% weight reduction (RR 3.60, 95% CI 2.44 to 5.30; $I^2$ = 86%; 5 studies, 4455 participants; moderate-certainty evidence; Analysis 1.4) and a 10% weight reduction (RR 6.79, 95% CI 4.84 to 9.54; $I^2$ = 18%; 5 studies, 4457 participants; moderate-certainty evidence; Analysis 1.5) in the medium-term.

#### Adverse events

Tirzepatide may result in an increase in non-serious adverse events in the medium-term (RR 1.33, 95% CI 1.03 to 1.71; $I^2$ = 85%; 5 studies, 4582 participants; low-certainty evidence; Analysis 1.6).

Tirzepatide may have little to no effect on serious adverse events in the medium-term, but the evidence is very uncertain (RR 0.99, 95% CI 0.88 to 1.12; $I^2$ = 0%; 8 studies, 6359 participants; very low-certainty evidence; Analysis 1.7).

Tirzepatide may result in little to no difference in adverse events leading to withdrawal in the medium term (RR 2.06, 95% CI 1.21 to 3.52; $I^2$ = 52%; 8 studies, 6359 participants; low-certainty evidence; Analysis 1.8).

#### Major adverse cardiovascular events (MACE)

Tirzepatide likely results in little to no difference in major adverse cardiovascular events (MACE) in the medium term (RR 0.75, 95% CI 0.34 to 1.66; $I^2$ = 0%; 7 studies, 5628 participants; moderate-certainty evidence; Analysis 1.9).

#### Quality of life

Tirzepatide likely results in little to no clinically important difference in quality of life as measured by the SF-36 mental component (MD 1.09, 95% CI 0.42 to 1.76; 1 study, 2539 participants; moderate-certainty evidence; Analysis 1.10), SF-36 physical component score (MD 2.07, 95% CI 1.51 to 2.64; $I^2$ = 0%; 2 studies, 3360 participants; moderate-certainty evidence; Analysis 1.11), IWQOL-Lite-CT total score (MD 10.30, 95% CI 8.77 to 11.83; 1 study, 2539 participants; moderate-certainty evidence; Analysis 1.12) and IWQOL-Lite-CT physical function (MD 9.91, 95% CI 7.81 to 12.02; $I^2$ = 46%; 6 studies, 5020 participants; moderate-certainty evidence; Analysis 1.13) in the medium-term.

#### Mortality

Tirzepatide likely results in little to no difference in mortality in the medium term (RR 0.79, 95% CI 0.34 to 1.83; $I^2$ = 0%; 7 studies, 5628 participants; moderate-certainty evidence; Analysis 1.14).

#### Other critical and important outcomes

The full details of additional measurements of critical outcomes and important outcomes can be found in Supplementary material 11.

### 2. Tirzepatide versus placebo (long-term follow-up)

#### Weight

Tirzepatide likely results in a greater percentage reduction in body weight from baseline, compared to placebo, in the long-term (MD −15.66, 95% CI −19.14 to −12.18; 1 study, 1032 participants; moderate-certainty evidence; Analysis 2.1). Tirzepatide likely results in a reduction in weight in kg from baseline in the long-term (MD −18.31, 95% CI −20.72 to −15.90; 1 study, 1032 participants; moderate-certainty evidence; Analysis 2.2).

Weight change in BMI in the long term was not reported.

Tirzepatide likely results in an increase in the number of people achieving a 5% weight reduction (RR 2.81, 95% CI 2.33 to 3.38; 1 study, 1032 participants; moderate-certainty evidence; Analysis 2.3), and 10% weight reduction (RR 2.13, 95% CI 1.63 to 2.78; 1 study, 577 participants; moderate-certainty evidence; Analysis 2.4) in the long-term.

#### Adverse events

Tirzepatide may result in an increase in non-serious adverse events in the long term (RR 1.05, 95% CI 0.98 to 1.11; 1 study, 1032 participants; low-certainty evidence; Analysis 2.5).

Tirzepatide may have little to no effect on serious adverse events in the long-term, but the evidence is very uncertain (RR 1.14, 95% CI 0.79 to 1.65; 1 study, 1032 participants; very low-certainty evidence; Analysis 2.6).

Tirzepatide may result in little to no difference in adverse events leading to withdrawal in the long term (RR 1.64, 95% CI 0.97 to 2.76; 1 study, 1032 participants; low-certainty evidence; Analysis 2.7).

#### Major adverse cardiovascular events (MACE)

Tirzepatide likely results in little to no difference in MACE in the long term (RR 0.56, 95% CI 0.22 to 1.42; $I^2$ not applicable; 1 study, 1032 participants; moderate-certainty evidence; Analysis 2.8).

### Quality of life

Tirzepatide may result in little to no clinically important difference in quality of life as measured by SF-36 physical component score in the long term (MD 2.70, 95% CI 0.00 to 5.40; 1 study, 1032 participants; low-certainty evidence; Analysis 2.9).

### Mortality

Tirzepatide may result in little to no difference in mortality in the long term (RR 0.83, 95% CI 0.22 to 3.17; $I^2$ not applicable; 1 study, 1032 participants; low-certainty evidence; Analysis 2.10).

### Other critical and important outcomes

The full details of additional measurements of critical outcomes and important outcomes can be found in Supplementary material 12.

### 3. Subgroup and sensitivity analyses

We were unable to conduct subgroup analyses because there were too few studies per comparison.

We conducted sensitivity analyses for the medium-term critical outcomes of the comparison 'tirzepatide versus placebo', excluding studies at high risk of bias, and the main findings were robust, although less precise (Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 3.4; Analysis 3.5; Analysis 3.6; Analysis 3.7; Analysis 3.8; Analysis 3.9; Analysis 3.10; Analysis 3.11; Analysis 3.12).

## 4. Tirzepatide versus semaglutide (medium-term follow-up)

### Weight

Tirzepatide may result in a greater percentage reduction in body weight from baseline in the medium term than semaglutide (MD −6.50, 95% CI −8.13 to −4.87; $I^2$ not applicable; 1 study, 750 participants; low-certainty evidence; Analysis 4.1).

Tirzepatide likely results in a reduction in weight in kg from baseline in the medium term (MD −7.80, 95% CI −9.64 to −5.96; $I^2$ not applicable; 1 study, 750 participants; moderate-certainty evidence; Analysis 4.2).

Tirzepatide likely results in a reduction in BMI from baseline in the medium term (MD −2.70, 95% CI −3.41 to −1.99; $I^2$ not applicable; 1 study, 750 participants; moderate-certainty evidence; Analysis 4.3).

Tirzepatide may result in an increase in the number of people achieving a 10% weight reduction in the medium term (RR 1.35, 95% CI 1.22 to 1.48; $I^2$ not applicable; 1 study, 750 participants; low-certainty evidence; Analysis 4.4).

### Adverse events

Tirzepatide may result in little to no difference in non-serious adverse events in the medium term (RR 0.97, 95% CI 0.90 to 1.05; $I^2$ not applicable; 1 study, 750 participants; low-certainty evidence; Analysis 4.5).

Tirzepatide may have little to no effect on serious adverse events in the medium term, but the evidence is very uncertain (RR 1.39, 95% CI 0.69 to 2.80; $I^2$ not applicable; 1 study, 750 participants; very low-certainty evidence; Analysis 4.6).

Tirzepatide likely results in little to no difference in adverse events leading to withdrawal in the medium term (RR 0.77, 95% CI 0.46 to 1.30; $I^2$ not applicable; 1 study, 750 participants; moderate-certainty evidence; Analysis 4.7).

#### Major adverse cardiovascular events (MACE)

The evidence is very uncertain about the effect of tirzepatide on MACE, as there were no events reported in either group.

### Quality of life

Quality of life was not reported.

### Mortality

The evidence is very uncertain about the effect of tirzepatide on mortality, as there were no events reported in either group.

### Other critical and important outcomes

The full details of additional measurements of critical outcomes and important outcomes can be found in Supplementary material 13.

## Equity assessment

### Distribution of effects across 'PROGRESS-PLUS' characteristics

We identified possible effect modification related to equity characteristics, including age, sex, dosage of tirzepatide, presence of comorbidities, and baseline BMI by geographical region; however, we were unable to assess the

distribution of effects due to the limited number of included studies for each comparison.

#### Interventions focusing on disadvantaged or at-risk populations

SUMMIT targeted patients with heart failure with preserved ejection fraction, while SURMOUNT-OSA included those with moderate-to-severe obstructive sleep apnoea. Both studies developed tailored interventions that targeted these groups. No other studies reported a focus on minority groups in other countries.

None of the studies were conducted in low-income countries. Seven studies were launched in multiple centres from several middle- and high-income countries (SUMMIT; SURMOUNT-1; SURMOUNT-2; SURMOUNT-3; SURMOUNT-4; SURMOUNT-5; SURMOUNT-OSA). One study recruited participants exclusively from one middle-income country (SURMOUNT-CN), and one from a high-income country (SURMOUNT-J).

### Reporting biases

We were unable to draft funnel plots due to the small number of included studies.

# Discussion

## Summary of main results

We included eight RCTs with 6361 participants that compared tirzepatide with placebo, with follow-up periods ranging from 52 weeks to 176 weeks, which constitute the main findings of the review. We also included one study that compared tirzepatide with semaglutide, with 751 participants and 72 weeks of follow-up.

The synthesised evidence of our main comparison indicates that, compared to placebo, tirzepatide likely reduces weight in the medium term and that this initial weight reduction is sustained in the long term. Tirzepatide may increase non-serious adverse events in the medium term. It may result in little to no difference in adverse events leading to withdrawal in both the medium and long term. The evidence is very uncertain about its effects on severe adverse events in the medium and long term. Tirzepatide may result in little to no clinically important difference in quality of life or the incidence of MACE in both the medium and long term. Tirzepatide likely results in little to no effect on mortality in the medium term, but the evidence in the long term is more uncertain.

## Limitations of the evidence included in the review

We identified some uncertainties in this review. Studies were conducted exclusively in middle- and high-income countries. They presented unclear or high risks of bias due to moderate to high attrition rates, likely related to the increased incidence of adverse events leading to withdrawal. Nearly all studies faced attrition attributed to the COVID-19 pandemic. We downgraded important outcomes, such as serious adverse events and mortality, due to significant imprecision, as there were very few events. Some studies focused solely on populations with distinct disease states, such as obstructive sleep apnoea, heart failure, and type 2 diabetes mellitus, which may contribute to indirectness. However, these are common comorbidities in people living with obesity. Additionally, a few studies exhibited inconsistency. Some had high statistical heterogeneity but slight variations in effect estimates beyond the minimally important difference; therefore, we did not downgrade due to inconsistency. We were unable to detect publication bias.

Although RoB 1 does not consider financial conflict of interest as a bias per se, 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 that there is a pressing need for structured approaches to assess studies involving conflicts of interest. To the best of our knowledge, the 'Tool for Addressing Conflicts of Interest in Trials' (TACIT) [177], 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 checklist to complement RoB 1 and aid interpretation of review findings, such as ours.

All our analyses and conclusions were driven by mostly compromised evidence, with conflicts of interest between the study authors and the drug manufacturer. We believe that independent investigations to make clinical and public policy decisions would better establish the role of tirzepatide in weight management.

## Limitations of the review processes

We conducted a comprehensive search in multiple databases and identified all relevant studies, secondary references and unpublished data (study protocols and outcome data in study registries). We tracked registered records, authors related to the study, clinical study reports from the companies, and conference reports. We then aligned study outcomes with medium-term and long-term results. Through these extensive searches and classifications, we believe it is unlikely that we have missed any relevant studies or outcomes.

Upon timely requests from WHO, we deviated from the original Cochrane protocol in several aspects, including expansion of inclusion criteria, intervention comparators, prioritisation of critical and important outcomes, and addition of equity considerations. Due to the large number of studies found by our comprehensive searches, we divided them into three separate systematic reviews, on liraglutide, semaglutide and tirzepatide (this review). We followed standard Cochrane methods, verified data extractions, and assessed risk of bias. We intended to conduct

subgroup analyses to explore heterogeneity based on predefined criteria, without making decisions based on data inspection, but rather on the evidentiary requirements for decision-making.

We relied on the complete reporting of the included studies, for which we examined multiple data sources. Nonetheless, we identified that some studies might fail to report prespecified results or lack long-term outcomes as planned (selective outcome reporting). Insufficient reporting about long-term effects also led to greater uncertainty regarding the evidence.

## Agreements and disagreements with other studies or reviews

Until now, Cochrane reviews have assessed the use of GLP-1 RAs for treating Parkinson's disease [178], chronic kidney disease and diabetes [179], cardiovascular disease [180], or diabetes in kidney transplant recipients [181]; no Cochrane reviews have addressed the application of GLP-1RAs in treating obese conditions. However, several other reviews indicated that tirzepatide had pronounced effects in treating overweight and obesity [24, 38, 39, 182, 183]. Tirzepatide might even have a dose-dependent effect on weight reduction, and its adverse effects were mild to moderate and transient [183]. However, these reviews used unclear comparators or included only a placebo and insulin in the control group, which did not align with the current set of guideline recommendations based on WHO needs [5].

Our review indicated consistent results when analysing parameters associated with obesity-related comorbidities. For instance, we found that tirzepatide might improve some diabetes-, MASLD- or dyslipidaemia-related parameters, but had uncertain or no effects on other comorbid abnormalities, consistent with previous reports [184, 185].

A pending subject is the examination of discontinuation of this drug class. A recent systematic review found that weight regain after discontinuation was proportional to the weight lost, regardless of the lifestyle interventions employed. Furthermore, it highlighted that sustained weight loss could be attainable with long-term use. The effect seemed to be rather obvious in tirzepatide and semaglutide as compared to liraglutide [186]. However, an observational study illustrated that discontinuation of GLP-1RAs was associated with several factors, including gastrointestinal side effects, individuals being aged over 60 years, and having a higher income [187]. A clinical benefit analysis of eight RCTs stated that a net benefit of 5% to 10% weight loss could be achieved in two years [188]. Still, the gap between halting and resuming timely treatment with GLP-1RAs might require further investigation.

# Authors' conclusions

## Implications for practice

Compared to placebo, tirzepatide likely results in weight loss at medium follow-up, and this initial weight loss is likely sustained at longer-term follow-up. The long-term impact on other patient-important outcomes, such as quality of life and overall mortality, may be limited or uncertain. Tirzepatide may cause little to no difference in the incidence of adverse events leading to withdrawal; however, the certainty of the evidence is low, which raises questions about the sustainability of the initial effects. Furthermore, the health effects of the withdrawal or discontinuation of these drugs, while outside the scope of this review, must be considered when implementing them in practice.

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

### Equity-related implications for practice

Obesity is often diagnosed based on weight status in adults, making weight loss a standard measure of treatment effectiveness. While weight loss may be the desirable goal for many, it might not be the main goal of all adults living with obesity. Considering the diversity in body composition, eating habits and overall health behaviours, it might be necessary to consider additional contextual factors when using these drugs in a target population. Obesity as a heterogeneously defined condition indicates that treatment needs differ for individuals with non-comorbid overweight versus severe obesity with complications. Moreover, considering the high prevalence of obesity, the implementation of these drugs may raise important questions about cost-effectiveness and affordability. In summary, without considering the social and commercial determinants of health for obesity, such as health insurance and public healthcare packages to ensure coverage, the widespread implementation of these drugs taken in isolation may increase existing inequities in people living with obesity.

## Implications for research

Considering that most of the weight loss was achieved in the first year and may be sustained for a longer follow-up, future research should investigate the reasons for the limited weight loss after this initial period and assess the long-term sustainability of the initial weight loss. Furthermore, additional research is necessary to address limitations in the current body of research, such as the marginal effect on quality of life and high dropout rates.

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 had a major role in the design, conduct, analysis and reporting of all nine studies. Several publications were written not by the researchers but by external writers, paid by the drug manufacturer. Considering the promising results, it would be advisable to rely on independent research that can confirm these findings. For resource-constrained settings, especially 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 21 ongoing, potentially eligible studies, of which 11 report funding by the drug manufacturer (Supplementary material 5). This is a very active research pipeline that will impact upcoming evidence syntheses. In a future update of this review, we plan to reassess the status of all these ongoing studies, aiming to refine our results further, and to assess the consistency of the results shown here with those published by independent authors.

Weight loss helps reduce the risk of chronic diseases. However, people may regain the lost weight, which can negatively impact metabolic disease risk parameters by reversing or worsening the achieved benefits. Therefore, our findings should be taken cautiously until independent studies assess weight regain after drug discontinuation and there has been a sufficient period of pharmacovigilance to ensure safety assessments have been completed.

### Equity-related implications for research

As a public health issue, obesity demands interventions that aim to reduce health inequities. Future studies should consider reporting equity-related characteristics following the PROGRESS-PLUS framework. Furthermore, although the included studies had a wide geographic spread, some regions and ethnicities, particularly in Africa and Central America, were underrepresented. Finally, evaluations of interventions that include these drugs in care pathways tailored to marginalised populations and adapted for low-resource settings are needed.

# Supplementary materials

[For display in the published PDF only] Supplementary materials are available with the online version of this article: 10.1002/14651858.CD016018.

[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**
CD016018-SUP-01-searchStrategy.html
Search strategies

**Supplementary material 2**
CD016018-SUP-02-characteristicsOfIncludedStudies.html
Characteristics of included studies

**Supplementary material 3**
CD016018-SUP-03-characteristicsOfExcludedStudies.html
Characteristics of excluded studies

**Supplementary material 4**
CD016018-SUP-04-characteristicsOfAwaitingStudies.html
Characteristics of studies awaiting classification

**Supplementary material 5**
CD016018-SUP-05-characteristicsOfOngoingStudies.html
Characteristics of ongoing studies

**Supplementary material 6**
CD016018-SUP-06-analyses.html
Analyses

**Supplementary material 7**

CD016018-SUP-07-dataPackage.zip

Data package

**Supplementary material 8**

CD016018-SUP-08-other.html

Threshold for minimally important differences

**Supplementary material 9**

CD016018-SUP-09-other.html

Funder involvement in included studies

**Supplementary material 10**

CD016018-SUP-10-other.html

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

**Supplementary material 11**

CD016018-SUP-11-other.html

Summary of findings table: Tirzepatide versus placebo in the medium term

**Supplementary material 12**

CD016018-SUP-12-other.html

Summary of findings table: Tirzepatide versus placebo in the long term

**Supplementary material 13**

CD016018-SUP-13-other.html

Summary of findings table: Tirzepatide versus semaglutide in the medium term

# Additional information

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### Editorial and peer-reviewer contributions

Cochrane Endocrine and Metabolic Disorders supported the authors in the development of this review. Juan Franco is a member of Cochrane Endocrine and Metabolic Disorders but was not involved in the editorial process or decision-making for this review.

The following people conducted the editorial process for this review.

- Sign-off Editor (final editorial decision): Solange Durão, Health Systems Research Unit, South African Medical Research Council (SAMRC)
- Managing Editor (conducted editorial policy checks, selected peer reviewers, collated peer-reviewer comments, provided editorial comments/guidance to authors, edited the article): Joey Kwong, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks, supported editorial team): Lisa Wydrzynski, Cochrane Central Editorial Service
- Copy Editor (copy-editing and production): Denise Mitchell, Cochrane Central Production Service
- Peer-reviewers (provided comments and recommended an editorial decision): Christy Bock, Children's National Hospital, Washington, DC (clinical/content review); Nicholas Chartres, Senior Research Fellow,

Faculty of Medicine and Health, The University of Sydney (clinical/content review); Tejaswini Arunachala Murthy, University of Adelaide (consumer review); Emma Axon, Cochrane Methods Support Unit (methods review); Andreas Lundh, Odense University Hospital, Centre for Evidence-Based Medicine Odense (CEBMO) (methods review); Jo Platt, Cochrane Evidence Production & Methods Directorate (search review); Denise Mitchell, Cochrane Central Production Service (PLS review).

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- Juan Franco: conceptualisation; methodology; writing, review, and editing
- Yang Guo: methodology; writing, review, and editing
- Lucia Varela: methodology; writing, review, and editing
- Zakariya Aqra: methodology, writing
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All authors approved the final version to be published and agree to be accountable for all aspects of the review.

## Declarations of interest

- Juan Franco: no relevant interests; Senior Editor for the *Cochrane Database of Systematic Reviews* and Managing Editor for the Cochrane Metabolic and Endocrine Disorders Group, but was not involved in the editorial process; published an editorial on the role of GLP-1RA for *BMJ*.
- Yang Guo: none known
- Lucia Varela: none known
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## Registration and protocol

Protocol (2022) DOI: 10.1002/14651858.CD015092 (this protocol is for the three systematic reviews (liraglutide, semaglutide and tirzepatide) [42].

Modified protocol (2025) PROSPERO: CRD420250654193; via www.crd.york.ac.uk/PROSPERO/view/CRD420250654193 [43].

## 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 studies included (Supplementary material 2), ongoing or excluded at the full-text screen, in the final review (Supplementary material 3; Supplementary material 5); study data, including study information, study arms, and study results or test data; consensus risk of bias assessments; and analysis data, including overall estimates and settings, subgroup estimates, and individual data rows] (Supplementary material 6; Supplementary material 7). Appropriate permissions have been obtained for such use. Analyses and data management were conducted using Cochrane's authoring tool, Review Manager, which utilises built-in computational methods.

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# Tables

**Table 1**

**Overview of included studies and syntheses: general characteristics**

| Study ID (Study period) | Country/setting | Intervention and comparison | No. of participants randomised (ratio) | Age[a] | Sex[b] | Weight (kg)[a] | BMI[a] | Subpopulation[c] | Follow-up |
|---|---|---|---|---|---|---|---|---|---|
| SUMMIT (2021-2024) | Argentina, Brazil, China, India, Israel, Mexico, Puerto Rico, Russian Federation, Taiwan, USA | Tirzepatide up to 15 mg vs placebo (weekly) | 731 (1:1) | 65.25 | 46.2% | 103.0 | 38.25 | Heart failure with preserved ejection fraction | 52 weeks (extended to 120 weeks) |
| SURMOUNT-1 (2019-2022) | Argentina, Brazil, China, India, Japan, Mexico, Russia, Taiwan, USA | Tirzepatide 5 mg, 10 mg and 15 mg vs placebo (weekly) | 2539 (1:1:1:1) | 44.9 | 32.5% | 104.8 | 38 | Prediabetes (for the extension phase) | 72 weeks + 4 weeks safety follow-up[d], 176 weeks (extension) + 17 weeks safety follow-up[d] |
| SURMOUNT-2 (2021-2023) | Argentina, Brazil, India, Japan, Russia, Taiwan, USA | Tirzepatide 10 mg, 15 mg vs placebo (weekly) | 938 (1:1:1) | 54.2 | 49% | 100.7 | 36.1 | T2DM | 72 weeks + 4 weeks safety follow-up[d] |
| SURMOUNT-3 (2021-2023) | Argentina, Brazil, Puerto Rico, USA | Tirzepatide 10 mg and 15 mg vs placebo (weekly) | 579 (1:1:1) | 45.6 | 37.1% | 101.9 | 35.9 | - | 72 weeks + 4 weeks safety follow-up[d] |
| SURMOUNT-4 (2021-2023) | Argentina, Brazil, Taiwan, USA | Continue tirzepatide vs switch to placebo (weekly) | 670 (1:1) | 48.5 | 29.4% | 85.2 | 30.5 | 36-week lead-in with tirzepatide 10 mg to 15 mg | 52 weeks (after 36-week lead-in period) |
| SURMOUNT-5 (2022-2025) | Puerto Rico, USA | Tirzepatide (10 mg or 15 mg) vs semaglutide (1.7 mg or 2.4 mg) (weekly) | 750 (1:1) | 44.7 | 64.7% | 113 | 39.4 | - | 72 weeks |
| SURMOUNT-CN (2021-2022) | China | Tirzepatide 10 mg and 15 mg vs placebo (weekly), plus a lifestyle intervention (in all arms) | 210 (1:1:1) | 36.1 | 50.95% | 91.8 | 32.30 | Chinese population[e] | 52 weeks |
| SURMOUNT-J (2021-2023) | Japan | Tirzepatide 10 mg, 15 mg (weekly) vs placebo | 225 (1:1:1) | 50.8 | 59.11% | - | - | Japanese population | 72 weeks + 4-week safety follow-up[d] |
| SURMOUNT-OSA (2022-2024) | Australia, Brazil, China, Czech Republic, Germany, Japan, Mexico, Puerto Rico, Taiwan, USA | Tirzepatide up to 10 mg-15 mg (weekly) vs placebo vs tirzepatide plus CPAP vs CPAP alone | 469 | 49.80 | 60.6% | 115.09 | 38.90 | Obstructive sleep apnoea | 52 weeks + 4 week safety follow-up[d] |

**CPAP:** continuous positive airway pressure; **T2DM:** type 2 diabetes mellitus

[a]Mean or median.
[b]Percentage of male population.
[c]Subsets of participants based on the study authors' specific requirements on the randomised population, including age, comorbidities, ethnicity, etc.
[d]Obesity was defined as BMI ≥ 28 kg/$m^2$ and overweight as BMI ≥ 24 kg/$m^2$.
[e]The safety follow-up was off-drug.

**Table 2**

**Overview of included studies and syntheses: additional details on populations and interventions**

| Study ID (Study period) | Intervention and comparison | SBP/DBP (mmHg) | TC/LDL/HDL | TG | Ethnicity | Race | Comorbidities |
|---|---|---|---|---|---|---|---|
| SUMMIT (2021-2024) | Tirzepatide up to 15 mg vs placebo (weekly) | 128.05/76.30 | - | - | 54.72% Hispanic or Latino<br>44.19% non-Hispanic or Latino<br>1.09% unknown or not reported | 70.04% White<br>17.92% Asian<br>6.84% American Indian or Alaska Native<br>4.92% Black or African American<br>0.27% more than one race | 48.15% T2DM<br>46.65% hospitalisation for heart failure within 12 months<br>29.69% coronary artery disease<br>25.44% atrial fibrillation |
| SURMOUNT-1 (2019-2022) | Tirzepatide 5 mg, 10 mg and 15 mg vs placebo (weekly) | 123.3/79.5 | 187.9/109.5/47.3 (mg/dL) | 128.4 (mg/dL) | 47.81% Hispanic<br>52.19% non-Hispanic | 70.58% White<br>10.87% Asian<br>9.10% American Indian or Alaska Native<br>7.92% Black or African American<br>0.35% Native Hawaiian or Pacific Islander<br>1.18% more than one race | 32.26% hypertension<br>29.81% dyslipidaemia<br>16.62% anxiety/ depression<br>12.84% osteoarthritis<br>10.52% asthma/COPD<br>7.76% OSA<br>7.09% MASLD<br>5.36% gout<br>3.07% ASCVD<br>1.54% PCOS |
| SURMOUNT-2 (2021-2023) | Tirzepatide 10 mg, 15 mg vs placebo (weekly) | 130.5/79.8 | 4.6/2.5/1.2 (mmol/L) | 2.1 (mmol/L) | 60% Hispanic<br>38% non-Hispanic<br>2% unknown or not reported | 76 % White<br>13% Asian<br>8% Black or African American<br>0.32% Native Hawaiian or Pacific Islander<br>2% more than one race | 66% hypertension<br>61% dyslipidaemia<br>10% ASCVD<br>17% MASLD<br>15% osteoarthritis<br>12% anxiety or depression<br>8% OSA<br>8% asthma/COPD<br>6% gout<br>0.64% PCOS |
| SURMOUNT-3 (2021-2023) | Tirzepatide 10 mg and 15 mg vs placebo (weekly) | 121/78.6 | 185.3/112.4/48.9 (mg/dL) | 120 (mg/dL) | 53% Hispanic<br>45% non-Hispanic<br>1% unknown or not reported | 86% White<br>11% Black or African American<br>1% American Indian or Alaska Native | 34.37% hypertension<br>26.25% dyslipidaemia<br>1.9% ASCVD<br>2.76% PCOS<br>10.19% OSA |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | | | | 0.7% Asian<br>1.4% more than one race | 15.72% osteoarthritis<br>20.03% anxiety/ depression<br>4.32% MASLD<br>8.98% asthma/COPD<br>2.59% gout |
| SURMOUNT-4<br>(2021-2023) | Continue tirzepatide vs switch to placebo (weekly) | 115/75.5 | 4.66/2.90/1.27 (mmol/L) | 1.09 (mmol/L) | 44.18% Hispanic<br>55.67% non-Hispanic<br>0.15% unknown or not reported | 80.15% White<br>11.19 % Black or African American<br>7.16% Asian<br>0.30% Native Hawaiian or Pacific Islander<br>1.19% more than one race | 35.22% hypertension<br>31.64% dyslipidaemia<br>22.54% anxiety/depression<br>19.85% osteoarthritis<br>12.09% OSA<br>10.30% asthma/COPD<br>7.16% MASLD<br>6.12% ASCVD<br>3.43% PCOS<br>3.58% gout |
| SURMOUNT-5 (2022-2025) | 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 (mmol/L) | 1.47 mmol/L | 26.13% Hispanic<br>73.87% non-Hispanic | 76.1% White<br>19.2% Black or African American<br>0.8% American Indian or Alaska Native<br>2.4% Asian<br>1.5% more than one race | 39.6% hypertension<br>24.3% dyslipidaemia<br>19.1% impaired glucose metabolism<br>18.3% anxiety<br>14.7% OSA<br>12.9% back pain<br>12.1% depression<br>9.7% asthma<br>10.8% gallbladder disease<br>8.9% osteoarthritis<br>3.6% MASLD<br>2.4% gout/hyperuricaemia |
| SURMOUNT-CN<br>(2021-2022) | Tirzepatide 10 mg and 15 mg vs placebo (weekly), plus a lifestyle intervention (in all arms) | 119.50/82 | 4.81/2.81/1.09 (mmol/L) | 1.67 (mmol/L) | - | 100% Asian | 72.86% dyslipidaemia<br>56.67% hyperuricemia<br>39.05% MASLD<br>25.24% hypertension<br>7.14% osteoarthritis<br>4.76% gout<br>3.81% OSA<br>3.33% PCOS<br>2.86% ASCVD<br>2.86% asthma/COPD<br>0.95% anxiety/depression |
| SURMOUNT-J | Tirzepatide 10 mg, 15 mg (weekly) vs placebo | - | - | - | - | 100% Asian | 60.44% glucose intolerance disorder |

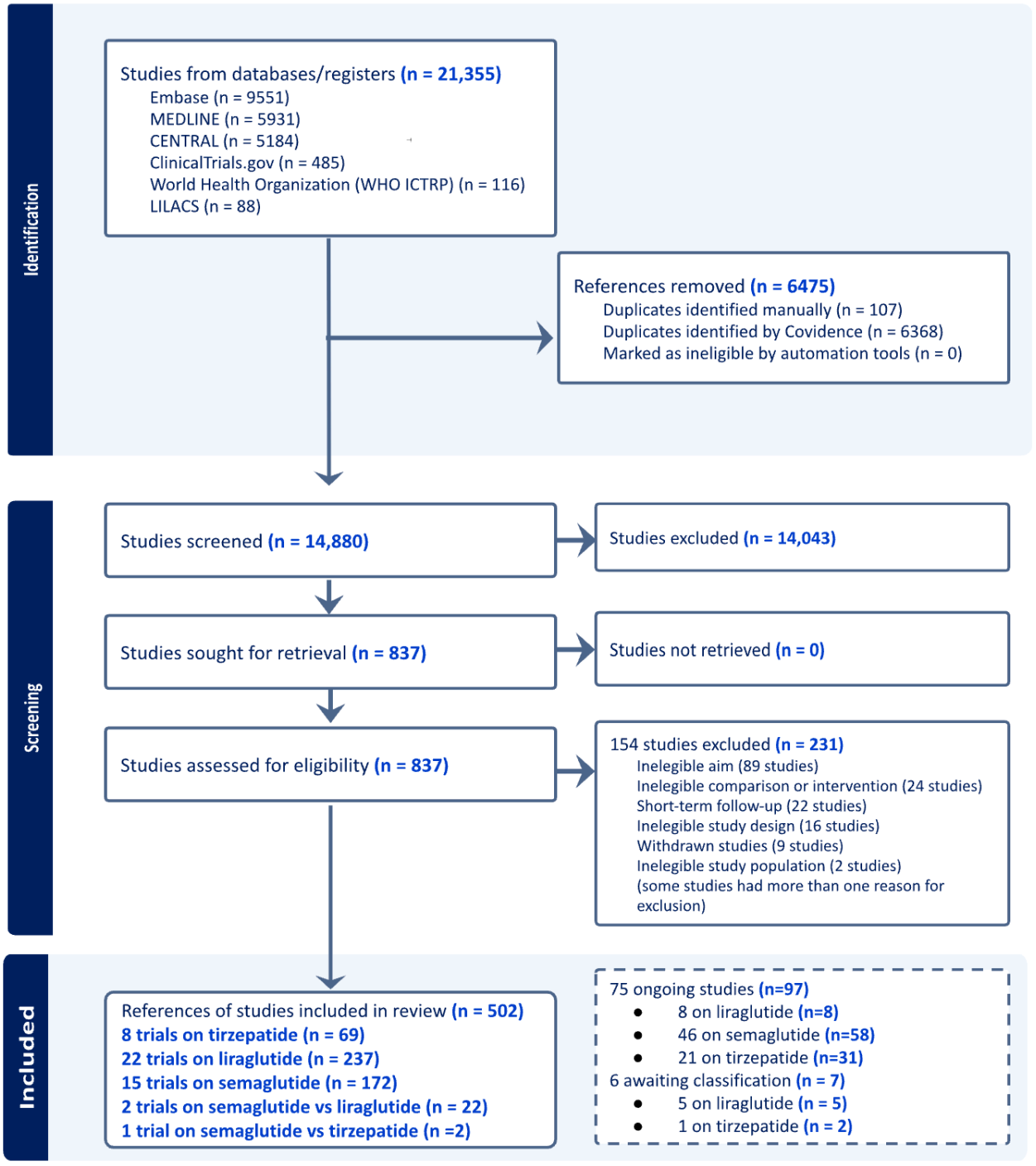
| | | | | | | | |
|---|---|---|---|---|---|---|---|
| (2021-2023) | | | | | | | 45.33% dyslipidaemia<br>80.89% MASLD[a] |
| SURMOUNT-OSA<br>(2022-2024) | Tirzepatide up to 10 mg-15 mg (weekly) vs placebo vs tirzepatide plus CPAP vs CPAP alone | 129.94/82.83 | - | - | 37.10% Hispanic or Latino | 83.80% White<br>23.67% Asian<br>9.81% American Indian or Alaska Native<br>7.25 % Black or African American<br>0.85 % more than one race | 100% moderate-to-severe OSA,<br>82.30% dyslipidaemia,<br>76.55 % hypertension,<br>60.77% prediabetes |

**ASCVD:** atherosclerotic cardiovascular disease; **COPD:** chronic obstructive pulmonary disease; **CPAP:** continuous positive airway pressure; **DBP:** diastolic blood pressure; **HDL:** high-density lipoprotein; **LDL:** low-density lipoprotein; **MASLD:** metabolic-dysfunction associated liver disease; **NASH:** nonalcoholic steatohepatitis; **OSA:** obstructive sleep apnoea; **PCOS:** polycystic ovary syndrome; **SBP:** systolic blood pressure; **T2DM:** type 2 diabetes mellitus; **TC:** total cholesterol, **TG:** triglyceride

[a]No publications were related. Data from the trial registry and baseline data.

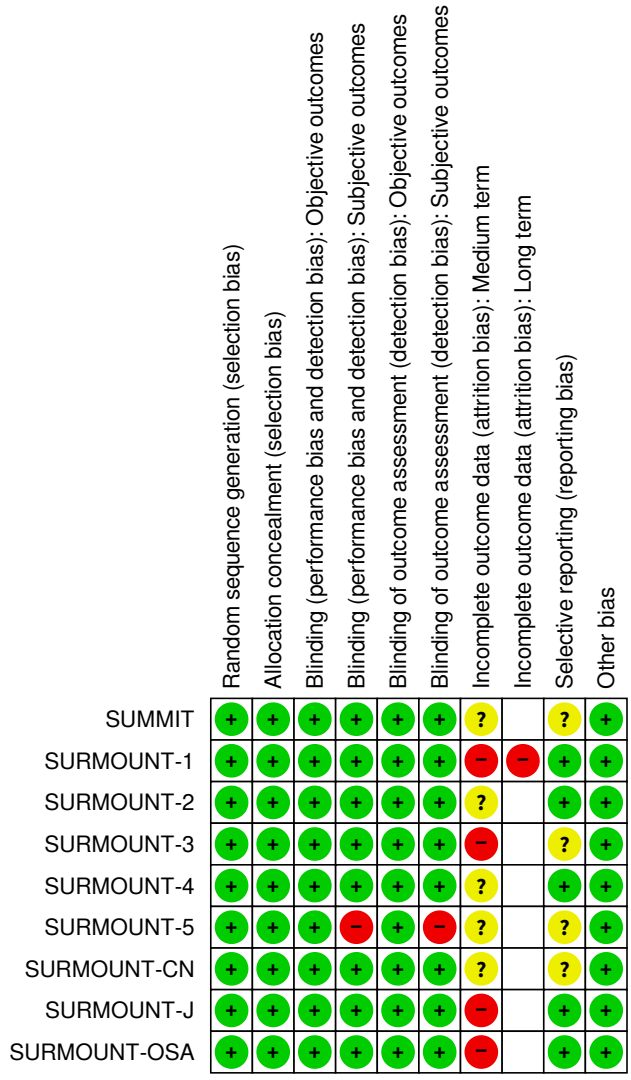
# Figures

**Figure 1**




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

**Figure 2**




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