nature medicine

Article

https://doi.org/10.1038/s41591-025-03978-z

A systematic review and meta-analysis of the efficacy and safety of pharmacological treatments for obesity in adults

Received: 14 April 2025

Accepted: 26 August 2025

Published online: 02 October 2025

Check for updates

Barbara McGowan[1,15] ✉, Andreea Ciudin[2,3,15] ✉, Jennifer L. Baker[4], Luca Busetto[5], Dror Dicker[6], Gema Frühbeck[7], Gijs H. Goossens[8], Matteo Monami[9], Paolo Sbraccia[10], Borja Martinez-Tellez[11,12], Euan Woodward[13] & Volkan Yumuk[14]

This systematic review and network meta-analysis evaluated the efficacy and safety of obesity management medications (OMMs) in terms of reducing body weight and impact on obesity-related complications. Here a Medline and Embase search was performed up to 31 January 2025 for randomized controlled trials comparing OMMs versus placebo/active comparators in adults. Primary endpoint was percentage of total body weight loss (TBWL%) at the end of the study. Secondary endpoints were TBWL% at 1, 2 and ≥3 years, lipid profile, blood pressure, hemoglobin A1c, fasting plasma glucose, mental health, serious adverse events, quality of life, cardiovascular morbidity and mortality, remission of obesity-related complications and all-cause mortality. Fifty-six clinical trials were identified—orlistat (22), semaglutide (14), liraglutide (11), tirzepatide (6), naltrexone/bupropion (5) and phentermine/topiramate (2)—enrolling 60,307 patients (32,598 OMM and 27,709 placebo). All OMMs showed a significantly greater TBWL% versus placebo ($P < 0.0001$), more than 10% for semaglutide and tirzepatide. Both tirzepatide and semaglutide showed normoglycemia restoration, remission of type 2 diabetes and reduction in hospitalization due to heart failure. Semaglutide was effective in reducing major adverse cardiovascular events and reducing pain in knee osteoarthritis. Tirzepatide was effective in remission of obstructive sleep apnea syndrome and metabolic dysfunction-associated steatohepatitis. These results support the need to individualize the selection of OMMs.

The prevalence of overweight and obesity is increasing at pace, with 3 billion adults expected to be living with overweight or obesity by 2030, compared to 1.6 billion in 2010 (ref. 1). This is leading to a rise in metabolic and cardiovascular diseases, cancer and overall mortality[2]. Considering the high prevalence of obesity and its harmful impact on health, its management represents a complex medical and economic[3] challenge for all healthcare systems. Currently, lifestyle intervention is the first-line treatment for people living with obesity. However, its mid-term and long-term effects as well as adherence data are limited[4,5].

Obesity is an adiposity-based chronic disease driven by biological mechanisms, resulting in dysregulation and/or excess accumulation of adipose tissue[6]. The biology of obesity includes genetic predisposition, neurohormonal signaling disruptions (particularly in the hypothalamus) and alterations in appetite-regulating hormones[7–9]. Furthermore, the body defends against fat loss through mechanisms

A full list of affiliations appears at the end of the paper. ✉e-mail: barbaramcgowan@nhs.net; andreea.ciudin@vallhebron.cat

including reduced resting energy expenditure and increased hunger, making long-term weight maintenance challenging. As a result, lifestyle interventions alone, such as diet and exercise, are often insufficient, and effective management typically requires a combination of strategies to address the underlying biology of obesity. Current guidelines recommend that, particularly for high-risk people with severe obesity or obesity-related complications, lifestyle programs can be combined with OMMs or metabolic bariatric surgery (MBS)[10–13], with recent evidence suggesting that these interventions can be risk stratified[14,15].

Recent advances in understanding of the biology of obesity have led to the development of novel medications, providing healthcare professionals with a broader range of therapeutic options[16]. Due to regulatory requirements, newer medications are supported by clinical trials on substantial numbers of patients, often including studies on longer-term cardiovascular outcomes[17,18]. However, the availability of head-to-head comparisons between different OMMs in randomized controlled trials (RCTs) is still limited[19], which makes assessment of differences in efficacy and safety across available molecules challenging. The method of network meta-analysis (NMA), which provides indirect comparisons of efficacy and safety, can overcome this challenge. Several NMAs[20–23] and a traditional meta-analysis[24] on different therapeutic options for overweight and obesity were published in the last few years, but they did not include more recently available OMMs, such as tirzepatide[20–22], or they included medications not approved for the treatment of overweight/obesity (for example, metformin, SGLT2 inhibitors or GLP-1 agonists, such as dulaglutide)[22], or they adopted different inclusion criteria (that is, irrespective of the trials' duration), including a considerable number of trials accounting for highly heterogeneous results[24].

The European Association for the Study of Obesity (EASO) has developed the first Grading of Recommendations Assessment, Development and Evaluation (GRADE)-based treatment algorithm for the pharmacological management of obesity (published in this same issue), as outlined in the 2024 EASO framework[25]. This algorithm was created using the findings of the present NMA, which aims to provide healthcare professionals involved in obesity care with a comprehensive overview based on published data of the efficacy and safety of all OMMs available in Europe until 31 January 2025.

Results

Retrieved trials

Supplementary Fig. 1 reports the trial flow summary showing the results of the search of Medline and Embase databases. Supplementary Table 1 reports the trials that were excluded ($n = 7$) after reading the full text. Fifty-six RCTs ($n = 60$ comparisons), performed with orlistat ($n = 22$ comparisons), semaglutide ($n = 14$ comparisons), liraglutide ($n = 11$ comparisons), tirzepatide ($n = 6$ comparisons), naltrexone plus bupropion ($n = 5$ comparisons) and phentermine plus topiramate ($n = 2$ comparisons), enrolling 60,307 patients (32,598 and 27,709 with active compound and placebo, respectively), were analyzed. All RCTs were placebo-controlled studies, except for two trials that reported multiple comparisons (that is, liraglutide versus either placebo or orlistat[19] and semaglutide versus either liraglutide or placebo[26]); therefore, the overall number of available comparisons was 60. The main characteristics of the included RCTs are reported in Supplementary Table 2. No studies reported a mean baseline body mass index (BMI) < 30 kg m^{-2}.

The quality of studies was heterogeneous (Supplementary Fig. 2). Most of the included RCTs were double blind (66%), with a few trials inadequately reporting attrition and/or description of allocation or blinding of assessors (29%).

Out of 60 comparisons, 58 were performed versus placebo. All except five[18,27–30] reported information on TBWL% at the endpoint ($n = 55$ comparisons). Only two head-to-head comparisons[19,26] between different OMMs were identified (that is, liraglutide versus orlistat and semaglutide versus liraglutide), showing a greater efficacy for liraglutide than for orlistat (weighted mean difference (WMD): 3.80% (0.73–6.87), $P = 0.020$) and for semaglutide than for liraglutide (WMD: 9.4% (6.8–12.0), $P < 0.001$).

Network meta-analysis

TBWL% at different timepoints. Figure 1 reports the number of available RCTs for each comparison, and Fig. 2 and Table 1 show the efficacy results with respect to TBWL% at the end of the different timepoints (52 weeks, 104 weeks and >156 weeks and at end of the study), based on the NMA.

At the endpoint (that is, primary endpoint of the present NMA), 55 comparisons reported information on TBWL% (Fig. 1a); all OMMs yielded a statistically significant greater TBWL% compared to placebo, with no evidence of inconsistency (H value = 1.51; Fig. 2a). The estimated TBWL% was greater than 10% only for semaglutide and tirzepatide (Fig. 2a). Details of direct and indirect estimates are reported in Supplementary Table 3. A visual analysis of funnel plots did not suggest publication bias (data not shown).

At 52 weeks ($n = 54$ comparisons, with evidence of inconsistency; H value = 3.90), all treatments showed a significantly greater TBWL% versus placebo except for orlistat (Fig. 2b). Similar to the endpoint analyses, only semaglutide and tirzepatide achieved a TBWL% of at least 10% (Fig. 2b). Details of direct and indirect estimates are reported in Supplementary Table 4.

A limited number of comparisons were possible at 53–104 weeks ($n = 25$; H value = 1.51; Fig. 2c and Supplementary Table 8), 105–156 weeks ($n = 3$, one trial each for liraglutide[31], orlistat[32] and semaglutide[17] reporting a placebo-subtracted TBWL of 4.2%, 3.0% and 8.7%, respectively) and more than 156 weeks (one trial with orlistat[32] reporting a 3% TBWL compared to placebo and one subgroup analysis of a trial with tirzepatide[33] reporting 19.3% TBWL). For all assessed treatments, the estimated efficacy at the endpoint ($n = 55$ comparisons; $H = 1.51$; Fig. 2a) was similar to that observed at 52 weeks and 104 weeks.

Weight regain after discontinuation of OMMs. Four trials reported information on weight regain after OMM discontinuation (one each for liraglutide[31] and tirzepatide[33] and two for semaglutide[34,35]). The discontinuation of liraglutide after 12 weeks[31] and semaglutide after 26 weeks[35] of treatment demonstrated, on average, a regain of 47% and 43% of the weight lost at the end of the active treatment period, respectively. Weight regain after discontinuation of semaglutide and tirzepatide treatment for 52 weeks was 67% and 53%[33,34], respectively.

Waist circumference, BMI and proportion of patients achieving ≥5–25% TBWL. Table 1 and Supplementary Figs. 3 and 4 report results of the effects of each OMM on endpoint waist circumference and BMI (percent reduction from baseline). Tirzepatide and semaglutide were associated with a greater reduction of both waist circumference and BMI.

The proportion of patients achieving different thresholds of TBWL% are reported in Table 1 and Supplementary Figs. 5 and 6. Patients treated with OMMs, except for orlistat, were more likely to achieve a TBWL of at least 5% compared to placebo. A higher degree of TBWL (>20%) was observed only with semaglutide and tirzepatide and, to a lesser extent, with liraglutide. Only tirzepatide was associated with a greater proportion of patients achieving at least 25% TBWL reduction (odds ratio [95% confidence interval]: 33.8 [18.4–61.9], $P < 0.001$). Five trials[19,36–39] reported results on body composition parameters assessed using heterogeneous methods (often in a smaller subgroup of included patients). Two studies on semaglutide[38,39] did not report any information about dispersion measurements and, therefore, were not included in any formal analyses. Semaglutide showed a greater reduction of total[40] and regional visceral fat mass[38,39] and a greater increase in total lean body mass compared to placebo[39]. Tirzepatide was associated with a greater reduction of total body fat mass and a

https://doi.org/10.1038/s41591-025-03978-z

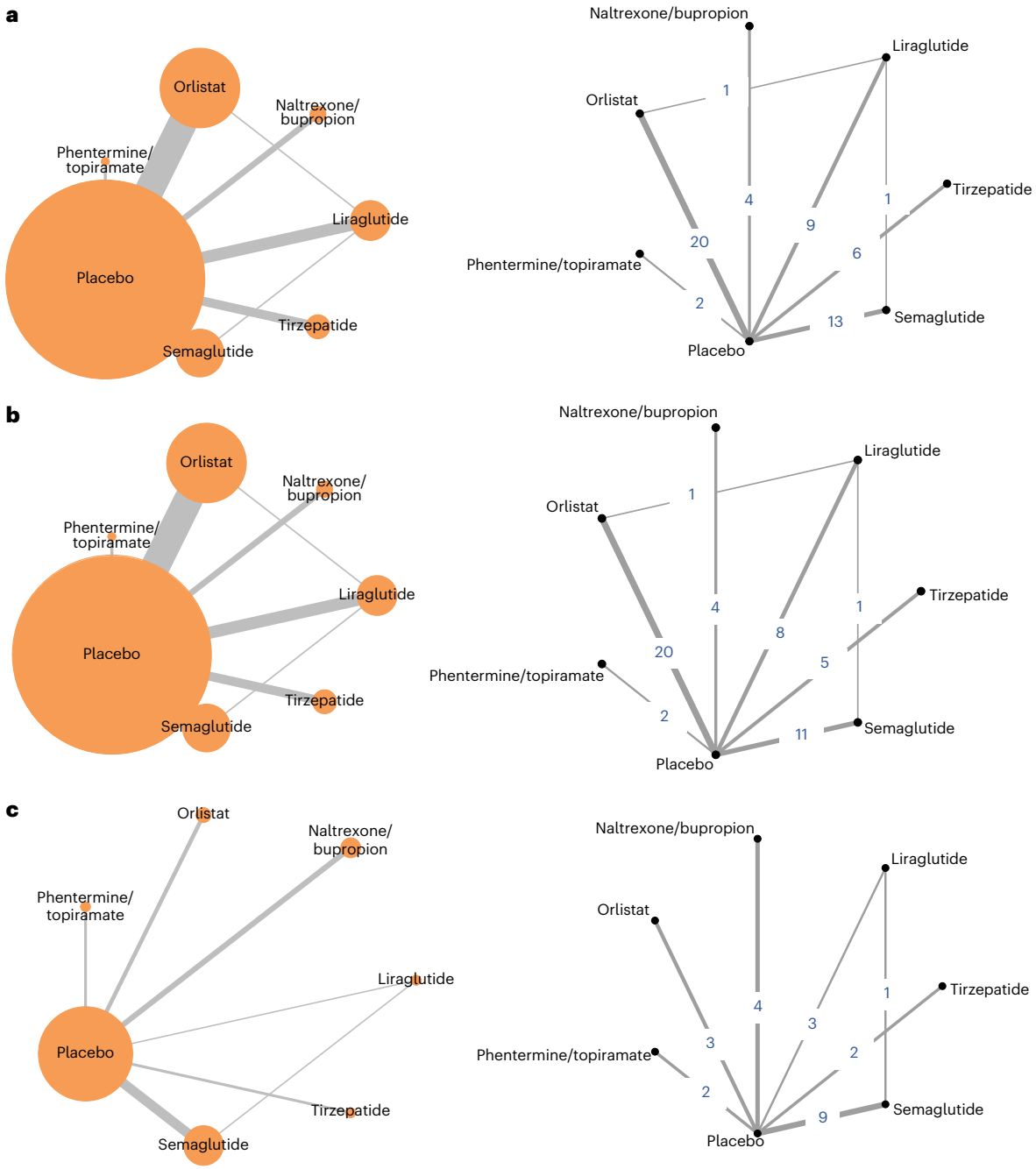

Fig. 1 | Graphical representations of networks of interventions. Graphical representation of the geometry of all networks of interventions with respect to TBWL% at the endpoint (**a**), 52 weeks (**b**) and 53–104 weeks (**c**).

significantly lower reduction in total fat-free mass[41]; similar results, despite to a lesser extent, were observed with liraglutide[19,37].

When subdividing trials by baseline BMI (<30, 30–34.9, 35–39.9 and ≥40.0 kg m^{-2}; Table 2), no RCTs on OMMs reported results for patients with overweight; only two OMMs (semaglutide and tirzepatide) provided data for class III obesity (BMI ≥ 40.0 kg m^{-2}; Table 2). Most of the information on the effects of each included OMM was available for the class II obesity (35–39.9 kg m^{-2}) category, which showed the highest body weight reduction for tirzepatide and semaglutide (TBWL% >10%). A further post hoc subgroup analysis was performed for RCTs specifically designed for body weight reduction. The results of these analyses, after excluding RCTs with a primary endpoint other than body weight reduction[17,18,30,41–44], are reported in Table 3. Results from these analyses were similar to those of the primary endpoint analysis.

Effects on glycemic control, blood pressure and lipid profile. Data were obtained considering all RCTs reporting data on each metabolic endpoint, irrespective of the proportion of patients with type 2 diabetes (T2D) or prediabetes. Table 1 reports results for metabolic parameters (n = 25, 33, 30, 36 and 33 RCTs for hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), total and high-density lipoprotein (HDL) cholesterol and triglycerides, respectively) and blood pressure (n = 36 and 30 RCTs for systolic and diastolic blood pressure, respectively). Tirzepatide produced a significantly greater reduction in HbA1c compared to other OMMs, whereas liraglutide and semaglutide were associated with a greater reduction of FPG in contrast to the other OMMs (Table 1). T2D remission was reported in a low number of RCTs (n = 5), and, therefore, we performed traditional meta-analyses for semaglutide only, and we showed the estimates of the other three studies in the same figures for

https://doi.org/10.1038/s41591-025-03978-z

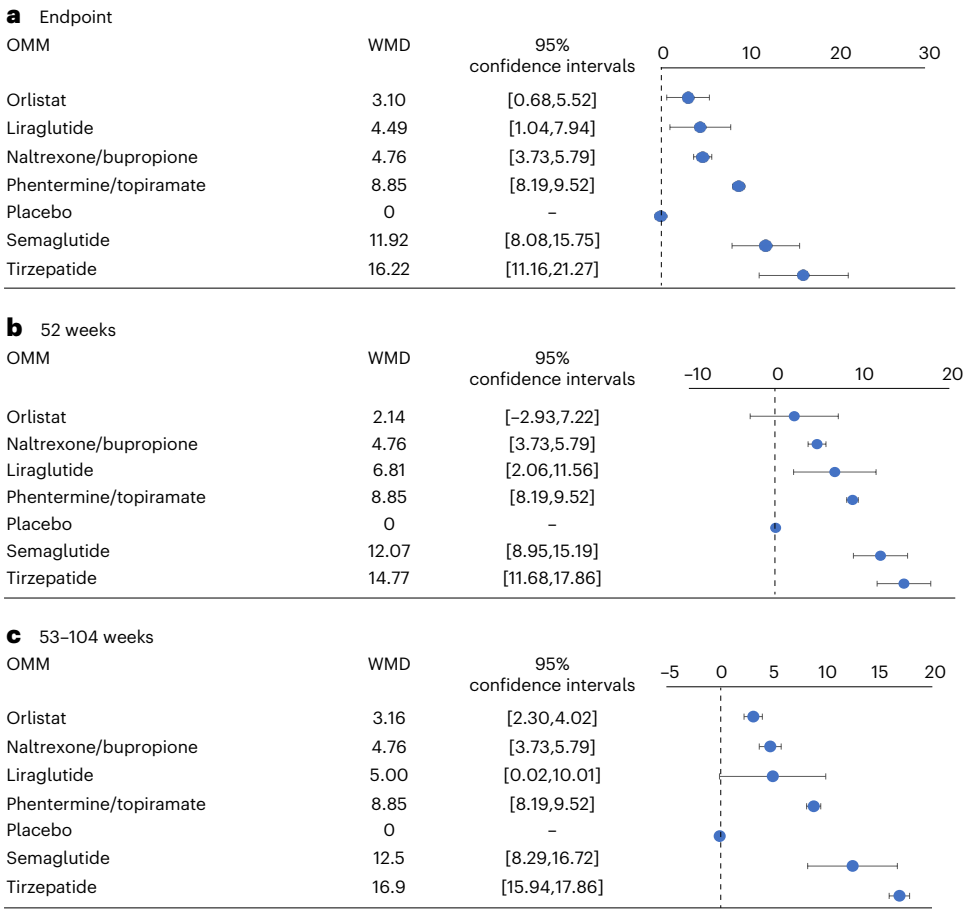

Fig. 2 | Network forest plots. Network forest plots showing the effects of each OMM on TBWL% at the endpoint (**a**), 52 weeks (**b**) and 53–104 weeks (**c**).

convenience (that is, naltrexone plus bupropion, liraglutide, semaglutide and tirzepatide; Table 1). All studies reported significant results (Table 1). Eight trials reported data on incident T2D; meta-analyses were possible only for orlistat and semaglutide, whereas, for phentermine plus topiramate and liraglutide, we reported only estimates derived from the original publication (Table 1). All OMMs, except orlistat, reported significant results (Table 1). Semaglutide and tirzepatide (only one trial), but not liraglutide, were associated with a higher chance of restoring normoglycemia in patients with pre-existing glycemic alterations (Table 1).

Orlistat was associated with the highest total cholesterol reduction, and statistically significant results versus placebo were also obtained for phentermine plus topiramate. Tirzepatide, naltrexone plus bupropion and liraglutide were associated with a greater increase in HDL cholesterol values; semaglutide, phentermine plus topiramate, orlistat and liraglutide resulted in a significant reduction of triglyceride circulating levels (Table 1). Table 1 shows the effects of each OMM on blood pressure, with naltrexone plus bupropion associated with a significant increase in systolic, but not diastolic, blood pressure. All other OMMs, but not liraglutide and semaglutide, exerted significant favorable effects on systolic blood pressure and some (phentermine plus topiramate, tirzepatide and orlistat) on diastolic blood pressure (Table 1).

Only a few RCTs reported data on hypertension and dyslipidemia remission, with clinically inconsequential effects (Table 1).

Effects on cardiovascular morbidity and mortality. In total, 33, 37 and seven RCTs reported information on (externally adjudicated) major adverse cardiovascular events (MACE), cardiovascular mortality and hospitalization due to heart failure (HHF), respectively (Supplementary Figs. 7–9). Table 1 and Supplementary Figs. 7–9 show results on these endpoints. Only semaglutide was associated with a significantly lower risk for MACE, with all OMMs reporting odds ratios below 1, except for phentermine plus topiramate (odds ratio = 2.00 [0.18–22.1], $P > 0.50$; Supplemtnary Fig. 8b). No information on cardiovascular mortality was reported for phentermine plus topiramate. Semaglutide and naltrexone plus bupropion were associated with a lower risk for cardiovascular mortality (Supplementary Fig. 8c). HHF was significantly reduced by tirzepatide ($n = 2$ RCTs), whereas semaglutide ($n = 4$ RCTs) showed a non-significant trend toward a reduction. Liraglutide reported zero events in both arms, and, therefore, the overall risk was not estimable (Supplementary Fig. 9).

Effects on quality of life and mental health. Only a few trials reported data on quality of life (QoL), using different scales (eight, two, seven and one with Impact of Weight on Quality of Life-Lite (IWQOL-Lite), Short Form-36 General Health, Short Form-36 Physical Role Functioning and Short Form-36 Physical Components, respectively). The paucity of data did not support an NMA but only traditional meta-analyses (when at least two studies were available) and presentation of individual studies for some outcomes (Table 1). Naltrexone plus bupropion and semaglutide were associated with an improvement of IWQOL versus placebo (Table 1). Only one active-controlled trial (liraglutide versus orlistat) reported data on IWQOL, showing better scores for liraglutide[19]. No other significant differences were observed across the remaining scales, except for semaglutide, which showed improved scores in the Short Form-36 Physical Functioning domain (Table 1).

Suicide attempts and major depression were reported as serious adverse events (SAEs) (with no external adjudication) in a large number of RCTs (Table 1). No significant association was observed between

https://doi.org/10.1038/s41591-025-03978-z

Table 1 | Summary report of NMAs on all critical outcomes at endpoint (placebo-subtracted effect), if not otherwise specified

Outcome	Orlistat	Naltr./Bupr.	Liraglutide	Phen./Topir.	Semaglutide	Tirzepatide
Body weight						
TBWL (WMD, %)						
Endpoint (overall)	**3.1** [0.7,5.5]	**4.8** [3.7,5.8]	**4.5** [1.0,7.9]	**8.8** [8.2,9.5]	**11.9** [8.1,15.7]	**16.2** [11.2,21.3]
At 52 weeks	2.1 [−2.9,7.2]	**4.8** [3.7,5.8]	**6.8** [2.1,11.6]	**8.8** [8.2,9.5]	**12.1** [9.0,15.2]	**14.8** [11.7,17.9]
At 53–104 weeks	**3.1** [2.3,4.0]	**4.8** [3.7,5.8]	**5.0** [0.1,10.0]	**8.8** [8.2,9.5]	**12.5** [8.3,16.8]	**16.9** [15.9,17.9]
Waist circumference (WMD, cm)	−0.9 [−3.7,1.8]	−1.4 [−4.5,1.8]	**−3.2** [−5.6,−0.8]	**−6.9** [−7.6,−5.9]	**−8.4** [−11.5,−5.2]	**−11.2** [−14.6,−7.7]
BMI (WMD, kg m^{-2})	**−1.8** [−2.4,−1.2]	–	**−1.6** [−1.8,−1.3]	–	**−4.0** [−5.4,−2.6]	**−5.1** [−8.0,−2.3]
BW reduction (OR)						
5%	2.1 [0.5,8.7]	**3.4** [2.1,5.4]	**4.2** [1.8,9.5]	**9.2** [6.8,12.3]	**9.8** [7.1,13.6]	**13.3** [7.8,22.6]
10%	2.0 [0.4,9.9]	**3.4** [2.2,5.2]	2.6 [0.9,6.9]	**10.9** [7.5,15.9]	**9.2** [5.6,15.0]	**17.2** [14.2,20.8]
15%	–	**4.2** [2.3,7.4]	**2.9** [1.5,5.4]	–	**16.2** [8.6,30.4]	**19.6** [14.2,27.0]
20%	–	–	**2.6** [1.4,4.9]	–	**18.0** [10.7,30.2]	**23.3** [11.8,45.9]
25%	–	–	–	–	–	**33.8** [18.4,61.9]
Metabolic parameters and blood pressure						
HbA1c (WMD, mmol mol^{-1})	**−5.2** [−8.4,−2.0]	**−5.5** [−7.2,−3.7]	**−1.7** [−2.7,−0.6]	–	**−2.8** [−4.1,−1.5]	**−14.4** [−17.7,−11.1]
FPG (WMD, mg dl^{-1})	−3.1 [−6.3,0.1]	−1.3 [−2.9,0.3]	**−6.7** [−11.4,−1.9]	**−2.5** [−3.8,−1.2]	**−9.6** [−14.3,−4.9]	−9.5 [−46.1,27.1]
Total cholesterol (WMD, mg dl^{-1})	**−15.1** [−20.4,−9.8]	–	2.8 [−10.1,15.7]	**−5.7** [−8.5,−3.0]	−12.3 [−25.2,0.6]	−3.9 [−9.1,1.4]
HDL cholesterol (WMD, mg dl^{-1})	0.1 [−0.5,0.8]	**3.5** [2.2,4.8]	**2.9** [1.4,4.4]	0.6 [−6.9,8.1]	−0.1 [−0.3,0.1]	**4.5** [0.5,8.5]
Triglycerides (WMD, mg dl^{-1})	**−7.7** [−13.8,−1.5]	−12.8 [−28.3,2.6]	**−6.6** [−12.4,−0.8]	**−20.9** [−26.0,−15.8]	**−21.0** [−22.0,−20.0]	−19.5 [−50.6,11.7]
SBP (WMD, mmHg)	**−1.8** [−2.6,−0.9]	**1.5** [0.6,2.4]	−2.9 [−6.9,1.2]	**−4.1** [−5.0,−3.2]	**−3.6** [−8.0,−2.9]	**−5.4** [−7.9,−2.9]
DBP (WMD, mmHg)	**−1.4** [−2.6,−0.9]	0.4 [−0.1,0.9]	−0.91 [−4.5,4.4]	**−2.2** [−3.2,−1.2]	−1.9 [−6.1,2.3]	**−1.5** [−2.9,−0.1]
Obesity-associated comorbid conditions						
Hypertension remission (OR)	–	–	–	–	1.9 [0.7,5.6]	–
Dyslipidemia remission (OR)	–	–	–	–	0.7 [0.3,1.6]	–
T2D remission (OR)	–	**2.3** [1.3,4.1]	**6.8** [4.4,10.4]	–	**27.8** [3.5,220.1]	**28.0** [19.2,40.8]
MASH[a] resolution (OR)	–	–	–	–	2.0 [0.6,6.2]	**11.8** [4.3,32.5]
Liver fibrosis[a] reduction (OR)	–	–	–	–	0.3 [0.1,1.0]	**2.5** [1.2,5.2]
OSAS[b] remission (OR)	–	–	–	–	–	**4.2** [3.1,7.6]
CVD effects						
MACE (OR)	0.8 [0.1,4.4]	0.9 [0.7,1.2]	0.8 [0.3,1.8]	2.0 [0.2,22.1]	**0.8** [0.4,7.3]	0.8 [0.3,1.8]
Cardiovascular mortality (OR)	0.80 [0.1,4.7]	**0.5** [0.3,0.9]	1.0 [0.3,3.4]	–	**0.8** [0.7,1.0]	1.2 [0.5,3.0]

https://doi.org/10.1038/s41591-025-03978-z

Table 1 (continued) | Summary report of NMAs on all critical outcomes at endpoint (placebo-subtracted effect), if not otherwise specified

Outcome	Orlistat	Naltr./Bupr.	Liraglutide	Phen./Topir.	Semaglutide	Tirzepatide
HHF (OR)	–	–	NE	–	0.4 [0.2,1.0]	**0.4** [0.2,0.9]
QoL						
IWQOL-Lite (WMD)[c]	–	**2.3** [0.8,3.8]	3.0 [−2.0,8.0]	–	**5.7** [0.8,10.6]	−0.9 [−3.5,1.7]
SF-General Health (WMD)[c]	2.2 [−1.8,6.2]	–	−3.6 [−7.5,0.3]	–	–	–
SF-36 Physical Functioning (WMD)[c]	1.7 [−2.5,5.9]	–	−2.8 [−6.7,1.1]	–	**1.6** [1.2,2.1]	1.1 [−0.6,2.9]
SF-36 Physical Component (WMD)[c]	–	–	–	–	0.5 [−0.7,1.7]	–
Mental health						
Suicide attempt* (OR)	1.1 [0.1,11.3]	0.6 [0.1,2.3]	1.4 [0.4,4.9]	1.0 [0.0,50.7]	0.7 [0.4,1.3]	0.9 [0.2,4.9]
Anxiety* (OR)	–	2.2 [0.8,6.1]	1.6 [0.4,6.1]	0.3 [0.0,3.2]	NE	0.5 [0.0,8.2]
Depression* (OR)	–	**0.4** [0.2,0.7]	1.7 [0.5,5.5]	0.4 [0.4,1.3]	0.6 [0.1,5.6]	0.3 [0.1,1.3]
Safety						
All-cause mortality (OR)	1.2 [0.4,3.2]	0.5 [0.3,1.0]	0.8 [0.2,2.4]	0.3 [0.0,8.2]	**0.8** [0.7,0.9]	1.1 [0.6,1.9]
SAEs (OR)	1.1 [0.3,3.9]	**1.2** [1.1,1.4]	1.3 [0.9,1.8]	1.3 [0.9,1.7]	0.9 [0.5,1.4]	1.0 [0.8,1.2]
Treatment discontinuation (OR)	0.7 [0.4,1.3]	0.7 [0.2,2.5]	0.9 [0.4,2.1]	–	0.1 [0.4,1.4]	0.7 [0.4,1.3]

Data are expressed as WMD or odds ratio (OR) [95% confidence interval]. NMAs have been performed only for outcomes with at least 10 RCTs. For all the other outcomes, we performed traditional meta-analyses. Bold character: $P<0.05$; *reported as SAEs. The ORs express the chance to obtain a BW loss of at least 5%, 10%, 15%, 20% and 25% with the interventional drug in comparison to the placebo group. '–' indicates data not available. BW, body weight; DBP, diastolic blood pressure; NE, not estimable (zero cases in the interventional and placebo arms); SBP, systolic blood pressure; SF, Short Form. [a]Liver fibrosis reduction: improvement (decrease) of at least one fibrosis stage without worsening of MASH; MASH resolution: steatosis score of 0 without worsening of fibrosis. [b]OSAS remission: defined as AHI < 5 or AHI of 5–14. [c]Higher values mean QoL improvements.

Table 2 | Effects of OMM on endpoint TBWL% (placebo-subtracted effect) for different baseline BMI categories

Drug	BMI <30 kg m^{-2}	BMI 30–34.9 kg m^{-2}	BMI 35.0–39.9 kg m^{-2}	BMI ≥40 kg m^{-2}
Orlistat	–	**2.4** [1.7,3.0]	**3.2** [3.7,5.8]	–
Naltrexone/bupropion	–	–	**4.8** [3.7,5.8]	–
Liraglutide	–	**5.8** [4.4,7.3]	4.2 [0.0,8.4]	–
Phentermine/topiramate	–	–	**8.6** [7.8,9.4]	**9.3** [8.3,10.3]
Semaglutide	–	**9.4** [3.1,15.7]	**11.9** [8.2,15.6]	**10.6** [10.0,11.2]
Tirzepatide	–	**19.5** [17.7,21.3]	**16.1** [10.8,21.5]	–

Data are derived from traditional meta-analysis versus placebo. Data are expressed as median [interquartile range]; '–' indicates data not available. Bold character: $P<0.05$ versus placebo.

treatment with any OMM and the risk for either suicide attempt or depression, except for naltrexone plus bupropion, which was associated with a significantly lower risk of depression (Table 1). Few studies reported on anxiety ($n=9$); thus, an NMA was not possible, and low event numbers precluded a formal meta-analysis. No significant associations were found for any OMM (Table 1).

Safety outcomes. Results on all-cause mortality are reported in Table 1 and Supplementary Fig. 8. Semaglutide was associated with a lower risk of all-cause mortality; the other OMMs did not show any significant effect on this endpoint (Supplementary Fig. 8a). SAEs (Table 1) were reported in most included studies, and no OMM was significantly associated with an increased risk of SAEs compared to placebo, except for naltrexone plus bupropion. The treatment discontinuation rate was similar to that observed in the placebo arms, with no significant between-group differences (Table 1).

GRADE evaluation for the primary endpoint. The evaluation of the quality of evidence for the primary endpoint (that is, TBWL%) was rated as 'high' (Supplementary Table 6) for each OMM.

Subgroup analyses for patients' pre-existing conditions

As reported in a previously published article[26], EASO identified several subgroups of patients with pre-existing comorbid conditions

https://doi.org/10.1038/s41591-025-03978-z

Table 3 | Effects of different OMM on body weight parameters (placebo-subtracted effect) in RCTs specifically designed for body weight reduction

Outcome	Orlistat	Naltr./Bupr.	Liraglutide	Phen./Topir.	Semaglutide	Tirzepatide
TBWL (%)						
Endpoint (overall)	3.0 [0.7,5.3]	**4.8** [3.7,5.8]	**4.5** [1.1,7.9]	**8.8** [8.2,9.5]	**11.9** [8.1,15.8]	**16.2** [9.6,23.5]
At 52 weeks	1.8 [−3.2,2.7]	**4.8** [3.7,5.8]	**6.5** [1.8,11.3]	**8.8** [8.2,9.5]	**13.2** [10.5,15.8]	**15.5** [9.9,21.2]
At 53–104 weeks	**2.8** [2.2,3.4]	**4.8** [3.7,5.8]	**4.3** [3.7,4.9]	**8.8** [8.2,9.5]	**10.5** [8.6,12.3]	**16.5** [8.2,24.7]
Waist circumference (cm)	**−2.0** [−2.9,−1.1]	**−3.6** [−4.5,−2.8]	**−3.5** [−4.4,−2.6]	**−6.8** [−7.6,5.9]	**−8.8** [−10.6,7.0]	**−11.2** [−14.6,−7.7]
BMI (kg m^{-2})	**−1.8** [−2.5,−1.2]	–	**−1.6** [−1.8,−2.3]	–	**−4.0** [−5.4,−2.6]	**−5.1** [−8.0,−2.3]
BW reduction (OR)						
5%	2.1 [0.5,8.7]	**3.4** [2.1,5.4]	**4.2** [1.8,9.5]	**9.2** [6.8,12.3]	**9.8** [7.1,13.6]	**13.3** [7.8,22.6]
10%	2.0 [0.4,9.9]	**3.4** [2.2,5.2]	2.6 [0.9,6.9]	**10.9** [7.5,15.9]	**9.2** [5.6,15.0]	**17.2** [14.2,20.8]
15%	–	**4.2** [2.4,7.8]	**2.9** [1.5,5.4]	–	**16.2** [8.6,30.4]	**19.6** [14.2,27.0]
20%	–	–	**2.6** [1.4,4.9]	–	**18.0** [10.6,30.2]	**23.3** [11.8,45.9]
25%	–	–	–	–	–	**33.8** [18.4,61.9]

Bold character: $P<0.05$; '–' indicates data not available. BW, body weight; NA, not available; Phen./Topir., phentermine/topiramate; Naltr./Bupr., naltrexone/bupropion. Data are expressed as median [interquartile range] and odds ratio (OR) [95% confidence interval] for TBWL%, waist circumference, BMI and BW reduction, respectively. OR indicates the 'risk' of achieving 5%, 10%, 15%, 20% and 25% of BW reduction (from baseline) compared to placebo.

(Supplementary Table 3). In this section, we analyze the effects of each OMM on several prespecified critical outcomes in specifically designed RCTs or in reported subgroups of patients affected by that comorbid condition.

Established CVD. Only two trials, one with semaglutide[17] and one with naltrexone plus bupropion[18], were designed to explore the effects on cardiovascular safety in patients with obesity. Information on TBWL% was available only for semaglutide, with results similar to those obtained in non-cardiovascular outcome trials (CVOTs) (8.7%; Table 4). Semaglutide, but not naltrexone plus bupropion, was associated with a significantly lower risk of MACE and acute myocardial infarction in patients with established CVD, whereas cardiovascular mortality was reduced by naltrexone plus bupropion but not by semaglutide. By contrast, both OMMs reported a significantly lower risk for all-cause mortality compared to placebo (Table 4).

The GRADE evaluation of the evidence retrieved for the primary endpoint (MACE; Supplementary Table 3) was rated as 'high' and 'moderate' for semaglutide and naltrexone plus bupropion, respectively (Supplementary Table 6).

HHF. Three trials (two with semaglutide[45,46] and one with tirzepatide[44]) included patients with previously diagnosed heart failure; thus, individual study results are presented. The effects of the two medications for TBWL% were not different from other non-CVOTs (Table 4). The risk of HHF was significantly reduced for both semaglutide and tirzepatide, with increased specific-disease QoL questionnaire (Kansas City Cardiomyopathy Questionnaire (KCCQ)) scores and performance on the 6-minute walking test. No relevant effects on all-cause and cardiovascular mortality were observed for the two medications (Table 4).

The GRADE evaluation of the evidence retrieved for the primary endpoint (HHF; Supplementary Table 3) was rated as 'high' for both tirzepatide and semaglutide (Supplementary Table 6).

Prediabetes. Two studies (one with liraglutide[31] and one with semaglutide[35]) were specifically designed for patients affected by overweight/obesity and prediabetes, and two more studies (one with orlistat[32] and one with tirzepatide[36]) reported a longer-term analysis on a subgroup of patients with prediabetes; thus, individual study results are presented. All of these four OMMs (orlistat, liraglutide, semaglutide and tirzepatide) were capable of effectively reducing TBWL%, HbA1c and FPG in patients with prediabetes. Orlistat, liraglutide and tirzepatide, but not semaglutide, were associated with a significant reduction of incident diabetes. Normoglycemia restoration was more likely to be achieved in the intervention group for liraglutide, semaglutide and tirzepatide, but not orlistat, compared to placebo (Table 4). The GRADE evaluation of the evidence retrieved for the primary endpoint (normoglycemia restoration; Supplementary Table 3) was rated as 'high' for all OMMs reporting this outcome, except for orlistat ('low'; Supplementary Table 6).

T2D. Eleven trials were performed in patients with T2D (Table 4). Tirzepatide was associated with a greater effect on TBWL%; semaglutide, tirzepatide and naltrexone plus bupropion were all associated with significant effects on HbA1c and FPG. Liraglutide and orlistat did not have significant effects (Table 4). Fewer studies ($n=4$) examined effects on complete and partial diabetes remission rates; these study-specific estimates are presented, and all showed significant effects (Table 4).

The GRADE evaluation of the evidence retrieved for the primary endpoint (diabetes remission; Supplementary Table 3) was rated as 'high' for liraglutide, naltrexone plus bupropion, semaglutide and tirzepatide (Supplementary Table 6).

Metabolic dysfunction-associated steatotic liver disease. Semaglutide[42] and tirzepatide[41] were the only two OMMs assessed in patients with metabolic dysfunction-associated steatotic liver disease (MASLD); thus, study-specific results are presented. Tirzepatide resulted in a greater effect on TBWL% versus semaglutide in those patients.

https://doi.org/10.1038/s41591-025-03978-z

Table 4 | Summary report of OMM effects on critical outcomes at the endpoint for different subpopulations of patients

Outcome	Orlistat	Naltr./Bupr.	Liraglutide	Phen./Topir.	Semaglutide	Tirzepatide
CVD (*n*=2 RCTs)						
TBWL (%)	–	NE	–	–	**8.7** [8.4,9.0]	–
MACE (OR)	–	0.9 [0.7,1.2]	–	–	**0.8** [0.7,0.9]	–
All-cause mortality (OR)	–	**0.4** [0.2,0.9]	–	–	**0.8** [0.7,0.9]	–
Acute myocardial infarction (OR)	–	1.0 [0.7,1.4]	–	–	**0.7** [0.6,0.8]	–
Stroke (OR)	–	1.0 [0.6,1.9]	–	–	0.9 [0.7,1.2]	–
Cardiovascular mortality (OR)	–	**0.5** [0.3,0.9]	–	–	0.8 [0.7,1.0]	–
Heart failure (*n*=3 RCTs)						
TBWL (%)	–	–	–	–	**8.5** [4.3,12.7]	**11.7** [10.5,11.9]
HHF (OR)	–	–	–	–	**0.2** [0.1,0.9]	**0.4** [0.2,0.9]
All-cause mortality (OR)	–	–	–	–	0.9 [0.3,2.4]	1.3 [0.6,2.6]
Cardiovascular mortality (OR)	–	–	–	–	0.3 [0.1,1.7]	1.6 [0.5,5.0]
KCCQ change (WMD)	–	–	–	–	**9.3** [7.8,10.9]	**7.5** [4.8,10.2]
6-minute walk distance (m)	–	–	–	–	**14.5** [4.8,24.3]	**20.3** [8.4,32.1]
Prediabetes (*n*=3 RCTs)						
TBWL (%)	**2.5** [1.6,3.4]	–	**4.2** [3.6,4.8]	–	**11.2** [9.5,12.9]	**19.3** [16.1,22.5]
HbA1c (WMD, mmol mol^{-1})	–	–	**−1.1** [−1.6,−0.6]	–	**−5.0** [−6.2,−3.8]	**−6.0** [−6.5,−5.5]
FPG (WMD, mg dl^{-1})	–	–	**−8.8** [−9.7,−7.9]	–	**−13.5** [−16.8,−10.1]	**−14.1** [−15.5,−12.3]
Incident diabetes (OR)	**0.6** [0.4,0.8]	–	**0.3** [0.2,0.4]	–	0.2 [0.1,1.7]	**0.1** [0.0,0.2]
Normoglycemia (OR)	–	–	**3.2** [2.7,3.9]	–	**19.6** [8.8,43.6]	**8.3** [5.5,12.4]
T2D (*n*=11 RCTs)						
TBWL (%)	**2.7** [2.1,3.2]	**3.2** [2.2,4.2]	**4.0** [3.4,4.7]	–	**6.4** [6.1,6.7]	**10.5** [9.3,11.7]
HbA1c (WMD, mmol mol^{-1})	−4.3 [−9.3,0.7]	**−5.5** [−7.2,−3.7]	−4.4 [−9.5,0.8]	–	**−15.1** [−17.0,−13.2]	**−17.0** [−18.3,−15.7]
FPG (WMD, mg dl^{-1})	−1.6 [−10.8,7.7]	**−11.9** [−19.9,−3.9]	−29.5 [−60.0,1.0]	–	**−37.8** [0.4,7.3]	**−36.0** [−44.5,−31.1]
Diabetes remission (complete, OR)	–	**2.3** [1.3,4.1]	**6.8** [4.4,10.4]	–	**12.3** [8.5,17.6]	**15.6** [11.1,21.9]
MASLD (*n*=2 RCTs)						
TBWL (%)	–	–	–	–	**8.7** [5.7,11.6]	**14.8** [13.4,16.2]
MASH remission[a]	–	–	–	–	2.0 [0.6,6.2]	**11.8** [4.3,32.5]
AST (IU l^{-1})	–	–	–	–	−7.8 [−21.2,5.6]	**−25.1** [−32.8,−17.4]
ALT (IU l^{-1})	–	–	–	–	−8.5 [−19.9,2.9]	**−29.7** [−40.2,−19.2]
Liver stiffness (kPa)	–	–	–	–	0.2 [−1.5,1.1]	**−4.3** [−6.1,−2.5]
Decrease ≥1 fibrosis stage (OR)	–	–	–	–	0.3 [0.1,1.0]	**2.5** [1.2,5.2]

https://doi.org/10.1038/s41591-025-03978-z

Table 4 (continued) | Summary report of OMM effects on critical outcomes at the endpoint for different subpopulations of patients

Outcome	Orlistat	Naltr./Bupr.	Liraglutide	Phen./Topir.	Semaglutide	Tirzepatide
Liver fat content (%)	–	–	–	–	**−4.2** [−6.0,−2.4]	**−6.0** [−8.5,−3.5]
OSAS (*n*=1 RCT)						
TBWL (%)	–	–	–	–	–	**16.7** [11.4,21.3]
OSAS[b] remission (OR)	–	–	–	–	–	**4.9** [3.1,7.6]
Reduction of at least 50% of AHI (%)	–	–	–	–	–	**−52.0** [−68.7,−35.3]
Reduction AHI (WMD, events per hour)	–	–	–	–	–	**−21.9** [−27.8,−16.3]
KOA (*n*=2 RCTs)						
TBWL (%)	–	–	–	–	**10.5** [9.8,11.2]	–
WOMAC pain score[c]	–	–	–	–	**−8.6** [−11.9,−5.3]	–
WOMAC physical function score[c]	–	–	–	–	**−14.9** [−11.9,−5.3]	–
KOOS pain subscale	–	–	1.0 [−4.2,6.2]	–	–	–
6-minute walk distance (m)	–	–	–	–	–	–
Opioid use (OR)	–	–	–	–	0.8 [0.4,1.8]	–

Data are expressed as median [interquartile range] or odds ratio (OR) [95% confidence intervals]. The ORs express the chance to obtain a BW loss of at least 5%, 10%, 15%, 20% and 25% with the interventional drug compared to the placebo group. NMA was performed only for outcomes with at least 10 RCTs; for all the other outcomes, we performed traditional meta-analyses. Bold character: $P<0.050$; '–' indicates data not available. *reported as SAEs. KOOS, Knee Injury and Osteoarthritis Outcome Score; kPa, kilopascal; Naltr./Bupr., naltrexone/bupropion; NE, not evaluated; Phen./Topir., phentermine/topiramate; SF, Short Form. KCCQ: 0–100-point scale, where lower scores represent more severe symptoms and/or limitations. [a]MASH remission: no steatotic liver disease (steatosis score of 0) or simple steatosis without steatohepatitis. [b]OSAS remission: AHI<5 or AHI of 5–14. [c]WOMAC Osteoarthritis Index expressed in points: a negative value means a reduction of pain or physical impairment.

Tirzepatide, but not semaglutide, was capable of reducing aspartate aminotransferase (AST), alanine aminotransferase (ALT) and liver stiffness levels, and it was associated with a significantly higher rate of metabolic dysfunction-associated steatohepatitis (MASH) remission and a decrease of at least one stage of liver fibrosis. Semaglutide and tirzepatide were both associated with a greater reduction of liver fat content compared to placebo (Table 4).

The GRADE evaluation of the evidence retrieved for the primary endpoint (diabetes remission; Supplementary Table 3) was rated as 'high' and 'low' for tirzepatide and semaglutide, respectively (Supplementary Table 6).

Obstructive sleep apnea syndrome. One trial with tirzepatide enrolled patients living with obesity and obstructive sleep apnea syndrome (OSAS)[43], reporting a reduction of the Apnea-Hypopnea Index (AHI) (that is, the number of apneas and hypopneas during an hour of sleep) and a higher percent reduction of AHI (Table 4).

The GRADE evaluation of the evidence retrieved for the primary endpoint (reduction of AHI episodes; Supplementary Table 3) was rated as 'moderate' for tirzepatide (Supplementary Table 6).

Knee osteoarthritis. Semaglutide[47] and liraglutide[27] were assessed in patients with obesity and knee osteoarthritis (KOA). Semaglutide, but not liraglutide[27], was capable of reducing knee pain and ameliorating physical function assessed through the Western Ontario and McMaster Universities (WOMAC) scale, as shown in the individual studies (Table 4).

The GRADE evaluation of the evidence retrieved for the primary endpoint (reduction of knee pain; Supplementary Table 3) was rated as 'moderate' for semaglutide (Supplementary Table 6) and 'low' for liraglutide.

Discussion

This systematic review and meta-analysis was aimed at investigating the efficacy of different OMMs by analyzing available evidence from clinical trials across different patient categories and obesity-related complications up until 31 January 2025. The results of the present analysis were used for the development of the EASO algorithm to guide clinicians with the pharmacological management of patients living with obesity according to specific goals, in some cases beyond weight loss, and focused on obesity-related complications.

The efficacy of currently available OMMs on TBWL is widely heterogeneous, with tirzepatide, semaglutide and, to a lesser extent, phentermine plus topiramate showing a greater efficacy than other OMMs. These differences in %TBWL were also evident in the proportion of patients reaching predefined targets of weight loss (for example, 5%, 10%, etc., of initial body weight). The results of different OMMs on waist circumference and BMI are consistent with those for TBWL. These results are in line with those reported in previous NMA and meta-analysis[20–22,24]; however, different from the above-cited papers, the main focus of this systematic review and NMA was to provide the basis for a management algorithm for the use of OMMs approved in European countries, specifically focusing on obesity-related complications. Several landmark trials, not included in the previous meta-analyses, specifically focusing on obesity-related complications (for example, osteoarthritis (STEP-9 (ref. 47)), remission of prediabetes (STEP-10 (ref. 35)), improvement in OSAS (SURMOUNT-OSA[43]) and improvement in MASH[41,42] and heart failure[44–46] (for both semaglutide and tirzepatide)), were published over the last year and have markedly moved the field forward, away from weight loss alone.

Several patient-related factors can affect the amount of weight lost with each treatment. It is plausible that patients with a higher body weight at baseline experience a greater weight loss with treatment, as

already reported in particular for MBS[40]. Differences in mean baseline BMI of patients enrolled in trials with different OMMs should be considered in the interpretation of the results of the present NMA. To address this possibility, we performed a subgroup analysis of trials, which enrolled patients in different BMI classes. Notably, few data (only with semaglutide) were available for patients with BMI over 40 kg m^{-2}, and none could be retrieved for those with BMI 27–30 kg m^{-2}. The large majority of data were collected in patients with a BMI between 35.0 kg m^{-2} and 39.9 kg m^{-2}; in this category, differences in TBWL were similar to those observed in the whole sample. However, due to the paucity of data, observed differences in efficacy cannot be generalized to patients affected by overweight (that is, with BMI 27–30 kg m^{-2}) or to those with a BMI ≥ 40 kg m^{-2}.

Most trials included in the analysis were designed with TBWL as the primary endpoint. However, some studies were designed for other purposes[17,18,30,41–44]—for example, prevention of CVD or T2D. The results on TBWL after the exclusion of trials that did not have TBWL as primary endpoint were similar to the primary analysis, strengthening the reliability of comparisons.

The presence of T2D is a negative moderator of the effects of some treatments, such as MBS, on body weight reduction[48]; however, scarce evidence is available for OMMs. The present NMA suggests that patients with T2D experience less TBWL than those without T2D; this could be partly due to differences in baseline BMI and age, because patients with T2D enrolled in trials on obesity show, on average, a lower BMI and a higher age than patients without T2D. A reduction in incretin effect in participants with T2D could contribute to the observed findings[49]. In addition, some of the patients with T2D enrolled in clinical trials may have relevant glycosuria. The improvement of glucose control, directly determined by the medication (as in the case of GLP-1 receptor and dual GLP-1/GIP receptor agonists) or consequent to weight loss, can reduce glycosuria, hampering weight loss. Moreover, background therapy, particularly some medications such as thiazolidinediones, sulfonylureas and insulin, could negatively affect the efficacy of OMM in patients with T2D.

In patients with T2D, when analyzed separately, semaglutide and tirzepatide were associated with a greater reduction of HbA1c and FPG compared to other agents, producing a T2D remission (discontinuing pharmacological treatment) in a relevant proportion of cases. In addition, semaglutide and tirzepatide appeared to be more effective than other medications in preventing incident T2D in patients with prediabetes. This is not surprising, considering that tirzepatide and semaglutide evoked more pronounced TBWL and also have glucose-lowering effects by slowing gastric emptying, stimulating insulin secretion and inhibiting glucagon secretion in a glucose-dependent manner, independent of their effects on body weight[50,51].

As anticipated, all OMMs contributed to improvements in lipid profiles, with orlistat demonstrating a greater effect on total cholesterol reduction than other agents. This aligns with its known mechanism of action, which involves the inhibition of intestinal fat absorption, leading to a reduction in serum lipid levels[52]. Most OMMs induced a reduction in triglycerides, which appeared to be greater with OMMs producing a greater weight loss, as expected[53]. Consistent with previous literature, OMMs inducing weight loss also improved blood pressure, with the notable exception of naltrexone plus bupropion, which was associated with an increase in systolic blood pressure[48]. This is a well-known side effect of naltrexone plus bupropion, and it is contraindicated in patients with uncontrolled hypertension[54].

Weight loss generally improves markers of cardiovascular risk. However, a reduction in cardiovascular risk has only been demonstrated thus far in cardiovascular outcome trials specifically designed in patients with obesity for semaglutide, whereas naltrexone plus bupropion did not show significant cardiovascular benefits. For tirzepatide, CVOTs are still not published. HHFs are reduced for both semaglutide and tirzepatide, highlighting their potential role in managing patients with concomitant heart failure. Cardiovascular mortality was significantly reduced with semaglutide and naltrexone plus bupropion, whereas the impact of tirzepatide cannot yet be established, as CVOTs are currently being analyzed.

Weight reduction has long been considered a cornerstone in the management of OSAS and KOA. Tirzepatide produces a significant reduction in the AHI, reinforcing its potential role in OSAS management. Similarly, semaglutide demonstrated efficacy in reducing knee pain and improving physical function in patients with KOA. Although those benefits have been demonstrated only for specific OMMs (that is, tirzepatide for OSAS and semaglutide for KOA), it is plausible that these effects are largely driven by weight reduction rather than by unique pharmacodynamic properties of each molecule[55,56].

Only one phase 2 trial performed on tirzepatide[41] showed promising results in improving MASH and liver fibrosis. After 31 January 2025 (deadline for our trials retrieval process), a further trial on semaglutide reported significant improvement of MASH and liver fibrosis[57]; this trial will, therefore, be considered in the next update of the present systemic review and meta-analysis.

Despite their critical role in clinical practice, QoL and mental health have been infrequently studied in clinical trials, limiting the strength of conclusions regarding the impact of OMMs on these outcomes. In the few trials that assessed QoL, semaglutide and naltrexone plus bupropion determined marginal improvements. Future studies should prioritize the inclusion of QoL assessments to better understand the real-world impact of these treatments. Notably, there were no concerns regarding suicide risk or major depressive events across the included trials[55,56]. This finding is reassuring given previous concerns regarding potential psychiatric adverse effects of weight loss pharmacotherapies[58].

All OMMs demonstrated a generally favorable safety profile, but there were differences in SAE rates across interventions. SAEs were not significantly increased with any OMM, except for naltrexone plus bupropion, which showed a higher SAE rate compared to placebo. However, the long-term safety of these medications, including their potential associations with cancer risk[59] and other uncommon events, warrants further investigation.

It is important to acknowledge that obesity is a chronic disease, and OMMs should be used long term to manage the disease. However, it is increasingly evident that OMMs are often used only for limited durations, with discontinuation rates of 50–60% within 1 year[60], which can have an impact on weight regain and remission of obesity-related complications. Evidence from the SCALE Obesity and Prediabetes trial[31], the SURMOUNT-4 trial with tirzepatide[33] and the STEP-1 extension trial[33] and STEP-10 (ref. 35) with semaglutide has clearly shown significant weight regain after discontinuation of treatment. The STEP-10 trial with semaglutide in patients with prediabetes has shown increased rates of progression to T2D after stopping OMM after 28 weeks[35]. As more trials emerge in the future showing the effect of discontinuation of OMMs on weight and obesity-related complications, the extent of weight regain and worsening of clinical outcomes will become clearer[60].

The scope of this NMA was to compare the effectiveness of OMMs for the treatment of obesity and obesity-related complications. For this reason, only RCTs on OMMs were considered, whereas studies on lifestyle and bariatric surgery were not included in this systematic review. Of note, it is important to highlight that lifestyle interventions can significantly improve cardio-metabolic and mental health. For example, lifestyle interventions can lead to remission of early T2D and prediabetes[61]. MBS can achieve sustained long-term remission of T2D[62], although remission rates decrease significantly over time. MBS has shown reductions in MACE and improvements in heart failure and nephropathy[63], among other obesity-related complications in people living with obesity. The choice between different interventions is beyond the scope of this paper, and the clinical decision should be individualized and based on multidisciplinary discussions.

However, for the present NMA, several limitations should be acknowledged. Heterogeneity in study populations, with variability in baseline BMI, age and obesity-related complication among trial participants, may influence treatment effects. Notably, limited data were available for people with BMI ≥ 40 kg m^{-2}, the elderly, adolescents and people with overweight (BMI ≥ 25 kg m^{-2} and <30 kg m^{-2}). Most trials were placebo controlled, limiting the number of head-to-head comparisons that could be performed. In addition, the varying intensity of lifestyle interventions in the placebo groups of the different trials may further influence the results for comparative purposes. Furthermore, many trials lacked comprehensive reporting for key outcomes such as body composition changes, long-term safety, lifestyle interventions and metabolic effects beyond glycemic control. Data on weight maintenance, metabolic effects and SAEs longer than 2 years remain scarce, limiting insights into the durability of treatment benefits. Another relevant limitation of this NMA is the potential for inconsistency. NMAs integrate evidence from multiple trials by assuming that the relative effect of a given intervention is consistent across all included studies. This requires homogeneity in study design and participant characteristics, which may have not always been met. Although no significant inconsistency was detected in the primary analyses ($H < 3$), differences in trial populations and methodologies should be considered when interpreting results.

Furthermore, despite the importance of tailoring the treatment for obesity to the characteristics of the patients, only a few trials reported subgroup analyses (for example, BMI and age categories, ethnicity, gender, etc.), making the assessment of the effects of these parameters on TBWL and remission of obesity-related complications very difficult.

Disparities exist in the regulatory approval and availability of OMMs across different countries[64–66]. For instance, although phentermine is an approved pharmacological agent in some countries, it is not approved by the regulatory authorities in others. These regulatory inconsistencies raise equity concerns, as access to effective obesity pharmacotherapy remains variable across populations. Addressing these disparities is crucial to ensuring equitable management opportunities for people with obesity worldwide.

This network meta-analysis concludes the need to tailor obesity pharmacotherapy to the severity and type of obesity-related complications, as certain medications demonstrate more pronounced effects on body weight and/or specific obesity complications than others. Although the focus of this analysis is on the choice of OMMs for individual obesity-related complications, we strongly advocate intervention with OMMs early in the obesity pathway to prevent the development of obesity-related complications. Overall, most OMMs are effective and safe for promoting total body weight loss and improving obesity-related complications. However, the impact of OMMs on specific complications still requires further investigation, and the information already published in 2025 reflects a rapidly evolving field that will need ongoing updates.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-025-03978-z.

References

1. *World Obesity Atlas 2025*. https://www.worldobesityday.org/assets/downloads/World_Obesity_Atlas_2025.pdf (World Obesity Federation, 2025).
2. Lingvay, I., Cohen, R. V., Roux, C. W. L. & Sumithran, P. Obesity in adults. *Lancet* **404**, 972–987 (2024).
3. Nagi, M. A. et al. Economic costs of obesity: a systematic review. *Int. J. Obes. (Lond.)* **48**, 33–43 (2024).
4. Wadden, T. A. et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int. J. Obes. (Lond.)* **37**, 1443–1451 (2013).
5. Wadden, T. A. et al. Four-year weight losses in the Look AHEAD study: factors associated with long-term success. *Obes. (Silver Spring)* **19**, 1987–1998 (2011).
6. Frühbeck, G. et al. The ABCD of obesity: an EASO position statement on a diagnostic term with clinical and scientific implications. *Obes. Facts* **12**, 131–136 (2019).
7. Sominsky, L. & Spencer, S. J. Eating behavior and stress: a pathway to obesity. *Front. Psychol.* **5**, 434 (2014).
8. Hall, K. D. et al. The energy balance model of obesity: beyond calories in, calories out. *Am. J. Clin. Nutr.* **115**, 1243–1254 (2022).
9. Herrera, B. M. & Lindgren, C. M. The genetics of obesity. *Curr. Diab. Rep.* **10**, 498–505 (2010).
10. De Luca, M. et al. Development of the International Federation for Surgery of Obesity and Metabolic Disorders-European Chapter (IFSO-EC) grade-based guidelines on the surgical treatment of obesity using multimodal strategies: design and methodological aspects. *J. Clin. Med.* **13**, 5106 (2024).
11. De Luca, M. et al. SICOB Italian clinical practice guidelines for the surgical treatment of obesity and associated diseases using GRADE methodology on bariatric and metabolic surgery. *Updates Surg.* **77**, 1603–1625 (2024).
12. Di Lorenzo, N. et al. Clinical practice guidelines of the European Association for Endoscopic Surgery (EAES) on bariatric surgery: update 2020 endorsed by IFSO-EC, EASO and ESPCOP. *Surg. Endosc.* **34**, 2332–2358 (2020).
13. Jeon, E., Lee, K. Y. & Kim, K. K. Approved anti-obesity medications in 2022 KSSO guidelines and the promise of phase 3 clinical trials: anti-obesity drugs in the sky and on the horizon. *J. Obes. Metab. Syndr.* **32**, 106–120 (2023).
14. Sandforth, A. et al. Mechanisms of weight loss-induced remission in people with prediabetes: a post-hoc analysis of the randomised, controlled, multicentre Prediabetes Lifestyle Intervention Study (PLIS). *Lancet Diabetes Endocrinol.* **11**, 798–810 (2023).
15. Sandforth, L. et al. Subphenotype-dependent benefits of bariatric surgery for individuals at risk for type 2 diabetes. *Diabetes Care* **48**, 996–1006 (2025).
16. Perdomo, C. M., Cohen, R. V., Sumithran, P., Clément, K. & Frühbeck, G. Contemporary medical, device, and surgical therapies for obesity in adults. *Lancet* **401**, 1116–1130 (2023).
17. Lincoff, A. M. et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N. Engl. J. Med.* **389**, 2221–2232 (2023).
18. Nissen, S. E. et al. Effect of naltrexone-bupropion on major adverse cardiovascular events in overweight and obese patients with cardiovascular risk factors: a randomized clinical trial. *JAMA* **315**, 990–1004 (2016).
19. Astrup, A. et al. Safety, tolerability and sustained weight loss over 2 years with the once-daily human GLP-1 analog, liraglutide. *Int. J. Obes. (Lond.)* **36**, 843–854 (2012).
20. Khera, R. et al. Effects of weight-loss medications on cardiometabolic risk profiles: a systematic review and network meta-analysis. *Gastroenterology* **154**, 1309–1319 (2018).
21. Iannone, A. et al. Clinical outcomes associated with drugs for obesity and overweight: a systematic review and network meta-analysis of randomized controlled trials. *Diabetes Obes. Metab.* **25**, 2535–2544 (2023).
22. Shi, Q. et al. Pharmacotherapy for adults with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet* **403**, e21–e31 (2024).

23. De Luca, M. et al. Bariatric surgery for patients with overweight/obesity. a comprehensive grading methodology and network metanalysis of randomized controlled trials on weight loss outcomes and adverse events. *Obes. Surg.* **33**, 4147–4158 (2023).
24. Liu, L. et al. Safety and effects of anti-obesity medications on weight loss, cardiometabolic, and psychological outcomes in people living with overweight or obesity: a systematic review and meta-analysis. *EClinicalMedicine* **79**, 103020 (2025).
25. Busetto, L. et al. A new framework for the diagnosis, staging and management of obesity in adults. *Nat. Med.* **30**, 2395–2399 (2024).
26. Rubino, D. M. et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. *JAMA* **327**, 138–150 (2022).
27. Gudbergsen, H. et al. Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. *Am. J. Clin. Nutr.* **113**, 314–323 (2021).
28. Karhunen, L. et al. Effect of orlistat treatment on body composition and resting energy expenditure during a two-year weight-reduction programme in obese Finns. *Int. J. Obes. Relat. Metab. Disord.* **24**, 1567–1572 (2000).
29. Richelsen, B. et al. Effect of orlistat on weight regain and cardiovascular risk factors following a very-low-energy diet in abdominally obese patients: a 3-year randomized, placebo-controlled study. *Diabetes Care* **30**, 27–32 (2007).
30. Swinburn, B. A. et al. Effect of orlistat on cardiovascular disease risk in obese adults. *Diabetes Obes. Metab.* **7**, 254–262 (2005).
31. le Roux, C. W. et al. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet* **389**, 1399–1409 (2017).
32. Torgerson, J. S., Hauptman, J., Boldrin, M. N. & Sjöström, L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* **27**, 155–161 (2004).
33. Aronne, L. J. et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: the SURMOUNT-4 randomized clinical trial. *JAMA* **331**, 38–48 (2024).
34. Wilding, J. P. H. et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. *Diabetes Obes. Metab.* **24**, 1553–1564 (2022).
35. McGowan, B. M. et al. Efficacy and safety of once-weekly semaglutide 2·4 mg versus placebo in people with obesity and prediabetes (STEP 10): a randomised, double-blind, placebo-controlled, multicentre phase 3 trial. *Lancet Diabetes Endocrinol.* **12**, 631–642 (2024).
36. Jastreboff, A. M. et al. Tirzepatide for obesity treatment and diabetes prevention. *N. Engl. J. Med.* **392**, 958–971 (2025).
37. Lundgren, J. R. et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. *N. Engl. J. Med.* **384**, 1719–1730 (2021).
38. Wilding, J. P. H. et al. Once-weekly semaglutide in adults with overweight or obesity. *N. Engl. J. Med.* **384**, 989–1002 (2021).
39. Kadowaki, T. et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. *Lancet Diabetes Endocrinol.* **10**, 193–206 (2022).
40. Valera-Mora, M. E. et al. Predictors of weight loss and reversal of comorbidities in malabsorptive bariatric surgery. *Am. J. Clin. Nutr.* **81**, 1292–1297 (2005).
41. Loomba, R. et al. Tirzepatide for metabolic dysfunction-associated steatohepatitis with liver fibrosis. *N. Engl. J. Med.* **391**, 299–310 (2024).
42. Loomba, R. et al. Semaglutide 2·4 mg once weekly in patients with non-alcoholic steatohepatitis-related cirrhosis: a randomised, placebo-controlled phase 2 trial. *Lancet Gastroenterol. Hepatol.* **8**, 511–522 (2023).
43. Malhotra, A. et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. *N. Engl. J. Med.* **391**, 1193–1205 (2024).
44. Packer, M. et al. Tirzepatide for heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* **392**, 427–437 (2025).
45. Kosiborod, M. N. et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N. Engl. J. Med.* **389**, 1069–1084 (2023).
46. Kosiborod, M. N. et al. Semaglutide in patients with obesity-related heart failure and type 2 diabetes. *N. Engl. J. Med.* **390**, 1394–1407 (2024).
47. Bliddal, H. et al. Once-weekly semaglutide in persons with obesity and knee osteoarthritis. *N. Engl. J. Med.* **391**, 1573–1583 (2024).
48. Müller, T. D., Blüher, M., Tschöp, M. H. & DiMarchi, R. D. Anti-obesity drug discovery: advances and challenges. *Nat. Rev. Drug Discov.* **21**, 201–223 (2022).
49. Nauck, M. A. & Meier, J. J. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol.* **4**, 525–536 (2016).
50. Nauck, M. A. & D'Allesio, D. A. Tirzepatide, a dual GIP/GLP-1 receptor co-agonist for the treatment of type 2 diabetes with unmatched effectiveness regrading glycaemic control and body weight reduction. *Cardiovasc. Diabetol.* **21**, 169 (2022).
51. Heise, T. et al. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. *Lancet Diabetes Endocrinol.* **10**, 418–429 (2022).
52. Mittendorfer, B., Ostlund, R. E. Jr., Patterson, B. W. & Klein, S. Orlistat inhibits dietary cholesterol absorption. *Obes. Res.* **9**, 599–604 (2001).
53. Purnell, J. Q. et al. Effect of weight loss with reduction of intra-abdominal fat on lipid metabolism in older men. *J. Clin. Endocrinol. Metab.* **85**, 977–982 (2000).
54. Sherman, M. M., Ungureanu, S. & Rey, J. A. Naltrexone/bupropion ER (Contrave): newly approved treatment option for chronic weight management in obese adults. *P T* **41**, 164–172 (2016) .
55. Pierret, A. C. S. et al. Glucagon-like peptide 1 receptor agonists and mental health: a systematic review and meta-analysis. *JAMA Psychiatry* **82**, 643–653 (2025).
56. Schoretsanitis, G., Weiler, S., Barbui, C., Raschi, E. & Gastaldon, C. Disproportionality analysis from World Health Organization data on semaglutide, liraglutide, and suicidality. *JAMA Netw. Open* **7**, e2423385 (2024).
57. Sanyal, A. J. et al. Phase 3 trial of semaglutide in metabolic dysfunction-associated steatohepatitis. *N. Engl. J. Med.* **392**, 2089–2099 (2025).
58. Harding, S. Mental health implications of weight loss medications: a narrative review. *J. Nurse Pract.* **20**, 105207 (2024).
59. Silverii, G. A. et al. Glucagon-like peptide-1 receptor agonists and risk of thyroid cancer: a systematic review and meta-analysis of randomized controlled trials. *Diabetes Obes. Metab.* **26**, 891–900 (2024).

60. Rodriguez, P. J. et al. Discontinuation and reinitiation of dual-labeled GLP-1 receptor agonists among US adults with overweight or obesity. *JAMA Netw. Open* **8**, e2457349 (2025).
61. Lean, M. E. et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* **391**, 541–551 (2018).
62. Courcoulas, A. P. et al. Long-term outcomes of medical management vs bariatric surgery in type 2 diabetes. *JAMA* **331**, 654–664 (2024).
63. Mentias, A. et al. Trends and outcomes associated with bariatric surgery and pharmacotherapies with weight loss effects among patients with heart failure and obesity. *Circ. Heart Fail.* **17**, e010453 (2024).
64. Heal, D. J., Gosden, J. & Smith, S. L. Regulatory challenges for new drugs to treat obesity and comorbid metabolic disorders. *Br. J. Clin. Pharm.* **68**, 861–874 (2009).
65. Roser, P., Bajaj, S. S. & Stanford, F. C. International lack of equity in modern obesity therapy: the critical need for change in health policy. *Int. J. Obes. (Lond.)* **46**, 1571–1572 (2022).
66. Berning, P. et al. Longitudinal analysis of obesity drug use and public awareness. *JAMA Netw. Open* **8**, e2457232 (2025).

[1]Department of Endocrinology and Diabetes, Guy's & St. Thomas' Hospital NHS Trust, London, UK. [2]Diabetes and Metabolism Research Group, VHIR, Department of Endocrinology, Vall d'Hebron University Hospital, Autonomous University Barcelona, Barcelona, Spain. [3]CIBERDEM (Instituto de Salud Carlos III), Madrid, Spain. [4]Center for Clinical Research and Prevention, Copenhagen University Hospital-Bispebjerg and Frederiksberg, Frederiksberg, Denmark. [5]Department of Medicine, University of Padova, Padova, Italy. [6]Internal Medicine D and Obesity Clinic, Hasharon Hospital-Rabin Medical Center, Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel. [7]Department of Endocrinology & Nutrition, Clínica Universidad de Navarra, CIBEROBN - Instituto de Salud Carlos III, IdiSNA, Pamplona, Spain. [8]Department of Human Biology, Institute of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Center+, Maastricht, The Netherlands. [9]Diabetes Unit, Careggi Teaching Hospital and University of Florence, Florence, Italy. [10]Department of Systems Medicine, University of Rome Tor Vergata, Rome, Italy. [11]Department of Nursing, Physiotherapy and Medicine, CIBIS Research Center, University of Almería, Almería, Spain. [12]CIBEROBN, Instituto de Salud Carlos III, Granada, Spain. [13]European Association for the Study of Obesity, Teddington, Ireland. [14]Division of Endocrinology, Metabolism and Diabetes, Istanbul University-Cerrahpaşa, Cerrahpaşa Medical Faculty, Istanbul, Turkey. [15]These authors contributed equally: Barbara McGowan, Andreea Ciudin. ✉e-mail: barbaramcgowan@nhs.net; andreea.ciudin@vallhebron.cat

Methods

This NMA is reported following the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 7).

Study search and selection

The protocol for this meta-analysis and NMA was published on the PROSPERO website (https://www.crd.york.ac.uk/prospero/#recordDetails; registration number CRD42024625338) and in a previous article[67]. The present analysis included all placebo-controlled or active-controlled RCTs that enrolled adults (≥18 years) with obesity (BMI ≥ 30 kg m^{-2}) or overweight (BMI > 25 kg m^{-2}), with a treatment duration of at least 48 weeks, which compared OMMs with the specific indication of obesity treatment with either placebo or other OMM. Furthermore, the RCTs needed to be performed on OMMs approved by the European Medicines Agency and on OMMs available in at least one EASO member country as of 31 January 2025. The OMMs and doses included were as follows: orlistat (360 mg), phentermine plus topiramate (15/92 mg), naltrexone plus bupropion (32/360 mg), liraglutide (3.0 mg), semaglutide (2.4 mg) and tirzepatide (10–15 mg).

A Medline and Embase search was performed up to 31 January 2025 using the following search string: "(obesity or overweight) AND (orlistat OR phentermine OR topiramate OR naltrexone OR bupropion OR liraglutide OR semaglutide OR tirzepatide)".

Medline: (("obeses"[All Fields] OR "obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields] OR "obesities"[All Fields] OR "obesity s"[All Fields] OR ("overweight"[MeSH Terms] OR "overweight"[All Fields] OR "overweighted"[All Fields] OR "overweightness"[All Fields] OR "overweights"[All Fields])) AND ("orlistat"[MeSH Terms] OR "orlistat"[All Fields] OR "orlistat s"[All Fields] OR ("phentermine"[MeSH Terms] OR "phentermine"[All Fields]) OR ("topiramate"[MeSH Terms] OR "topiramate"[All Fields] OR "topiramate s"[All Fields]) OR ("naltrexone"[MeSH Terms] OR "naltrexone"[All Fields] OR "naltrexon"[All Fields] OR "naltrexone s"[All Fields]) OR ("bupropion"[MeSH Terms] OR "bupropion"[All Fields] OR "amfebutamone"[All Fields] OR "bupropion s"[All Fields] OR "bupropione"[All Fields]) OR ("liraglutid"[All Fields] OR "liraglutide"[MeSH Terms] OR "liraglutide"[All Fields] OR "liraglutide s"[All Fields]) OR ("semaglutide"[Supplementary Concept] OR "semaglutide"[All Fields]) OR ("tirzepatide"[MeSH Terms] OR "tirzepatide"[All Fields]))) AND (randomizedcontrolledtrial[Filter])

Translations

obesity: "obeses"[All Fields] OR "obesity"[MeSH Terms] OR "obesity"[All Fields] OR "obese"[All Fields] OR "obesities"[All Fields] OR "obesity's"[All Fields] overweight: "overweight"[MeSH Terms] OR "overweight"[All Fields] OR "overweighted"[All Fields] OR "overweightness"[All Fields] OR "overweights"[All Fields] orlistat: "orlistat"[MeSH Terms] OR "orlistat"[All Fields] OR "orlistat's"[All Fields] phentermine: "phentermine"[MeSH Terms] OR "phentermine"[All Fields] topiramate: "topiramate"[MeSH Terms] OR "topiramate"[All Fields] OR "topiramate's"[All Fields] naltrexone: "naltrexone"[MeSH Terms] OR "naltrexone"[All Fields] OR "naltrexon"[All Fields] OR "naltrexone's"[All Fields] bupropion: "bupropion"[MeSH Terms] OR "bupropion"[All Fields] OR "amfebutamone"[All Fields] OR "bupropion's"[All Fields] OR "bupropione"[All Fields] liraglutide: "liraglutid"[All Fields] OR "liraglutide"[MeSH Terms] OR "liraglutide"[All Fields] OR "liraglutide's"[All Fields] semaglutide: "semaglutide"[Supplementary Concept] OR "semaglutide"[All Fields]

tirzepatide: "tirzepatide"[MeSH Terms] OR "tirzepatide"[All Fields]

Embase: ('obesity'/exp OR obesity OR 'overweight'/exp OR overweight) AND ('orlistat'/exp OR orlistat OR 'phentermine'/exp OR phentermine OR 'topiramate'/exp OR topiramate OR 'naltrexone'/exp OR naltrexone OR 'bupropion'/exp OR bupropion OR 'liraglutide'/exp OR liraglutide OR 'semaglutide'/exp OR semaglutide OR 'tirzepatide'/exp OR tirzepatide) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND ('phase 3 clinical trial'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial topic'/de).

Duplicate records were removed with EndNote X9 (Clarivate Analytics).

Data extraction

Information on the baseline characteristics of the samples enrolled included age, gender, proportion of patients with T2D, baseline BMI, TBWL%, waist circumference, body composition, proportion of patients achieving at least 5%, 10%, 15%, 20%, and 25% body weight reduction, remission or improvement/resolution of obesity-related complications, SAE, mortality, MACE, FPG, HbA1c, lipid profile, estimated glomerular filtration rate (eGFR), creatinine, albuminuria, mental health parameters and QoL. Two authors performed data extraction independently (B.R. and E.M), and conflicts were resolved by a third investigator (M.M.).

Quality assessment

The risk of bias was assessed using the Cochrane-recommended tool to determine the risk of bias in RCTs[68]. The risk of bias was described and evaluated in seven specific domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases. The results of these domains were graded as low, high or uncertain risk of bias. Two researchers (B.R. and E.M.) independently assessed the risk of bias in individual studies, with discrepancies resolved by a third researcher (M.M.).

Data analysis

All included trials. The principal endpoint was TBWL% at the end of the trial period; secondary endpoints included:

a. TBWL% at 52 weeks, 53–104 weeks, 105–156 weeks and >156 weeks
b. Change in endpoint BMI and waist circumference
c. Change in total fat mass, subcutaneous fat mass and visceral fat mass
d. Change in fat-free mass
e. The proportion of patients achieving at least 5%, 10%, 15%, 20% and 25% body weight reduction
f. T2D, hypertension and dyslipidemia remission. T2D remission was defined as HbA1c < 6.5% at endpoint[69].
g. MASH resolution (defined as no steatotic liver disease without worsening of fibrosis) and improvement of liver fibrosis (defined as a decrease of at least one fibrosis stage without worsening of MASH[29,30]). OSAS resolution (defined as AHI < 5 or AHI of 5–14 (ref. 31)) and improvement of KOA (improvement in pain/physical functioning items of any validated scale assessing QoL in patients with KOA).
h. Reduction in HHF, considering only studies in which these events were formally adjudicated
i. Any SAE
j. All-cause mortality
k. MACE (composite of non-fatal myocardial infarction, non-fatal stroke and cardiovascular mortality), considering only studies in which these events were formally adjudicated
l. Endpoint FPG, HbA1c, lipid profile, eGFR, creatinine and albuminuria
m. Change in mental health parameters
n. QoL

All the endpoints, except point (a), were collected at the end of the trials.

Trials performed in populations with pre-existing comorbid conditions. Trials performed in specific populations of patients with obesity and other comorbid conditions were also analyzed separately. For all the above-reported conditions, only adjudicated events were considered.

T2D: Primary endpoint: complete T2D remission

Other critical endpoints: body weight reduction (TBWL%), lipid and blood pressure profile, renal function and improvement of metabolic control (HbA1c and FPG)

Pre-diabetes: Primary endpoint: normoglycemia restoration*

Other critical endpoints: body weight reduction (TBWL%), lipid and blood pressure profile, renal function, reduction of incident T2D* and improvement of metabolic control (HbA1c and FPG)

Established CVD: Primary endpoint: incidence reduction of MACE*

Other critical endpoints: body weight reduction (TBWL%) and all-cause and cardiovascular mortality reduction

Heart failure: Primary endpoint: reduction of HHF

Other critical endpoints: body weight reduction (TBWL%), incidence of MACE*, improvement of KCCQ clinical summary score, change in 6-minute walking test distance and all-cause and cardiovascular mortality reduction

OSAS: Primary endpoint: OSAS remission

Other critical endpoints: body weight reduction (TBWL%) and improvement of parameters evaluating apnea*

MASLD: Primary endpoint: MASH remission

Other critical endpoints: body weight reduction (TBWL%) and improvement of fibrosis and liver indexes

KOA: Primary endpoint: KOA improvement assessed with scales evaluating osteoarthritis outcome scores (WOMAC Osteoarthritis Index–pain and physical function score)

Other critical endpoints: body weight reduction (TBWL%), improvement of 6-minute walking distance and opioid use

Statistical analyses

NMAs were performed only for outcomes with at least 10 RCTs. For all other outcomes, when supported by data, traditional meta-analyses were performed, as specified in a previous publication[67]. As there is still a lack of RCT data for some outcomes and subgroup analyses, in cases where there was only one RCT in each subgroup we presented the findings descriptively, as a meta-analysis may have been misleading. Mean and 95% confidence intervals for continuous variables and Mantel–Haenzel odds ratio for categorical variables were calculated, using random effect models. When data were reported as least-squares mean and s.e., the s.d. was obtained for each group using the following formula: s.d. = √(number of patients) × (confidence interval upper limit − confidence interval lower limit) / 3.92 and s.d. = √(number of patients) × s.e., respectively (http://handbook-5-1.cochrane.org/chapter_7/7_7_3_2_obtaining_standard_deviations_from_standard_errors_and.htm).

Prespecified subgroup analyses were performed for the following baseline variables: different OMMs, BMI categories (mean BMI at enrollment <30, 30–34.9, 35–39.9 and >40 kg m^{-2}), T2D (RCT enrolling at least 75% of patients with diabetes), prediabetes[70] and previous established CVD, heart failure, KOA, MASLD and OSAS. A further subgroup analysis was performed only for body weight parameters (that is, TBWL%, waist circumference, BMI and proportion of patients achieving at least 5%, 10%, 15%, 20% and 25% of body weight reduction) in RCTs specifically designed for body weight reduction.

Supplementary Table 3 reports the principal endpoints (together with other critical endpoints) for all these subpopulations of patients with obesity.

Heterogeneity was assessed by using the I^2 statistic. Random effect models were applied for all the analyses reported above.

We performed an NMA[71] for all outcomes listed above to examine differences across individual OMMs and their effects on primary and secondary endpoints. These analyses allowed indirect comparisons when direct trials were unavailable, using differences from common comparators and then combining direct and indirect comparisons for a final estimate of effects. The reference category was placebo. We performed NMA within a generalized pairwise modelling framework using the software program MetaXL (https://www.epigear.com/). *H* values were calculated to test consistency between direct and indirect evidence; $H < 3$ indicates minimal inconsistency of treatment effects.

All other analyses were performed using Review Manager (RevMan) version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

The GRADE methodology[72] was used to assess the quality of the body of retrieved evidence for the principal endpoint, with GRADEpro GDT software (GRADEpro Guideline Development Tool; https://www.gradepro.org/).

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

All data and results associated with the dataset are available in the main text and in the Supplementary Information. Any other material associated with this paper will be shared upon reasonable request.

References

67. McGowan, B. et al. Development of the European Association for the Study of Obesity (EASO) grade-based framework on the pharmacological treatment of obesity: design and methodological aspects. *Obes. Facts* https://doi.org/10.1159/000546855 (2025).
68. Higgins, J. P. et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* **343**, d5928 (2011).
69. Diabetes UK interim position statement on remission in adults with type 2 diabetes (Diabetes UK, 2018); https://www.diabetes.org.uk/sites/default/files/2021-08/DIABETES%20UK%20UPDATED%20POSITION%20STATEMENT%20ON%20REMISSION%20IN%20ADULTS%20-%20FINAL_0.pdf
70. Stepanek, L. et al. Significance of prediabetes as a nosological entity. *Biomed. Pap. Med. Fac. Univ. Palacky Olomouc Czech Repub.* https://doi.org/10.5507/bp.2018.057 (2018).
71. Madden, L. V., Piepho, H. P. & Paul, P. A. Statistical models and methods for network meta-analysis. *Phytopathology* **106**, 792–806 (2016).
72. Guyatt, G. H. et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *J. Clin. Epidemiol.* **66**, 158–172 (2013).

Acknowledgements

The authors would like to thank E. Mannucci and B. Ragghianti for their external support in collecting data and revising the final draft of the present manuscript.

Author contributions

All authors approved the final version of the manuscript. B.M. takes full responsibility for the work as a whole, including the study design, access to data and the decision to submit and publish the manuscript[2]. Authors involvement in each of the following points include: design: B.M., A.C., L.B., M.M., D.D., G.F., G.H.G., P.S. and V.Y.; data collection: M.M., B.R. and B.M.-T.; analysis: M.M. and B.R.; editing the manuscript: B.M., A.C., M.M., D.D., B.M.-T., G.H.G. and P.S.; and review of the final draft: all authors.

Competing interests

B.M. has received speaker and/or advisory fees from Novo Nordisk, Eli Lilly, AstraZeneca, Janssen, Pfizer and Merck Sharp & Dohme and a research grant from Novo Nordisk. B.M. is a shareholder of Reset Health. A.C. has received speaking fees from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sanofi and Menarini and research grants from Eli Lilly, Novo Nordisk and Menarini. A.C. is also a member of the Data Monitoring Committee of Boehringer Ingelheim. J.L.B. has received a consulting fee and is an advisory board member for Novo Nordisk, with fees paid to her institution. L.B. has received payment of honoraria from Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Pfizer, Bruno Farmaceutici, Regeneron, Rythm Pharmaceuticals and Pronokal as speaker and/or member of advisory boards. D.D. has received speaker and advisory board fees from Boehringer Ingelheim, Eli Lilly, Novo Nordisk and AstraZeneca and research grants from Eli Lilly, Novo Nordisk and Boehringer Ingelheim. G.F. has received payment of honoraria from Eli Lilly, Novo Nordisk, Regeneron and AstraZeneca as speaker and/or member of advisory boards and payment of honoraria as member of the OPEN Spain Initiative. G.H.G. has no relevant conflicts of interest to declare related to this article. M.M. has received speaking fees from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi and Novartis and research grants from Bristol Myers Squibb. P.S. received payment of honoraria and consulting fees from Boehringer Ingelheim, Chiesi, Novo Nordisk, Eli Lilly, Pfizer and Roche as a member of advisory boards. B.M.-T. has received grants from the EASO New Clinical Investigator Award 2024 and the EFSD Rising Star 2024, both supported by the Novo Nordisk Foundation. E.W. has no conflicts of interest to declare. V.Y. was engaged in advisory boards and lectures with Novo Nordisk, Eli Lilly, Rhythm and Regeneron.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41591-025-03978-z.

Correspondence and requests for materials should be addressed to Barbara McGowan or Andreea Ciudin.

Peer review information *Nature Medicine* thanks Andreas Birkenfeld and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. Primary Handling Editor: Ming Yang, in collaboration with the *Nature Medicine* team.

nature portfolio

Corresponding author(s): Andreea Ciudin

Last updated by author(s): 2025/08/04

Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐	☒ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Endnote; MetaXL; GRADEpro; RevMan 5.0
Data analysis	RevMan 5.0 was used to perform traditional meta-analyses. MetaXL was usewd for network meta-analyses; Endnote was used for storing and removing duplicates; GRADE Pro was uiede for rating the quality of the retrieved evidence.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

"The authors confirm that the data supporting this study's findings are available within the article and its supplementary materials. A full version of the dataset containing all the extracted variables is available from the corresponding author (A.C.) on request."

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	NA; this study is a meta-analysis. We did not report any analyses stratified for gender.
Reporting on race, ethnicity, or other socially relevant groupings	NA; this study is a meta-analysis. We did not report any analyses stratified for ethnicity.
Population characteristics	NA; this study is a meta-analysis.
Recruitment	NA; this study is a meta-analysis.
Ethics oversight	NA; this study is a meta-analysis.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	NA; this study is a meta-analysis.
Data exclusions	The present analysis excluded RCTs perfomed in subjects aged <18 years, with body mass index<25 kg/m2. RCTs with a treatment duration/ follow-up <48 weeks and comparing obesity management medications not used in EASO member countries were excluded as well.
Replication	NA; this study is a meta-analysis.
Randomization	NA; this study is a meta-analysis.
Blinding	NA; this study is a meta-analysis.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	NA; this study is a meta-analysis on humans.
Novel plant genotypes	NA; this study is a meta-analysis on humans.
Authentication	NA; this study is a meta-analysis on humans.