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Research Article

The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review

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Abstract

Background: Glucagon-like peptide 1 receptor agonists are a class of drug originally developed to treat type 2 diabetes but now increasingly used for weight loss, especially in people living with obesity. Despite an abundance of evidence about the effectiveness and safety of glucagon-like peptide 1 receptor agonists for weight loss, network meta-analyses are inconsistent in their quality and scope, and this is a fast-moving field.

Objectives: We sought to identify the most recent network meta-analyses evaluating the effectiveness of glucagon-like peptide 1 receptor agonists for weight loss; critically appraise included network meta-analyses; provide an overview of the quality and findings of existing network meta-analyses, and identify any pertinent gaps in the evidence; and consider the value of updating the most recent, comprehensive and high-quality network meta-analyses.

Methods: On 6 June 2023, we searched MEDLINE, EMBASE, the Cochrane Database of Systematic Reviews and Epistemonikos for systematic reviews with network meta-analyses published since 2020 in adults (18 or above) with body mass index ≥ 25 (or ≥ 23 for Asian populations), including at least one relevant glucagon-like peptide 1 receptor agonist and weight loss outcomes. We screened and selected reviews in duplicate and independently, and appraised reviews using a modified A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2) and a network meta-analysis reliability checklist. The highest-quality reviews were then extracted in depth, and the most relevant network meta-analysis models identified, focusing on weight loss and safety outcomes. A top-up search for trials published since October 2022 was also undertaken to identify relevant trials not included in published network meta-analyses. A further search for new network meta-analyses was conducted on 26 September 2024.

Results: Of 22 systematic reviews identified, 14 were prioritised for analysis as the remaining 8 reviews were rated as low or critically low quality. We focused on network meta-analyses of weight loss outcomes measured at 6 months, 12 months, longer than 12 months or over a mix of time points. At 6 months, subcutaneous tirzepatide was the most effective drug associated with 9 kg (at 5 mg) to 12 kg (at 15 mg) of weight loss. However, the largest effects were seen for subcutaneous semaglutide 2.4 mg, which was associated with between 11.5 and 12.5 kg of weight loss, though this came from two network meta-analyses, both informed by six trials, and both merging findings across multiple time points. The relative effectiveness among glucagon-like peptide 1 receptor agonists followed a pattern suggested by their performance against placebo, with tirzepatide and semaglutide standing out as the most effective drugs for weight loss. No network meta-analyses compared tirzepatide and semaglutide 2.4 mg. The drugs associated with the greatest weight loss, tirzepatide and semaglutide 2.4 mg, were generally associated with increased risk of safety issues compared to placebo. The update trial search identified 11 new trials, which, though largely small, could make a new network meta-analysis useful. The update search for network meta-analyses yielded 13 new includes. Among

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other novel comparisons, tirzepatide was indirectly compared with semaglutide 2.4 mg, outperforming it at 15 mg, but not 5 or 10 mg. Data again came from merged time points.
Discussion: To our knowledge, this is the first review of network meta-analyses of glucagon-like peptide 1 receptor agonists. The evidence presented regarding weight loss is in general agreement with the wider literature, though data on tirzepatide were not as resounding as reported in some meta-analyses.
Limitations: Current network meta-analyses of glucagon-like peptide 1 receptor agonists with weight loss outcomes often lack clarity about the network meta-analysis methods, such as which trials were included. The tendency to combine multiple doses of drugs, and to merge findings from multiple time points, limits our understanding of dose and time effects.
Future work: Head-to-head trials of tirzepatide versus semaglutide 2.4 mg are required to determine their relative effectiveness and safety, as the two most promising options for weight loss, as are longer-term trials to establish the effectiveness and safety of glucagon-like peptide 1 receptor agonists when taken for durations of > 72 weeks.
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Background

Obesity is a chronic disease associated with increased risks of developing several serious and potentially life-threatening conditions, including cardiovascular disease, stroke and type 2 diabetes mellitus (T2DM).[1] In the UK, 26% of men and 29% of women are classified as obese [body mass index (BMI) ≥ 30 kg/m^2 or ≥ 27.5 kg/m^2 in Asian populations].[2] The economic burden on the NHS due to obesity and related illnesses is estimated at £6.1B each year.[3]

The latest generation of antiobesity drugs include glucagon-like peptide 1 receptor agonists (GLP-1 RAs). Their mode of action involves increasing insulin secretion, suppressing glucagon secretion and slowing gastric emptying. They can also reduce appetite.[4]

This review examines those GLP-1 RAs currently authorised for use in the UK: semaglutide and liraglutide are indicated for the treatment of obesity, while lixisenatide, exenatide and dulaglutide are licenced for the treatment of T2DM. Tirzepatide (Mounjaro, Eli Lilly) is a dual gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, which has recently been approved by the National Institute for Health and Care Excellence (NICE) for the treatment of adults with poorly controlled T2DM as an adjunct to diet and exercise.[5] Tirzepatide is under consideration for approval by NICE for managing overweight and obesity and, as such, is of interest in this review.

There is an abundance of evidence about the effectiveness and safety of GLP-1 RAs for the management of both T2DM and obesity, including publication of several network meta-analyses (NMAs) in recent years. NMAs allow the comparison of relevant drugs and doses, even when they have not been directly compared in trials. However, the quality and scope of published NMAs are variable and warrant close analysis.

This review sets out to provide a critical overview of the findings of recent NMAs analysing weight loss outcomes, with a focus on evaluating the evidence for effectiveness and safety of GLP-1 RAs authorised in the UK.

Aims and objectives

The aims and objectives of this review were:

- To identify the most recent (published since 2020) NMAs evaluating the effectiveness of GLP-1 RAs for weight loss.
- To critically appraise and prioritise the included NMAs.
- To provide an overview of the quality and findings of existing NMAs, and to identify any pertinent gaps in the evidence.
- To consider the value of updating the most recent, comprehensive and high-quality NMA(s) with trials published since the search date(s) in those NMA(s).

Research questions

1. What is the quantity, quality and scope of recent NMAs evaluating the effectiveness of GLP-1 RAs for weight loss in overweight and obese adults?
2. What is the effectiveness of GLP-1 RAs for weight loss in overweight and obese patients, according to recent, high-quality NMAs?
3. What adverse events (AEs) are associated with GLP-1 RAs in overweight and obese patients, according to recent, high-quality NMAs?

Methods

Search methods

The search strategy was developed by two information specialists (JB, AB) in MEDLINE and translated to the other databases. The searches used a combination of relevant controlled vocabulary terms (e.g. medical subject headings) and free text terms. The MEDLINE search strategy is shown in *Appendix 1*.

Information sources

Four bibliographic databases were searched on 6 June 2023: MEDLINE (1946–current), EMBASE (1974–current) via OvidSP, Cochrane Database of Systematic Reviews (2003–current) via Wiley Cochrane Library and the systematic review database Epistemonikos. The databases were searched from inception to June 2023 with no date or language restrictions. Forward citation chasing was conducted in Scopus (1788–present) and SpiderCite. Backward citation searching was conducted manually (MN, SF). The results of citation searching were downloaded into EndNote (Version 20, Clarivate Analytics, Philadelphia, PA, USA), deduplicated against the database search results, then a simple search of the term 'network' was carried out to identify relevant papers.

An update search was conducted on 26 September 2024 and is described in *Appendix 10*.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria according to population, intervention, control/comparison, outcome (PICO) framework were applied:

Participants/population

Adults (18 or above) with BMI ≥ 25 (or ≥ 23 for Asian populations).

Intervention

Network meta-analyses must have included trials of the following GLP-1 RAs:

- semaglutide
- liraglutide
- tirzepatide
- exenatide
- dulaglutide
- lixisenatide.

Any dose or mode of delivery (e.g. oral or subcutaneous) was of interest. Interventions could be drug-only or as part of multimodal interventions, for example, GLP-1 RA with lifestyle modifications.

Comparator(s)/control

Another GLP-1 RA, placebo or usual care.

Outcomes

A measure of weight loss such as change in mass or BMI from baseline was required for inclusion. Other relevant outcomes related to weight loss, such as body composition, were extracted but were not necessary for inclusion. Safety outcomes were extracted but were not necessary for inclusion.

Study design

Systematic reviews of randomised controlled trials (RCTs), with NMAs.

Date limit

Articles published in 2020 or later.

Process for applying inclusion criteria

The title and abstract of each record retrieved by the search was screened by two independent reviewers (MN, SF) to identify records that were clearly irrelevant. The full text of each remaining record was then sought, and screened by two independent reviewers (MN, SF) to determine inclusion. Disagreements at each stage were resolved through discussion. Articles excluded at the full-text screening stage were coded to indicate the first reason for exclusion.

Critical appraisal

Each included systematic review was critically appraised using a modified version of A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2).[6] Items 1–10, 13, 14 and 16 were included, thus omitting questions related to synthesis, which was evaluated with a separate tool, and focusing on the methodological rigour of the systematic review. Reviews that contained no fatal flaws [critical items: 2 (protocol), 4 (search), 9 (risk of bias assessment)] were prioritised for full data extraction and further appraisal using the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) checklist for assessing the reliability of NMAs.[7] Reviews that were identified as having at least one critical flaw were subjected to top-level data extraction, and their findings were briefly summarised. The assessment with the ISPOR checklist was used to inform the discussion of findings.

Data extraction

For each included record, one reviewer (SF, MN, JB) completed data extraction, and a second reviewer (MN, SF, RA, RW) checked the extracted data for accuracy. Data were extracted in relation to the study details, funding information, review inclusion criteria, NMA methods,

sample characteristics and any inequalities investigated using the PROGRESS-Plus acronym for guidance. This stands for Place of residence, Race/ethnicity/culture/language, Occupation, Gender or sex, Religion, Education, Socioeconomic status, Social capital. 'Plus' represents other factors associated with discrimination, exclusion, marginalisation or vulnerability such as personal characteristics, relationships that limit opportunities for health, or environmental situations which provide limited control of opportunities for health.[8]

Network estimates were extracted for each comparison of GLP-1 RA versus placebo or another GLP-1 RA of interest, from NMAs of weight loss (including BMI, body composition, achievement of weight loss thresholds) and any safety outcomes. A full list of data extraction items is provided in the protocol.

Patient and public involvement and engagement

This review benefited from several interactions with PERSPEX, a group of 14 public collaborators who bring their carer, patient or public perspective to the work of Isca Evidence. PERSPEX members meet monthly online, and membership is culturally, geographically and demographically diverse (www.exeter.ac.uk/research/groups/medicine/esmi/workstreams/perspex/).

PERSPEX contributed to the protocol by reviewing a plain language version; members raised questions about the potential of weight loss drugs to cause harm to patients, promoting regular review team discussions about incorporating harms and side effects. The group discussed the review on two occasions in their regular monthly meetings. Discussion highlighted safety and maintenance of weight loss as key areas of interest to patients and carers and contextualised the use of weight loss drugs within a broader societal context, with concerns about industry sponsorship. These discussions foregrounded patient and carer concerns for the review team.

Equality, diversity and inclusion

To incorporate a diverse range of experience and views into this work, the research team drew upon the knowledge and expertise of the PERSPEX team throughout the conduct of this review. The PERSPEX team represents individuals living with a range of health conditions, who have different communication preferences. Hence, the research team used a variety of modes of communication to engage with the group, including face-to-face verbal updates and plain-language protocols. The size of the research team makes it difficult to ask team members to disclose information on diversity while respecting their confidentiality.

The inclusion criteria for this review reflect that the definition of obesity differs among certain minority ethnic groups. Where possible, this was considered alongside reported health inequalities data within the synthesis of our findings. A summary of health inequality data considered within the systematic reviews prioritised for full data extraction is provided within this report. The relevance of specific findings to different population groups is considered where applicable.

This report is prefaced by the plain language summary approved by the PERSPEX team, representing our desire to make the processes and findings associated with this review accessible to non-research audiences.

Synthesis

Extracted data were tabulated and summarised with accompanying text. The synthesis focused on the key characteristics and quality of included evidence, the effectiveness of GLP-1 RAs for weight loss, and safety outcomes. Overviews of the evidence are provided in the main body of the report, with detailed descriptions of findings available in the appendices.

We looked for common time points in the NMAs for grouping evidence. Forest plots were used to summarise network estimates for comparisons explored across multiple NMAs. Findings relating to safety were described using a narrative approach.

The drugs licensed for weight loss in the UK, or anticipated to be licensed soon, were prioritised in the synthesis (semaglutide, liraglutide, tirzepatide).

Study registration details

The protocol was hosted at the following link: http://hdl.handle.net/10871/133388 and on Research Registry (reviewregistry1711).

Results

Study selection

From the bibliographic database searches, 693 references were retrieved. After deduplication, 359 references were screened at title and abstract. At full text, 61 articles were screened, resulting in 22 includes. The most common reasons for exclusion at the full-text stage were publication status, where only abstracts were available (n = 13 studies), and BMI being too low or not reported at baseline (n = 10 studies). No additional studies were found through supplementary searching. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow

diagram is shown in *Figure 1*.[9] Reasons for exclusion for each article screened at full text are available in *Report Supplementary Material 1*, *Table 1*. The update search exercise is summarised in *Appendix 10*.

Review characteristics

Appendix 2 displays key characteristics of the 22 included systematic reviews. Fourteen reviews were rated as being of moderate quality, having no critical flaws, and thus prioritised for full data extraction and synthesis.[10–23] Note that our update search identified that the 2022 review by Shi and colleagues[19] was retracted, revised and resubmitted in a new article.[24]

Four reviews received funding from private companies: Novo Nordisk (Bagsværd, Denmark) sponsored reviews by Chubb and colleagues,[25] and Smith and colleagues[26] (both non-prioritised); Merck Sharp & Dohme Corp. (Rahway, NJ, USA) sponsored the review by Lautsch and colleagues;[14] the review by Tsapas and colleagues[21] was supported by a grant from AstraZeneca (Cambridge, UK). Nine reviews received public/government funding,[15,16,18,20,22,24,27–29] and the rest received no funding (*n* = 6[11,13,17,23,30,31]) or included no declaration (*n* = 3[10,12,32]).

Weight loss was a primary outcome in 12 reviews,[11,14,16,21,22,24–30] the others prioritising glycated haemoglobin (HbA1c) (*n* = 5),[10,12,23,31,32] safety outcomes (*n* = 3[13,17,20]) or liver function in patients with non-alcoholic fatty liver disease (NAFLD).[15,18] Twelve reviews specifically sought participants with T2DM,[11,12,14,17,20,21,23,25,28,30–32] of which four were prioritised.[17,20,21,23] The 'intervention' inclusion criteria of 10 reviews specified GLP-1 RAs,[11,22,23,25–28,30–32] and of these, 4 specified that the trial comparator had to be another GLP-1 RA or placebo/usual care.[27,30–32] None of those reviews were prioritised, therefore all prioritised reviews potentially included drugs in their NMAs that were not of interest in this review. The most recent search was conducted in February 2023.[13]

Sample characteristics

Appendix 3 displays the sample characteristics of the 14 prioritised reviews.[10–18,20–24] The number of trials included in the reviews ranged from 9[11] to 816.[20] The number of trials in the body weight NMA was calculable in 12 of the reviews,[11,13–18,20–24] ranging from 8[11] to 531.[20] Two reviews added all of their included trials to their body weight NMAs.[15,22] Sample size ranged from 1812[15] to 49,810 (or 42,148 for body weight NMA).[20] Baseline mean BMI ranged from 25.5[14] to 35.8 kg/m^2.[13] Participant mean age ranged from 41.1[10] to 57.7[20] years, and percentage of female participants ranged from 43.8%[11] to 79.9%.[15] Ten reviews reported diabetes as a comorbidity,[10–14,16–18,23,24] eight of these specifying T2DM.[11–14,17,18,23,24] Other baseline comorbidities were hypertension,[13,24] NAFLD,[18,24] non-alcoholic steatohepatitis (NASH),[18] metabolic syndrome, polycystic ovary syndrome (PCOS), obstructive sleep apnoea and dyslipidaemia,[24] and cardiovascular disease.[20]

Nine reviews included semaglutide; semaglutide 0.5 and 1.0 mg was included in four reviews,[11,16,22,23] semaglutide 2.4 mg in two reviews,[16,22] oral semaglutide 3.0 and 7 mg in one review[23] and oral semaglutide 14 mg in two reviews.[14,23] Liraglutide was included in 11 reviews,[10–13,15,16,20–24] tirzepatide in two.[20,23] Eight reviews included exenatide.[10–12,15,16,20,21,24] Dulaglutide[12,16] and lixisenatide[20,21] were included in two reviews each. Three reviews reported GLP-1 RAs as a single intervention.[17,18,24] Safety outcomes were reported in nine reviews.[10,12,13,16,17,20,22–24]

PROGRESS-Plus data

Eight papers refer to further analyses (sensitivity or subgroup) based on PROGRESS-Plus criteria. Of these, only one analysed results based on race/ethnicity, omitting one study with an Asian population.[14] All other studies used 'other personal characteristics' for their subgroup analyses. One review discussed findings of analyses based on the previous or background treatment.[21] Seven studies based their further analyses on those with or without other health conditions, including four looking at patients with or without diabetes,[16,18,26,29] three looking at baseline BMI,[13,20,21] one looking at presence of liver disease,[18] one looking at presence of pre-diabetes[26] and one looking at patients with normal glucose tolerance.[26]

Critical appraisal

A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR-2)

The included systematic reviews (22 studies) were critically appraised using AMSTAR-2,[6] which indicated that the overall confidence in the findings of the reviews was mostly moderate (14 studies),[10–18,20–24] with six reviews assessed as low[26–31] and two as critically low.[25,32] None of the systematic reviews were assessed as having a high overall level of confidence. The ratings are shown in *Appendix 4*.

For the prioritised reviews (those assessed as moderate quality), all were assessed as reporting a protocol and having an adequate search strategy. All moderate reviews used a satisfactory technique for assessing the risk of bias of included studies and included discussion of this in the findings. None of the prioritised reviews provided details

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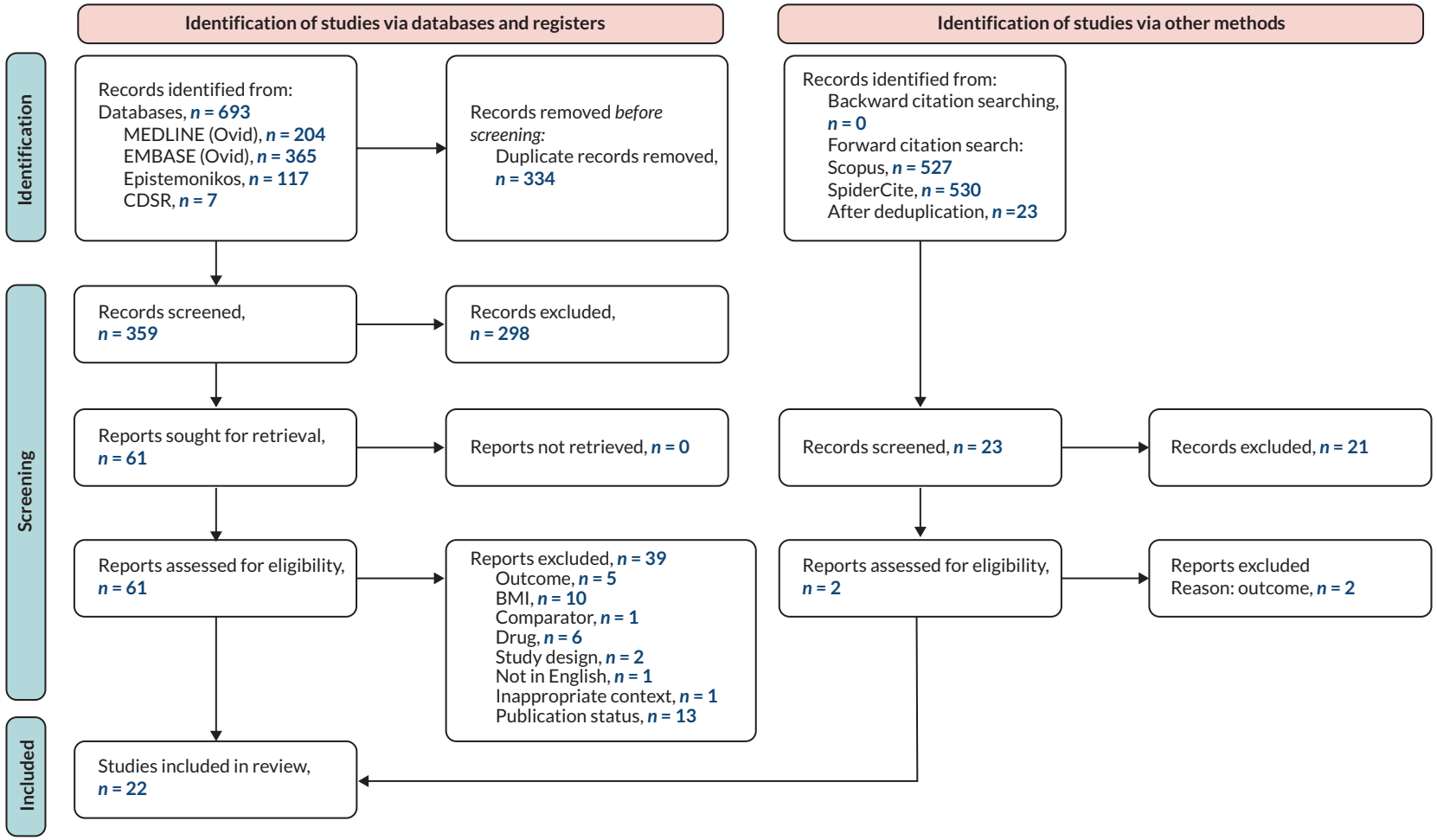


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart summarising the results of the literature search and study selection. CDSR, Cochrane Database of Systematic Reviews.

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of the excluded studies, and only one review justified the choice of study design inclusion.[23]

For the reviews assessed as low or critically low quality, none reported the use of a protocol, and three of the reviews may have had inadequate search strategies.[25,27,32] While all used satisfactory techniques to assess risk of bias in their included RCTs, only five of the eight reviews adequately discussed the risk of bias in their findings.[26,27,29,31,32] None of these reviews justified the choice of study design inclusion, and only one provided details of the excluded studies.[25] Low and critically low-quality reviews may not provide an accurate and comprehensive summary of the available studies of interest.

International Society of Pharmacoeconomics and Outcomes Research appraisal of network meta-analyses (ISPOR)

The outcome of assessment with the ISPOR tool is provided in *Appendix 5* for the 14 prioritised reviews. All but two reviews[20,23] were missing some of the GLP-1 RAs of interest to this review, and 10 reviews included poor-quality studies.[10–17,20,21] All but two reviews included trials in their systematic review that were subsequently not included in their NMAs of body weight outcomes, introducing potential bias due to selective reporting.[15,22] One review displayed the number of trials included per comparison in the evidence network diagram,[24] though all reviews provided a diagram.

Of 26 items, the median number of negative responses was 8, ranging from 6[18] to 10.[12,13] The review by Zaazouee and colleagues received seven negative responses, and a further five items were unclear, reflecting a significant lack of clarity about the methods used to conduct their analyses.[23] The review by Hussein and colleagues received 10 negative responses with 2 items unclear, reflecting significant uncertainty about the validity of their analyses.[12]

Overview of findings relating to the effectiveness of glucagon-like peptide 1 receptor agonists for weight loss

This section provides an overview of comparisons between GLP-1 RAs and placebo/usual care, and comparisons between GLP-1 RAs of interest. NMAs were conducted for outcomes at specific time points, or included trials with a wide range of time points. We grouped outcomes at the following intervals: 6 months, 12 months, longer than 12 months, a mix of time points (see *Figure 1* in *Report Supplementary Material 1* for details). In this section, network estimates extracted from the prioritised reviews are presented at the above intervals. *Appendix 6* contains detailed descriptions of findings, including forest plots (see *Appendix 6*, *Figures 5–19*) of comparisons and all individual network estimates for absolute weight loss (in kg) for specific GLP-1 RAs versus placebo or standard care where available at 6 months, 12 months, more than 12 months, and where reviews combined findings across a range of time points (see *Appendix 6*, *Table 6*). All network estimates and confidence intervals (CIs) for all outcomes are provided in *Report Supplementary Material 1*, *Table 2*.

Effectiveness of glucagon-like peptide 1 receptor agonists versus placebo

Findings at 6 months

At 6 months (23–26 weeks), subcutaneous tirzepatide was the most effective drug, associated with 9 kg (at 5 mg) to 12 kg (at 15 mg) of weight loss. Subcutaneous semaglutide was the next most effective, associated with almost 8 kg (1.0 mg) and 5.5 kg (0.5 mg) weight loss. Oral semaglutide 14 mg and at a variety of doses combined into one variable (referred to hereafter as 'combined doses') provided around 3 kg weight loss, the remaining comparisons were associated with 0.8–2.3 kg weight loss. Notably, there were no data available at the 6-month time point for semaglutide 2.4 mg or liraglutide 3.0 mg versus placebo/usual care. *Table 1* orders the available comparisons for the 6-month time point by magnitude of effect in each network estimate.

Findings at 12 months

At 12 months, combined doses of subcutaneous semaglutide were associated with 9 kg of weight loss. Liraglutide 3.0 mg and data for combined oral and subcutaneous doses of semaglutide were associated with around 5 kg of weight loss. Oral doses of semaglutide were associated with weight loss increasing with greater doses (3.0–14 mg), but to a lesser extent than subcutaneous doses (up to 3.86 kg lost). There were no data for tirzepatide versus placebo at the 12-month time point. *Table 2* orders the available comparisons for the 12-month time point by magnitude of effect in each network estimate.

Findings beyond 12 months

For follow-up periods longer than 12 months, exenatide and subcutaneous semaglutide at 0.5 and 1.0 mg were associated with around 4–4.5 kg greater weight loss than placebo. Combined doses of liraglutide were associated with 3.4 kg weight loss, but estimates for specific doses (0.6/1.2/1.8/3.0 mg) were not statistically significant due to wide CIs. There were no data available for tirzepatide versus placebo at the > 12 months time period. *Table 3* orders the available comparisons for follow-up periods > 12 months by magnitude of effect.

TABLE 1 Most effective GLP-1 RAs for weight loss at 6 months vs. placebo (sorted by magnitude of network estimate)

Drug	Dose	Network estimate of absolute weight loss in kg (95% CI)
Tirzepatide (SC)	15 mg	−12.11 (−16.14 to −8.09)[23]
Tirzepatide (SC)	10 mg	−11.21 (−15.21 to −7.21)[23]
Tirzepatide (SC)	5 mg	−9.23 (−13.24 to −5.22)[23]
Semaglutide (SC)	1.0 mg	−7.72 (−11.68 to −3.75)[23]
Semaglutide (SC)	0.5 mg	−5.51 (−9.45 to −1.57)[23]
Semaglutide (oral)	nr	−3.40 (−4.51 to −2.33)[12]
Semaglutide (oral)	14 mg	−3.06 (−3.57 to −2.55)[23]
Liraglutide (SC)	3.0 mg	−2.44 (−2.87 to −2.04)[12]
Liraglutide (SC)	1.8 mg	−2.35 (−3.20 to −1.50)[23]
Semaglutide (oral)	14 mg	−2.16 (−3.37 to −0.97)[14]
Semaglutide (SC)	0.1 mg	−2.02 (−8.60 to 4.56)[23]
Semaglutide (oral)	7 mg	−1.87 (−2.58 to −1.16)[23]
Exenatide (SC)	Short-acting (nr)	−1.71 (−2.12 to −1.29)[12]
Exenatide (SC)	Long-acting (nr)	−1.63 (−2.13 to −1.11)[12]
Semaglutide (SC)	0.05 mg	−1.51 (−8.25 to 5.23)[23]
GLP-1 RAs (nr)	nr	−1.45 (−1.72 to −1.18)[17]
Dulaglutide (SC)	nr	−1.23 (−1.80 to −0.64)[12]
Lixisenatide (SC)	nr	−0.91 (−1.32 to −0.52)[12]
Semaglutide (oral)	3.0 mg	−0.78 (−1.45 to −0.12)[23]

Grey shading, non-significant estimate; nr, not reported or combined doses; SC, subcutaneous.

Note
Values are individual network estimates from prioritised reviews.

TABLE 2 Most effective GLP-1 RAs for weight loss at 12 months vs. placebo or usual care (sorted by magnitude of network estimate)

Drug	Dose	Network estimate of absolute weight loss in kg (95% CI)
Semaglutide (SC)	nr	−9.02 (−10.42 to −7.63)[13]
Liraglutide (SC)	3.0 mg	−5.01 (−5.95 to −4.07)[13]
Semaglutide (SC/oral)	nr	−5.00 (−9.62 to −0.41)[12]
Semaglutide (oral)	14 mg	−3.86 (−5.26 to −2.47)[23]
Semaglutide (oral)	7 mg	−2.66 (−4.05 to −1.26)[23]
Semaglutide (oral)	3.0 mg	−1.71 (−3.04 to −0.37)[23]
Exenatide (SC)	Long-acting (nr)	−1.21 (−4.73 to 2.25)[12]

Grey shading, non-significant estimate; nr, not reported or combined doses; SC, subcutaneous.

Note
Values are individual network estimates from prioritised reviews.

TABLE 3 Most effective GLP-1 RAs for weight loss at beyond 12 months, vs. placebo (sorted by magnitude of network estimate)

Drug	Dose	Network estimate of absolute weight loss in kg (95% CI)
Exenatide (SC)	nr	−4.50 (−6.93 to −2.07)[10]
Liraglutide (SC)	3.0 mg	−4.30 (−9.20 to 0.57)[11]
Semaglutide (SC)	1.0 mg	−4.04 (−5.61 to −2.47)[11]
Semaglutide (SC)	0.5 mg	−3.84 (−5.94 to −2.09)[11]
Liraglutide (SC)	3.0 mg	−3.39 (−4.18 to −2.60)[10]
Liraglutide (SC)	1.8 mg	−3.09 (−6.32 to 0.20)[11]
Liraglutide (SC)	1.2 mg	−2.72 (−6.43 to 1.09)[11]
Liraglutide (SC)	0.6 mg	−1.45 (−6.08 to 3.20)[11]
Exenatide (SC)	2.0 mg	−0.31 (−4.93 to 4.30)[11]

Grey shading, non-significant estimate; nr, not reported or combined doses; SC, subcutaneous.

Note
Values are individual network estimates from prioritised reviews.

Data from multiple time points

Where reviews combined data from multiple time points, spanning a maximum of 8–281 weeks, there were data for comparisons covering a greater range of drugs and doses. The largest effects were seen for subcutaneous semaglutide 2.4 mg, which was associated with between 11.5 and 12.5 kg greater weight loss than placebo. Tirzepatide was also associated with a large effect, with more than 8.5 kg weight loss compared with placebo (combined doses). Around 4–5 kg of weight loss was seen with combined doses of subcutaneous semaglutide, semaglutide 1.0 mg, liraglutide 3.0 mg and some (unreported/combined) doses of exenatide. Short- and long-acting exenatide, dulaglutide and lixisenatide were associated with under 2 kg of weight loss. *Table 4* orders the available comparisons for data from combined time points, by magnitude of effect. *Report Supplementary Material 1*, *Figure 1* provides an overview of the time points covered by NMAs providing estimates from merged or multiple time points.

Other indicators of weight loss

Effects were also reported in terms of percentage of body weight reduction, reduction in BMI and reduction in waist circumference. Results for these outcomes followed the same pattern as those for absolute body weight reduction, and no additional comparisons were covered.

Semaglutide (combined doses) was associated with 13 times greater likelihood of achieving 10% weight loss than lifestyle modification alone, while the odds were nearly 5 times greater with liraglutide (combined doses). Participants were nearly 10 and 5 times more likely to achieve 5% weight loss with semaglutide and liraglutide, respectively. Full detail is available in *Appendix 6*.

Summary of effects of glucagon-like peptide 1 receptor agonists versus placebo/usual care

Across all time points, the largest effects were seen for subcutaneous semaglutide 2.4 mg, which was associated with between 11.5 and 12.5 kg of weight loss compared to placebo. Data came from NMAs in two reviews,[16,22] both informed by six trials.

Tirzepatide 10 mg (11.2 kg) and 15 mg (12.1 kg) were associated with similar weight loss effects as semaglutide 2.4 mg, this effect seen after 6 months, but only informed by one trial. At combined doses and time points, tirzepatide was associated with 8.5 kg weight loss.[20] This estimate came from a NMA which included data from seven tirzepatide trials, including SURPASS-J and SURPASS 1–5.[33–38] These trials all included doses of 5, 10 and 15 mg, and had follow-ups spanning 6–13 months, with the SURPASS trials all covering 10–13 months. Therefore, it can be deduced that the effects for tirzepatide (8.5 kg weight loss) are relevant to the 12-month interval.

The next best-performing GLP-1 RAs were subcutaneous doses of semaglutide, with 1.0 mg associated with greater weight loss than the 0.5 mg dose. At 6 months, 7.7 kg was achieved with semaglutide 1.0 mg, 5.5 kg with 0.5 mg, and combined doses of subcutaneous semaglutide were associated with 9 kg of weight loss at 12 months. However, the data for follow-up beyond 12 months indicated a smaller effect, with only around 4 kg of weight loss.

TABLE 4 Most effective GLP-1 RAs for weight loss at combined or multiple time points, vs. placebo or usual care (sorted by magnitude of network estimate)

Drug	Dose	Network estimate of absolute weight loss in kg (95% CI)	Time points included in NMA (weeks)
Semaglutide (SC)	2.4 mg	−12.47 (−13.25 to −11.69)[22]	20–68
Semaglutide (SC)	2.4 mg	−11.51 (−12.83 to −10.21)[16]	12–72
Tirzepatide (oral)	nr	−8.57 (−9.40 to −7.75)[20,a]	24 +[b]
Semaglutide (SC)	1.0 mg	−5.67 (−7.84 to −3.52)[16]	12–72
Liraglutide (SC)	3.0 mg	−5.24 (−5.82 to −4.67)[22]	20–68
Liraglutide (SC)	3.0 mg	−4.65 (−5.60 to −3.69)[16]	12–72
Semaglutide (SC)	nr	−4.62 (−5.22 to −4.03)[20,a]	24 +[b]
Exenatide (SC)	nr	−4.35 (−5.53 to −3.17)[10]	4–52
Liraglutide (SC)	3.0 mg	−4.34 (−6.27 to −2.41)[15]	8–96
Exenatide (SC)	nr	−4.04 (−8.64 to −0.57)[15]	8–96
Liraglutide (SC)	3.0 mg	−3.85 (−4.35 to −3.35)[10]	4–52
Semaglutide (SC)	nr	−3.80 (−4.46 to −3.14)[21]	24–281
Semaglutide (SC)	1.0 mg	−3.74 (−4.87 to −2.61)[22]	20–68
Liraglutide (SC)	1.8 mg	−3.29 (−4.04 to −2.53)[22]	20–68
Liraglutide (SC)	1.8 mg	−3.24 (−4.43 to −2.04)[16]	12–72
Semaglutide (oral)	nr	−2.98 (−3.66 to −2.29)[16,a]	12–72
Semaglutide (oral)	nr	−2.41 (−3.13 to −1.69)[21]	24–281
Exenatide (SC)	nr	−2.37 (−2.87 to −1.87)[21]	24–281
Liraglutide (SC)	3.0 mg	−2.37 (−2.75 to −1.98)[21]	24–281
Liraglutide (SC)	nr	−2.21 (−2.58 to −1.85)[20,a]	24 +[b]
Exenatide (SC)	Short-acting (nr)	−1.77 (−2.47 to −1.07)[20,a]	24 +[b]
Dulaglutide (SC)	nr	−1.40 (−1.93 to −0.88)[20]	24 +[b]
Exenatide (SC)	Long-acting (nr)	−1.05 (−1.67 to −0.42)[20,a]	24 +[b]
Lixisenatide (SC)	nr	−1.04 (−1.56 to −0.52)[21]	24–281
Dulaglutide (SC)	1.5 mg	−1.04 (−2.96 to 0.90)[16,a]	12–72
Exenatide (SC)	Long-acting (nr)	−1.03 (−1.68 to −0.38)[21]	24–281
Exenatide (SC)	10 µg	−1.03 (−2.18 to 0.09)[16]	12–72
Lixisenatide (SC)	nr	−0.83 (−1.4 to −0.26)[20,a]	24 +[b]

Grey shading, non-significant estimate; nr, not reported or combined doses; SC, subcutaneous.
a Compared with usual care.
b No upper limit provided.

Note
Values are individual network estimates from prioritised reviews.

Comparative effectiveness of glucagon-like peptide 1 receptor agonists

The following section summarises network estimates comparing GLP-1 RAs with one another at 6 months, 12 months, > 12 months, and where review authors have combined data for multiple time points. A detailed description of the evidence is available in *Appendix 6*.

Findings at 6 months

Figure 2 summarises comparisons between GLP-1 RAs at 6 months. Tirzepatide at 5, 10 and 15 mg outperformed semaglutide 1.0 and 0.5 mg, with a dose-related response. The largest difference in body weight reduction was for tirzepatide 15 mg versus semaglutide 0.5 mg, with 6.6 kg greater weight loss (95% CI −8.25 to −4.95 kg). Evidence for tirzepatide came from one trial included in the review by Zaazouee and colleagues, which performed poorly on ISPOR evaluation.[23] Oral doses of semaglutide, at 3.0, 7 and 14 mg, were of equivalent effectiveness to low subcutaneous doses (0.1, 0.05 mg).[23]

Combined doses of semaglutide were associated with greater weight loss at 6 months than exenatide (long- and short-acting), dulaglutide and lixisenatide, with differences ranging from 1.7 to 2.5 kg. There was no difference between this composite variable and the equivalent composite for liraglutide. While liraglutide outperformed exenatide, dulaglutide and lixisenatide, the magnitude of differences in all cases was around 1 kg less than with semaglutide.

Findings at 12 months

Five comparisons between GLP-1 RAs were available at 12 months. The review by Zaazouee and colleagues compared oral semaglutide at 14, 7 and 3.0 mg, reporting around 1 kg additional weight loss per dose increment.[23] Subcutaneous semaglutide (combined doses) was associated with 4 kg of additional weight loss at 12 months compared with liraglutide 3.0 mg.[13] A similar effect was seen when combined doses of subcutaneous semaglutide were compared with long-acting exenatide, with 3.8 kg additional weight loss for semaglutide.[12] Full detail is available in *Appendix 6*.

Findings beyond 12 months

As shown in *Figure 3*, the NMA by Alsugair and colleagues, including 9 trials with over 9600 participants, provided 21 of the 22 network estimates at time points beyond 12 months, focusing on various doses of semaglutide and liraglutide.[11] Semaglutide 1.0 was associated with 3 kg greater weight loss versus liraglutide 0.6 and 3.8 kg greater weight loss versus exenatide 2.0 mg. Semaglutide 0.5 mg performed similarly against the same comparators (2.4 and 2.1 kg greater weight loss with semaglutide, respectively).

Data from multiple time points

Network estimates were available for absolute body weight loss for all GLP-1 RAs of interest, with further data on treatment responders (patients achieving 5% or 10% weight loss) and BMI available for a subsection of drugs (*Figure 4*). Network estimates in this section came from six systematic reviews with NMAs,[10,15,16,20–22] all covering a range of time points from 4–52 weeks[10] to 24–281 weeks.[21] All reviews covered the period from 24 to 52 weeks, and three included trials up to 96 weeks' duration.[15,20,21]

Estimates for combined doses of tirzepatide (5–15 mg), semaglutide 2.4 mg and combined subcutaneous doses of semaglutide were superior to their comparators. Semaglutide 2.4 mg was associated with 6–8.7 kg greater weight loss than the next strongest dose (1.0 mg), and was associated with greater odds of achieving 5% weight loss than liraglutide 3.0 mg (2.5 times better odds) and 1.8 mg (2.9 times better odds). Combined doses of subcutaneous semaglutide were associated with between 1.4 and 3.8 kg greater weight loss than oral semaglutide, semaglutide 1.0 and 0.5 mg, liraglutide, exenatide, dulaglutide and lixisenatide.

There was no NMA, including both tirzepatide and semaglutide 2.4 mg; nor was either drug compared to the same comparator.

Summary of comparisons between glucagon-like peptide 1 receptor agonists

Across all time points, the ordering of drugs in terms of efficacy versus placebo or usual care holds true for comparisons with one another. Tirzepatide and semaglutide were the most effective drugs for weight loss; however, there were no NMAs comparing tirzepatide and semaglutide 2.4 mg. The only mutual comparator across reviews was semaglutide 1.0 mg. At 6 months, tirzepatide was superior to semaglutide 1.0 mg by up to 4.4 kg (at 15 mg). At combined time points, semaglutide 2.4 mg was associated with 5.8 and 8.7 kg greater weight loss than semaglutide 1.0 (data from two NMAs), suggesting that semaglutide 2.4 mg may be more effective for weight loss than tirzepatide.

Lower (1.0, 0.5 mg) doses of subcutaneous semaglutide were associated with similar weight loss performance to liraglutide 3.0 and 1.8 mg at > 12 months and when time points were combined, but combined data for subcutaneous semaglutide were associated with 4 kg

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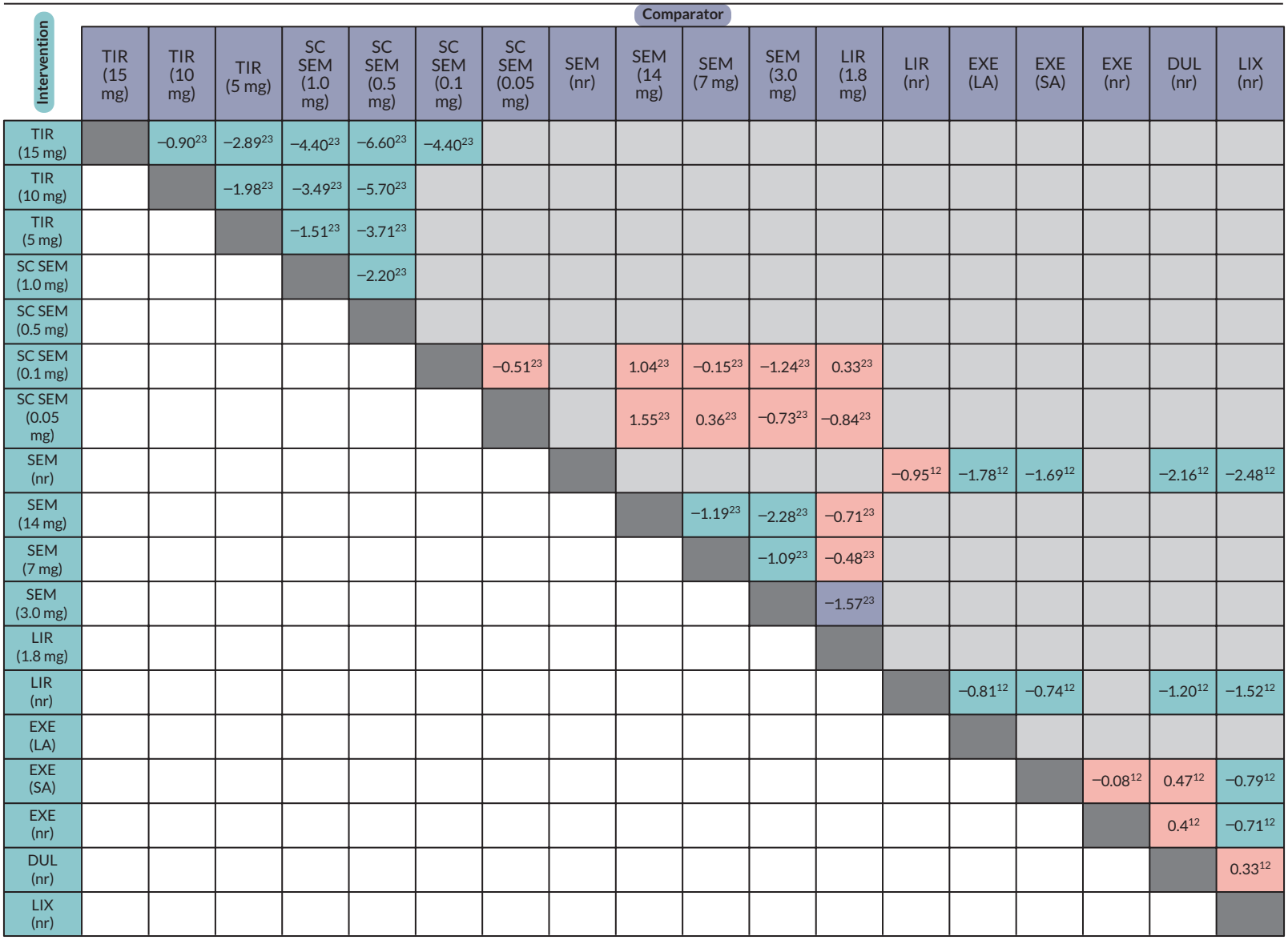


FIGURE 2 Summary of effects for active comparisons at 6 months. Top right of grid contains mean network estimate for absolute reduction in body mass (kg) for the comparison, and the review providing the estimate. Cell colour indicates which comparator is favoured: light blue cell, evidence is statistically significant in favour of the intervention (row labels); grey cell, no data; dark blue cell, evidence is statistically significant in favour of the comparator (column labels); orange cell, evidence of no statistically significant difference between drugs being compared. DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; nr, not reported or combined doses; SA, short-acting; SC, subcutaneous; SEM, semaglutide; TIR, tirzepatide.

Intervention \ Comparator	SEM (1.0 mg)	SEM (0.5 mg)	LIR (3.0 mg)	LIR (1.8 mg)	LIR (1.2 mg)	LIR (0.6 mg)	LIR (nr)	EXE (2.0 mg)	EXE (nr)
SEM (1.0 mg)		−0.35[11]	−0.82[11]	−1.58[11]	−1.23[11]	−3.06[11]		−3.80[11]	
SEM (0.5 mg)			−0.48[11]	−0.27[11]	−0.89[11]	−2.42[11]		−2.13[11]	
LIR (3.0 mg)				−1.22[11]	−1.56[11]	−2.85[11]		−1.66[11]	−1.66[11]
LIR (1.8 mg)					−0.34[11]	−1.63[11]			
LIR (1.2 mg)						−1.31[11]			−1.36[11]
LIR (0.6 mg)									−1.74[11]
LIR (nr)									1.11[10]
EXE (2.0 mg)									
EXE (nr)									

FIGURE 3 Summary of effects for active comparisons at longer than 12 months. Top right of grid contains mean network estimate for absolute reduction in body mass (kg) for the comparison, and the review providing the estimate. Cell colour indicates which comparator is favoured: light blue cell, evidence is statistically significant in favour of the intervention (row labels); grey cell, no data; orange cell, evidence of no statistically significant difference between drugs being compared. EXE, exenatide; LIR, liraglutide; nr, not reported or combined doses; SEM, semaglutide.

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Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

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Intervention \ Comparator	TIR (nr)	SEM (2.4 mg)	SC SEM (nr)	SEM (nr)	SEM (1.0 mg)	LIR (nr)	LIR (3.0 mg)	LIR (1.8 mg)	EXE (LA)	EXE (SA)	EXE (nr)	EXE (10 µg)	DUL (nr)	DUL (1.5 mg)	LIX (nr)
TIR (nr)			−3.95[20]	−5.59[20]		−6.36[20]			−7.52[20]	−6.8[20]			−7.17[20]		−7.74[20]
SEM (2.4 mg)					−5.84[16] −8.73[22]		−6.86[16] −7.32[22]	−8.38[16] −9.19[22]				−10.23[16]		−10.11[16]	
SC SEM (nr)				−1.39[21]	−1.65[20]	−1.43[21] −2.41[20]			−2.77[21] −3.58[20]	−2.85[20]	−1.43[21]		−3.22[20]		−2.76[21] −3.79[20]
SEM (nr)						−0.76[20] −0.04[21]			−1.38[21] −1.93[20]	−1.21[20]	−0.04[21]			−1.58[20]	−1.37[21] −2.15[20]
SEM (1.0 mg)		OR 5% 0.65[16]					−1.02[16] 1.51[22]	−0.45[22] −2.54[16]				−4.39[16]		−4.27[16]	
LIR (nr)									−1.34[21] −1.17[20]	−0.44[20]	0.5[10] 0.0[21] 0.3[15]			0.81 [20]	−1.33[21] −1.38[20]
LIR (3.0 mg)		OR 5% 0.45[16]			OR 5% 0.69[16]			−1.96[22] −1.51[16]				−3.38[16]		−3.25[16]	
LIR (1.8 mg)		OR 5% 0.35[16]			OR 5% 0.54[16]		OR 5% 0.78[16]					−1.86[16]		−1.74[16]	
EXE (LA)										0.72[20]	−1.34[21]			0.36[20]	−0.01[23] −0.21[20]
EXE (SA)														−0.37[20]	−0.94[20]
EXE (nr)						BMI −1.14[15]									−1.33[21]
EXE (10 µg)		OR 5% 0.19[16]			OR 5% 0.30[16]		OR 5% 0.43[16]	OR 5% 0.55[16]						0.11[16]	
DUL (nr)														−0.57[20]	
DUL (1.5 mg)															
LIX (nr)															

FIGURE 4 Summary of effects for active comparisons at mixed/combined time points. Top right of grid contains network estimates for absolute reduction in body mass (kg) for the comparison, and the reference of the review providing the network estimate(s). Bottom left of grid contains ORs for the odds of meeting 5% weight loss, or absolute reduction in BMI (kg/m^2), and the reference of the review providing the network estimate. Cell colour indicates which comparator is favoured: light blue cell, evidence is statistically significant in favour of the intervention (row labels); grey cell, no data; dark blue cell, evidence is statistically significant in favour of the comparator (column labels); light orange cell, evidence of no statistically significant difference between drugs being compared; dark orange cell, conflicting evidence for comparison. DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; nr, not reported or combined doses; OR, odds ratio; SA, short-acting; SC, subcutaneous; SEM, semaglutide; TIR, tirzepatide.

greater weight loss than liraglutide 3.0 mg at 12 months. This estimate came from a review that included 13 different doses of semaglutide in the data; thus this comparison does not clearly illustrate differences between the two drugs.[13]

Summary of non-prioritised reviews

Appendix 7 summarises the eight reviews that scored below 'moderate' on critical appraisal.[25–32] All included trials of patients with T2DM, with five specifically seeking them.[25,28,30–32] Data from one review compared tirzepatide and semaglutide 2.4 mg; the authors concluded that tirzepatide 10 and 15 mg were associated with greater weight loss at 52–72 weeks than semaglutide 2.4 mg, with similar safety profiles.[27]

Two reviews found that oral semaglutide (up to 14 mg) performed similarly to equivalent subcutaneous alternatives.[25,32] However, while Alhindi and colleagues found oral semaglutide to be non-inferior to semaglutide 1.0 mg,[32] contrasting with the evidence from prioritised reviews, others concluded that semaglutide 1.0 mg was superior to oral semaglutide 14 mg.[25]

Ida and colleagues observed that weight loss achieved with semaglutide was also associated with a decrease in fat-free mass.[30] Jiang and colleagues reported mixed effects for GLP-1 RAs versus placebo but did not include semaglutide or tirzepatide.[31] The findings of the remaining reviews were in agreement with the evidence from prioritised reviews, including further evidence of the effectiveness of semaglutide 2.4 mg [26,27,29] and tirzepatide 5, 10, 12 and 15 mg.[27,28]

Additional relevant randomised controlled trials

To assess whether there would be value in updating the NMA evidence, we searched for RCTs published since October 2022, comparing GLP-1 RAs of interest with one another or placebo, that were not already included in the prioritised systematic reviews. This exercise is described in *Appendix 8*.

We identified 11 trials not included in the prioritised reviews.[39–49] *Appendix 8*, *Table 7* displays the key characteristics of these 11 trials. Eight trials randomised fewer than 120 participants, and only one novel comparison was offered by the trials, with the study by Knop and colleagues evaluating oral semaglutide escalated to 50 mg.[45] Two-year data from the STEP-5 trial[41] of semaglutide 2.4 mg, and the SURMOUNT-2 trial of tirzepatide 5/10/15 mg in people with T2DM were notable discoveries. STEP-5 showed around 12.6% greater body weight reduction with semaglutide 2.4 mg than placebo at 104 weeks, with 77.1% versus 34.4% of patients achieving 5% weight loss.[41] The SURMOUNT-2 trial gave estimates at 72 weeks, with patients receiving 15 and 10 mg of tirzepatide found to have lost around 11.6 and 9.6% more weight than those allocated to placebo.[42]

Given the gaps in the evidence in existing NMAs, particularly the absence of a NMA, including both tirzepatide and semaglutide 2.4 mg, and the availability of new trials, albeit with limited novel, high-quality evidence or information power, an updated NMA may be of benefit.

Overview of findings relating to the safety of glucagon-like peptide 1 receptor agonists

The following section provides an overview of NMAs of safety outcomes for liraglutide, semaglutide and tirzepatide. Comparisons with placebo are prioritised, supplemented with information from interdrug comparisons where available. We focus on serious adverse events (SAEs), any AE, total AEs and discontinuation due to AEs. *Appendix 9* provides a detailed description of findings, with all network estimates and CIs provided in *Report Supplementary Material 1*, *Table 3*. Nine of the 14 prioritised reviews conducted safety NMAs.[10,12,13,16,17,20,22–24] None of these reviews provide a definition for AE or SAE. A standard definition for AEs and SAEs is available from the European Medicines Agency.[50]

Table 5 displays the risks/odds of patients experiencing SAEs, AEs and discontinuation compared with placebo/standard care/lifestyle modifications only. *Appendix 9*, *Table 8* provides an overview of the risks/odds of SAEs, AEs, total AEs and discontinuation due to AEs between interventions, with ORs/RRs and CIs provided for statistically significant findings.

Liraglutide

Across eight comparisons with placebo, liraglutide was associated with similar risk of SAEs across all doses, except at 3.0 mg, where Xie and colleagues found an increased risk of SAEs with liraglutide 3.0 mg (OR 1.47, 95% CI 1.07 to 2.02),[22] but Ma and colleagues found no increased risk.[16] For total AEs, liraglutide 3.0 mg was linked with an increased risk (OR 2.35, 95% CI 1.82 to 3.02),[22] and it was further associated with 2.4 and 2.9 times increased risk of discontinuation in two reviews.[13,16] The risk was greater when the same dose was compared to standard care (OR 5.68, 95% CI 1.64 to 19.63),[13] albeit wide CIs suggest ambiguity. The composite variable of combined doses of liraglutide was associated with 3.8 times greater risk of discontinuation compared to placebo,[10] and 2.45 times greater risk compared to lifestyle modifications alone.[24]

TABLE 5 Risks of AEs for GLP-1 RAs compared to placebo/standard care/lifestyle modifications only

	SAEs	Any AEs	Total AEs	Discontinuation due to AEs
Liraglutide (combined doses)				OR: 3.80[10] OR: 2.45[24]
Liraglutide 1.2 mg				
Liraglutide 1.8 mg				OR: 2.48[16] RR: 1.70[23]
Liraglutide 3.0 mg	OR: 1.47;[22] similar risk[16]		OR: 2.35[22]	OR: 2.43; OR: 5.68 (St.c);[13] OR: 2.88[16]
Subcutaneous semaglutide (combined doses)				OR: 1.95; OR: 4.55 (St.c);[13] OR: 1.98 (LMA)[24]
Subcutaneous semaglutide 0.5 mg (QW)				RR: 1.74 (52 weeks)[23]
Subcutaneous semaglutide 1.0 mg (QW)			OR: 1.82[22]	RR: 2.25 (52 weeks);[23] similar risk[16]
Subcutaneous semaglutide 2.4 mg	OR: 1.42;[22] similar risk[16]		OR: 2.36[22]	OR: 1.88[16]
Oral semaglutide 3 mg (OD)				
Oral semaglutide 7 mg (OD)				
Oral semaglutide 14 mg (OD)		RR: 1.79 (30–40 weeks); RR: 1.14 (52 weeks)[23]		RR: 3.07 (26 weeks); RR: 1.90 (52 weeks)[23]
Oral semaglutide 40 mg				
Tirzepatide 5 mg	RR: 3.16 (30–40 weeks)[23]			RR: 5.93 (30–40 weeks)[23]
Tirzepatide 10 mg		RR: 1.21(30–40 weeks)[23]		RR: 8.48 (30–40 weeks)[23]
Tirzepatide 15 mg	RR: 2.59 (30–40 weeks)[23]	RR: 1.22 (30–40 weeks)[23]		RR: 8.47 (30–40 weeks)[23]

LMA, lifestyle modification alone; OD, once daily; QW, once weekly; St.c, standard care.

Note
Light blue cell indicates intervention is no more harmful than placebo/standard care; red cell indicates intervention more harmful than placebo/standard care; orange cell indicates conflicting results between reviews; dark blue cell indicates no data available. RR/OR are intervention compared to placebo unless otherwise stated.

There were no associated increased risks of AEs, total AEs, SAEs or discontinuations due to AEs when reported doses of liraglutide (1.2, 1.8, 3.0 mg and combined doses) were compared with any other intervention (see *Appendix 9*).

Semaglutide

Across 13 comparisons of semaglutide versus placebo, the risk of SAEs was similar, except where subcutaneous semaglutide 2.4 mg was associated with a higher risk of SAEs (OR 1.42, 95% CI 1.01 to 1.97),[16] although risks were reported to be similar for the same comparison in another review.[22] For AEs, oral semaglutide 14 mg was associated with a small increased risk of AEs compared to placebo at 52 weeks (RR 1.14, 95% CI 1.05 to 1.24).[23] Total AEs were likely to be greater with semaglutide 1.0 and 2.4 mg than placebo, with no data available for other doses. When compared with other drugs, risk of greater total AEs was similar for all comparisons (see *Appendix 9*).

Discontinuation was between 1.7 and 4.55 times more likely with all doses of semaglutide than with placebo/standard care/lifestyle modifications alone, except for oral doses of 3.0 and 7 mg, which were of similar risk to placebo.

Tirzepatide

All NMA data relating to SAEs and AEs involving tirzepatide came from one review.[23] Tirzepatide 5, 10 and 15 mg were compared to placebo, oral semaglutide 14 mg, semaglutide 0.5 and 1.0 mg and liraglutide 1.2 mg at 30–40 weeks.[23]

Compared with placebo, the odds of experiencing SAEs and AEs were greater at 15 mg, SAEs were more likely with 5 mg but not 10 mg, and the reverse was true for AEs. Discontinuation was 6–8.5 times more likely with any dose of tirzepatide. Wide CIs for all outcomes suggest uncertainty, with data coming from a single trial.[35] When compared with active comparators, there was an inconclusive mix of outcomes both in favour of tirzepatide, or comparators (see *Appendix 9*).

All-cause mortality/death

All-cause mortality was lower with GLP-1 RAs when compared with placebo (one comparison; OR 0.88, 95% CI 0.83 to 0.94)[17] and standard treatment (two comparisons: mean OR 0.81, 95% CI 0.69 to 0.95).[17,20] Risks were similar for semaglutide (a variety of doses combined into one variable, referred to hereafter as 'combined doses'), liraglutide 3.0 mg and placebo,[13] and for tirzepatide (combined doses) compared with standard treatment and GLP-1 RAs.[20] Similar risks were found with semaglutide 0.5, 0.75, 1.0 mg, dulaglutide 1.5 mg and tirzepatide 5, 10 and 15 mg after 30–40 weeks and semaglutide 0.5 and 1.0 mg after 52 weeks.[23]

Discussion

This scoping review provides the first overview of either effectiveness or safety NMAs for GLP-1 RAs and the dual GLP-1 RA/GIP agonist tirzepatide that have been approved for use in the UK. We focused on the effectiveness of these drugs for weight loss, as well as safety outcomes, with an emphasis on the two drugs currently approved for weight loss in the UK (semaglutide and liraglutide), and one that is under consideration by NICE (tirzepatide).

Summary of findings

We identified 22 systematic reviews with NMAs that included GLP-1 RAs of interest, with comparators including placebo/usual care or other GLP-1 RAs of interest and were published in 2020 or later. Of these, 14 were deemed of sufficient quality to be fully examined. Weight loss was most frequently reported in terms of absolute change in mass from baseline (kg) at 6 months, 12 months, beyond 12 months, and at a range of time points. Nine of the 14 prioritised reviews also conducted NMAs of safety outcomes, including AEs, SAEs, discontinuation and mortality. A brief update exercise identified 13 new relevant NMAs published in the 15 months since the original search.

Summary of effectiveness for weight loss

Compared with placebo or usual care, all GLP-1 RAs were associated with statistically significant increased weight loss at a minimum of one time point. Most data were for 23–72 weeks, with much of it included in aggregated estimates. Longer-term follow-up data were limited, particularly in a disaggregated form.

The greatest weight loss was seen with semaglutide 2.4 mg, and tirzepatide 10 and 15 mg, which were associated with between 11.2 and 12.5 kg of weight loss compared to placebo. In general, semaglutide 1.0 mg was the next most effective dose, but weight loss was in the region of 7.5 kg at 6 months, reducing to 4 kg beyond 12 months. Liraglutide 3.0 mg was associated with similar weight loss to semaglutide 0.5 and 1.0 mg at 12 months and beyond.

For tirzepatide, the largest effects were seen at 6 months, but only one trial provided data for the drug in this NMA. In total, eight trials were available for tirzepatide across the prioritised reviews, with the SURPASS trials dominating the evidence.[33–38] One prioritised review included seven of these trials[20] but amalgamated data for doses (5, 10, 12, 15 mg) and time points (covering 6–13 months), so their network estimate of 8.5 kg weight loss did not provide insight on the relative effectiveness of the available doses, or at time points of interest. The data for 6 months indicate increasing effectiveness as the dose increased from 5 to 15 mg.

None of the prioritised reviews included both tirzepatide and semaglutide 2.4 mg in a NMA. The relative performance of semaglutide 2.4 and tirzepatide versus semaglutide 1.0 mg indicates that semaglutide 2.4 mg may be associated with the greater weight loss. One non-prioritised review compared these drugs, concluding that tirzepatide was more effective than semaglutide 2.4 mg at both the 10 and 15 mg doses.[27] That review was not prioritised because it did not have a protocol or comprehensive search strategy. Only seven trials were included in the NMA, and the network estimates came from indirect comparisons between tirzepatide and semaglutide 2.4 mg; therefore the evidence regarding the superiority of these drugs versus each other remains inconclusive.[27]

Two reviews from the update search included indirect comparisons of tirzepatide and semaglutide 2.4 mg.[22,51] This incorporated data from 3 trials not included in the

14 prioritised reviews,[52–54] and found that tirzepatide was associated with greater weight loss at 15 mg, but there was no difference at 5 or 10 mg. Again, network estimates came from merging a range of time points.

Summary of safety evidence

It was not the purpose of this review to exhaustively capture all data regarding the safety of GLP-1 RAs, but we reported on NMAs of safety outcomes presented in the prioritised reviews. The drugs associated with the greatest weight loss, tirzepatide and semaglutide 2.4 mg, were generally associated with increased risk of safety issues compared to placebo. Evidence for semaglutide 2.4 mg was mixed with respect to SAEs, but patients were more than twice as likely to experience AEs and nearly twice as likely to discontinue treatment than those receiving placebo. For all doses of tirzepatide, patients were 6–8.5 times more likely to discontinue treatment than those receiving placebo, and the risk of experiencing SAEs was over 3 times greater with the 5 mg dose, and 2.5 times greater at 15 mg. Despite these concerns, data came from a single trial, with wide CIs for all outcomes indicating uncertainty.

Other doses of semaglutide were associated with some increased risk of discontinuation, but not of SAEs. Liraglutide was similar to placebo in terms of risk of SAEs and AEs, but discontinuation was more likely with 1.8 and 3.0 mg. No drugs were associated with increased risk of early death, and when GLP-1 RAs were combined, the risk of all-cause mortality/death was reduced by 12–19%. There were dozens of comparisons for specific AEs, notable findings including increased risk of gastrointestinal AEs with GLP-1 RAs.

Evidence in context

To our knowledge, this is the first review of NMAs of GLP-1 RAs. We aimed to capture the relative effectiveness of drugs licenced for use in the UK, or anticipated to be licensed, with respect to weight loss management. The evidence presented regarding weight loss is in general agreement with the wider literature, as is expected when capturing that provided by systematic reviews. However, data on tirzepatide were not as resounding as reported in some meta-analyses, partly due to the nature of the NMAs included herein: an estimate of effectiveness at 6 months came from only one trial, while the estimate informed by seven trials combined all doses. Recent systematic reviews with pairwise meta-analyses have suggested weight loss of between 8.4 and over 12.5 kg versus placebo, with a dose-related response.[55–58] The most recent tirzepatide trial, from SURMOUNT-2, saw tirzepatide associated with up to 11.5% greater weight loss than placebo.[42]

Safety outcomes were not required for inclusion in this review, and more comprehensive reviews of safety have been conducted. Recent NMAs of safety outcomes highlight the benefits of GLP-1 RAs for reducing risk of all-cause mortality and cardiovascular safety outcomes, with semaglutide performing particularly well.[59,60] Tirzepatide has been shown to have a similar safety profile as semaglutide[55] and to not increase the risk of major cardiovascular events in participants with T2DM versus controls in the SURPASS trials.[61] Data in our review suggest that there was an increased risk of discontinuations, SAEs and AEs with tirzepatide, compared to placebo, albeit with uncertainty over the magnitude of effects. Further evidence may be required to develop a clear picture of the safety of GLP-1 RAs and dual GIP/GLP-1 RAs, particularly where trials include patients with comorbidities.

The 13 NMAs captured by our update search provided some novel comparisons, including indirect comparisons of tirzepatide and semaglutide 2.4 mg, and network estimates for oral doses of semaglutide.

Future research

Head-to-head trials of tirzepatide versus semaglutide 2.4 mg are required to determine their relative effectiveness and safety, as the two most promising options for weight loss. This applies for emerging treatments. Trials with longer-term follow-ups are required to establish the effectiveness and safety of GLP-1 RAs when taken for durations of > 72 weeks, where the coverage of trials in this review drops off significantly. Future NMAs should consider disaggregating data for both multiple doses of a drug, and data from a wide range of time points. Trials are emerging, which consider larger doses of oral semaglutide as an alternative to subcutaneous doses,[45] which may naturally represent the next step into wider treatment acceptability for this category of weight loss drug. It may be of benefit to conduct a NMA, including trials evaluating tirzepatide, semaglutide 2.4 mg and liraglutide 3.0 mg; however, the rate of publication of de novo NMAs at a rate exceeding the availability of new trial data will only further clutter the field, and a living NMA approach may be more appropriate.

Limitations

Systematic reviews with NMAs are considered among the highest levels of evidence, but scrutiny of the NMAs included in this scoping review reveals several limitations. It was often unclear which trials were

included in each NMA, or how many informed direct comparisons. The tendency to combine both multiple doses of drugs, and outcomes at different time points, restricts understanding. Evaluation with ISPOR highlighted several technical limitations at the NMA level, including frequent inclusion of studies at high risk of bias (without sensitivity analysis or accounting for potential bias) and failure to account for heterogeneity in treatment effect modifiers.

It was beyond the scope of this review to provide comprehensive evaluations of the safety profiles of included drugs, or to consider other outcomes which may be of value to evidence users. It was beyond the scope of this review, and a limitation of NMAs that we reviewed, to examine the nature of, or variations in, standard care or diet and exercise regimes prescribed alongside drug interventions, which may influence weight loss or treatment acceptability.

The majority of trials of GLP-1 RAs (and two of the prioritised reviews) were privately sponsored, and there may be conflicts of interest associated with this. It was fervently noted by PERSPEX, our patient and public involvement and engagement (PPIE) group, that the role of industry sponsorship should be considered, particularly with respect to the possible diversion of funds and focus from societal/public health interventions to drug-based interventions. We acknowledge the need to consider commercial determinants of health in this field, and the potential implications for bias.[62]

Conclusions

Key learning points

Semaglutide, liraglutide and tirzepatide appear to be effective drugs for weight loss. Tirzepatide 10 and 15 mg, and semaglutide 2.4 mg are associated with the greatest effects and appear to have similar safety profiles. More evidence is needed comparing semaglutide 2.4 mg with tirzepatide, and to explore longer-term safety and effectiveness. Despite an abundance of recent NMAs, findings are inconsistent, particularly for safety outcomes, and the methodological rigour of future NMAs could be improved.

What this adds to existing knowledge

This scoping review provides necessary clarity about the state of evidence in the field, including a critique of NMAs. We identify areas of overlap and gaps in the data, and provide direction for future research.

Additional information

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Ethics statement

No ethical approval was required for this project, which exclusively involved secondary analysis of data.

Information governance statement

During the conduct of this report, we were not required to handle any personal information.

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Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/SKHT8119

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Glossary

Adverse event Any unfavourable or unintended symptom, medical occurrence or sign temporarily associated with the use of a medicinal product.

Body mass index A measure to help decide if adults are a healthy weight or underweight, overweight or obese. It is defined as weight in kilograms divided by the square of height in metres (kg/m^2).

Confidence interval A measure of the uncertainty around the main finding of a statistical analysis. Wider intervals indicate lower precision, and narrow intervals indicate greater precision.

Glucose-dependent insulinotropic polypeptide One of the incretin hormones secreted by the gut after food intake.

Glucagon-like peptide 1 receptor agonists A family of medication, also known as glucagon-like peptide 1 analogues. These drugs increase hormones called 'incretins', which help the body make more insulin, reduce the amount of sugar the liver produces and slow digestion speed. They also reduce appetite. Examples include semaglutide and liraglutide.

Glycated haemoglobin Indicates blood sugar levels over the last 1–2 months, and used as an indicator of diabetes control.

Meta-analysis A statistical technique for combining data from multiple independent studies. This enables

conclusions to be drawn when each individual data set is too small to provide reliable evidence.

Network estimate The pooled result of the direct and indirect evidence for a given comparison, or only the indirect evidence if no direct evidence is available.

Network meta-analysis A way of comparing many different treatments at the same time by using both direct and indirect evidence from studies that have tested them. Direct evidence comes from studies that have compared two treatments head to head. Indirect evidence comes from combining the results of studies that have compared different pairs of treatments. A network meta-analysis can give us more information and more precise estimates of the effects of each treatment than a single comparison. It can also help us rank the treatments according to how effective or safe they are. A network meta-analysis is more complex and requires more expertise and resources than a standard meta-analysis.

Obesity The term 'obese' describes a person who has excess body fat. Obesity is a serious health concern that increases the risk of many other health conditions, including type 2 diabetes, coronary heart disease, hypertension, stroke and depression. Obesity and overweight is caused when extra calories, particularly those from foods high in fat and sugar, are stored in the body as fat.

Overweight Having a body mass index above the healthy range. For people of white heritage, a body mass index:

- below 18.5 is underweight
- between 18.5 and 24.9 is healthy
- between 25 and 29.9 is overweight
- of 30 or over is obese.

Black, Asian and some other minority ethnic groups have a higher risk of developing some long-term conditions, such as type 2 diabetes with a lower body mass index. People from these groups with a body mass index of:

- 23 or more are at increased risk (overweight)
- 27.5 or more are at high risk (obese).

Odds ratio The ratio between the odds of exposure to a factor among people with a condition or disease (cases) and the odds of exposure to a factor among those who do not have the condition or disease (control group).

Placebo An inactive substance or procedure administered to a participant, usually to compare its effects with those of a real drug or other intervention, but sometimes for the psychological benefit of the belief of receiving treatment. Placebos are used in clinical trials to blind people to their treatment allocation. Placebos should be indistinguishable from the active intervention to ensure adequate blinding.

Randomised controlled trial A type of clinical trial where two or more groups of people are compared in a way that reduces bias. In a randomised controlled trial, one (or more) experimental group(s) receive a new treatment, and a control group, receives the current standard treatment (or no treatment or a placebo). Randomisation is the best way of ensuring that the results of trials are not biased by the way participants in each group are selected. Randomised controlled trials are considered the 'gold standard' in research design for demonstrating a cause-and-effect relationship between an intervention and an outcome.

Serious adverse event Any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/ incapacity, or
- is a congenital anomaly/birth defect.

Systematic review A process that addresses a specific research question. It involves searching for and collating all the existing primary research on a topic that meets certain criteria; the research is then assessed using stringent guidelines, to establish whether there is conclusive evidence about a specific treatment or intervention. Systematic reviews are an important source of evidence for clinicians, researchers, consumers and policy-makers.

List of abbreviations

AE	adverse event
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
BMI	body mass index
GIP	glucose-dependent insulinotropic polypeptide
GLP-1 RA	glucagon-like peptide 1 receptor agonist
HbA1c	glycated haemoglobin

ISPOR	International Society of Pharmacoeconomics and Outcomes Research
NAFLD	non-alcoholic fatty liver disease
NASH	non-alcoholic steatohepatitis
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMA	network meta-analysis
PCOS	polycystic ovary syndrome
PICO	population, intervention, control/comparison, outcome
PPIE	patient and public involvement and engagement
PROGRESS-Plus	Place of residence, Race/ethnicity/culture/language, Occupation, Gender or sex, Religion, Education, Socioeconomic status, Social capital-Plus
RCT	randomised controlled trial
SAE	serious adverse event
SGLT-2i	sodium-glucose cotransporter-2 inhibitors
T2DM	type 2 diabetes mellitus

List of supplementary material

Report Supplementary Material 1 Supplementary material

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/SKHT8119).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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Appendix 1

MEDLINE search strategy
Database: MEDLINE(R)
Host: Ovid
Issue: 1946 to 1 June 2023
Date searched 6 June 2023

Search strategy:

1 network metaanalys*.tw.
2 network meta-analysis/
3 network meta analys*.tw.
4 nma.tw.
5 1 or 2 or 3 or 4
6 Semaglutide*.tw.
7 Ozempic*.tw.
8 Rybelsus*.tw.
9 Wegovy*.tw.
10 Liraglutide*.tw.
11 Victoza*.tw.
12 Saxenda*.tw.
13 Tirzepatide*.tw.
14 Mounjaro*.tw.
15 Exenatide*.tw.
16 Byetta*.tw.
17 Dulaglutide*.tw.
18 Trulicity*.tw.
19 Lixisenatide*.tw.
20 Lyxumia*.tw.
21 or/6-20
22 glucagon like peptid* one.tw.
23 "glucagon like peptid* 1".tw.
24 *glucagon-like peptides/ or exp glucagon-like peptide 1/
25 glp-1*.tw.
26 21 or 22 or 23 or 24 or 25
27 5 and 26

DOI: 10.3310/SKHT8119

Appendix 2 Table of network meta-analysis characteristics

First author, year	Review funding	Review aims	Primary outcome	PICO inclusion criteria				Search date (mm/yy)	AMSTAR-2 rating
				Participants	Intervention	Comparator	Outcome		
Alhindi, 2022[32]	NR	Efficacy and safety of oral semaglutide compared to that of subcutaneous semaglutide, placebo, and other GLP-1 RAs in the treatment of T2DM	Change in HbA1c	Adults with T2DM	Once weekly subcutaneous semaglutide or oral semaglutide	Placebo or another GLP-1 RA comparator [liraglutide (1.2 mg), exenatide ER (2.0 mg) and dulaglutide (1.5 mg)]	CFB HbA1c, body weight, AEs, hypoglycaemic events	02/21	Critically low
Alkhezi, 2023[27]	King Saud University	Compare the efficacy and safety of all GLP-1 RAs, including tirzepatide, in adult patients with overweight or obesity without diabetes	Weight loss	Obesity without diabetes BMI ≥ 30 kg/m^2 or, alternatively, BMI ≥ 27 kg/m^2 with comorbidity	GLP-1 RA	GLP-1 RA or placebo	NR	06/22	Low
Alsugair, 2021[11]	No external funding	Compare the long-term efficacy of semaglutide and liraglutide.	HbA1c, body weight	Adults with T2DM and duration of ≥ 52 weeks on intervention	Once-weekly semaglutide (0.5 or 1.0 mg) and liraglutide (1.2 or 1.8 mg)	Active intervention or placebo	Any or all of the following: HbA1c level, FPG level, SBP, DBP, heart rate, lipid profile and weight changes from baselines	06/19	Moderate
Avgerinos, 2021[10]	NR	To assess the efficacy and safety of glucose-lowering drugs used as an adjunct to insulin therapy in adults with type 1 diabetes.	HbA1c	Adults with T1DM	RCTs with parallel or cross-over design and with a treatment duration of at least 4 weeks that evaluated any glucose-lowering agent as an adjunct to insulin therapy	Comparisons between glucose-lowering drugs or against placebo	NR	01/20	Moderate

First author, year	Review funding	Review aims	Primary outcome	PICO inclusion criteria				Search date (mm/yy)	AMSTAR-2 rating
				Participants	Intervention	Comparator	Outcome		
Chubb, 2021[25]	Novo Nordisk	Assess the relative efficacy and safety of once-daily oral semaglutide (7 and 14 mg) compared with injectable GLP-1 RAs as an add-on to insulin therapy in people with T2DM inadequately controlled on basal insulin.	Change in HbA1c, weight and blood pressure	People with T2DM inadequately controlled on basal insulin	Once daily oral semaglutide 7 and 14 mg	All licensed doses of injectable GLP-1 RAs approved for treatment in T2DM: exenatide (BID), liraglutide (once daily), lixisenatide once daily, dulaglutide once weekly	Subjects achieving HbA1c < 7%, ≤ 6.5%, proportion achieving a composite end point (HbA1c < 7%, no weight gain and no hypoglycaemia), incidence of nausea, vomiting and diarrhoea	07/19	Critically low
Guan, 2022[28]	National Natural Science Funds of China MHHFDU-SPFDU Joint Research Fund	Systematically estimate the efficacy and safety of tirzepatide to provide basis for its future use	HbA1c, body weight and FBG	Individuals with T2DM	Tirzepatide 5, 10, 12 mg	Placebo or therapeutic interventions	Blood glucose parameters or body weight, and safety	05/22	Low
Hussein, 2020[12]	NR	Investigate the efficacy and tolerability profiles between and within GLP-1 RAs and SGLT-2i in adults with type 2 diabetes	HbA1c	Adults with T2DM	Long-acting GLP-1 RAs (albiglutide, dulaglutide, exenatide once weekly, liraglutide, semaglutide and taspoglutide), short-acting GLP-1 RAs (exenatide BID and lixisenatide) and SGLT-2i (canagliflozin, dapagliflozin, empagliflozin and ertugliflozin)	Compared interventions with each other at international guideline-recommended doses, or with placebo/standard care	CFB in HbA1c. Reported follow-up data at 24 (± 8) and/or 52 (± 8) weeks	04/19	Moderate
Iannone, 2023[13]	None	Compare benefits and harms of drugs for weight loss in obese or overweight adults	Cardiovascular death	Adults with obesity (BMI ≥ 30 kg/m^2) or overweight (BMI 25–29.9 kg/m^2)	Orlistat, liraglutide (3 mg daily only), semaglutide, phentermine/topiramate, naltrexone/bupropion and lorcaserin. Only drugs specifically approved for the treatment of obesity.	Comparisons of the drugs of interest against each other, placebo, or standard management	Cardiovascular death	02/23	Moderate

continued

This article should be referenced as follows: Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

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First author, year	Review funding	Review aims	Primary outcome	PICO inclusion criteria				Search date (mm/yy)	AMSTAR-2 rating
				Participants	Intervention	Comparator	Outcome		
Ida, 2021[30]	None	Comparatively examine the effects of GLP-1 RAs and oral antidiabetic drugs, including SGLT-2i and metformin on muscle mass and body weight in patients with T2DM	Muscle weight and body	Patients with T2DM (excluding gestational diabetes)	GLP-1 RAs with or without diet and exercise	Placebo/conventional treatment	Body weight and muscle weight	01/20	Low
Jiang, 2021[31]	None	Examine whether GLP-1 RAs have differential efficacy and safety profiles	Change in HbA1c	Individuals with T2DM	GLP-1 RAs	Other GLP-1 RAs or control (placebo or no treatment) with or without the same add on therapy	At least one of: CFB HbA1c, proportions of patients achieving HbA1c < 7% and < 6.5%; changes in FPG, PPG2h, body weight, SBP, DBP, TC, HDL, LDL, TG; hypoglycaemia, severe hypoglycaemia, and any AE	06/19	Low
Lautsch, 2021[14]	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA	Evaluate the comparative efficacy of single and dual initiated approved oral doses of SGLT-2i, DPP4 inhibitors, and GLP-1 receptor agonists (all in combination with metformin) at 24–26 weeks in adult T2DM patients uncontrolled on metformin	Efficacy outcomes including change in weight from baseline	Adults with T2DM and uncontrolled HbA1c (7%) while on metformin	Approved oral doses of SGLT-2i, DPP4 inhibitors, and GLP-1 agonists, as single or dual initiation therapies adjunctive to metformin	Placebo	CFB in HbA1c, weight, SBP, DBP, proportion of patients achieving HbA1c 7% at 24–46 weeks of follow-up	11/19	Moderate
Lian,2021[15]	Funded by National Natural Science Foundation of China	Evaluate the therapeutic effects of various hypoglycaemic agents that have been approved for the treatment for NAFLD patients with or without diabetes	ALT, AST, and triglyceride levels	Adults between 18–70 years with NAFLD with or with diabetes	Hypoglycaemic agents in the treatment of NAFLD	Other hypoglycaemic agents or placebo	NR	09/20	Moderate

First author, year	Review funding	Review aims	Primary outcome	PICO inclusion criteria				Search date (mm/yy)	AMSTAR-2 rating
				Participants	Intervention	Comparator	Outcome		
Ma, 2023[16]	Natural Science Foundation of Fujian Province, China	Estimate the difference of the efficacy and safety between and within GLP-1 RAs and SGLT-2i treatments in obesity patients with or without diabetes	Change in body weight, glucose levels and blood pressure	Overweight (BMI ≥ 25 kg/m^2, Asian ≥ 23 kg/m^2) or obese adults (BMI ≥ 30 kg/m^2)	Long and short-acting GLP-1 RAs and SGLT-2i	Placebo or other GLP-1 RAs or SGLT-2i	Changes in body weight, proportion or patients reaching at least 5% weight loss, HbA1c, FPG, SBP, DBP, SAEs and discontinuation due to AEs	01/22	Moderate
Palmer, 2021[17]	None	Evaluate SGLT-2i and GLP-1 RAs in patients with T2DM at varying cardiovascular and renal risk	All cause and cardiovascular mortality	Adults with T2DM	SGLT-2i or GLP-1 RAs. Either as monotherapy or added to non-randomised background glucose-lowering management and other treatments	Other SGLT-2i or GLP-1 RAs, other glucose-lowering treatments, placebo, or standard care	All-cause mortality, cardiovascular mortality. Outcomes at 24 weeks or longer	08/20	Moderate
Park, 2023[18]	Supported by a National Research Foundation of Korea grant funded by the Korean government	Compare the effects of GLP-1 RAs and TZD on NAFLD or NASH	Liver biopsy-based outcomes: NAS, fibrosis stage and NASH resolution	Adults with NAFLD or NASH detected by biopsy or other imaging methods	TZD or GLP-1 RAs for at least 3 months	Active control (TZD or GLP-1 RA) or placebo	Liver biopsy-based, non-invasive technique-based, biological or anthropometric parameters as outcomes	07/21	Moderate
Shi, 2022[24]	Project for Disciplines of Excellence, West China Hospital, Sichuan University	Assess the weight-lowering effects and safety of drugs, provided in addition to lifestyle modification, for the management of body weight	Percentage body weight CFB to end of follow-up, proportion patients reducing body weight by 5% or >, AEs leading to discontinuation, weight regain after discontinuation, change in QoL score	Overweight or obese adults	Lifestyle modification and a candidate weight-lowering drug	Lifestyle modification alone with or without placebo or an alternative active drug	Absolute or percentage weight CFB or pre-treatment and post-treatment absolute body weight or any type of QoL score; and had a treatment duration of 12 weeks or more	03/21	Moderate

continued

This article should be referenced as follows: Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

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First author, year	Review funding	Review aims	Primary outcome	PICO inclusion criteria				Search date (mm/yy)	AMSTAR-2 rating
				Participants	Intervention	Comparator	Outcome		
Shi, 2023[20]	Supported by Sichuan Science and Technology Programme and Clinical Research Incubation Project	Compare benefits and harms of adding nsMRAs (including finerenone) and tirzepatide to previously existing treatment options	Cardiovascular and kidney outcomes	Adults with T2DM	Any of the following drug classes: SGLT-2i, GLP-1 RAs, DPP4, TZD, sulfonylureas, metformin, α-glucosidase inhibitors, meglitinides, insulins, dual GIP/GLP-1 receptor agonists, and nsMRAs	Standard treatment	NR	10/22	Moderate
Smith, 2022[26]	Novo Nordisk	Compared RCT evidence for weekly semaglutide 2.4 mg with that of relevant pharmacological comparators for weight management in people who have overweight or obesity	Weight CFB % at 52 weeks, proportion losing ≥ 5% baseline fasting body weight at 12 weeks at full therapeutic dose	Adults overweight and obese – BMI ≥ 27 kg/m^2 and one weight-related comorbidity; BMI ≥ 30 kg/m^2 (with weight-related comorbidities); BMI ≥ 30 kg/m^2 (without weight-related comorbidities)	Weekly 2.4 mg semaglutide	To include pharmacological agents, surgical intervention, and diet, liraglutide 3 mg (daily), placebo, diet and exercise	Proportion of subjects losing at least 5, 10 and 15% of baseline fasting body weight, CFB weight change in kg, CFB weight change in %, CFB SBP, CFB total cholesterol, CFB HDL, CFB HbA1c in %, incidence of patients reverting from prediabetes to normal glucose tolerance, incidence of patients reducing antihypertensive treatment, incidence of patients reducing glucose-lowering drugs, CFB waist circumference, incidence of hypoglycaemia, incidence of SAEs, discontinuations due to AEs	09/20	Low
Tsapas, 2021[21]	European Foundation for the Study of Diabetes: PACT Programme supported by an unrestricted educational grant from AstraZeneca	Compare the effects of glucose-lowering drugs on body weight and blood pressure in people with T2DM	Body weight and blood pressure	Adults with T2DM	Glucose-lowering medications that have been approved or have applied for authorisation for treating T2DM in Europe or US with or without background therapy (metformin alone or metformin plus other antidiabetic medication)	Control/placebo	Body weight, SBP, DBP	09/20	Moderate

First author, year	Review funding	Review aims	Primary outcome	PICO inclusion criteria				Search date (mm/yy)	AMSTAR-2 rating
				Participants	Intervention	Comparator	Outcome		
Vosoughi, 2021[29]	There was no funding used to conduct this study other than support of research time for the PI's research program on a GLP-1 agent in obesity from NIH R01-DK67071	Compare the associations of each GLP-1 agonist or analogue with weight loss and adverse effects	Weight loss and adverse effects, in particular discontinuation due to adverse effects	Adults with obesity or overweight (BMI) > 25 kg/m^2 in white, Hispanic, and black individuals, and BMI> 23 kg/m^2 in Asian populations. Patients with or without diabetes mellitus or NAFLD	GLP-1 agonist or analogue drug	Placebo	NR	10/21	Low
Xie, 2022[22]	Supported by the National Key Specialty Construction Project (Clinical Pharmacy) and the High-level Clinical Key Specialty of Guangdong Province, funders were the central finance subsidy fund for the improvement of medical services and guarantee capacity	The effect and safety of subcutaneous injection of semaglutide and liraglutide on weight loss in people with obesity or overweight	Weight loss	Adults with BMI ≥ 25 kg/m^2 with or without type 2 diabetes	Subcutaneous injection of liraglutide and semaglutide	Placebo, other GLP-1 RAs or other hypoglycaemic drugs (i.e. sitagliptin, glimepiride)	Body weight, HbA1c, total number of AEs, SAEs and hypoglycaemic events	04/22	Moderate

continued

This article should be referenced as follows:
Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;30(63):429–502. https://doi.org/10.3310/SKHT8119

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First author, year	Review funding	Review aims	Primary outcome	PICO inclusion criteria				Search date (mm/yy)	AMSTAR-2 rating
				Participants	Intervention	Comparator	Outcome		
Zaazouee, 2022[23]	None	To assess the safety and efficacy of semaglutide compared with placebo and other AHAs in T2DM	HbA1c	Patients with T2DM	Semaglutide	Other AHAs or placebo	HbA1c, FBG, SMPG, body weight, % HbA1c < 7%, any AEs, SAEs, hypoglycaemia, any GI AEs, nausea, vomiting, dyspepsia, diarrhoea, constipation, discontinuation, and death	12/20	Moderate

Unless otherwise stated, 'adults' is defined as 18 years old and above. AHA, antihyperglycaemic agent; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CFB, change from baseline; DBP, diastolic blood pressure; DPP4, dipeptidyl peptidase-4 inhibitor; ER, extended release; FBG, fasting blood glucose; FPG, fasting plasma glucose; GI, gastrointestinal; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NAS, NAFLD activity score; NR, not reported; nsMRAs, non-steroidal mineralocorticoid receptor agonists; PI, principal investigator; PPG2h, postprandial plasma glucose at 2 hours; QoL, quality of life; SBP, systolic blood pressure; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; SMPG, self-measured plasma glucose; T1DM, type 1 diabetes mellitus; TC, total cholesterol; TG, triglycerides; TZD, thiazolidinedione.

Appendix 3 Sample characteristics

First author, year	Sample characteristics							
	Trials in BW NMA/total included trials (*n*/*N*)*	Participants in BW NMA/overall sample size (*n*/*N*)*	For overall sample or * if calculated for BW NMA (** if BW NMA was whole sample)					
			BMI (kg/m²)	Age (years)	% female	Comorbidities	Drugs and doses of interest	Safety outcomes
Alsugair, 2021[11]	8/9	9115/9618	32.6 (6.1)*	57.3 (9.8)*	43.8*	T2DM	Semaglutide (0.5, 1.0 mg) (QW); liraglutide (1.2, 1.8, 3.0 mg) (OD); exenatide 2.0 mg	nr
Avgerinos, 2021[10]	nr/58	nr/13,216	27.0 (2.5)	41.1 (6.3)	45.0	Mean duration of T1DM 18.3 (6.3)	Exenatide daily (doses nr); liraglutide (doses nr)	Incidence of SAEs, discontinuation due to AEs, diabetic ketoacidosis, severe hypoglycaemia, nausea and genital infections

First author, year	Sample characteristics					Comorbidities	Drugs and doses of interest	Safety outcomes
	Trials in BW NMA/total included trials (*n*/*N*)*	Participants in BW NMA/ overall sample size (*n*/*N*)*	For overall sample or * if calculated for BW NMA (** if BW NMA was whole sample)					
			BMI (kg/m²)	Age (years)	% female			
Hussein, 2020[12]	nr/64	nr/31,384	32.6 (range 28.16–41.16)	55 (range 52–63)	nr	T2DM	Semaglutide (doses nr); liraglutide (doses nr); exenatide (short-acting) (BID); exenatide (long-acting) (QW); dulaglutide (doses nr)	Hypoglycaemic events, urinary tract infections, genital infections, diarrhoea (24 and 52 weeks), nausea, vomiting, injection site reactions, abdominal pain, bone fractures, pancreatitis and cancer events (24 weeks only)
Iannone, 2023[13]	33/168	nr/97,938	35.8 (median)	46.9 (median)	74.5 (median)	43 (25.6%) trials included people with diabetes; 41 (24.4%) patients with hypertension	Semaglutide (doses nr); Liraglutide 3.0 mg daily	Cardiovascular mortality, all-cause death, non-fatal stroke, non-fatal myocardial infarction, treatment withdrawals due to AEs, serious GI AEs
Lautsch, 2021[14]	22/25	12,488/13,975	25.5*	55.6*	46.1*	T2DM	Oral semaglutide (OD) 14 mg	nr
Lian, 2021[15]	26/26	1812/1812	30.4**	51.2**	79.9**	nr	Liraglutide (dose nr); exenatide (dose nr)	nr
Ma, 2023[16]	56/61	nr/17,281	33.6 (median) (range 27.3–40.1)	54.1 (median) (range 24–68)	nr	Mean duration of diabetes 8.72 (4.93) years	Semaglutide 1.0, 2.4 mg; liraglutide 1.8, 3.0 mg; dulaglutide 1.5 mg; exenatide 10 µg	SAE, discontinuation due to AEs
Palmer, 2021[17]	469/764	226,361/421,346	30.1	57.1	44.4	T2DM	GLP-1 RAs (grouped)	All-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, kidney failure, admission to hospital for HF, severe hypoglycaemia, blindness, eye disease requiring intervention, amputation, neuropathic pain, diabetic ketoacidosis, serious hyperglycaemia, genital infection, Fournier gangrene, severe gastrointestinal events, pancreatic cancer and pancreatitis

continued

This article should be referenced as follows: Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

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First author, year	Sample characteristics					Comorbidities	Drugs and doses of interest	Safety outcomes
	Trials in BW NMA/total included trials (*n*/*N*)*	Participants in BW NMA/ overall sample size (*n*/*N*)*	For overall sample or * if calculated for BW NMA (** if BW NMA was whole sample)					
			BMI (kg/m²)	Age (years)	% female			
Park, 2023[18]	22/25 (BMI NMA); 11/25 (WC NMA)	nr/2237	34	51.9	57.2	NAFLD/NASH, some T2DM, prediabetes	GLP-RAs grouped (liraglutide, semaglutide, dulaglutide)	nr
Shi, 2022[24]	122/143 (absolute BW change NMA)	42,148/49,810 (absolute BW change NMA)	35.3 (33.1–36.8) (median)	46.7 (IQR 43.0–53.6) (median)	75 (IQR 54–89) (median)	26.6% of studies had at least 60% sample with T2DM; 9% PCOS; 2.8% metabolic syndrome; 1.4% obstructive sleep apnoea; 2.1% NAFLD; 4.9% dyslipidaemia; 2.8% hypertension	Semaglutide; liraglutide; exenatide (doses nr); GLP-1 RAs (grouped)	Discontinuation due to AEs, severe GI AEs, GI events
Shi, 2023[20]	531/816	279,118/471,038	30	57.7	43.4	Overall, about 60% had CVD at baseline	Semaglutide (oral and SC); liraglutide; tirzepatide; exenatide (immediate and extended release); lixisenatide (doses nr)	All-cause death, cardio-vascular death, non-fatal myocardial infarction, non-fatal stroke, admission to hospital for HF, end-stage kidney disease, severe hyperglycaemia, severe GI events, genital infections, amputation, diabetic ketoacidosis, hyperkalaemia
Tsapas, 2021[21]	407/424	264,578/276,336	At baseline was within the overweight or obesity range in most trials while mean BMI was below 25 kg/m² in only 10 trials	56.6 (4.66)	nr	nr	Semaglutide (oral and SC); liraglutide; exenatide (extended release) (QW); exenatide (BID); lixisenatide (doses nr)	nr
Xie, 2022[22]	23/23	11,545/11,545	30.3** (range 25.1–43.9)	49.9** (range 31.1–65.3)	71.8** (range 0–84)	nr	Semaglutide 1.0, 2.4 mg; liraglutide 1.8, 3.0 mg	Hypoglycaemic events, total AEs, SAEs
Zaazouee, 2022[23]	22/26	18,382/22,868	32 (range 25.1–34.5)	52.7–71 (range)	10–56.4 (range)	Mean duration of diabetes 2–15.1 years (T2DM)	Semaglutide (SC) 0.05, 0.1 (OD) 0.5, 1.0 mg (QW); semaglutide (oral) 3, 7, 14 mg; liraglutide 1.8 mg; tirzepatide (SC) 5, 10, 15 mg	AEs, SAEs, GI side effects, death, discontinuation, hypoglycaemia, nausea, vomiting, dyspepsia, diarrhoea, constipation.

BID, twice daily; CVD, cardiovascular disease; GI, gastrointestinal; HF, heart failure; IQR, interquartile range; nr; not reported; OD, once daily; SC, subcutaneous; T1DM, type 1 diabetes mellitus; WC, waist circumference.

Appendix 4 Results of assessment of included reviews with a measurement tool to assess systematic review-2 tool

Study	PICO components	Protocol	Study design explanation	Comprehensive search strategy	Duplicate study selection	Duplicate data extraction	Details of excluded studies	Description of included studies	Risk of bias assessment	Funding sources	Risk of bias discussed	Heterogeneity	Reports conflicts of interest	Overall rating
Alhindi[32]	Yes	No	No	No	No	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes	Critically low
Alkhezi[27]	Yes	No	No	No	Yes	Yes	No	Partial yes	Yes	No	Yes	No	Yes	Low
Alsugair[11]	Yes	Yes	No	Partial Yes	Yes	Yes	No	Partial yes	Yes	Yes	Yes	Yes	Yes	Moderate
Avgerinos[10]	Yes	Yes	No	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Moderate
Chubb[25]	Yes	No	No	No	Yes	NR	Yes	Partial yes	Yes	No	No	Yes	No	Critically low
Guan[28]	Yes	No	No	Partial yes	Yes	Yes	No	Yes	Yes	No	No	Yes	Yes	Low
Hussein[12]	Yes	Yes	No	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	No	Moderate
Iannone[13]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Moderate
Ida[30]	No	No	No	Partial yes	Yes	No	No	Partial yes	Partial yes	No	No	No	Yes	Low
Jiang[31]	No	No	No	Partial yes	Yes	Yes	No	No	Partial yes	No	Yes	Yes	Yes	Low
Lautsch[14]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Moderate
Lian[15]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Moderate
Ma[16]	Yes	Partial yes	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Moderate
Palmer[17]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Moderate
Park[18]	Yes	Yes	No	Partial yes	Yes	Yes	No	Partial yes	Partial yes	No	Yes	Yes	Yes	Moderate
Shi[24]	Yes	Yes	No	Partial yes	Yes	Yes	No	Partial yes	Partial yes	No	Yes	Yes	Yes	Moderate
Shi[20]	Yes	Yes	No	Partial yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Moderate
Smith[26]	Yes	No	No	Partial yes	Yes	Yes	No	Partial yes	Partial yes	No	Yes	No	No	Low
Tsapas[21]	Yes	Partial yes	No	Partial yes	Yes	Yes	No	Partial yes	Partial Yes	No	Yes	Yes	No	Moderate
Vosoughi[29]	Yes	No	No	Yes	Yes	Yes	No	Partial yes	No	Yes	Yes	Yes	No	Low
Xie[22]	Yes	Yes	No	Partial yes	Yes	Yes	No	Partial yes	Yes	No	Yes	Yes	Yes	Moderate
Zaazouee[23]	Yes	Yes	Yes	Partial yes	No	No	No	Partial yes	Yes	No	Yes	Yes	Yes	Moderate

NR, not reported.

Note
Blue shading indicates critical items.

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Appendix 5 Results of assessment of prioritised reviews with International Society of Pharmacoeconomics and Outcomes Research tool

Question	Alsugair[11]	Avgerinos[10]	Iannone[13]	Hussein[12]	Lautsch[14]	Lian[15]	Ma[16]	Palmer[17]	Park[18]	Shi[19]	Shi[20]	Tsapas[21]	Xie[22]	Zaazouee[23]
1. Is the population relevant?	Y	P	Y	P	P	P	Y	P	P	Y	P	P	Y	P
2. Are any critical interventions missing?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	N
3. Are any relevant outcomes missing?	N	N	N	N	N	N	N	N	N	N	N	N	N	N
4. Is the context (e.g. settings and circumstances) applicable to your population?	Y	Y	Y	Y	N	N	Y	Y	N	Y	Y	Y	Y	Y
5. Did the researchers attempt to identify and include all relevant RCTs?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
6. Do the trials for interventions of interest form one connected network of RCTs?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
7. Is it apparent that poor quality studies were included, thereby leading to bias?	Y	Y	Y	Y	Y	Y	N	CT	N	Y	Y	Y	N	Y
8. Is it likely that bias was induced by selective reporting of outcomes in the studies?	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y
9. Are there systematic differences in treatment effect modifiers across the different treatment comparisons in the network?	Y	N	N	CT	Y	N	Y	N	Y	Y	N	CT	CT	CT
10. Were imbalances in effect modifiers across the different treatment comparisons identified before reviewing individual study results?	N	N/A	N/A	CT	Y	N/A	N	N/A	Y	Y	N/A	CT	CT	N/A
11. Were statistical methods used that preserve within study randomisation?	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
12. If both direct and indirect comparisons are available for pairwise contrasts was agreement evaluated or discussed?	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CT
13. In the presence of consistency, were both direct and indirect evidence included in the NMA?	N/A	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CT
14. With inconsistency or an imbalance in the distribution of treatment effect modifiers across the different types of comparisons in the network of trials, did researchers attempt to minimise this bias with the analysis?	Y	N/A	N	Y	N	N/A	N	CT	Y	Y	Y	N	N/A	CT

Question	Alsugair[11]	Avgerinos[10]	Iannone[13]	Hussein[12]	Lautsch[14]	Lian[15]	Ma[16]	Palmer[17]	Park[18]	Shi[19]	Shi[20]	Tsapas[21]	Xie[22]	Zaazouee[23]
15. Was a valid rationale provided for the use of RE or FE models?	N	N	N	N	Y	Y	N	N	Y	N	N	N	N	N
16. If a RE model was used, were assumptions about heterogeneity explored or discussed?	N	Y	Y	Y	Y	N/A	Y	Y	Y	Y	Y	Y	CT	N/A
17. If there are indications of heterogeneity, were subgroup analyses or meta-regression analysis with pre-specified covariates performed?	Y	Y	N	N	Y	Y	N	N	Y	Y	Y	Y	N	N/A
18. Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
19. Are the individual study results reported?	Y	N	N	Y	Y	Y	N	N	N	N	N	N	N	N
20. Are direct results reported separately from results of indirect comparisons or NMAs?	N/A	N	Y	N	N	N	Y	Y	Y	Y	N	N	N	N
21. Are all pairwise contrasts between interventions as obtained with NMA reported along with measure of uncertainty?	Y	Y	Y	N	Y	N	Y	Y	N	Y	N	Y	Y	Y
22. Is a ranking of interventions provided given the reported treatment and its uncertainty outcome?	Y	Y	N	Y	Y	N	Y	N	Y	N	Y	Y	Y	N
23. Is the impact of important patient characteristics on treatment effects reported?	N	N	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y	N
24. Are the conclusions fair and balanced?	Y	Y	Y	Y	Y	Y	Y	Y	Y	y	Y	Y	Y	CT
25. Were there any potential conflicts of interest?	N	Y	N	Y	Y	N	N	Y	N	Y	Y	Y	N	N
26. If yes, were steps taken to address these?	N/A	Y	N/A	Y	Y	N/A	N/A	Y	N/A	Y	Y	Y	N/A	N/A
Number of negative ratings (number of 'can't tell' items)	8	9	10	10 (2)	9	9	9	8 (2)	6	7	8	8 (2)	7 (3)	7 (5)

CT, can't tell (not enough information provided); FE, fixed effect; N, no; N/A, not applicable; P, partly; RCT, RE, random effect; Y, yes.

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Appendix 6 Detailed description of findings relating to effectiveness of glucagon-like peptide 1 receptor agonists for weight loss

Effects at 6 months

All glucagon-like peptide 1 receptor agonists versus placebo

Four reviews provided NMAs for GLP-1 RA versus placebo at the 6 month time point (23–26 weeks).[12,14,17,23] The forest plot in *Figure 5* shows that 17 of 19 comparisons indicated a statistically significant reduction in body weight at 6 months for GLP-1 RAs versus placebo. The two exceptions were subcutaneous semaglutide 0.1 and 0.05 mg daily, where wide CIs denote considerable uncertainty about effectiveness. The largest effect sizes were observed for the three doses of subcutaneous tirzepatide, which came from indirect evidence; 15 mg [mean difference (MD): −12.11 kg, 95% CI −16.14 to −8.09 kg], 10 mg (MD −11.21 kg, 95% CI −15.21 to −7.21 kg) and 5 mg (MD −9.23 kg, 95% CI −13.24 to −5.22 kg). Subcutaneous semaglutide 1.0 mg delivered weekly was of similar magnitude of effectiveness (MD −7.72 kg, 95% CI −11.68 to −3.75 kg). However, wide CIs for these comparisons indicate uncertainty in the true magnitude of effect. Palmer and colleagues grouped all GLP-1 RAs together, estimating a statistically significant reduction in weight loss compared to placebo overall (MD −1.45, 95% CI −1.72 to −1.18).[17] Exenatide (short- and long-acting), dulaglutide and lixisenatide were all associated with statistically significant reductions in body weight, with similar MDs (range 0.91–1.71 kg) and narrow CIs.

Effectiveness of semaglutide, liraglutide and tirzepatide

Semaglutide versus all comparators

Three reviews provided NMAs for weight loss at 6 months that included semaglutide, the data from these NMAs is presented in *Figure 6*.[12,14,23] Semaglutide was associated with greater weight loss than placebo at five doses (subcutaneously at 1.0 and 0.5 mg weekly, orally at 14, 7 and 3 mg daily), with subcutaneous doses giving the largest effects, albeit with wide CIs indicating an uncertain magnitude of effect (1 mg subcutaneous MD −7.72 kg, 95% CI −11.68 to −3.75 kg; 0.5 mg subcutaneous MD −5.51 kg, 95% CI −9.45 to −1.57 kg).

Several comparisons of semaglutide with liraglutide were available, with the comparison of combined doses for each failing to reach statistical significance, despite the point estimate favouring semaglutide (MD −0.95 kg, 95% CI −2.14 to 0.19 kg).[12] Liraglutide 1.8 mg was associated with greater weight loss than semaglutide 3 mg daily (subcutaneous, MD 1.57 kg, 95% CI 0.57 to 2.57 kg).

All doses of tirzepatide (5/10/15 mg) were associated with greater weight loss than semaglutide comparisons (0.5/1.0/3.0 mg), with the largest difference between subcutaneous semaglutide 0.5 mg and tirzepatide 15 mg.[23]

Tirzepatide versus all comparators

The evidence for tirzepatide at 6 months came from one review,[23] including data from one trial[35] comparing tirzepatide to semaglutide in a study of 1879 patients with T2DM. Three doses of tirzepatide (5, 10 and 15 mg subcutaneously) were associated with greater weight loss than the two semaglutide doses (0.5 and 1.0 mg subcutaneously) (*Figure 7*). Effects were greater with increasing doses, the largest being tirzepatide 15 mg versus semaglutide 0.5 mg (MD −6.60 kg, 95% CI −8.25 to −4.95 kg).

Liraglutide versus all comparators

Two reviews provided NMAs for weight loss at 6 months that included liraglutide (see *Figure 8*).[12,23] Liraglutide was most effective versus placebo, at 1.8 mg (MD −2.35 kg, 95% CI −3.20 to −1.50 kg) and with combined evidence for all doses (MD −2.44 kg, 95% CI −2.87 to −2.04 kg). Liraglutide 1.8 mg was shown to be associated with greater weight loss at 6 months than daily semaglutide 3.0 mg (MD −1.57 kg, 95% CI −2.57 to −0.57 kg), but similar to daily oral semaglutide 7 and 15 mg, and daily subcutaneous semaglutide 0.05 and 0.01 mg. Liraglutide was associated with greater weight loss than short (MD −0.74 kg, 95% CI −1.27 to −0.22 kg) and long-acting (MD −0.81 kg, 95% CI −1.39 to −0.25 kg) exenatide, dulaglutide (MD −1.20 kg, 95% CI −1.86 to −0.60 kg) and lixisenatide (MD −1.52 kg, 95% CI −2.07 to −1.01 kg).

12-month data

All glucagon-like peptide 1 receptor agonists versus placebo

Three reviews provided NMAs showing the effects of GLP-1 RAs versus placebo on weight loss, measured in terms of absolute body mass loss in kilograms after 52 weeks (*Figure 9*).[12,13,23] The largest effect was seen for semaglutide (all doses combined in the analysis), which was associated with a loss of 9.02 kg versus placebo (95% CI −10.24 to −7.63 kg). Liraglutide at 3.0 mg daily, and semaglutide (all doses) were both associated with around 5 kg weight loss at 52 weeks, but the indirect estimate

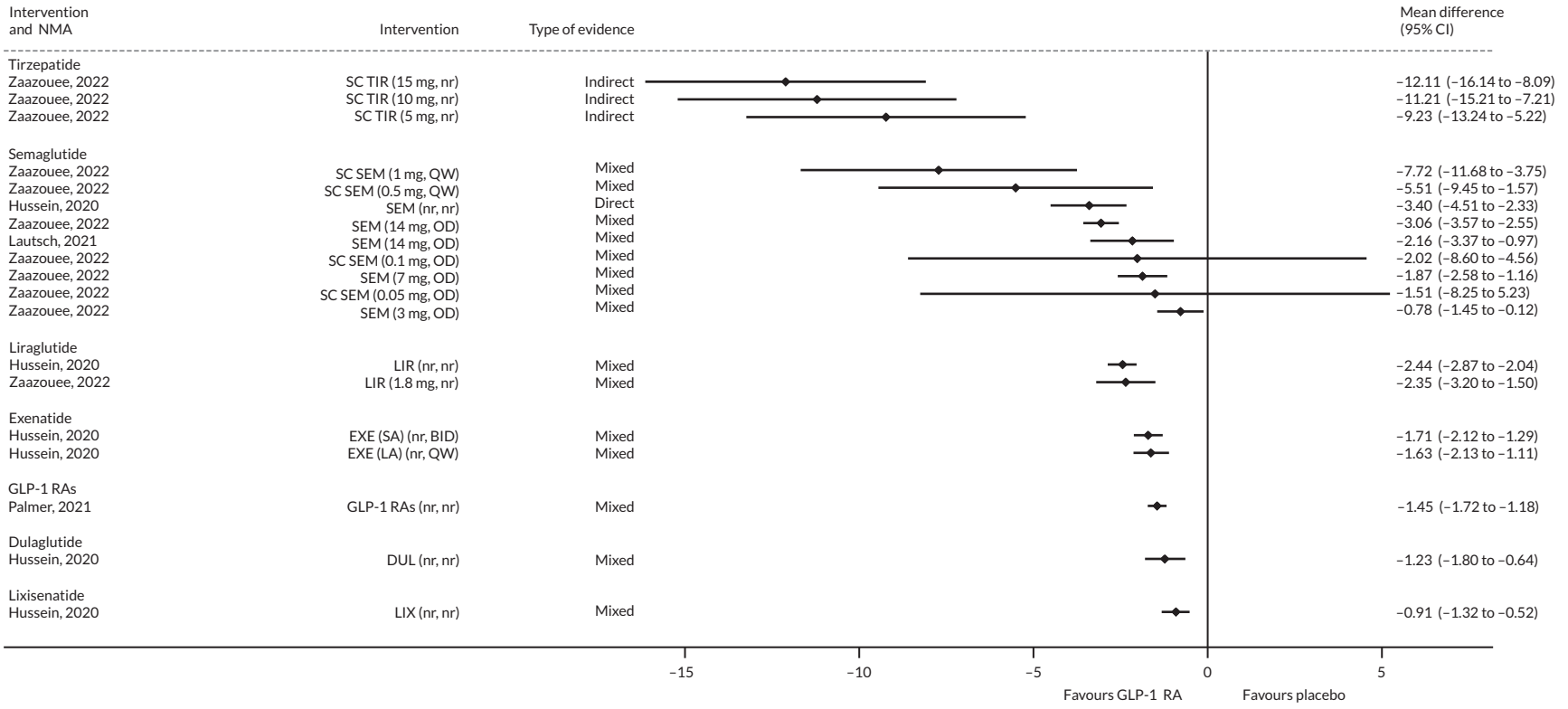


FIGURE 5 Effect of GLP-1 RAs vs. Placebo on change in body mass (kg) after 23–26 weeks. BID, twice daily; DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; nr, not reported or combined doses; OD, once daily; QW, once weekly; SA, short-acting; SC, subcutaneous; SEM, semaglutide; TIR, tirzepatide. Direct, evidence comes from direct comparisons in the network only; Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

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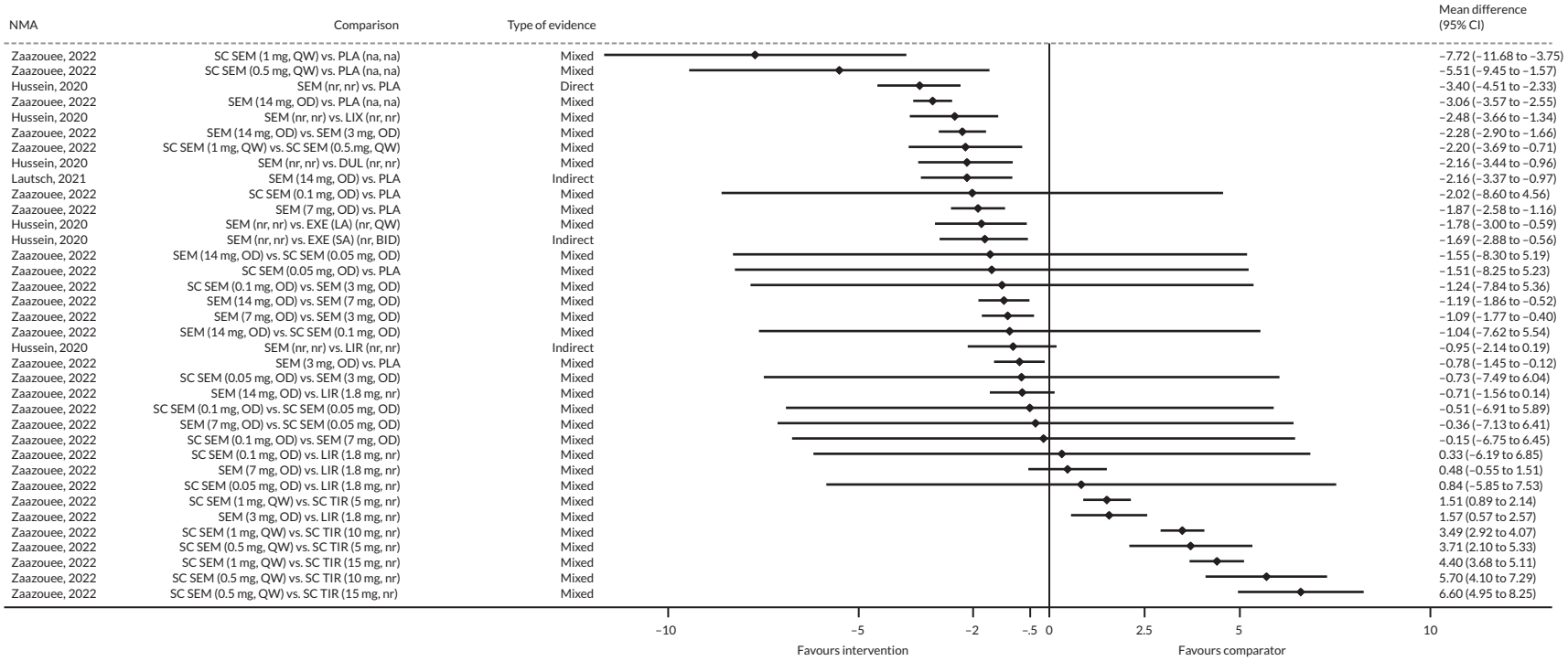


FIGURE 6 Comparison of the effect of semaglutide (SEM) vs. all other comparators on change in body mass (kg) after 23–26 weeks. BID, twice daily; DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; na, not applicable; nr, not reported or combined doses; OD, once daily; PLA, placebo; QW, once weekly; SA, short-acting; SC, subcutaneous; TIR, tirzepatide. Direct, evidence comes from direct comparisons in the network only; Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

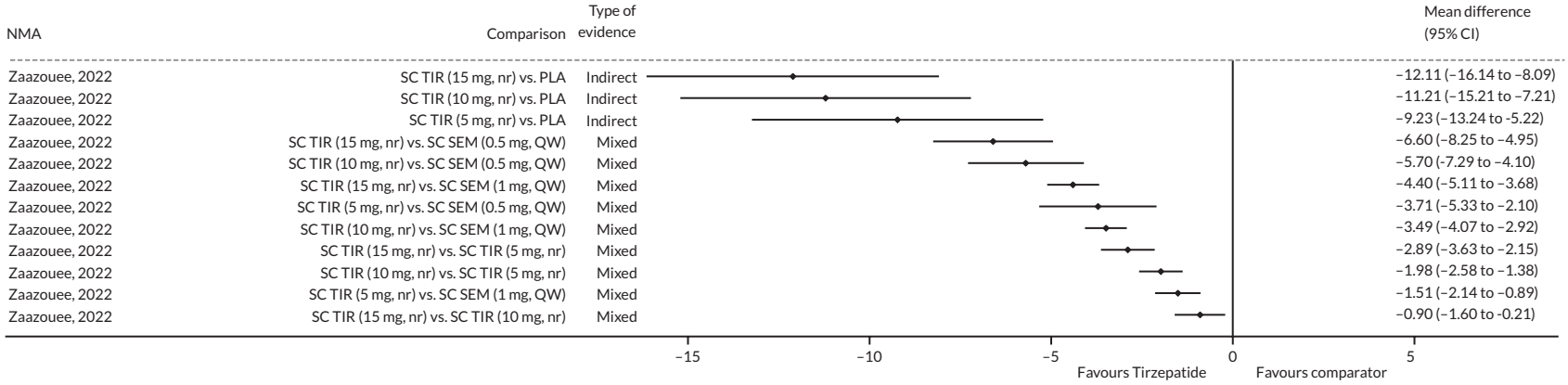


FIGURE 7 Comparison of the effect of tirzepatide (TIR) vs. all other comparators on change in body mass (kg) after 23–26 weeks. nr, not reported or combined doses; PLA, placebo; QW, once weekly; SEM, semaglutide; SC, subcutaneous. Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

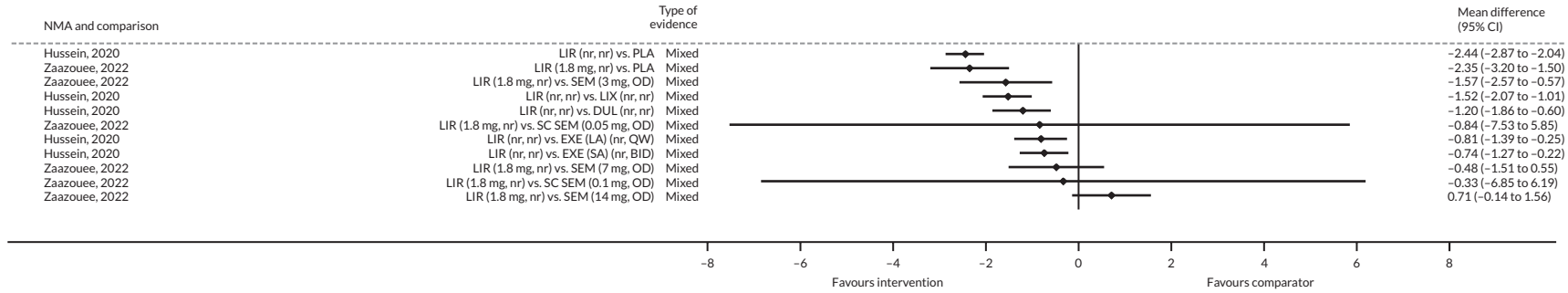


FIGURE 8 Comparison of the effect of liraglutide (LIR) vs. all other comparators on change in body mass (kg) after 23–26 weeks. BID, twice daily; DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIX, lixisenatide nr, not reported or combined doses; OD, once daily; PLA, placebo; QW, once weekly; SA, short-acting; SC, subcutaneous; SEM, semaglutide. Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

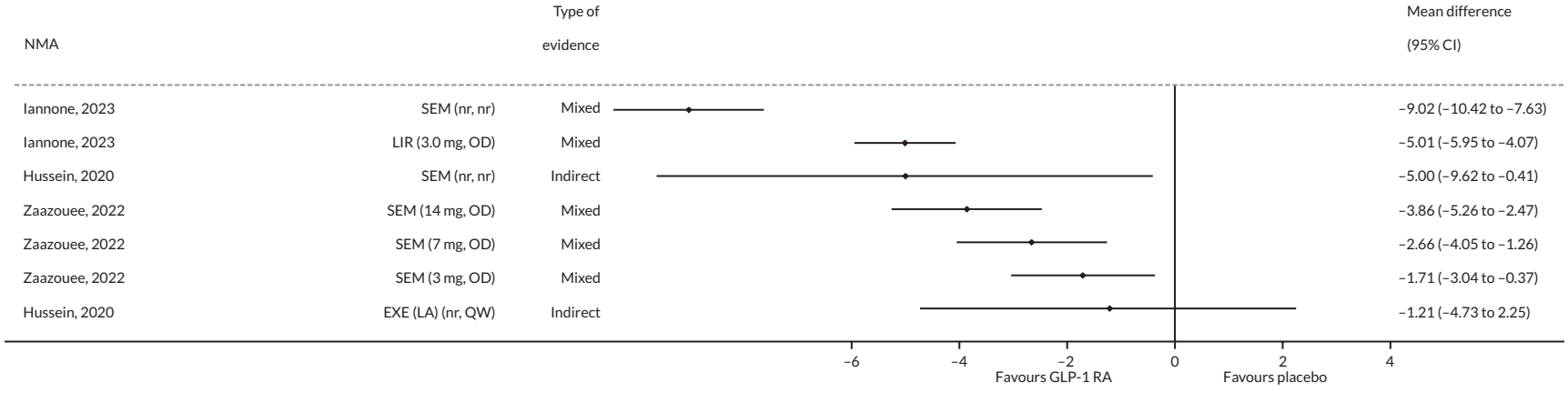


FIGURE 9 Effect of GLP-1 RAs vs. placebo on change in body mass (kg) at 52 weeks. EXE, exenatide; LA, long-acting; LIR, liraglutide; nr, not reported or combined doses; OD, once daily; QW, once weekly; SEM, semaglutide. Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

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coming from the NMA in the review by Hussein and colleagues included wide CIs approaching zero.[12]

Three doses of oral semaglutide (14, 7 and 3.0 mg) reported by Zaazouee and colleagues were associated with statistically significant decreases in body mass at 12 months., the magnitude of the effect increasing with the dose (range 1.71–3.86 kg decrease).[23] There was no difference between weekly long-acting exenatide and placebo, according to indirect evidence from Hussein *et al.*[12]

Iannone and colleagues provided three additional indications of weight loss, with percentage body mass lost, reduction in BMI (kg/m^2) and reduction in waist circumference, for three comparisons: semaglutide (all doses) versus placebo, liraglutide 3.0 mg daily versus placebo and the two drugs compared. Semaglutide was associated with the largest effects in all metrics. Versus placebo, both drugs were associated with statistically significant effects [semaglutide: −8.91% (95%: CI −10.88% to −6.94%) body mass loss; −7.84 cm (95% CI −9.34 to −6.34 cm) waist circumference reduction; −3.31 kg/m^2 (95% CI −4.02 to −2.60 kg/m^2) reduction in BMI]. Liraglutide: −4.61% (95% CI −5.84% to −3.38%) body mass loss; −3.71 cm (95% CI −4.46 to −2.96 cm) waist circumference reduction; −1.82 kg/m^2 (95% CI −2.39 to −1.25 kg/m^2) reduction in BMI]. Semaglutide was associated with approximately 4% greater loss of body mass, 4 cm reduction in waist circumference, and 1.5 kg/m^2 reduction in BMI, compared to liraglutide.[13]

Comparison of glucagon-like peptide 1 receptor agonists

At 52 weeks, three reviews provided data about the comparative effectiveness of GLP-1 RAs in reducing body mass (kg) (*Figure 10*).[12,13,23] Mixed evidence was available for semaglutide (all doses combined) versus liraglutide 3.0 mg daily (MD −4.01 kg, 95% CI −5.59 to −2.43 kg) and for the comparison of three doses of oral semaglutide. The latter analysis, from Zaazouee and colleagues, showed that a daily dose of 14 mg oral semaglutide was associated with greater weight loss than 3 mg daily (MD −2.15 kg, 95% CI −3.19 to −1.12 kg) and 7 mg daily (MD −1.20 kg, 95% CI −2.39 to −0.09 kg), but no statistically significant difference between the two lower doses, with CIs narrowly crossing zero.[23]

Direct evidence for long-acting exenatide versus all doses of semaglutide showed that semaglutide was associated with nearly 4 kg greater weight loss over a year, however the CIs suggest this difference might be as little as < 1 kg (MD −3.77 kg, 95% CI −6.80 to −0.78 kg).

Evidence for longer than 12 months

All glucagon-like peptide 1 receptor agonists versus placebo

The evidence for GLP-1 RAs versus placebo at time points of above 52 weeks comes from two reviews (*Figure 11*).[10,11] Liraglutide at four doses and with all doses combined, semaglutide at 0.5 and 1 mg weekly (assumed delivered subcutaneously) and exenatide at 2 mg and an unknown daily dose, were included. All four estimates regarding liraglutide at daily doses of 0.6, 1.2, 1.8 and 3.0 mg suffered from very wide CIs which crossed zero, despite point estimates suggestive of body weight reduction with the drug. Direct evidence from the review by Avgerinos and colleagues indicates that liraglutide was associated with a 3.39 kg reduction in body weight, compared with placebo (95% CI −4.18 to −2.60 kg).[10] Similar findings were reported for semaglutide 0.5 mg weekly (MD −3.84 kg, 95% CI −5.94 to −2.09 kg) and 1 mg weekly (MD −4.04 kg, 95% CI −5.61 to −2.47 kg). Exenatide was associated with a 4.5 kg reduction in body weight (95% CI −6.93 to −2.07 kg).

Effectiveness of semaglutide and liraglutide

Liraglutide versus all comparators

Twenty-four comparisons involving liraglutide were available for time points > 52 weeks, in two reviews,[10,11] with 22 provided by one review.[11] The comparisons are displayed in *Figure 12*, grouped by dose. Only three comparisons reached statistical significance: the combined doses versus placebo comparison from Avgerinos and colleagues' review indicated a 3.39 kg weight loss (95% CI −4.18 to −2.60 kg) with liraglutide; both semaglutide 1.0 mg weekly and 0.5 mg weekly were associated with greater weight loss than liraglutide 0.6 mg. However, both comparisons were accompanied by skewed CIs (vs. semaglutide 0.5 mg MD 2.42 kg, 95% CI 1.44 to 6.22 kg; vs. semaglutide 1.0 mg MD 3.06 kg, 95% CI 0.82 to 6.02 kg).

Liraglutide 3.0 mg, which is the approved dose for weight loss, was not associated with statistically significant weight loss when compared to placebo, exenatide 2.0 mg, semaglutide 1 or 0.5 mg weekly. The comparison with placebo suggested over 4 kg of weight loss, but the upper CI crossed zero, and the finding was not statistically significant (MD −4.30 kg, 95% CI −9.20 to 0.57 kg). Data were from mixed evidence, and it was unclear how many trials were in the NMA, or how many provided data for each drug and dose. Wide CIs for the majority of comparisons are indicative of significant heterogeneity and statistical uncertainty.

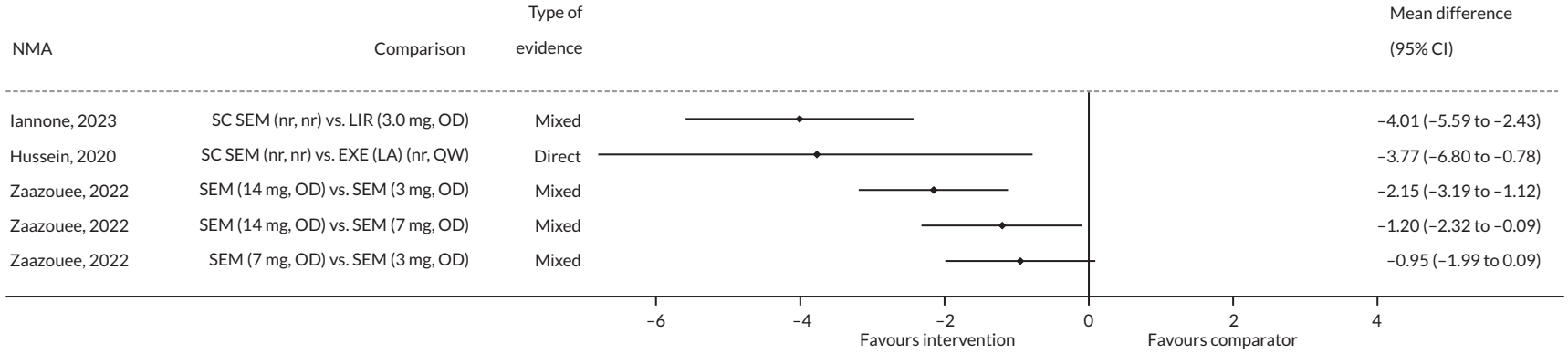


FIGURE 10 Comparison of the effect of different type or dose of GLP-1 RAs on change in body mass (kg) at 52 weeks. EXE, exenatide; LA, long-acting; LIR, liraglutide; nr, not reported or combined doses; OD, once daily; QW, once weekly; SC, subcutaneous; SEM, semaglutide. Direct, evidence comes from direct comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

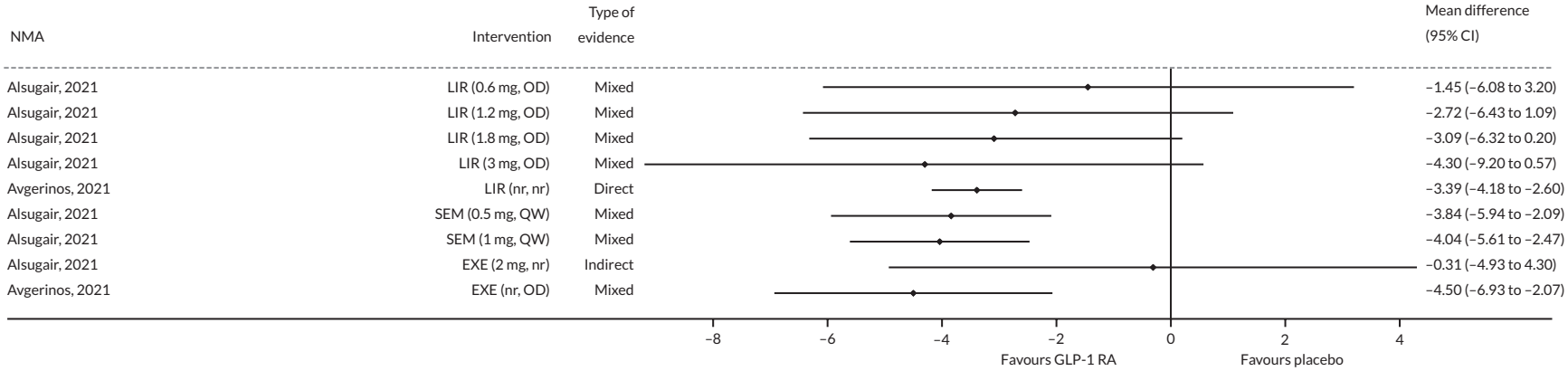


FIGURE 11 Effect of GLP-1 RAs vs. placebo on change in body mass (kg) at longer than 52 weeks. EXE, exenatide; LIR, liraglutide; nr, not reported or combined doses; OD, once daily; QW, once weekly; SEM, semaglutide. Direct, evidence comes from direct comparisons in the network only; Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

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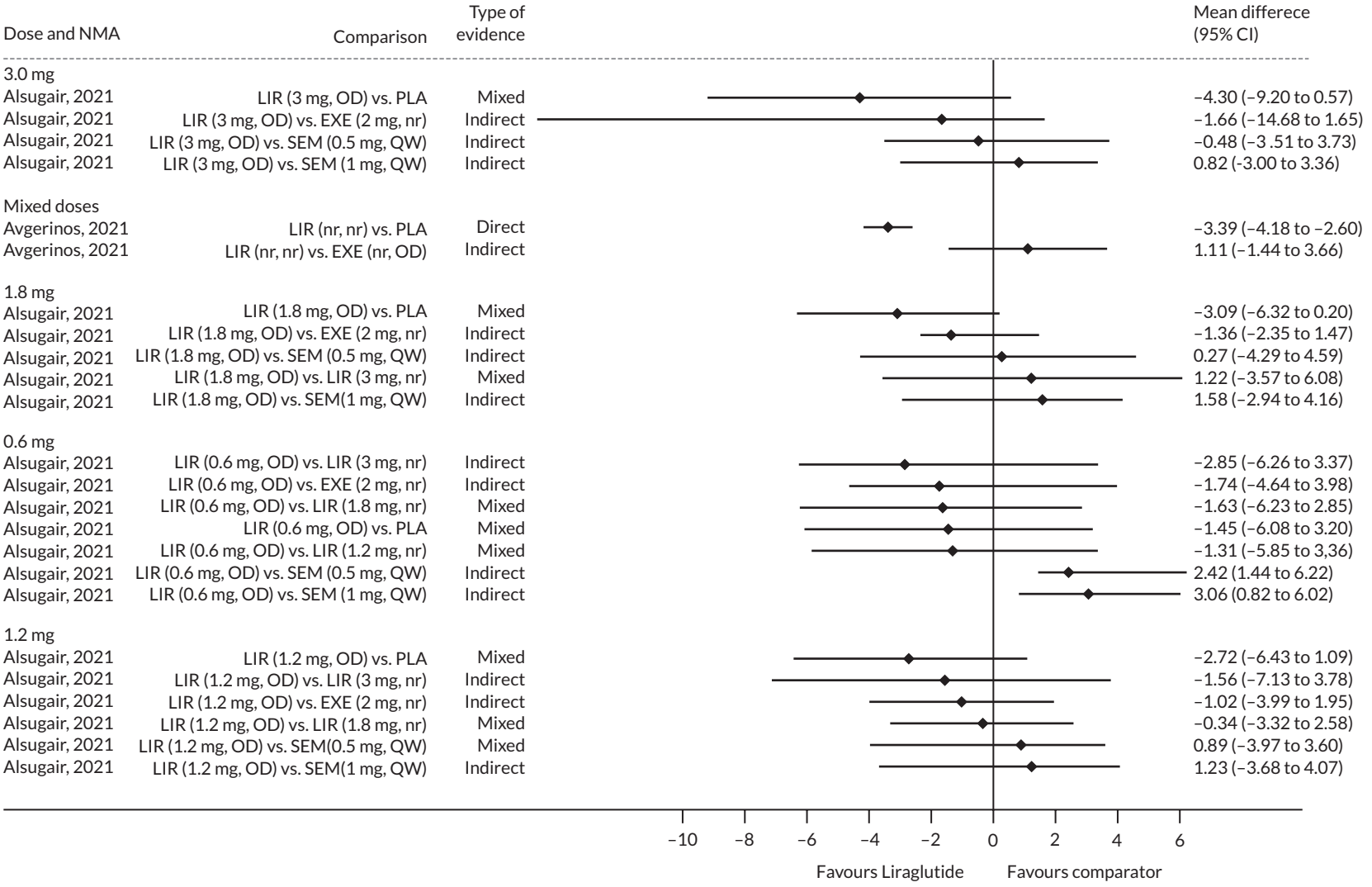


FIGURE 12 Effect of liraglutide (LIR) vs. comparators on change in body mass (kg) at longer than 52 weeks. EXE, exenatide; nr, not reported or combined doses; OD, once daily; PLA, placebo; QW, once weekly; SEM, semaglutide. Direct, evidence comes from direct comparisons in the network only; Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

Semaglutide versus all comparators

Figure 13 displays the 13 available comparisons for semaglutide doses at > 52 weeks, all taken from the review by Alsugair and colleagues.[11] Semaglutide 1.0 mg weekly was associated with statistically significant weight loss when compared with placebo (MD −4.04 kg, 95% CI −5.61 to −2.47 kg), exenatide 2.0 mg (MD −3.80 kg, 95% CI −4.60 to −2.96 kg) and liraglutide 0.6 mg, though the latter was accompanied by wide CIs (MD −1.58 kg, 95% CI −4.16 to −0.82 kg). There was no difference in weight loss when semaglutide 1.0 mg weekly was compared with liraglutide at 1.8, 1.2 and 3.0 mg daily.

The same pattern of results and magnitudes of effect were seen with semaglutide 0.5 mg weekly, with statistically significant differences in the same comparisons as for 1.0 mg weekly. However, CIs were highly skewed for the comparisons with liraglutide 0.6 mg daily (MD −2.42 kg, 95% CI −6.22 to −1.44 kg) and exenatide 2.0 mg (−2.13 kg, 95% CI −4.15 to −1.89 kg).

Evidence at multiple, combined or unstated time points

All glucagon-like peptide 1 receptor agonists versus placebo

The forest plot in *Figure 14* shows 20 comparisons of a GLP-1 RA versus placebo, reported across five reviews.[10,15,16,21,22] Semaglutide 2.4 mg was associated with the greatest weight loss as shown in two NMAs, with reductions of 12.47 kg (95% CI 13.25 to 11.69 kg) and 11.51 kg (95% CI 12.83 to 10.21 kg) of weight loss shown over time periods in the range of 12–72 weeks.[16,22] Semaglutide 1.0 mg, and combined doses, administered both orally and subcutaneously, were associated with statistically significant weight loss ranging from 3.80 to 2.41 kg.

All doses of liraglutide were associated with weight loss versus placebo, with the greatest effects at the 3.0 mg dose, confirmed by two NMAs (MD −5.24 kg, 95% CI −5.82 to −4.67 kg; MD −4.65 kg, 95% CI −5.60 to −3.69 kg).[16,22] Combined doses were associated with 2.37–4.34 kg of weight loss,[10,15,21] while 1.8 mg liraglutide was associated with 3.42 and 3.29 kg weight loss in two NMAs.[16,22]

Results for exenatide were equivocal: mixed evidence from Avgerinos and colleagues, which included 15 other glucose-lowering drugs in the network, indicated 4.35 kg weight loss with exenatide (95% CI 5.53 to 3.17 kg).[10] Lian and colleagues reported a similar point estimate, but with wide CIs indicating uncertainty over the effect.[15] Exenatide twice daily was associated with statistically significant weight loss equivalent to that of liraglutide in the review by Tsapas and colleagues (MD −2.37 kg, 95% CI −2.87 to −1.87 kg).[21] Long-acting weekly exenatide was linked with a small reduction in body weight, while exenatide at 10 micrograms was not more effective than placebo, thanks to CIs narrowly crossing zero.

Lixisenatide was equivalent to long-acting exenatide, while direct evidence for dulaglutide showed that it was not associated with additional weight loss versus placebo. *Appendix 6*, *Table 6* contains all individual network estimates for absolute weight loss (in kg) for specific GLP-1 RAs versus placebo or standard care where available at 6 months, 12 months, more than 12 months, and where reviews combined findings across a range of time points. All GLP-1 RAs were associated with greater weight loss than placebo, except for the following specific comparisons: liraglutide 0.6/1.2/1.8/3.0 mg at > 12 months (wide CIs crossing zero in all cases); long-acting exenatide at 12 months, exenatide 2.0 mg at > 12 months, dulaglutide 1.5 mg across multiple time points.

All glucagon-like peptide 1 receptor agonists versus lifestyle modification alone

The 2023 review by Shi and colleagues featured lifestyle modification alone as a comparator.[20] Results from these analyses are displayed in *Figure 15*. All six comparisons showed that drugs were more effective than lifestyle modification/treatment as usual (TAU). Tirzepatide was the most effective treatment, associated with over 8.5 kg of weight loss (MD −8.57, 95% CI −9.40 to −7.75 kg), followed by subcutaneous semaglutide (MD −4.62 kg, 95% CI −5.22 to −4.03 kg), with oral semaglutide, liraglutide, exenatide (short-acting), dulaglutide, exenatide (long-acting) and lixisenatide associated with point estimates of between 2.21 and 0.83 kg weight loss. Dose and frequency were not reported for any drug.

Effectiveness of semaglutide, liraglutide and tirzepatide

Semaglutide versus all comparators

Figure 16 displays the network estimates for semaglutide at 1.0 and 2.4 mg subcutaneously, as well as combined and unreported doses orally and subcutaneously, taken from four systematic reviews.[16,20–22]

At 2.4 mg, semaglutide was associated with the largest effects, with between 12.47 and 6.86 kg weight loss versus placebo, exenatide, dulaglutide and liraglutide. Mixed evidence for semaglutide 2.4 mg indicated superiority versus

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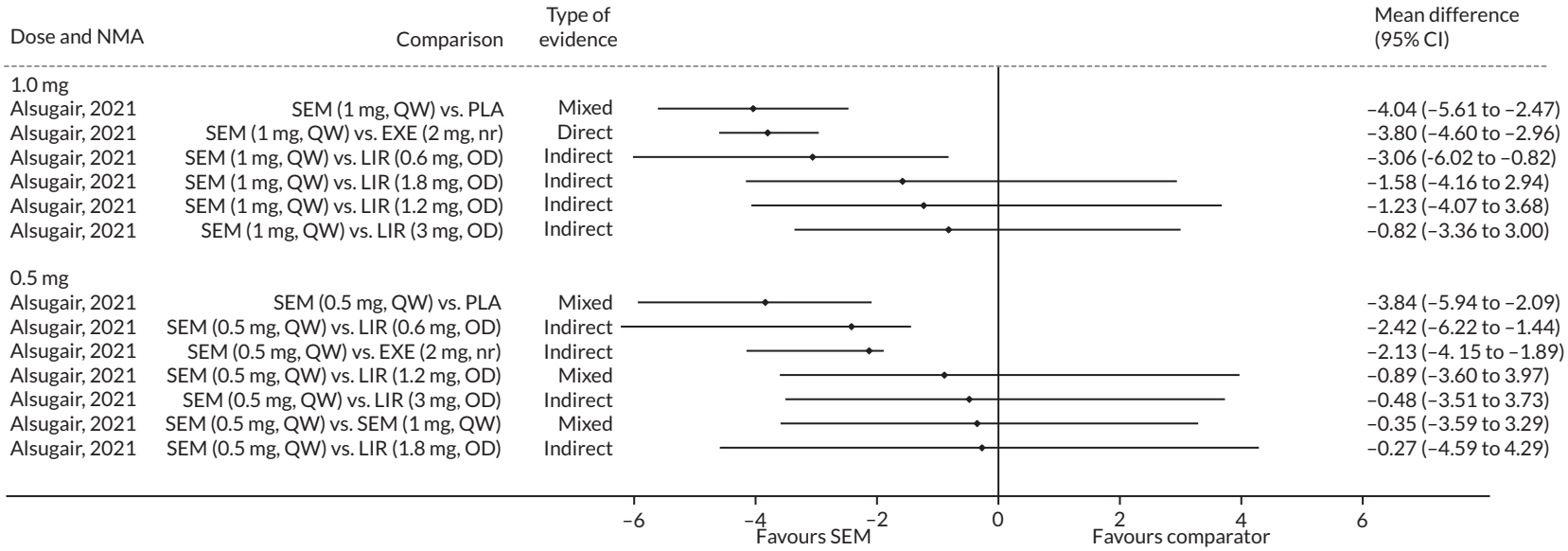


FIGURE 13 Effect of semaglutide (SEM) vs. comparators on change in body mass (kg) at longer than 52 weeks. EXE, exenatide; LIR, liraglutide; nr, not reported or combined doses; OD, once daily; PLA, placebo; QW, once weekly. Direct, evidence comes from direct comparisons in the network only; Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

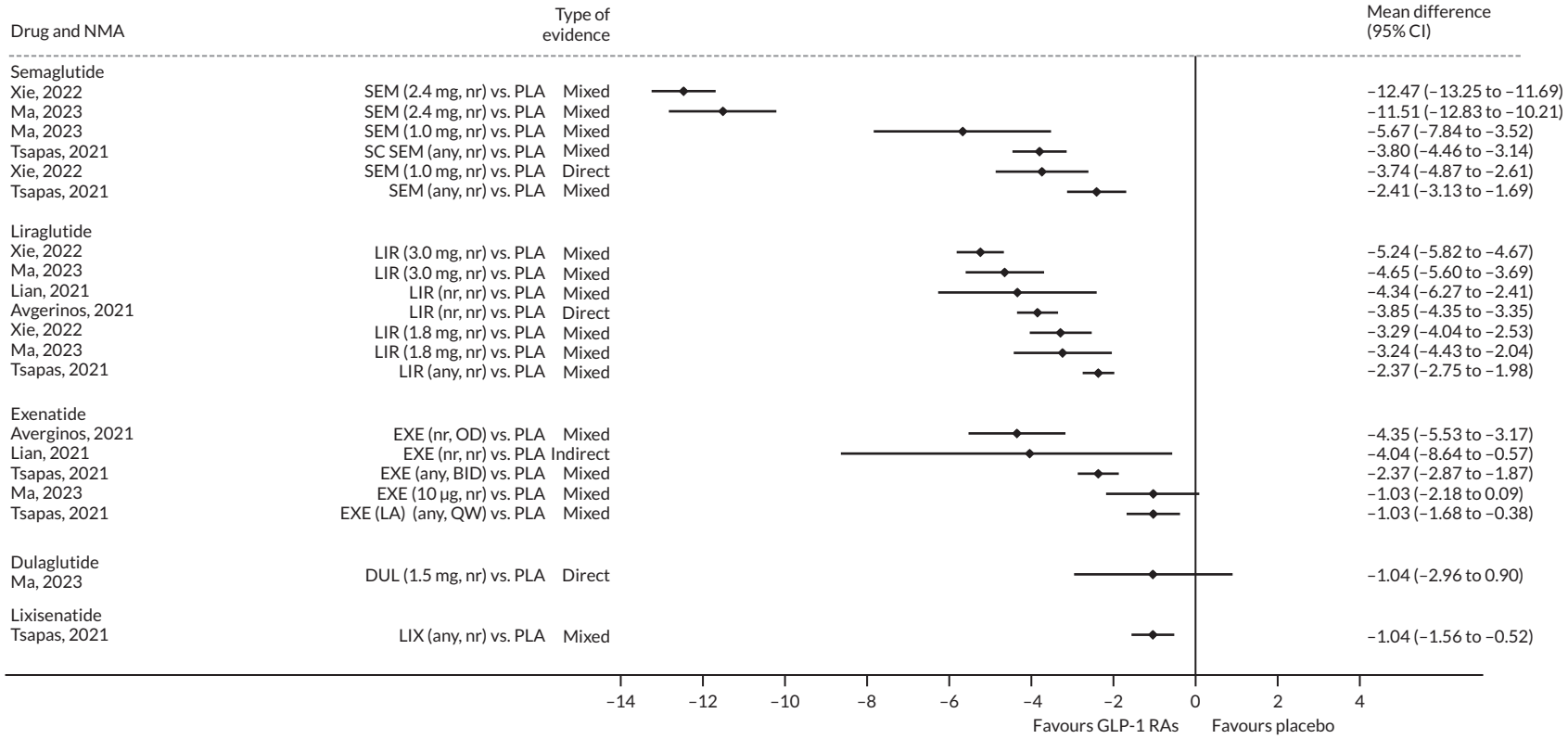


FIGURE 14 Effect of GLP-1 RAs vs. placebo (PLA) on change in body mass (kg) at multiple, combined or undefined time points. DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; nr, not reported or combined doses; QW, once weekly; SC, subcutaneous; SEM, semaglutide; TIR, tirzepatide. Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

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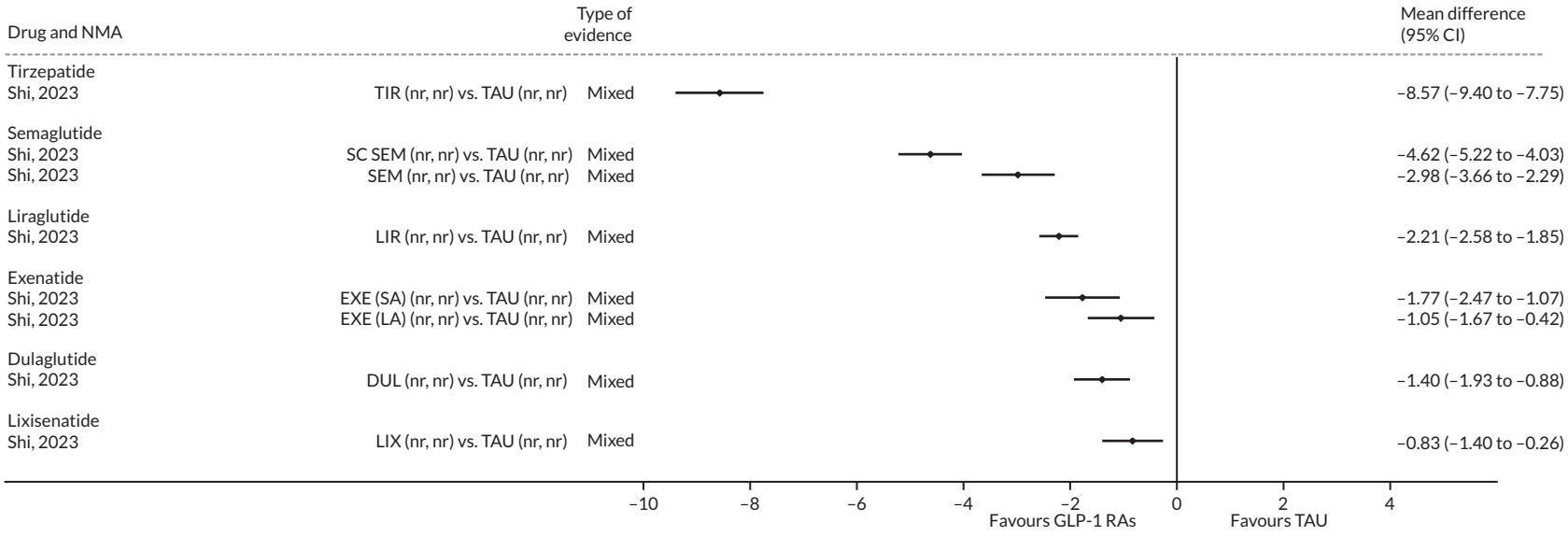


FIGURE 15 Effect of GLP-1 RAs vs. TAU (lifestyle modification alone) on change in body mass (kg) at multiple, combined or undefined time points. DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; nr, not reported or combined doses; SA, short-acting; SC, subcutaneous; SEM, semaglutide; TIR, tirzepatide. Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

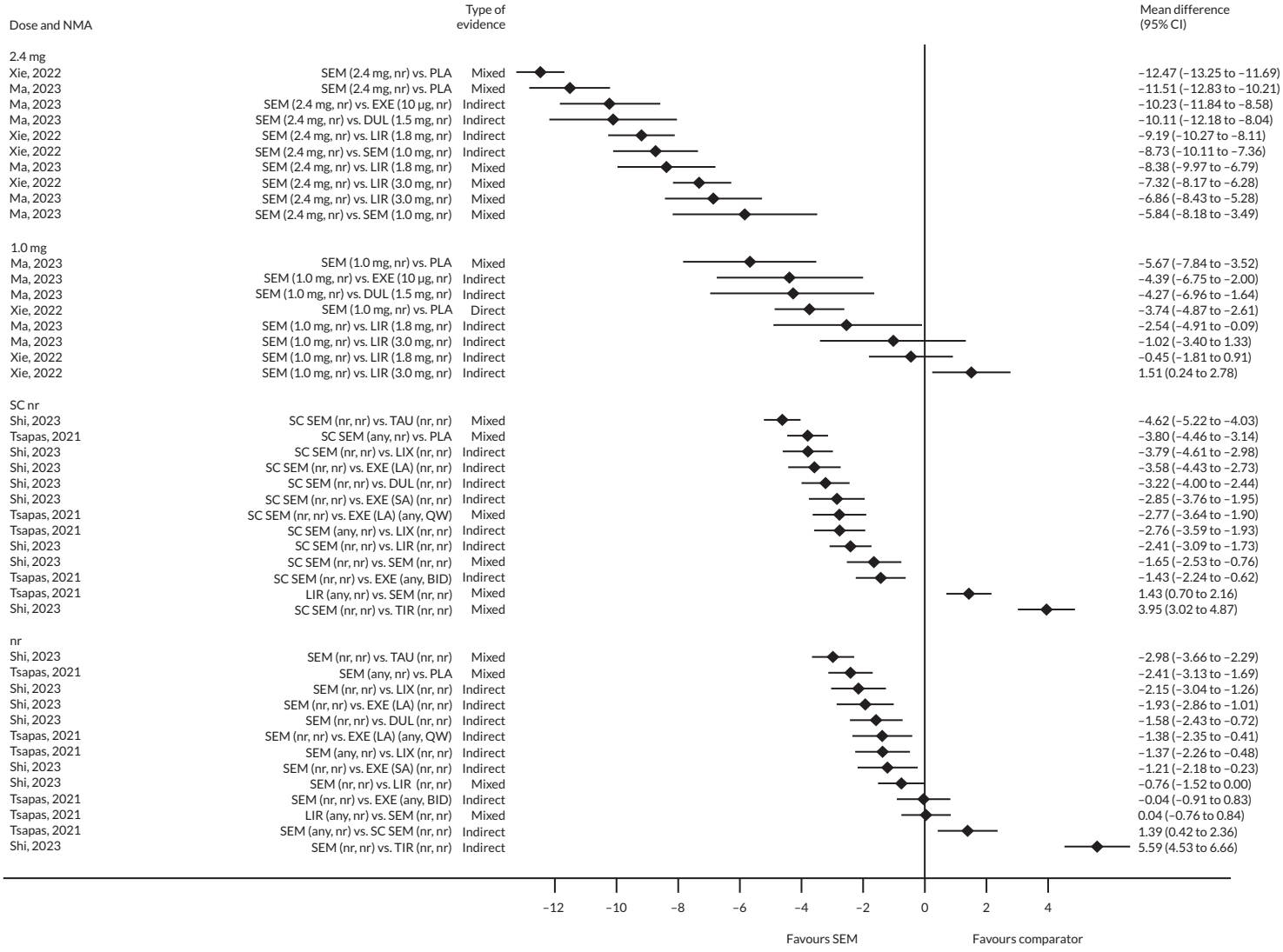


FIGURE 16 Effect of semaglutide (SEM) vs. all other treatments on change in body mass (kg) at multiple, combined or undefined time points. BID, twice daily; CI, confidence interval; DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; NMA, network meta-analysis; nr, not reported or combined doses; OD, once daily; PLA, placebo; QW, once weekly; SA, short-acting; SC, subcutaneous. Direct, evidence comes from direct comparisons in the network only; Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

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liraglutide 1.8 mg (MD −8.38 kg, 95% CI −9.97 to −6.79 kg) and 3.0 mg (MD −6.86 kg, 95% CI −8.43 to −5.28 kg). All network estimates for semaglutide 2.4 mg came from the reviews by Ma and colleagues, who included 56 RCTs of both GLP-1 RAs and sodium-glucose cotransporter-2 inhibitors (SGLT-2i),[16] and Xie and colleagues, who included 23 RCTs, with only GLP-1 RAs included in the network.[22] Both reviews provided estimates for semaglutide 2.4 mg versus placebo, liraglutide 1.8 and 3.0 mg, and semaglutide 1.0 mg, with estimates from the Xie review being slightly greater in each case.

Evidence for semaglutide 1.0 mg came predominantly from indirect comparisons with exenatide 10 µg, dulaglutide 1.5 mg and liraglutide 1.8 and 3.0 mg. In these comparisons, CIs were wide, reflecting uncertainty, however semaglutide was associated with statistically significant weight loss against all but liraglutide 3.0 mg, where there was no difference in weight loss, as reported by two reviews.[16,22] Two estimates of semaglutide versus placebo indicate weight loss of 5.67 kg (mixed evidence)[16] or 3.74 kg (direct evidence),[22] with CIs from the two estimates ranging from 2.61 to 7.84 kg.

Subcutaneous semaglutide was effective versus all comparators except tirzepatide. Comparators were TAU (lifestyle modification alone), placebo, lixisenatide, exenatide, dulaglutide, liraglutide and combined oral doses of semaglutide, with weight loss ranging from 1.43 to 4.62 kg across 11 comparisons.

The magnitude of effect against placebo compared with semaglutide 2.4 mg (3.80 kg weight loss vs. 12.47 or 11.51 kg for semaglutide 2.4 mg) suggests that the 2.4 mg dose was not represented in the data for combined/unreported oral doses. Tirzepatide was associated with nearly 4 kg greater weight loss than subcutaneous semaglutide (MD 3.95 kg, 95% CI 3.02 to 4.87 kg).

There were 13 comparisons involving oral semaglutide (doses combined or not reported). Semaglutide was associated with between 1.21 and 2.15 kg weight loss versus exenatide, lixisenatide and dulaglutide. When compared with liraglutide, Shi and colleagues[20] reported a point estimate of −0.76 kg with semaglutide, but the upper CI hit 0, while the network estimate produced by Tsapas and colleagues[21] showed no difference between semaglutide and liraglutide. The NMA from Tsapas and colleagues contained 22 nodes from 424 RCTs, with 7 representing GLP-1 RAs.[21] Both subcutaneous semaglutide (MD 1.39 kg, 95% CI 0.42 to 2.36 kg) and tirzepatide (MD 5.59 kg, 95% CI 4.53 to 6.66 kg) were associated with greater weight loss than oral semaglutide.

Liraglutide versus all comparators

There were 24 network estimates involving liraglutide across 5 reviews, presented in *Figure 17*.[10,15,20–22] Xie and colleagues provided effectiveness estimates at 1.8 and 3.0 mg, but the majority of estimates involved combined or unreported doses. At 3.0 mg, liraglutide was associated with greater weight loss than placebo (MD 5.24 kg, 95% CI −5.82 to −4.67 kg), liraglutide 1.8 mg (MD −1.96, 95% CI −2.87 to −1.05 kg) and semaglutide 1.0 mg (MD −1.51 kg, 95% CI −2.78 to −0.24 kg). However, as noted above semaglutide 2.4 mg was associated with more than 7 kg greater weight loss than liraglutide 3.0 mg. Following this trend, liraglutide 1.8 mg was similar in effect to semaglutide 1.0 mg, and significantly less effective than semaglutide 2.4 mg, which was associated with more than 9 kg additional weight loss (MD 9.19 kg, 95% CI 8.11 to 10.27 kg).

Data for combined or unreported doses of liraglutide place is as more effective than placebo, lifestyle modification alone, lixisenatide and long-acting exenatide, but less effective than subcutaneous semaglutide, dulaglutide and tirzepatide. There was no difference in weight loss when liraglutide was compared with short-acting exenatide, combined doses of exenatide twice daily or oral semaglutide (doses combined).

Tirzepatide versus all comparators

Data for tirzepatide came from the 2023 review by Shi and colleagues, which offered comparisons with lifestyle modification alone, lixisenatide, exenatide (short-, and long-acting), dulaglutide, liraglutide (doses not reported) and semaglutide, both orally and subcutaneously (doses not reported) (*Figure 18*).[20] In all comparisons, tirzepatide was associated with statistically significant weight loss, ranging from nearly 4 kg versus subcutaneous semaglutide (MD −3.95 kg, 95% CI −4.87 to −3.02 kg) to over 8.5 kg versus lifestyle modification alone (MD −8.57 kg, 95% CI −9.40 to −7.75 kg).

Other outcomes

% reduction in body weight

Shi and colleagues provided network estimates for % weight loss for semaglutide, liraglutide, exenatide and GLP-1 RAs versus lifestyle modification alone.[24] As a group, GLP-1 RAs were associated with a 5.79% weight loss than lifestyle modification alone (95% CI 6.34 to 5.25), with semaglutide performing best of the individual drugs (MD −11.40%, 95% CI −12.51% to −10.29%), followed by liraglutide (MD −4.67%, 95% CI −5.28% to −4.07%) and exenatide (MD −3.53%, 95% CI −4.70% to −2.36%).

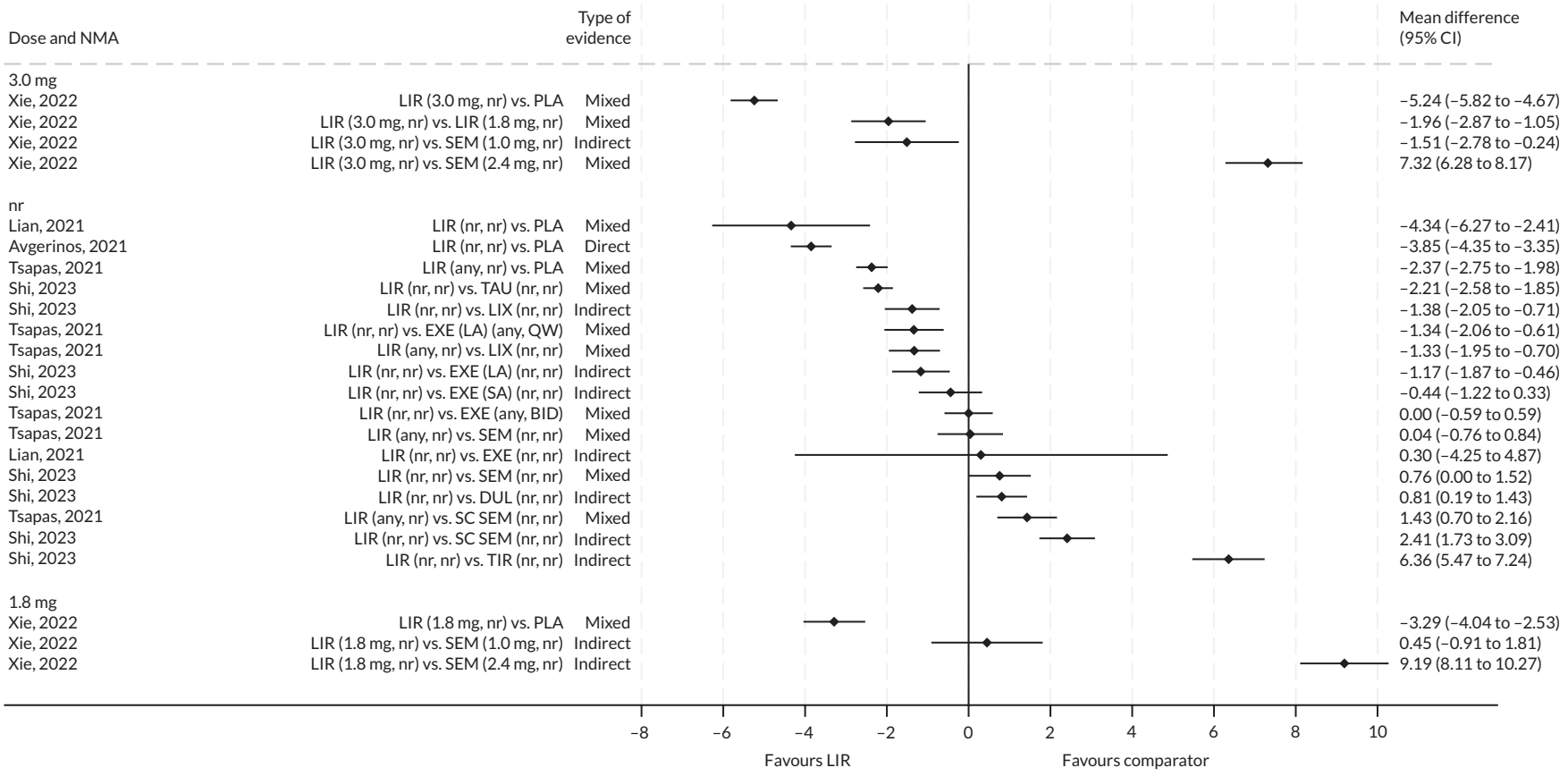


FIGURE 17 Effect of liraglutide (LIR) vs. all other treatments on change in body mass (kg) at multiple, combined or undefined time points. BID, twice daily; DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIX, lixisenatide; nr, not reported or combined doses; PLA, placebo; QW, once weekly; SA, short-acting; SC, subcutaneous; SEM, semaglutide. Direct, evidence comes from direct comparisons in the network only; Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

This article should be referenced as follows:
Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;30(63):429–502. https://doi.org/10.3310/SKHT8119

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FIGURE 18 Effect of tirzepatide (TIR) vs. all other treatments on change in body mass (kg) at multiple, combined or undefined time points. DUL, dulaglutide; EXE, exenatide; LA, long-acting; LIR, liraglutide; LIX, lixisenatide; nr, not reported or combined doses; SA, short-acting; SC, subcutaneous; SEM, semaglutide; (lifestyle modification alone). Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

Odds of achieving 5% weight loss

Figure 19 displays data from two reviews providing network estimates of the odds of participants achieving 5% weight loss.[16,24] Shi and colleagues reported that the GLP-1 RAs combined were more than six times more likely than lifestyle modification alone to achieve 5% weight loss, (OR 6.33, 95% CI 5.00 to 8.00).[24] From the same review, estimated network effects for semaglutide (OR 9.82, 95% CI 7.09 to 13.61), liraglutide (OR 4.91, 95% CI 3.78 to 6.38) and exenatide (OR 2.86, 95% CI 1.27 to 6.47) versus lifestyle modification alone were in the same direction, but with different magnitudes and levels of certainty.

Semaglutide 1.0 mg was associated with greater odds of achieving 5% weight loss than exenatide 10 µg, albeit with wide CIs (OR 3.35, 95% CI 1.03 to 11.38) and semaglutide 2.4 mg was 2.22–2.87 times more likely to achieve 5% weight loss than liraglutide 1.8 mg and 3.0 mg, respectively.

Odds of achieving 10% weight loss

Shi and colleagues provided network estimates for the odds of achieving 10% weight loss for semaglutide, liraglutide, exenatide and GLP-1 RAs versus lifestyle modification alone.[24] As a group, GLP-1 RAs were associated with a 7.83 greater likelihood of reaching 10% weight loss than lifestyle modification alone (95% CI 5.89 to 10.40), with semaglutide performing best (OR 13.32, 95% CI 9.94 to 17.83), followed by liraglutide (OR 4.80, 95% CI 3.60 to 6.41) and exenatide (OR 3.12, 95% CI 1.17 to 8.32).

Body mass index reduction

In terms of BMI reduction, Park and colleagues provided network estimates at < 48 weeks of treatment (MD −1.07 kg/m^2, 95% CI −1.79 to −0.35 kg/m^2), > 48 weeks of treatment (MD −1.39 kg/m^2, 95% CI −2.63 to −0.14 kg/m^2) and for all trial durations combined (MD −1.09 kg/m^2, 95% CI −1.70 to 0.47 kg/m^2).[18]

Lian and colleagues compared data for exenatide, liraglutide and placebo.[15] Both GLP-1 RAs were more effective than placebo (exenatide, MD −2.21 kg/m^2, 95% CI −3.92 to −0.44 kg/m^2; liraglutide, MD −1.07 kg/m^2, 95% CI −2.10 to −0.17 kg/m^2). There was no difference between the active conditions when they were compared.

Waist circumference reduction

Data for reduction in waist circumference was available from Park and colleagues.[18] GLP-1 RAs were associated with statistically significant loss in waist circumference at treatment durations of < 48 weeks (MD −4.33 cm, 95% CI −6.86 to −1.80 cm), and for all trial durations combined (MD −3.67 cm, 95% CI −5.98 to −1.36 cm), but not at durations > 48 weeks specifically (MD −1.78 cm, 95% CI −8.73 to 5.17 cm).[18]

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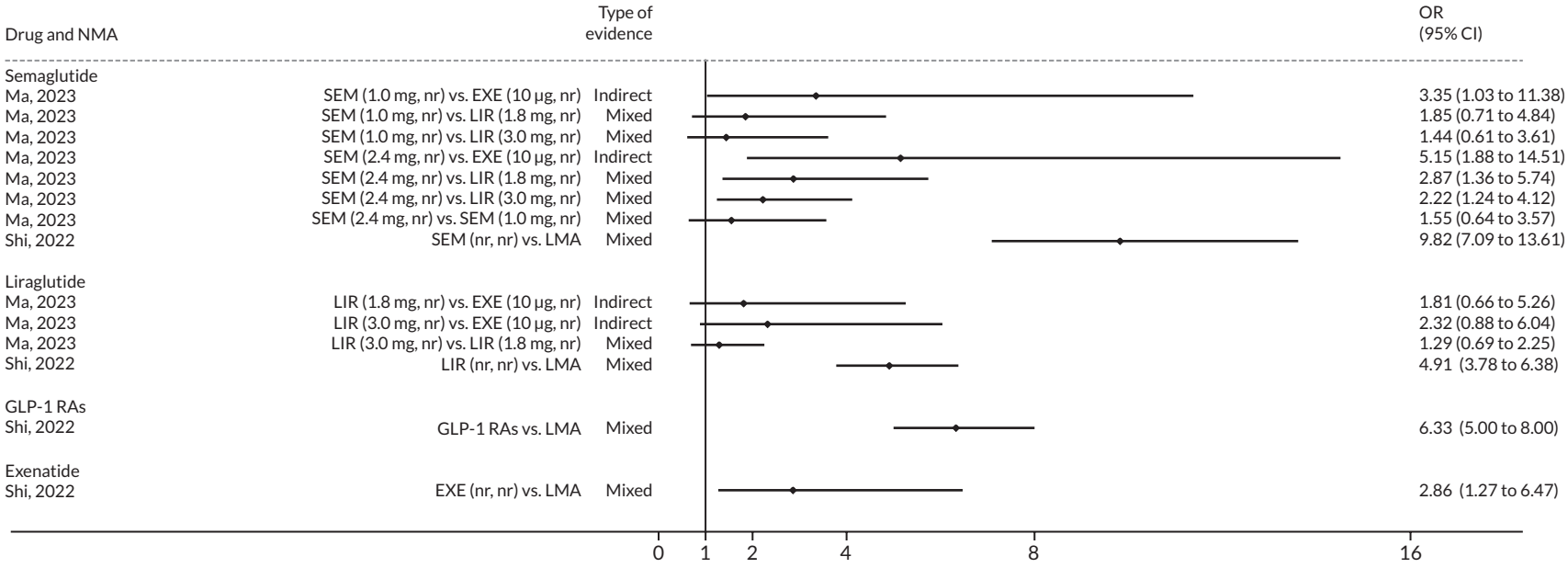


FIGURE 19 Odds of achieving 5% weight loss at multiple, combined or undefined time points, all comparisons. EXE, exenatide; LIR, liraglutide; LMA, lifestyle modification alone; nr, not reported or combined doses; SEM, semaglutide. Indirect, evidence comes from indirect comparisons in the network only; Mixed, evidence comes from a mix of direct and indirect comparisons in the network.

TABLE 6 Performance of GLP-1 RAs vs. placebo or lifestyle modification alone, in terms of absolute weight loss (kg) at 6 months, 12 months, > 12 months, and multiple combined time points

Drug	Dose	Weight loss at 6 months	Weight loss at 12 months	Weight loss at > 12 months	Weight loss at multiple/ combined time points
Semaglutide (oral, combined doses)	3 mg	**−0.78 (−1.45 to −0.12)**[23]	**−1.71 (−3.04 to −0.37)**[23]	–	–
	7 mg	**−1.87 (−2.58 to −1.16)**[23]	**−2.66 (−4.05 to −1.26)**[23]	–	–
	14 mg	**−2.16 (−3.37 to −0.97)**[23] **−3.06 (−3.57 to −2.55)**[14]	**−3.86 (−5.26 to −2.47)**[23]	–	–
	nr	**−3.40 (−4.51 to −2.33)**[12]	–	–	**−2.41 (−3.13 to −1.69)**[21] **−2.98 (−3.66 to −2.29)**[16+]
Semaglutide (SC)	nr	–	**−9.02 (−10.42 to −7.63)**[13] **−5.00 (−9.62 to −0.41)**[13]	–	**−3.80 (−4.46 to −3.14)**[21] **−4.62 (−5.22 to −4.03)**[20+]
	0.05 mg	**−1.51 (−8.25 to 5.23)**[23]	–	–	–
	0.1 mg	**−2.02 (−8.60 to 4.56)**[23]	–	–	–
	0.5 mg	**−5.51 (−9.45 to −1.57)**[23]	–	**−3.84 (−5.94 to −2.09)**[11]	–
	1.0 mg	**−7.72 (−11.68 to −3.75)**[23]	–	**−4.04 (−5.61 to −2.47)**[11]	**−5.67 (−7.84 to −3.52)**[16] **−3.74 (−4.87 to −2.61)**[22]
	2.4 mg	–		–	**−11.51 (−12.83 to −10.21)**[16] **−12.47 (−13.25 to −11.69)**[22]
Liraglutide	0.6 mg	–	–	−1.45 (−6.08 to 3.20)[11]	–
	1.2 mg	–	–	−2.72 (−6.43 to 1.09)[11]	–
	1.8 mg	**−2.35 (−3.20 to −1.50)**[23]	–	−3.09 (−6.32 to 0.20)[11]	**−3.24 (−4.43 to −2.04)**[16] **−3.29 (−4.04 to −2.53)**[22]
	3.0 mg	–	**−5.01 (−5.95 to −4.07)**[13]	−4.30 (−9.20 to 0.57)[11]	**−4.65 (−5.60 to −3.69)**[16] **−5.24 (−5.82 to −4.67)**[22]
	nr	**−2.44 (−2.87 to −2.04)**[12]	–	**−3.39 (−4.18 to −2.60)**[10]	**−2.37 (−2.75 to −1.98)**[21] **−3.85 (−4.35 to −3.35)**[10] **−4.34 (−6.27 to −2.41)**[15] **−2.21 (−2.58 to −1.85)**[20+]

continued

This article should be referenced as follows:
Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;30(63):429–502. https://doi.org/10.3310/SKHT8119

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TABLE 6 Performance of GLP-1 RAs vs. placebo or lifestyle modification alone, in terms of absolute weight loss (kg) at 6 months, 12 months, > 12 months, and multiple combined time points. Values indicate network estimates (95% CIs) (*continued*)

Drug	Dose	Weight loss at 6 months	Weight loss at 12 months	Weight loss at > 12 months	Weight loss at multiple/ combined time points
Exenatide	Short-acting	**−1.71 (−2.12 to −1.29)**[12]	–	–	**−1.77 (−2.47 to −1.07)**[20+]
	Long-acting	**−1.63 (−2.13 to −1.11)**[12]	−1.21 (−4.73 to 2.25)[12]	–	**−1.03 (−1.68 to −0.38)**[21] **−1.05 (−1.67 to −0.42)**[20+]
	nr	–	–	**−4.50 (−6.93 to −2.07)**[10]	**−2.37 (−2.87 to −1.87)**[21] **−4.04 (−8.64 to −0.57)**[15] **−4.35 (−5.53 to −3.17)**[10]
	2.0 mg	–	–	−0.31 (−4.93 to 4.30)[11]	–
	10 µg	–	–	–	−1.03 (−2.18 to 0.09)[16]
Tirzepatide (SC)	5 mg	**−9.23 (−13.24 to −5.22)**[23]	–	–	–
	10 mg	**−11.21 (−15.21 to −7.21)**[23]	–	–	–
	15 mg	**−12.11 (−16.14 to −8.09)**[23]	–	–	–
	nr				**−8.57 (−9.40 to−7.75)**[20+]
Dulaglutide	1.5 mg		–	–	−1.04 (−2.96 to 0.90)[16+]
	nr	**−1.23 (−1.80 to −0.64)**[12]	–	–	**−1.40 (−1.93 to −0.88)**[20]
Lixisenatide	nr	**−0.91 (−1.32 to −0.52)**[12]	–	–	**−1.04 (−1.56 to −0.52)**[21] **−0.83 (−1.4 to −0.26)**[20+]
GLP-1 RAs	nr	**−1.45 (−1.72 to −1.18)**[17]	–	–	

Bold formatting, statistically significant difference; [+], compared with TAU; nr, not reported or combined doses; SC, subcutaneous.

Note
Values indicate network estimates (95% CIs).

This article should be referenced as follows: Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;30(63):429–502. https://doi.org/10.3310/SKHT8119

Appendix 7 Summary of findings from non-prioritised reviews

First author, date	Population	NMA framework model used	RCTs in review (*n*)/ RCTs in BW NMA (*n*)	Intervention GLP-1 RAs (dose, frequency if available)	Comparator (dose, frequency if available)	Time point or range	Weight outcomes of interest	Summary of findings
Alhindi, 2022[32]	Adults with T2DM	Frequentist RE	12/12	Semaglutide Once-weekly subcutaneous semaglutide (0.5–1.0 mg) or oral semaglutide (3–14 mg)	Placebo or another GLP-1 RA comparator [liraglutide (1.2 mg), exenatide ER (2.0 mg), and dulaglutide (1.5 mg)]	26–52 weeks (amalgamated)	Body weight (kg) lost	Oral semaglutide 14.0 mg was associated with significant reduction in body weight [−3.17 kg (95% CI −3.89 to −2.45)] compared to placebo. Subcutaneous semaglutide was associated with greater weight loss than oral semaglutide [−1.08 kg (95% CI −2.04 to −0.12)]. The incidence of AEs (nausea, diarrhoea, dyspepsia and vomiting) was greater in oral semaglutide compared to placebo, liraglutide (1.2 mg), exenatide (ER, 2.0 mg), and dulaglutide 1.5 mg but not compared to subcutaneous Semaglutide. **Author conclusion: Oral semaglutide was non-inferior to subcutaneous semaglutide and superior to placebo and another GLP-1 RA in reducing body weight.**
Alkhezi, 2023[27]	Obesity without diabetes BMI ≥ 30 kg/m^2 or, alternatively, BMI ≥ 27 kg/m^2 with comorbidity	Bayesian RE	7/7	Semaglutide, liraglutide, tirzepatide Daily liraglutide 3 mg, daily semaglutide 0.05–0.4 mg, weekly semaglutide 2.4 mg and tirzepatide 5, 10, and 15 mg weekly	Placebo or another GLP-1 RA, or a different dose of the same	52–72 weeks (amalgamated)	Body weight (kg) lost Body weight (%) lost Proportion achieving targets of weight loss	Weekly tirzepatide 10 and 15 mg resulted in more weight loss than weekly semaglutide 2.4 mg, daily semaglutide 0.4 mg, or liraglutide 3 mg. Tirzepatide and weekly semaglutide demonstrated comparable results but with significantly higher odds of achieving ≥ 5–20% weight loss compared with liraglutide. GLP-1 RAs triggered more gastrointestinal AEs than placebo, with no in-between difference. **Author conclusion: Tirzepatide was associated with more significant weight loss outcomes than other GLP-1 RAs**
Chubb, 2021[25]	Adults with T2DM inadequately controlled on basal insulin	Bayesian FE	7/7	Semaglutide Once-daily oral 7 and 14 mg	Injectable GLP-1 RAs approved for the treatment of T2DM Exenatide twice-daily, liraglutide once daily, lixisenatide once-daily, dulaglutide once-weekly	24–30 weeks	Body weight (kg) lost	Once daily oral semaglutide 14 mg was associated with significantly greater loss than exenatide 2.0 mg and lixisenatide 20 µg (−2.21 and −2.39 kg, respectively). **Author conclusion: Once-daily oral semaglutide 14 mg was similar or more effective for weight loss than comparable injectable GLP-1 RAs.**

continued

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First author, date	Population	NMA framework model used	RCTs in review (*n*)/ RCTs in BW NMA (*n*)	Intervention GLP-1 RAs (dose, frequency if available)	Comparator (dose, frequency if available)	Time point or range	Weight outcomes of interest	Summary of findings
Guan, 2022[28]	Adults with T2DM	Bayesian RE	8/8	Tirzepatide Weekly 5, 10 and 12 mg	Placebo or therapeutic interventions (once weekly semaglutide or dulaglutide)	12–52 weeks (amalgamated)	Body weight (kg) lost	Weekly tirzepatide 15 mg resulted in significantly greater weight loss than once weekly semaglutide or dulaglutide combined [−8.60 (−12.08, −5.12)] or placebo [−4.40 (−7.80, −1.00)]. Weekly tirzepatide 10 mg resulted in significantly greater weight loss than once weekly semaglutide or dulaglutide [−6.00 (−9.40, −2.60)] or placebo [−1.45 (−5.36, 2.46)]. **Author conclusion: Compared with GLP-1 RAs (semaglutide and dulaglutide once weekly), 10 and 15 mg of tirzepatide showed statistically significant reductions in body weight.**
Ida, 2021[30]	Adults with T2DM (excluding gestational diabetes)	NR NR	18/3	Semaglutide, liraglutide Doses were collapsed into individual treatment arms	Placebo	8–52 weeks (amalgamated)	Body weight (kg) lost Fat-free mass (kg) lost	When compared with placebo, semaglutide showed a significant weight loss (MD −4.10, 95% CI −5.77 to −2.43). Semaglutide showed a significant decrease in fat-free mass compared with placebo (MD −1.68, 95% CI −2.84 to −0.52). **Author conclusion: Although semaglutide has a large weight loss effect, it is important to pay attention to muscle loss because a decrease in fat-free mass was observed.**
Jiang, 2021[31]	Adults with T2DM	Frequentist RE	54/52	Dulaglutide, liraglutide, exenatide, lixisenatide, loxanitide At various doses and regimens	Placebo	24–30 weeks	Body weight (kg) lost	Nine of the 18 regimens significantly reduced body weight in relation to placebo. **Author conclusion: The effects of GLP-1 regimens on weight were relatively mixed.**
Smith, 2022[26]	Adults overweight and obese – BMI ≥ 27 kg/m^2 and one weight-related comorbidity; BMI ≥ 30 kg/m^2 (with weight-related comorbidities); BMI ≥ 30 kg/m^2 (without weight-related comorbidities)	Bayesian FE	41/6	Semaglutide 2.4 mg weekly	Liraglutide and placebo (and diet and exercise)	52 weeks	% weight CFB *N* losing > 5% body weight	In all populations, semaglutide 2.4 mg was associated with a greater percentage weight loss with 52 weeks of treatment vs. all available comparators. In all populations, semaglutide was associated with a higher likelihood of participants losing ≥ 5% of baseline fasting body weight at 12 weeks vs. all available comparators. **Author conclusion: Semaglutide 2.4 mg demonstrated effective weight loss (≥ 5%) in the total population and all subpopulations of glucose tolerance vs. active comparators**

First author, date	Population	NMA framework model used	RCTs in review (*n*)/ RCTs in BW NMA (*n*)	Intervention GLP-1 RAs (dose, frequency if available)	Comparator (dose, frequency if available)	Time point or range	Weight outcomes of interest	Summary of findings
Vosoughi, 2021[29]	Adults with obesity or overweight (BMI) > 25 kg/m^2 in white, Hispanic, and black individuals, and BMI > 23 kg/m^2 in Asian populations. Patients with or without diabetes mellitus or NAFLD were included	Frequentist RE	64/60	Semaglutide, dulaglutide, liraglutide, exenatide, lixisenatide At various doses and regimens	Placebo	12–160 weeks (median 26)	Body weight (kg) lost	Compared with placebo, dulaglutide 1.5 mg, exenatide IR, liraglutide 1.8 mg, liraglutide > 1.8 mg, semaglutide subcutaneous < 2.4 mg, semaglutide subcutaneous 2.4 mg, and semaglutide oral were all associated with significant excess weight loss. Dulaglutide < 1.5 mg, exenatide ER, lixisenatide; and taspoglutide did not show a statistically significant excess weight loss in comparison with placebo. **Author conclusion: Semaglutide subcutaneous 2.4 mg was associated with excess weight loss compared to all other active agents**

Unless otherwise stated, 'adults' is defined as 18 years old and above. ER, extended release; FE, fixed effect; IR, immediate-release; MD, mean difference; NR, not reported; RE, random effect; T1DM, type 1 diabetes mellitus.

This article should be referenced as follows:
Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

Appendix 8 Summary of exercise to identify new, relevant randomised controlled trial

We searched for RCTs published since October 2022, comparing liraglutide, semaglutide and/or tirzepatide with placebo, usual care, or one another. Trials had to be conducted in overweight or obese adults, and not already be included in systematic reviews included in our scoping review.

Methods

Search

We searched MEDLINE (via Ovid) on 1 August 2023, with the following search strategy:

Ovid MEDLINE(R) ALL <1946 to 31 July 2023>

1 randomized controlled trial.pt.597462
2 controlled clinical trial.pt.95394
3 randomized.ab.612072
4 placebo.ab.240333
5 drug therapy.fs.2611770
6 randomly.ab.413620
7 trial.ab.658293
8 groups.ab.2550454
9 1 or 2 or 3 or 4 or 5 or 6 or 7 or 85719422
10 exp animals/ not humans.sh.5142879
11 9 not 104992963
12 Obesity/216640
13 overweight/33567
14 Weight Loss/43674
15 overweight.tw.87328
16 obes*.tw.374566
17 (weight loss or weight control).tw. 112625
18 (reduc* adj5 weight).tw.55966
19 (body mass index adj5 "25").tw. 7241
20 (body mass index adj5 "30").tw. 7934
21 or/12-20551101
22 semaglutide*.tw.1129
23 wegovy*.tw.10
24 Ozempic*.tw.13
25 Tirzepatide*.tw.239
26 Mounjaro*.tw.9
27 liraglutide*.tw.3662
28 Saxenda*.tw.30
29 Victoza*.tw.63
30 Dulaglutide*.tw.653
31 Trulicity*.tw.19
32 glucagon like peptid* one.tw.10
33 "glucagon like peptid* 1".tw.14887
34 *glucagon-like peptides/ or exp glucagon-like peptide 1/11603
35 glp-1*.tw.15001
36 or/22-3522456
37 11 and 21 and 363629
38 **limit 37 to dt=20221001-20230801383**

We also searched Cochrane Central Register of Controlled Trials (CENTRAL).

Inclusion criteria

Participants/population

Adults (18 or above) with mean/median BMI of 25 or above (or 23 in Asian populations) at baseline.

Intervention

Randomised controlled trials which evaluate any of the following:

- Semaglutide (also known as Ozempic, Rybelsus, Wegovy)
- Liraglutide (also known as Victoza, Saxenda)
- Tirzepatide (also known as Mounjaro)

Any dosage or mode of delivery (e.g. oral or subcutaneous) is of interest. Interventions may be drug-only or as part of multimodal interventions, for example, GLP-1 RA with dietary modifications.

Comparator(s)/control

Another GLP-1 RA or placebo/usual care.

Outcomes

A measure of weight loss such as change in mass or BMI from baseline was required for inclusion.

Date

Studies published since October 2022, based on the search dates in included systematic reviews.

Process

Records identified at title and abstract were independently screened by two reviewers (MN, SF) with disagreements resolved by discussion. The full-texts of studies included at title and abstract were sought and taken forward to full-text screening. An additional stage at full-text screening involved checking that studies were not already captured by the systematic reviews included in the main scoping review.

Results

Study selection

Database searches identified 900 records. After deduplication, we screened 574 records at title and abstract, with 25 taken forward to full-text screening. Reasons for exclusion at full-text screening were:

- 3 studies were conference abstracts
- 1 study did not have a relevant intervention
- 4 studies did not have a relevant outcome
- 6 studies were already captured by reviews in our scoping review.

Appendix 8, *Table 7* displays key characteristics of the 11 novel trials identified by the exercise.

This article should be referenced as follows:
Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

DOI: 10.3310/SKHT8119

TABLE 7 Key characteristics of RCTs identified by further scoping

Study	Title	Trial arms	*N*	Relevant outcomes	Outcome time points (weeks)	Setting	Country	Major comorbidities
Allison, 2022[39]	A pilot RCT of liraglutide 3.0 mg for binge eating disorder	Liraglutide 3.0 mg vs. placebo	37	BW, WC	1, 7, 9, 11, 13, 15, 17	Community	USA	Binge eating disorder
Elkind-Hirsch, 2022[40]	Liraglutide 3 mg on weight, body composition, and hormonal and metabolic parameters in women with obesity and PCOS: a randomised placebo-controlled-phase 3 study	Liraglutide 3.0 mg vs. placebo	82	BW, WC, BMI, RA5%	32	Hospital-based outpatient centre	USA	PCOS
Garvey, 2022[41]	Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial	Once-weekly subcutaneous semaglutide 2.4 mg vs. placebo (both plus behavioural intervention)	304	BW, RA5%	104	Community	USA, Canada, Spain, Hungary, Italy	Adults with obesity or with overweight and at least one weight-related comorbidity, without diabetes.
Garvey, 2023[42]	Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial	Once-weekly, subcutaneous tirzepatide (10 mg or 15 mg) or placebo	938	BW, RA5/10/15/20%, WC	72	Multicentre, worldwide	77 sites across Argentina, Brazil, India, Japan, Russia, Taiwan and the USA	Type 2 diabetes
Heise, 2023[43]	Tirzepatide reduces appetite, energy intake and fat mass in people with type 2 diabetes	Once weekly 15 mg tirzepatide, 1 mg semaglutide, or placebo	118	BW, BC	5, 9, 13, 17, 21, 25, 28	Community	Germany	Type 2 diabetes
Jiang, 2022[44]	Efficacy and safety of liraglutide in patients with T2DM and severe obstructive sleep apnoea	Liraglutide was injected subcutaneously once daily up to 1.8 mg/day vs. control group (not placebo).	90	BW	4, 8, 12	Outpatients	China	Diabetes and severe obstructive sleep apnoea
Knop, 2023[45]	Oral semaglutide 50 mg taken once per day in adults with overweight or obesity (OASIS 1): a randomised, double-blind, placebo-controlled, phase 3 trial	Oral semaglutide escalated to 50 mg/day or placebo	667	BW%, BWkg, BMI, WC, RA5/10/15/20%	BW: 4, 8, 12, 16, 20, 28, 36, 44, 52, 60, 68, 75; WC: 36, 68	Outpatients	50 outpatient centres in 9 countries across east Asia, Europe and North America	*n*/a
Mashayekhi, 2023[46]	Comparative effects of weight loss and incretin-based therapies on vascular endothelial function, fibrinolysis and inflammation in individuals with obesity and prediabetes: A RCT	Liraglutide (up to 1.8 mg/day), hypocaloric diet or sitagliptin	93	BWkg	2, 14	Community	USA	Prediabetes

TABLE 7 Key characteristics of RCTs identified by further scoping (*continued*)

Study	Title	Trial arms	*N*	Relevant outcomes	Outcome time points (weeks)	Setting	Country	Major comorbidities
Mok, 2023[47]	Safety and efficacy of liraglutide, 3.0 mg, once daily vs. placebo in patients with poor weight loss following metabolic surgery: the BARI-OPTIMISE RCT	Liraglutide, 3.0 mg once daily vs. placebo	70	BW%, BWkg, BC, RA5%	24	Community	UK	Post-1 year metabolic surgery
Yu, 2022[48]	Effects of liraglutide or lifestyle interventions combined with other antidiabetic drugs on abdominal fat distribution in people with obesity and T2DM evaluated by the energy spectrum CT: a prospective randomised controlled study	Liraglutide up to 1.8 mg vs. control (lifestyle)	96	BWkg, WC, BMI, BC	12	Community	China	Type 2 diabetes
Zhang, 2023[49]	Effects of a dulaglutide plus calorie-restricted diet vs. a calorie-restricted diet on visceral fat and metabolic profiles in women with PCOS: a RCT	Dulaglutide (subcutaneous once-weekly) combined with CRD, or CRD alone	68	BW%, BWkg, BMI	Until 7% BW loss, median 6.0 (int) and 9.5 (con) weeks	Community	China	PCOS

BC, body composition; BW, body weight; BWkg, absolute change in body weight in kg; BW%, percentage change in body weight; CRD, calorie restricted diet; RA, responder analysis (e.g. how many participants achieved target weight loss) at 5/10/15/20%; WC, waist circumference.

This article should be referenced as follows:
Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

Appendix 9 Findings relating to the safety of glucagon-like peptide 1 receptor agonists

The following section provides a detailed description of NMAs of safety outcomes and their findings.

Nine of the 14 prioritised reviews conducted safety NMAs.[10,12,13,16,17,20,22–24] Seven produced NMAs for SAEs as a composite outcome,[10,16,20,23] five reviews produced NMAs on treatment discontinuation due to AEs,[10,13,16,19,23] and all but one review[16] provided NMA data on a range of specific AEs/SAEs. NMAs were also provided on total AEs[22] and any AEs as composite outcomes.[23] Two reviews provided NMA safety outcomes over specified time points: Zaazouee; 26, 30–40 and 52 weeks,[12] and Hussein; 24 and 52 weeks.[12,23] For the other reviews, the time points at which safety outcomes were collected were not disaggregated but ranged from 12 to 104 weeks.[10,13,17,20,22] provides an overview of the risks/odds of SAEs, AEs, total AEs and discontinuation due to AEs between interventions, with odds/risk ratios and CIs provided for statistically significant findings. Complete reporting of effects and CIs is provided in *Report Supplementary Material 1*, *Table 3*.

Serious adverse events and adverse events

Liraglutide

Four reviews provided NMAs for SAEs that included liraglutide.[10,16,22,23] Across these reviews, liraglutide was reported 35 times, doses of which included 1.0, 1.2, 1.8 and 3.0 mg. Liraglutide was compared against placebo eight times, at doses of 1.2, 1.8 and 3.0 mg (and one unspecified dose). The risk of SAEs was similar across doses of 1.2 and 1.8 mg. There were two comparisons of liraglutide 3.0 mg with placebo, one review found risks to be similar,[16] the other associated this dose with a higher risk of SAE (OR 1.47, 95% CI 1.07 to 2.02).[22]

Liraglutide was not associated with increased risks of SAE when compared with all other interventions (oral semaglutide 3.0, 7, 14 mg, subcutaneous semaglutide 0.5, 1.0, 2.4 mg exenatide 10 µg, dulaglutide 1.5 mg, tirzepatide 5, 10 and 15 mg).

The incidence of any AE was reported as a composite outcome in one review.[23] Liraglutide 1.2 mg was compared with placebo, subcutaneous tirzepatide 5, 10 and 15 mg, subcutaneous semaglutide 0.5, 1.0 mg (once weekly) and oral semaglutide 14 mg (once daily) at 30–40 weeks. At 52 weeks liraglutide 1.8 mg was compared with oral (once daily) semaglutide 3.0, 7 and 14 mg and placebo. There were no increased risks of AEs across all comparisons. Total AEs were reported in another review,[22] and liraglutide 1.8 and 3.0 mg were compared with placebo, semaglutide 1.0 and 2.4 mg. Liraglutide 3.0 mg was associated with an increased risk of AEs compared to placebo (OR 2.35, 95% CI 1.82 to 3.02), and risks were similar across all other comparisons.

Semaglutide

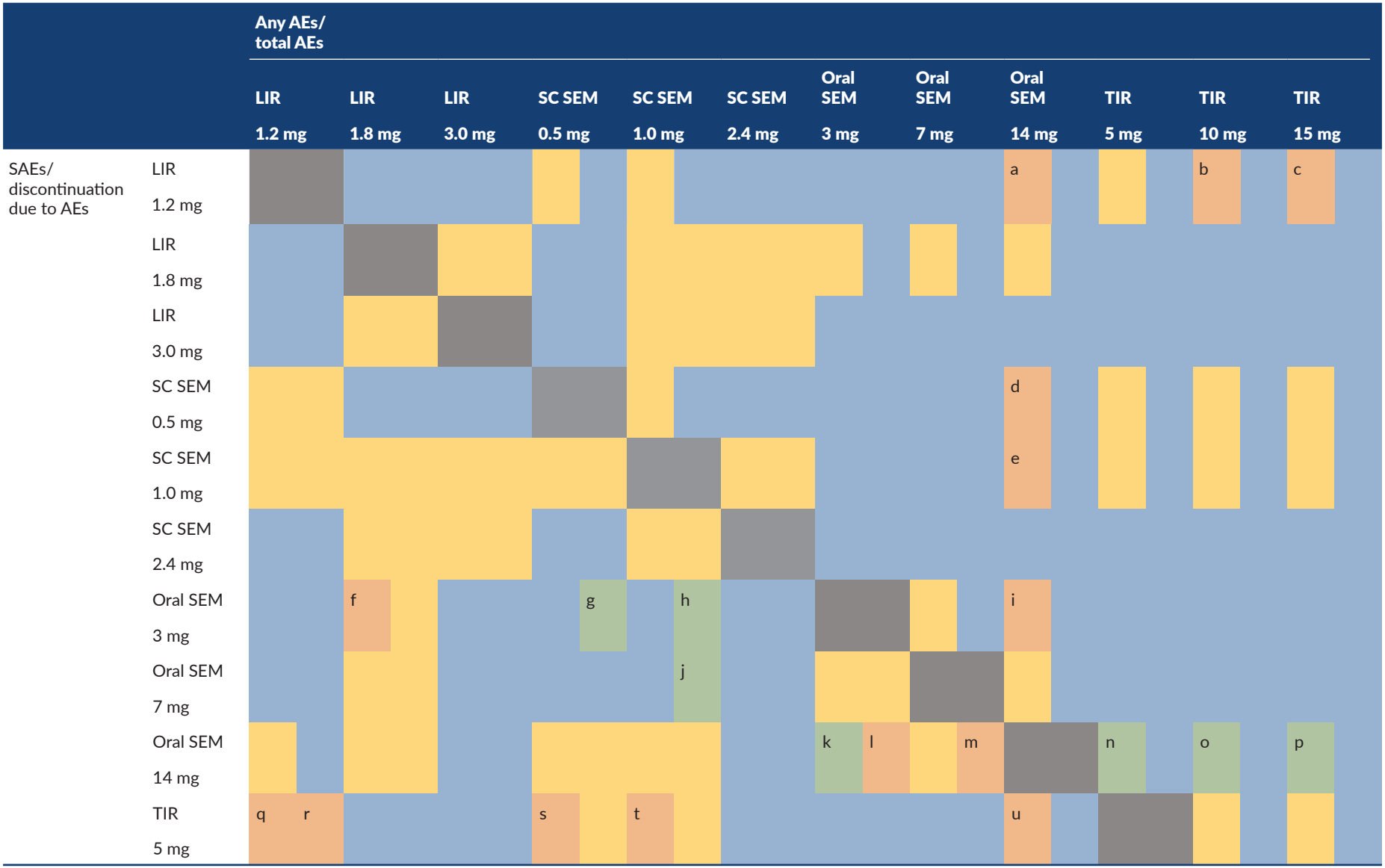
There were 46 comparisons involving semaglutide for assessment of SAEs at a NMA level, from three reviews.[16,22,23] Semaglutide doses included subcutaneous semaglutide (once weekly) 0.5, 1.0 and 2.4 mg and oral semaglutide (once daily) 3, 7, 14 mg. There were 13 comparisons of semaglutide against placebo, and across most comparisons, risks were found to be similar. The exception to this was in the review by Ma and colleagues who reported that subcutaneous semaglutide 2.4 mg was associated with a higher risk of SAEs (OR 1.42, 95% CI 1.01 to 1.97);[16] however, risks were reported to be similar for the same comparison in the review by Xie and colleagues.[22]

The risk of SAEs was similar when subcutaneous semaglutide 1.0 and 2.4 mg were compared with one another (two comparisons[16,22]), liraglutide 1.8 and 3.0 mg (two comparisons),[16,22] exenatide 10 µg (one comparison),[16] and dulaglutide 1.5 mg (one comparison).[16] Risks were also similar for total SAEs for doses of subcutaneous semaglutide 1.0 and 2.4 mg, compared with liraglutide 1.8 and 3.0 mg.[16,22]

Zaazouee compared oral semaglutide 3, 7 and 14 mg with one another at 26 weeks, and SAE risks were similar for all.[23] At 52 weeks, the same doses of oral semaglutide were compared, along with a comparison with liraglutide 1.8 mg, and risks were similar across most of these comparisons. The only dose of semaglutide that was found to increase the risk of SAE was oral semaglutide 3.0 mg when compared with liraglutide 1.8 mg (RR 2.44, 95% CI 1.19 to 5.0). At 30–40 weeks, Zaazouee compared oral semaglutide 14 mg; subcutaneous semaglutide 0.5 and 1.0 mg; liraglutide 1.2 mg; and subcutaneous tirzepatide 5, 10 and 15 mg.[23] Semaglutide was not associated with any increased risks of SAEs in those comparisons.

Zaazouee and colleagues reported 14 comparisons involving semaglutide for the assessment of any AE (as a composite outcome) at a NMA level.[23] At 26 weeks, risks were similar when doses of oral semaglutide 3.0, 7 and 14 mg were compared with one another and with placebo. Oral semaglutide 14 mg was associated with a small increased risk of AEs compared to placebo at 52 weeks (RR 1.14, 95% CI 1.05 to 1.24).[23] At 30–40 weeks, oral semaglutide 14 mg was associated with greater risk

TABLE 8 Summary of safety data comparing interventions for AEs, SAEs and discontinuation due to AEs



continued

This article should be referenced as follows: Nunns M, Febrey S, Buckland J, Abbott R, Whear R, Bethel A, *et al.* The quantity, quality and findings of network meta-analyses evaluating the effectiveness of GLP-1 RAs for weight loss: a scoping review. *Health Technol Assess* 2026;**30**(63):429–502. https://doi.org/10.3310/SKHT8119

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TABLE 8 Summary of safety data comparing interventions for AEs, SAEs and discontinuation due to AEs (*continued*)

	Any AEs/ total AEs											
	LIR 1.2 mg	LIR 1.8 mg	LIR 3.0 mg	SC SEM 0.5 mg	SC SEM 1.0 mg	SC SEM 2.4 mg	Oral SEM 3 mg	Oral SEM 7 mg	Oral SEM 14 mg	TIR 5 mg	TIR 10 mg	TIR 15 mg
TIR 10 mg									y			
TIR 15 mg									ae			

LIR, liraglutide; SC, subcutaneous; SEM, semaglutide; TIR, tirzepatide; a, RR 1.69, 95% CI 1.28 to 2.27;[23] b, RR 1.16, 95% CI 1.02 to 1.33;[23] c, RR 1.18, 95% CI 1.03 to 1.33;[23] d, RR 1.54, 95% CI 1.18 to 2.00;[23] e, RR 1.56, 95% CI 1.20 to 2.04;[23] f, RR 2.44, 95% CI 1.19 to 5.00 (52 weeks);[23] g, RR 0.56, 95% CI 0.35 to 0.88 (52 weeks);[23] h, RR 0.43, 95% CI 0.27 to 0.68 (52 weeks);[23] i, RR 1.14, 95% CI 1.02 to 1.27 (52 weeks);[23] j, RR 0.48, 95% CI 0.31 to 0.76 (52 weeks);[23] k, RR 0.55, 95% CI 0.31 to 0.98 (52 weeks);[23] l, RR 1.96, 95% CI 1.37 to 2.78 (52 weeks);[23] m, RR 1.75, 95% CI 1.23 to 2.4 (52 weeks);[23] n, RR 0.63, 95% CI 0.48 to 0.84;[23] o, RR 0.69, 95% CI 0.52 to 0.91;[23] p, RR 0.69, 95% CI 0.52 to 0.91;[23] q, RR 2.86, 95% CI 1.23 to 6.67;[23] r, RR 2.56, 95% CI 1.16 to 5.56;[23] s, RR 2.56, 95% CI 1.30 to 5.26;[23] t, RR 2.56, 95% CI 1.35 to 4.76;[23] u, RR 3.70, 95% CI 1.54 to 9.09;[23] v, RR 3.57, 95% CI 1.69 to 7.69;[23] w, RR 2.78, 95% CI 1.47 to 5.26;[23] x, RR 2.48, 95% CI 1.47 to 3.57;[23] y, RR 2.86, 95% CI 1.15 to 7.14;[23] z, RR 3.57, 95% CI 1.69 to 7.69;[23] aa, RR 2.13, 95% CI 1.04 to 4.00;[23] ab, RR 2.78, 95% CI 1.47 to 5.26;[23] ac, RR 2.08, 95% CI 1.09 to 4.00;[23] ad, RR 2.08, 95% CI 1.23 to 3.57;[23] ae, RR 3.03, 95% CI 1.25 to 7.69.[23]

Note

Top right of grid is for AEs (any/total), the risk estimate being for the column-defining intervention compared with row-defining intervention (comparator); bottom left is for the outcomes SAEs/discontinuation due to AEs, the risk estimate being for the row-defining intervention compared with column-defining intervention (comparator). Green cell, indicates lower risk for the intervention; yellow cell, indicates risks are similar between intervention and comparator; red cell, indicates increased risk for the intervention; blue cell, no comparisons available.

of AEs across all comparisons (placebo, subcutaneous semaglutide 0.5 and 1.0 mg, liraglutide 1.2 mg and tirzepatide 5, 10 and 15 mg), the risk being greatest when compared with placebo (RR 1.79, 95% CI 1.41 to 2.22). The risk of AEs was similar across all other comparisons. Total AEs reported by Xie and colleagues showed an increased odds with semaglutide 1.0 (OR 1.82, 95% CI 1.29 to 2.56) and 2.4 mg compared to placebo (OR 2.36, 95% CI 1.84 to 3.03), but risks were similar when semaglutide doses were compared with one another and with liraglutide 1.8 and 2.4 mg.[22]

Tirzepatide

All NMA data relating to SAEs and AEs (as a composite outcome) involving tirzepatide came from one review.[23] There were 18 comparisons for each outcome; these collected at 30–40 weeks. Doses of subcutaneous tirzepatide (once weekly) were 5, 10 and 15 mg, and these were compared to placebo, oral semaglutide 14 mg, subcutaneous semaglutide 0.5 and 1.0 mg and liraglutide 1.2 mg. Ten of these comparisons for SAEs suggested that tirzepatide was associated with increased risk (and four for AEs), though wide CIs suggest some ambiguity.

Tirzepatide at doses of 5 and 15 mg was associated with increased risk of SAEs when compared with placebo, subcutaneous semaglutide 0.5 and 1.0 mg; tirzepatide 5 mg versus placebo associated with the greatest risk (RR 3.16, 95% CI 1.31 to 7.62). The same comparisons with tirzepatide 10 mg, however, found no difference in risk. When all three tirzepatide doses were compared with liraglutide 1.2 mg, only the 5 mg dose was associated with an increased risk (RR 2.85, 95% CI 1.23 to 6.67). All doses of tirzepatide were associated with increased risk of SAEs (but not AEs) when compared with oral semaglutide 14 mg, the risk greatest again with tirzepatide 5 mg (RR 3.70, 95% CI 1.54 to 9.10). When all doses of tirzepatide were compared with one another, risks were found to be similar for both SAEs and AEs. Where tirzepatide 5 mg had been often associated with increased SAE risk, the picture was different for AEs. Compared with placebo and liraglutide 1.2 mg, risks were similar for tirzepatide 5 mg, while 10 and 15 mg increased AE risk. AE risks were similar for all three doses when compared to subcutaneous semaglutide 0.5 and 1.0 mg. NMA data for tirzepatide comparisons was informed by a single RCT.[35]

Discontinuation due to adverse events

Five reviews provided NMAs for discontinuation due to AEs that included liraglutide, semaglutide and tirzepatide.[10,13,16,23,24] Across these reviews for this outcome, liraglutide was reported 33 times (doses including 1.2, 1.8 and 3.0 mg and a variety of doses combined into one variable, referred to hereafter as 'combined doses'), semaglutide 105 times (doses including subcutaneous 0.5, 0.75, 1.0 mg); oral 2.5, 3.0, 5, 7, 10, 14, 20 and 40 mg and combined doses and tirzepatide 21 times (doses 5, 10 and 15 mg). Most comparisons came from the review by Zaazouee and colleagues.[23] Comparators included placebo, lifestyle modifications alone, standard care, exenatide (a range of doses, 10 µg and 2.0 mg) and dulaglutide 1.5 mg. Risks were similar when liraglutide 1.2 mg were compared with placebo at 30–40 weeks.[23] All other doses of liraglutide compared with placebo/standard care/lifestyle modifications alone were associated with an increased risk of discontinuations due to AEs.[10,13,16,23,24] Two reviews[13,24] compared semaglutide (combined doses) to either placebo/standard care/lifestyle modifications alone and found semaglutide to be associated with an increased risk of discontinuation (placebo: OR 1.95, 95% CI 1.35 to 2.81).[13] Zaazouee and colleagues reported risks to be similar with most oral doses of semaglutide compared to placebo, with the exception of oral semaglutide 14 mg (after 26 weeks), which was associated with an increased risk (RR 3.07, 95% CI 1.63 to 5.77).[23] Compared to placebo, risks were similar for subcutaneous semaglutide 1.0 mg after 26 weeks, but at the two other time points in the Zazaouee review (after 30–40 weeks and after 52 weeks), both subcutaneous semaglutide doses (0.5 and 1.0 mg) were associated with increased risks of discontinuation due to AEs.[23] Risks were reported to be similar for subcutaneous semaglutide 1.0 mg in the review by Ma and colleagues, but subcutaneous semaglutide 2.4 mg compared with placebo was associated with a higher risk of discontinuation (OR 1.88, 95% CI 1.12 to 2.99).[16] All three doses of tirzepatide were associated with a higher risk of discontinuation, the highest with tirzepatide 10 mg (RR 8.48, 95% CI 3.24 to 22.24), although very wide CIs suggests some caution should be taken when interpreting these results.[23]

Tirzepatide 10 and 15 mg were associated with higher risks of discontinuation compared with other interventions (subcutaneous semaglutide 0.5, 0.75 and 1.0 mg, liraglutide 1.2 mg and dulaglutide 1.5 mg).[23] Risks between all three doses of tirzepatide were similar, as were risks between subcutaneous semaglutide 0.5 and 1.0 mg, though both were associated with an increased risk when compared with subcutaneous semaglutide 0.75 mg after 30–40 weeks.[23] Discontinuation rates after 26 weeks were similar between most subcutaneous semaglutide and oral semaglutide doses, including 40 mg. Oral semaglutide 20 mg, however, was associated with an increased risk (RR 2.13, 95% CI 1.09 to 4.17).[23] At more than 52 weeks,

discontinuation risk was increased with subcutaneous semaglutide 0.5 and 1.0 mg when compared with oral semaglutide 3 and 7 mg, but risks were similar with oral semaglutide 14 mg.[23]

Glucagon-like peptide 1 receptor agonists

One review[16] grouped GLP-1 RAs (semaglutide 1.0, 2.4 mg, liraglutide 1.8, 3.0 mg, exenatide 10 µg and dulaglutide 1.5 mg) together to assess for SAEs. Compared with placebo, GLP-1 RAs were associated with a higher risk (OR 1.27, 95% CI 1.04 to 1.55). Two reviews provided NMAs for discontinuation due to AEs, grouping GLP-1 RAs together.[16,24] Compared to placebo and lifestyle modifications alone, GLP-1 RAs increased the risk of discontinuation (vs. placebo OR 2.46, 95% CI 1.22 to 4.97).

Specific adverse events

All-cause mortality/death

Four reviews[13,17,20,23] provided NMAs for all-cause mortality/death. All-cause mortality was lower with GLP-1 RAs when compared with placebo (one comparison; placebo OR 0.88, 95% CI 0.83 to 0.94) and standard treatment (two comparisons: mean OR 0.81, 95% CI 0.69 to 0.95). Risks were similar for semaglutide (mixed dose) liraglutide 3.0 mg and placebo,[13] and for tirzepatide (combined doses) compared with standard treatment and GLP-1 RAs.[20] Similar risks were reported by Zaazouee when subcutaneous semaglutide 0.5, 0.75, 1.0 mg, dulaglutide 1.5 mg and tirzepatide 5, 10 and 15 mg were compared after 30–40 weeks and subcutaneous semaglutide 0.5 and 1.0 mg after 52 weeks.[23]

Cardiovascular mortality

Two reviews[17,20] provided NMAs for cardiovascular mortality, and both grouped GLP-1 RAs together. Palmer reported that compared to placebo cardiovascular mortality was lowered with GLP-1 RAs (OR 0.88, 95% CI 0.83 to 0.94).[17] Risks were similar between GLP-1 RAs and standard therapy in the same review. However, the results from Shi and colleagues[20] found GLP-1 RAs to be associated with higher risk of cardiovascular mortality than standard treatment (OR: 1.97, 95% CI 1.39 to 2.80). Risks were similar between tirzepatide (combined doses), GLP-1 RAs and standard treatment.[20]

Gastrointestinal disorders

Five reviews[13,17,20,23,24] provided NMAs for gastrointestinal events, four of these reported odds of serious gastrointestinal events,[13,17,20,24] one incidence rate ratio (IRR) of total gastrointestinal events[24] and one RR of gastrointestinal AEs.[23]

For serious gastrointestinal events, GLP-1 RAs were grouped together in three reviews: Palmer *et al.* reported an associated increased risk compared to placebo (OR 2.46, 95% CI 1.22 to 4.97), but no difference in risks compared to standard therapy;[17] Shi *et al.* found GLP-1 RAs versus standard treatments were associated with an increased risk (OR 1.97, 95% CI 1.39 to 2.80),[20] but compared to lifestyle modifications alone, risks were similar.[24]

Semaglutide (combined doses) was associated with an increased risk of serious gastrointestinal events when compared with placebo (OR 1.95, 95% CI 1.35 to 2.81),[13] but risks were similar when compared with lifestyle modifications alone.[24] Risks were similar when liraglutide (3.0 mg and mixed dose) were compared with either placebo, standard care or lifestyle modifications alone.[13,24] Risks were also similar when liraglutide 3.0 mg and semaglutide (combined doses) were compared with exenatide (combined doses).[24] There were two comparisons between liraglutide and semaglutide. Iannone *et al.* reported similar risks when liraglutide 3.0 mg was compared with semaglutide (combined doses),[13] Shi *et al.*[24] found semaglutide (combined doses) to be associated with a much higher IRR compared to liraglutide (combined doses); however, the certainty of this result was rated as low to due severe imprecision.[24]

Total gastrointestinal AEs were reported by Shi and colleagues.[24] Compared to lifestyle modification alone, all interventions (GLP-1 RAs), semaglutide (combined doses), liraglutide (combined doses) and exenatide (combined doses) were associated with an increased IRR, the highest being with liraglutide (IRR 3.10, 95% CI 2.59 to 3.71).[24] Liraglutide and semaglutide were also associated with an increased incidence rate compared to exenatide but not compared to each other.[24]

Zaazouee and colleagues reported total gastrointestinal events across three different time points (after 26 weeks, after 30–40 weeks and after 52 weeks).[23] At 26 weeks, subcutaneous semaglutide (doses ranging from 0.05 to 1.6 mg), oral semaglutide (doses ranging from 2.5 to 40 mg) and liraglutide (0.3, 1.2 and 1.8 mg) were compared to one another and to placebo. Compared to placebo, risks were similar with liraglutide 0.3 and 0.6 mg, oral semaglutide 2.5 and 5 mg, and subcutaneous semaglutide 0.05 mg. All other comparisons with placebo were associated with an increased risk, the highest with subcutaneous 0.8 mg (RR 5.13, 95% CI 3.42 to 7.7). Risks were similar between subcutaneous semaglutide 0.8 and 1.6 mg, but both these doses were associated with increased risks in all other comparisons. Across all comparisons with oral semaglutide 40 mg, it was only compared to oral semaglutide 2.5 and

5 mg, where an associated increased risk was reported (RR 4, 95% CI 2.13 to 7.69).[23]

At 30–40 weeks, subcutaneous semaglutide 0.5, 0.75 and 1.0 mg, liraglutide 1.2 mg, dulaglutide 1.5 mg and tirzepatide 5, 10 and 15 mg were compared to one another and to placebo. All interventions were associated with an increased risk when compared to placebo, the highest with tirzepatide 10 mg (RR 3.05, 95% CI 2.15 to 4.33).[23] With the exception of liraglutide 1.2 mg, all other interventions were associated with an increased risk of gastrointestinal events when compared to subcutaneous semaglutide 0.75 mg. Risks were similar when all other interventions were compared with one another.[23] At 52 weeks, all interventions (subcutaneous semaglutide 0.5 and 1.0 mg and oral semaglutide 14 mg) compared with placebo, were associated with an increased risk, the highest with oral semaglutide 14 mg (RR 4.16, 95% CI 2.72 to 6.34). Compared with both doses of subcutaneous semaglutide, oral semaglutide 14 mg was associated with an increased risk (RR 2.86, 95% CI 1.85 to 4.35). Risks were similar between the two subcutaneous semaglutide doses.[23]

Other specific adverse events

Network meta-analyses were provided on other specific AEs in the following reviews: non-fatal stroke[13,17,20]; non-fatal myocardial infarction[13,17,20]; diabetic ketoacidosis[10,17,20]; severe/serious hyperglycaemia[10,17,20]; hyperglycaemic events[23]; nausea, vomiting, diarrhoea, constipation, dyspepsia[23]; genital infections[10,12,17,20]; urinary tract infections, injection site reactions, abdominal pain, cancer events, bone fractures[12]; pancreatitis[12,17]; kidney failure[17]; end-stage kidney disease[20]; hospitalisation due to heart failure[17,20]; pancreatic cancer, neuropathic pain, blindness[17]; and amputation.[17,20]

Appendix 10 Summary of update search

We performed an update search for new NMAs on 26 September 2024. Database searches were deduplicated against studies already identified, after which there were 59 new, unique records. We were able to retrieve the full text of 56 records, and these were independently screened by two reviewers (MN, SF, LS, RW), duplicating the methods described above.

After full-text screening, there were 14 new NMAs eligible for inclusion.[24,51,63–75]

The identification of 14 eligible new NMAs from this update search highlights how fast-paced this topic is. This volume of new eligible NMAs was, however, too large for us fully assess the methodological quality using ISPOR or to incorporate findings into the analyses as a post-submission update activity. Instead, we have:

- applied top-level critical appraisal using AMSTAR-2 to identify which of those reviews were of moderate quality or better
- briefly described the sample characteristics of moderate or high-quality NMAs
- identified any novel comparisons within these NMAs (and summarised network estimates for them)
- listed any key new trials and highlighted whether they add to our understanding.

Appraisal of critical domains with A MeaSurement Tool to Assess systematic Reviews 2

Two reviewers (MN, SF) completed top-level critical appraisal using questions 2, 4 and 9 of the modified version of AMSTAR-2[6] to identify whether any of these 14 eligible reviews contained any fatal flaws with regards to the protocol, search and risk of bias. Reviews with at least one critical flaw were noted and were not summarised any further.

Of the 14 reviews, 1 contained a fatal flaw under the heading of protocol.[68] While the authors reported the presence of a protocol, it was not registered, and insufficient details were provided. The remaining 13 reviews were all given a 'yes' with regards to q2 (protocol). In terms of search quality (q4), all reviews were given a 'partial yes'. Search details were often limited, with no mention of supplementary searches or searching of grey literature. All reviews were shown to use a satisfactory technique to assess risk of bias (q9).

Sample characteristics

There were 13 reviews with no fatal flaws in the conduct of the systematic review component.[24,63,64,65–67,69–76]

One of these reviews was a resubmission of an include in our review which had been retracted and revised.[24]

Of the 12 remaining reviews, 9 targeted patients with T2DM,[63,64,65,69–73,76] one of these specifically older diabetic patients (≥ 65 years);[69] 2 reviews sought patients with NAFLD[66,74]; and only 2 reviews focused specifically on an obese population.[67,75] As such, the primary outcome for most of the reviews (n = 5) was changes in HbA1c,[63,64,70,72,73] and weight loss was the primary outcome in just two.[67,75] Four reviews had a combination of primary outcomes of which a measure of weight loss featured alongside either safety outcomes,[65] lipid profiles or liver fat contents and/or HbA1c changes.[71,74,76]

Safety outcomes were reported in 11 reviews.[63,64,65–67,69,71,76]

None of the 12 reviews were funded by pharmaceutical companies. The majority were conducted in China (n = 6),[64,71,74–77] and the most common funder was the National Natural Science Foundation of China (n = 4).[67,71,74,76] The review by Caruso and colleagues reports some pharmaceutical industry-related conflict of interest.[63]

Glucagon-like peptide 1 receptor agonists

Within the body weight NMAs, seven of the reviews included tirzepatide, either as a network node combining doses[65,71] or as nodes representing individual doses of 5, 10 or 15 mg.[63,70,72,75,76] Semaglutide was included in six reviews,[63,64,67,70,71,75] and where provided, subcutaneous doses ranged from 0.5 to 2.4 mg and oral doses from 2.0 to 40 mg, all of which came from one review.[76] Liraglutide was included in six reviews,[67,70,71,74–76] and specific doses featured in three reviews, which ranged from 0.6[70] to 3.0 mg.[75] Other featured GLP-1 RAs included exenatide (n = 3),[64,67,76] and where a dose was mentioned, this was 2 mg;[64,76] dulaglutide (n = 6)[63,64,70,71,73,76] with doses ranging from 0.75[64,70,73,76] to 4.5 mg;[63,64] and lixisenatide (mixed dose).[71] Three reviews reported various GLP-1 RAs as a single network node.[65,66,69]

The length of follow-up of the included interventions was reported in 11 of the 12 reviews, and this ranged from 12 weeks[63,64,71,74,76] to 5.4 years.[65] Eight of these involved intervention periods extending to 72 weeks and beyond,[63,65,66,69,71–73,76] with three lasting ≥ 2 years.[65,69,76]

Novel comparisons

Three reviews incorporated novel comparisons of interest.[63,75,76] The NMA by Ding and colleagues introduced multiple novel comparisons, including a range of oral doses of semaglutide.[76] Of particular interest, their NMA compared subcutaneous semaglutide 2.4 mg with tirzepatide 5, 10 and 15 mg, merging data across multiple time points. Results were not statistically significant apart from the comparison between subcutaneous semaglutide 2.4 mg and tirzepatide 15 mg (MD −2.96 kg, 95% CI −5.22 to −0.69 kg). Data for these comparisons came from indirect evidence, drawing on 10 trials, one of which was novel to our prioritised NMAs, and included data for tirzepatide.[53] Furthermore, data from this review indicate parity in weight loss achieved between subcutaneous semaglutide 2.4 mg and oral doses at 20 and 40 mg.[76] Tirzepatide 10 mg was superior to all comparators except semaglutide 2.4 mg, tirzepatide 15 mg was superior to all comparators.[76] There were no differences in the incidence of gastrointestinal AEs (including nausea and diarrhoea) when comparing subcutaneous semaglutide 2.4 mg and all oral doses of semaglutide and tirzepatide.[76]

In the body weight NMA in the review by Caruso and colleagues, subcutaneous semaglutide 2.0 mg was compared with tirzepatide doses 5, 10, 15 mg, with data from multiple time points combined.[63] Data for these comparisons came from indirect evidence from 13 trials, two of which appear to not have been included in our prioritised NMAs, including data on tirzepatide[53] and semaglutide.[78] All doses of tirzepatide were more effective compared to semaglutide 2.0 mg, the greatest difference observed for tirzepatide 15 mg, which resulted in 6.56 kg more weight loss (MD −6.56 kg, 95% CI −7.38 to −5.73 kg).[63] There were no differences in the incidence of any AEs or SAEs between subcutaneous semaglutide 2.0 mg and tirzepatide 5, 10, 15 mg.[63]

The NMA by Xie and colleagues presented the comparison of subcutaneous semaglutide 2.4 mg with two doses of tirzepatide: 10 and 15 mg, with data from multiple time points combined.[75] The evidence of these data came from indirect comparisons from 13 trials, three of which were not included in our prioritised NMAs.[52–54] Weight loss outcomes were presented separately for those with and without T2DM. Only tirzepatide 15 mg was shown to result in significant percentage of weight loss compared to subcutaneous semaglutide 2.4 mg for patients without T2DM (MD −5.01%, 95% CI −7.42% to −2.06%) and with T2DM (MD −4.44%, 95% CI −5.92% to −2.97%).[75] The incidence of AEs, SAEs and withdrawals due to AEs did not significantly differ between the comparisons described above.

Summary

The size of the NMA literature featuring GLP-1 RAs and weight loss outcomes has almost doubled in the last year, reflecting the pace of evidence synthesis in this

area. Notably, only 6 unique trials, including the drugs of interest, were identified by the 12 higher-quality new NMAs.[52–54,79–81]

Several novel comparisons have been provided by the new NMAs, including, of note, tirzepatide versus semaglutide 2.4 mg. The inclusion of oral doses of semaglutide in networks is potentially informative. Several issues with the evidence remain, for example, even where specific doses were used to populate network nodes, data were still combined across multiple time points. There were no new head-to-head trials of higher doses of semaglutide with tirzepatide, and all but two of the new NMAs targeted patients with either T2DM or NAFLD, making it difficult to understand the pure weight loss effects.

Given the volume of new evidence identified by the update search, we were only able to briefly review it, and have not critically appraised the NMA methods of the new reviews. The rate of publication emphasises the value of a living NMA, where multiple new publications offer only incremental added value, if any.